UNIVERSITY OF BIRMINGHAM

Diastereoselective Synthesis of 2,4,5-Trisubstituted Piperidines – Application in Natural Product Synthesis

By

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Abstract

This thesis describes the diastereoselective synthesis of 2,4,5-trisubstituted piperidines using carbonyl-ene and Prins cyclisations and their application in natural product synthesis. Following on from previous work in the group, we investigated how a preinstalled substituent in the 2-position can help to control the sense of induction at the two newly forming stereocentres.

We utilised the Prins reaction in the formal synthesis of pseudodistomin F, a marine alkaloid that posses a 2,4,5-tribsubstituted piperidine core. An initial first generation synthesis focused on the construction of a cyclisation precursor containing a crotyl-ene component, however, cyclisation with anhydrous hydrogen chloride at -78 °C resulted in side product formation, presumably resulting from the relative instability of the secondary carbocation. Changing the ene component to a prenyl group resulted in successful cyclisation to yield the *trans*, *cis*-2,4,5-trisubstituted piperidine, with diastereomeric ratios of up to 200:1. An improved second generation synthesis completed the formal synthesis of pseudodistomin F on a multi-gram scale. Progress towards the total synthesis of pseudodistomin F by a third generation synthesis was undertaken.

An investigation into how varying the electronics of the Prins reaction would alter the diastereoselectivity was conducted with a range of *para*-substituted cinnamyl substrates. The results indicated that selectivity in favour of the *trans* diastereomer was favoured as the electron withdrawing power of the substituent increased.

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List of Abbreviations

Å	Angstrom (10^{-10} metre)
Ac	acetyl
app.	apparent
(aq)	aqueous
Ar	aromatic
atm	atmosphere
B	base
BA	Brønsted acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
n-Bu	butyl
Bz	benzoyl
c	concentration
°C	degrees Celsius
cat.	catalytic or catalyst
CDI	1,1'-carbonyldiimidazole
CSI	chlorosulfonyl isocyanate
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	dichloroethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DPPA	diphenylphosorylazide
dr	diastereoisomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-mehtylpyrdine
DTBS	di-*tert*-butyldimethylsilyl
ee	enantiomeric excess
EI	electron impact
eq	equivalent(s)
er	enantiomeric ratio
ES	electrospray ionization
Et	ethyl
FMO	frontier molecular orbital
g	gram(s)
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared (spectroscopy)

J	coupling constant
KHMDS	potassium hexamehtyldisilazide
L	litre(s)
LA	Lewis acid
lit.	literature value
LUMO	lowest occupied molecular orbital
m	milli or multiplet
M	molar
m/z	mass to charge ratio
M^+	parent molecular ion
Me	methyl
Mes	2,4,6-trimethylphenylsulfonyl (mesityl)
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
PCC	pyridinium chlorochromate
Ph	phenyl

pH	hydrogen ion concentration in aqueous solution
tol.	toluene
ppm	parts per million
Pr	propyl
i-Pr	*iso*-propyl
py	pyridine
q	quartet
R	alkyl
R_f	retention factor
R_t	retention time
rt	room temperature
s	seconds or singlet or strong
SAR	structure-activity relationship
sat.	saturated
)))	sonication
t	triplet
Temp	temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl (tosyl)
TS	transition state
w	weak
$[\alpha]_D$	specific rotation at wavelength of sodium D line
δ	chemical shift
Δ	heating
μ	micro or elemental analysis
$\tilde{\nu}$	wavenumber

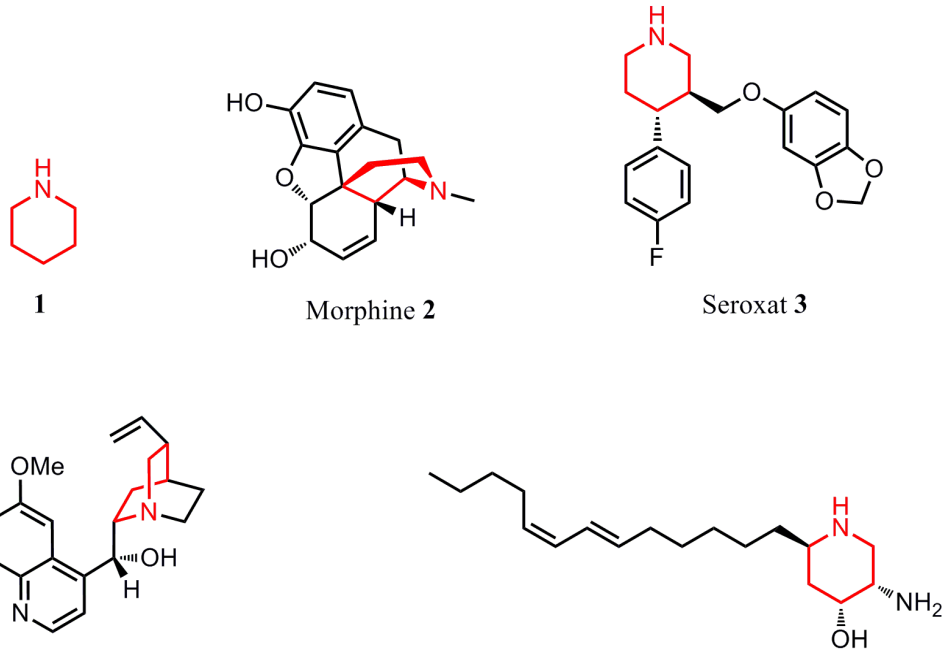
"Total synthesis has been hailed as a highly demanding and exacting science, but it is also recognized in its finest form as an art"

- K. C. Nicolaou

1. Introduction

1.1 Piperidines

The piperidine structural motif **1** appears frequently in natural products and synthetic compounds that possess potent biological activity. For example, the powerful analgesic morphine **2** extracted from the poppy, *Papaver somniferum,* has been used by mankind since antiquity.[1] The antidepressant Seroxat **3**, a synthetic drug, marketed by the pharmaceutical company GlaxoSmithKline has been listed in the top 100 best selling drugs with sales of over $1 billion.[2,3] Quinine **4** extracted from the bark of the cinchona tree, *Cinchona officinalis*, has been used for many centuries in the treatment of malaria.[4] Pseudodistomin A **5** isolated from the tunicate, *Pseudodistoma kanoko*, exhibits potent anti-tumour activity and is part of a wider family of marine alkaloids[5] (Figure 1).



1 Morphine **2** Seroxat **3**

Quinine **4** Pseudodistomin A **5**

Figure 1: The piperidine structural motif

The importance of biologically active molecules such as these drives research towards novel routes for the stereocontrolled synthesis of piperidines that display diverse substitution patterns. Molecules **4** and **5** both display a 2,4,5-trisubstituted piperidine ring pattern and methods in the literature for the synthesis of such systems are considerably underdeveloped.[6-9]

1.2 Pseudodistomins

At present there are six members of the pseudodistomin family, pseudodistomins A-F; they consist of a core containing a 2,4,5-trisubstituted piperidine ring and differ from one another in configuration at their stereogenic centres and nature of the alkyl side chain (Figure 2).

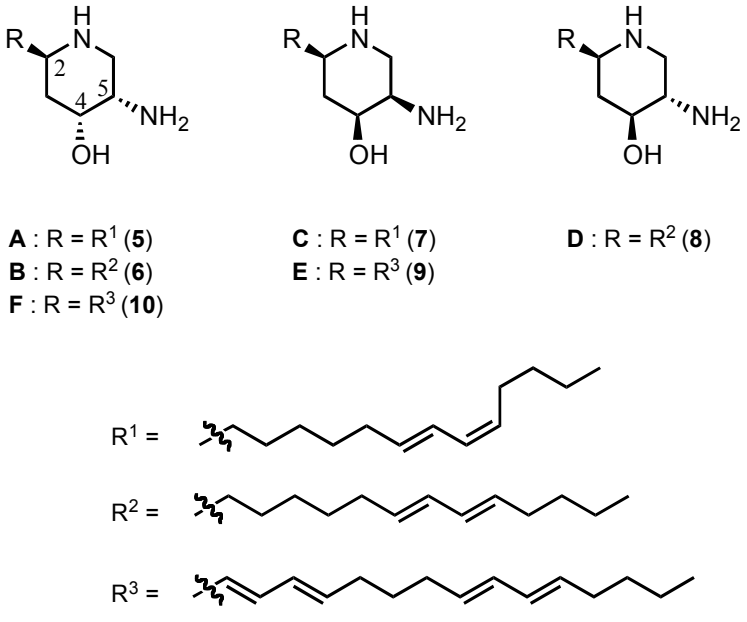


Figure 2: Pseudodistomins A-F **5-10**

Pseudodistomins A **5** and B **6** were isolated from the Okinawan tunicate *Pseudodistoma kanoko* (Image 1) by Kobayashi *et al* in 1987, making them the first piperidine alkaloids to be discovered from a marine source.[5] Their proposed side chains were later revised,[10,11] and

absolute configurations were subsequently determined.[12] Pseudodistomin C **7** was later isolated from the same tunicate.[13] It is considered unusual that pseudodistomins A **5** and B **6** possess the opposite absolute configurations at (4)-hydroxyl and (5)-amino compared to pseudodistomin C **7** isolated from the same tunicate because the proposed biosynthetic pathway for pseudoditomins A **5** and B **6** incorporates L-serine while pseudodistomin C **7** incorporates the much rarer D-serine.[14] Three new pseudodistomins D-F **8-10** were isolated along with known pseudodistomins B **6** and C **7** from the ascidian *Pseudodistoma megalarva* (Image 1) by Freyer *et al* in 1997 off the coast of Palau.[15]

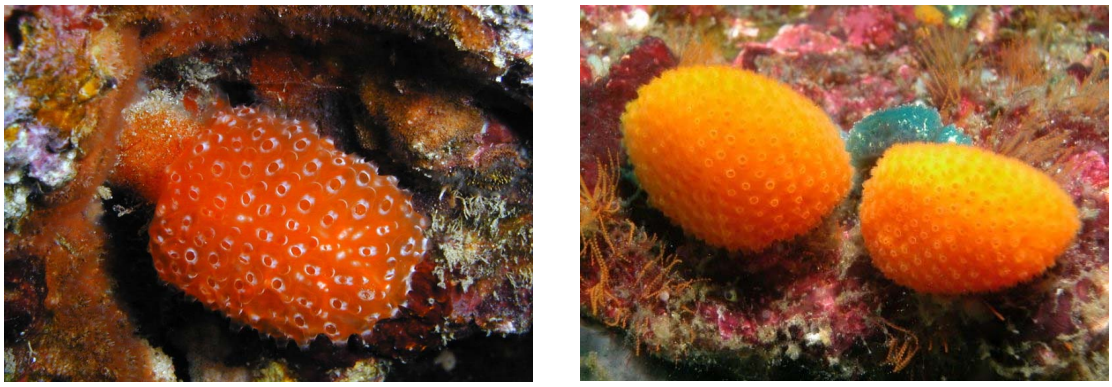
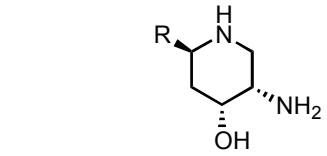


Image 1: From left to right: *Pseudodistoma kanoko*[16] and *Pseudodistoma megalarva*[17]

Their biological activities were investigated and the pseudodistomin alkaloids were shown to exhibit calmodulin antagonistic activity, potent *in vitro* activity against murine leukemia and human epidermoid carcinoma KB cells and were also found to be active in a cell-based assay for DNA damage induction.[5,13,15] In view of their interesting pharmacological activity and unusual structural features, they have become popular synthetic targets. However, a number of routes have been limited to the racemic syntheses or the synthesis of simpler analogues such as tetrahydropseudodistomin **11** (Figure 3).



11

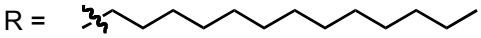


Figure 3: Tetrahydropseudodistomin **11**

A summary of the efforts made by the synthetic community towards the construction of the pseudodistomin alkaloids is listed below (Table 1).

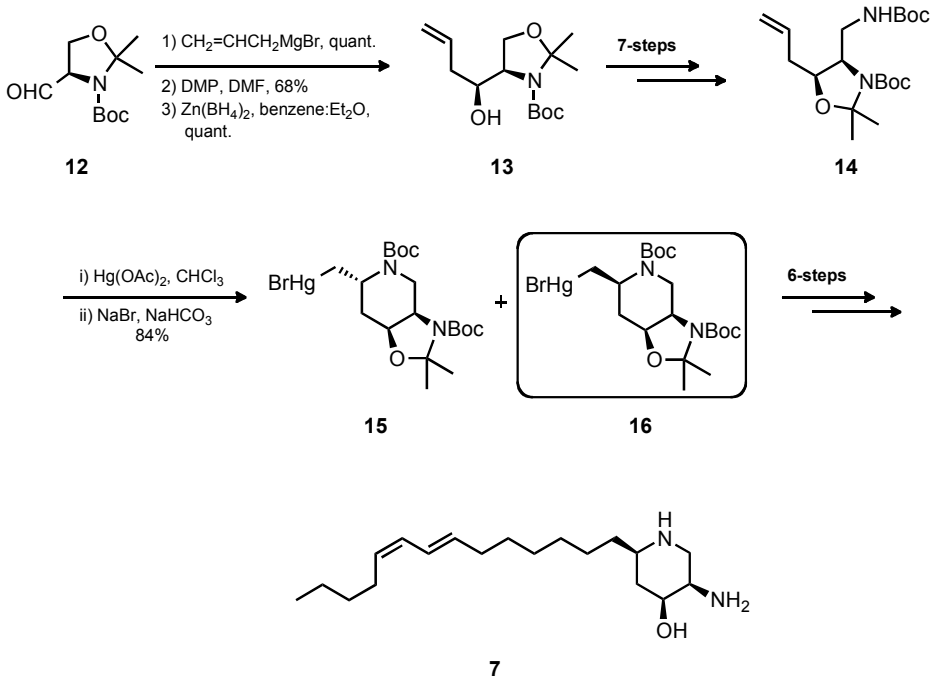
Year	Author	Achievement
1992	Naito, T.	(±)-tetrahydropseudodistomin[18]
1992	Natsume, M.	(±)-tetrahydropseudodistomin[19]
1992	Naito, T. and Kobayashi, J.	(±)-pseudodistomin B[10]
1993	Knapp, S.	(+)-tetrahydorpseudodistomin[12]
1996	Kobayashi, J.	(-)-pseudodistomin C[14]
1996	Naito, T.	(±)-pseudodistomin A[a, 20]
1996	Naito, T.	(±)-tetrahydropseudodistomin[21]
1997	Naito, T.	(±)-pseudodistomins A and B[22]
1998	Naito, T.	(+)-tetrahydorpseudodistomin[23]
2000	Ma, D. and Sun, H.	(-)-pseudodistomins B and F[24]
2002	Langlois, N.	(-)-pseudodistomin C[b, 25]
2005	Davis, F.A.	(-)-pseudodistomin B[b, 26]
2005	Trost, B.M.	(+)-pseudodistomin D[27]
2005	Haddad, M.	studies towards (+)-pseudodistomin D[28]
2006	Tanaka, K.	(-)-pseudodistomin C[b, 29]
2007	Chandrasekhar, S.	(+)-tetrahydorpseudodistomin[30]
2009	Woerpel, K.A.	studies towards (+)-pseudodistomin B[31]
2010	Davies, S.G.	(+)-pseudodistomin D[c, 32]

[a] Synthesis of incorrectly proposed structure. [b] Formal synthesis. [c] Ongoing research.

Table 1: Summary of pseudodistomin syntheses

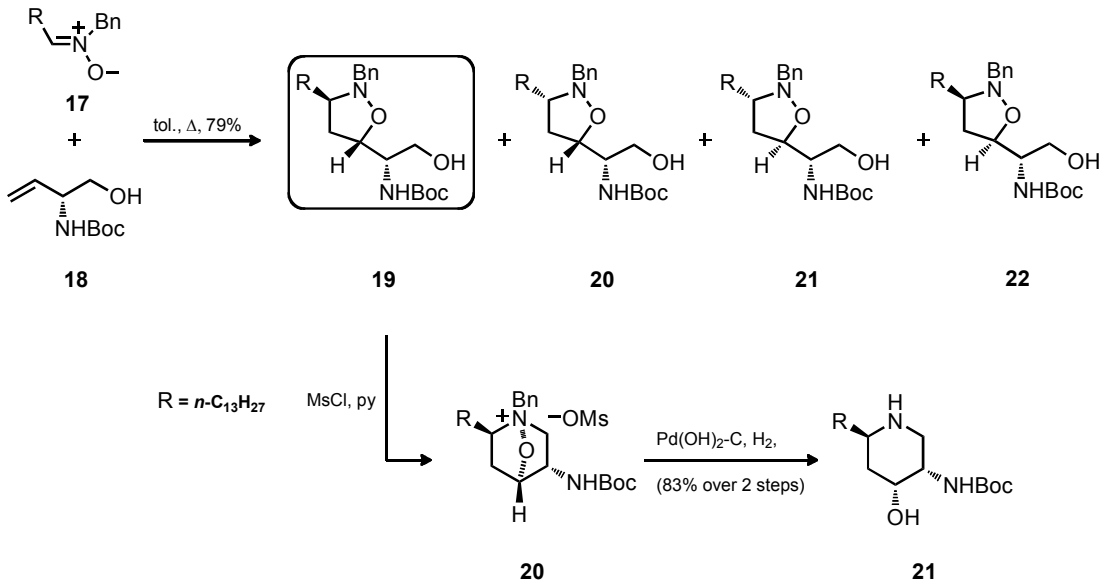
The literature examples presented below focus on the synthesis of these small but densely functionalised natural products in an attempt to show the development from initial attempts through to the state of the art in this area. Focus is on the key steps and examples are chosen based on diversity and stereocontrol.

The first total synthesis of pseudodistomin C **7** by Kobayashi (Scheme 1),[14] utilised D-serine derived Garner's aldehyde[33] **12** as a starting point. Grignard addition into **12** followed by an oxidation-reduction sequence gave the *erythro*-alcohol **13** with good diastereoselectivity of 96% de but disappointingly resulted in erosion of enantiopurity with a 60% ee. The *erythro*-alcohol **13** was converted to carbamate **14** in seven steps, which set up the key ring forming step, a intramolecular amidomercuration, to afford the piperidine products **15** and **16**, unfortunately with poor diastereocontrol of 1:1.5 in favour of the desired diastereomer **16**. A further six steps were required to complete the synthesis of pseudodistomin C **7**, which included a Julia olefination[34] to install the side chain. The overall yield was 0.4%, with seventeen steps in the longest linear sequence.



Scheme 1: Kobayashi's synthesis of pseudodistomin C **7**

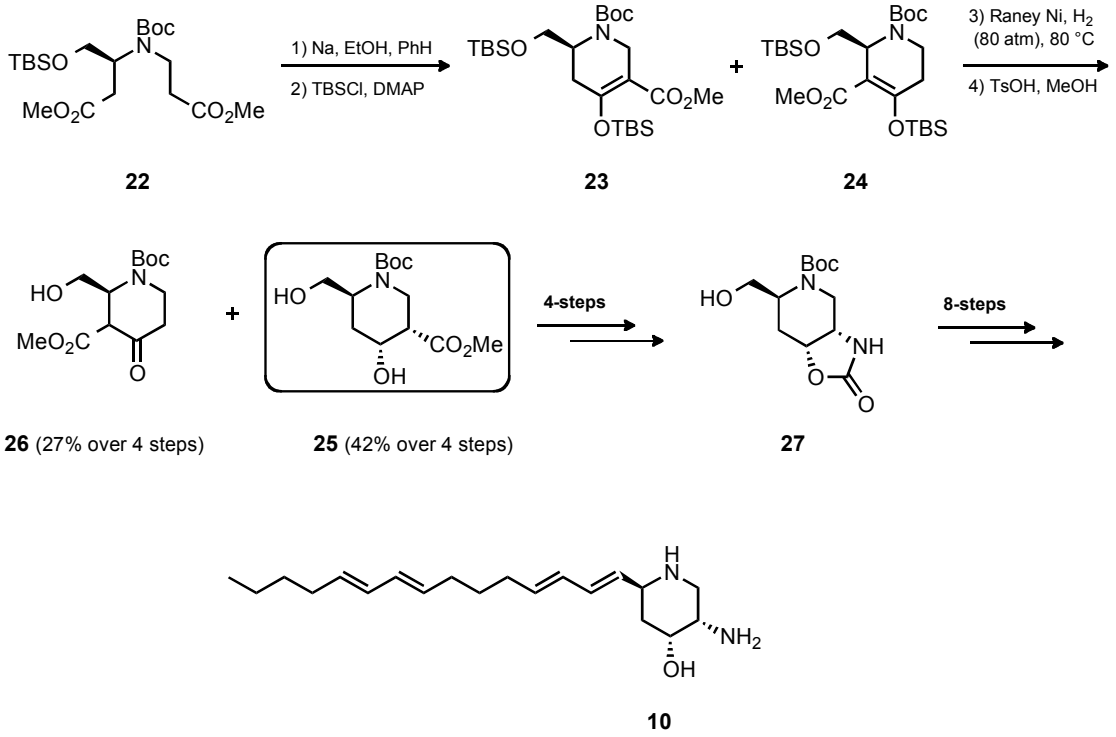
Naito's synthesis of (+)-tetrahydorpseudodistomin **11** (Scheme 2)[23] is notable for its brevity rather than its stereocontrol, requiring only eight synthetic steps to complete. The route involves two key reactions: first, an intermolecular [3+2] cycloaddition of nitrone **17** with vinyl glycinol **18**, derived from D-methionine *tert*-butylester, gave all four possible isoxazolidine stereoisomers **19**-**22** in a 2:3:3:5 mixture, respectively, with the desired isomer **19** as the minor component; secondly, bicycle formation with mesyl chloride gave the bridged piperidine **20**. Subsequent reduction by hydrogen in the presence of Pearlman's catalyst gave the corresponding 2,4,5-trisubstituted piperidine **21**; removal of the protecting group gave the product **11** in an overall yield of 3%.



Scheme 2: Key transformations in Naito's synthesis of (+)-tetrahydropseudodistomin **11**

Ma and Sun have developed a general method for the synthesis of pseudodistomins containing the (2*R,* 4*R*, *5S*)-piperidine core and have showcased the method through the synthesis pseudodistomins B & F.[24] The shorter synthesis of pseudodistomin F (Scheme 3) employed a Dieckmann condensation of diester **22** and silylation of the intermediate enolate

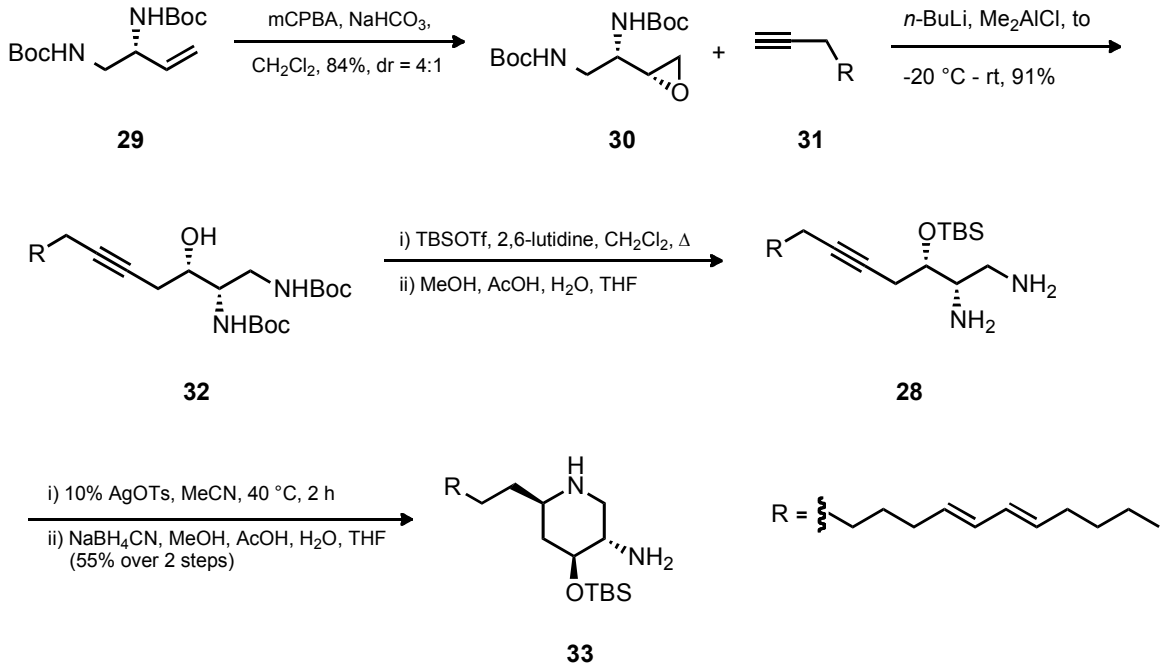
to afford a mixture of the two regioisomeric silyl enol ethers **23** and **24** with a poor selectivity of 1.6:1 in favour of the desired product. Serendipitously, Raney Nickel hydrogenation of the crude reaction mixture selectively reduced **23** over **24**, and this was followed by treatment with tosic acid in methanol to gave piperidine **25** and piperidinone **26**. Four steps were required convert the ester into a protected amine **27** and a further eight steps to complete the synthesis of the natural product in a total of twenty three steps and an overall yield of 4%.



Scheme 3: Key transformations in Ma and Sun's synthesis of pseudodistomin F **10**

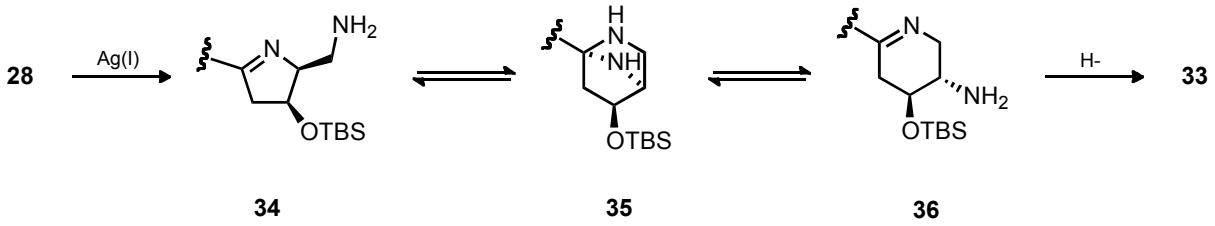
The Trost synthesis of Pseudodistomin D (Scheme 4)[27] employed a regio- and diastereoselective reductive intramolecular hydroamination step to construct the core. The cyclisation precursor **28** was obtained through a convergent synthesis, in a total of seventeen steps, which included: an epoxidation of alkene **29** that proceeded with modest diastereoselectivity of 4:1 in favour of the desired epoxide **30**; addition into the terminal end of the epoxide with alkyne **31** gave **32,** treatment with TBSOTf removed the Boc protecting

groups and simultaneously protected the hydroxyl. Treatment of diamino alkyne **28** with silver tosylate and sodium cyanoborohydride afforded piperidine **33**. They report that this step afforded a single detectable diastereomer and gave exclusively the piperidine without any pyrrolidine by-products, although the yield was a somewhat modest 55%.



Scheme 4: Trost's synthesis of pseudodistomin D **8**

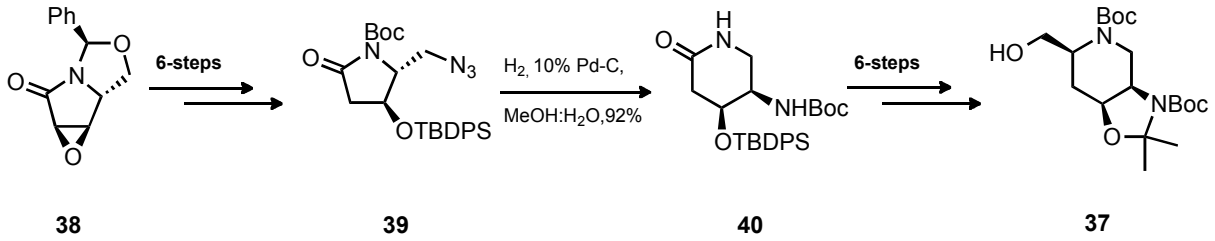
The authors put forward several explanations in order to rationalise the selective formation of the piperidine product **33**. One explanation is that the hydroamination of alkyne **28** proceeds through a kinetic 5-exo-dig cyclisation to afford imine **34**, which is in rapid equilibrium with imine **36** (Scheme 5). They reasoned that the reduction of imine **36** was favoured due to a faster rate of reduction of an sp^2 to an sp^3 carbon in a six-membered ring compared to five-membered ring. An alternative explanation offered relates to the equilibrium strongly favouring imine **36**, with the observed selectivity simply the result of the reduction of the dominant species.



Scheme 5: Trost's proposed mechanism for piperidine formation

The total synthesis was achieved in a 13% yield for the longest linear sequence. Installation of the side chain early on limits this approach for the synthesis of the whole family of pseudodistomin alkaloids.

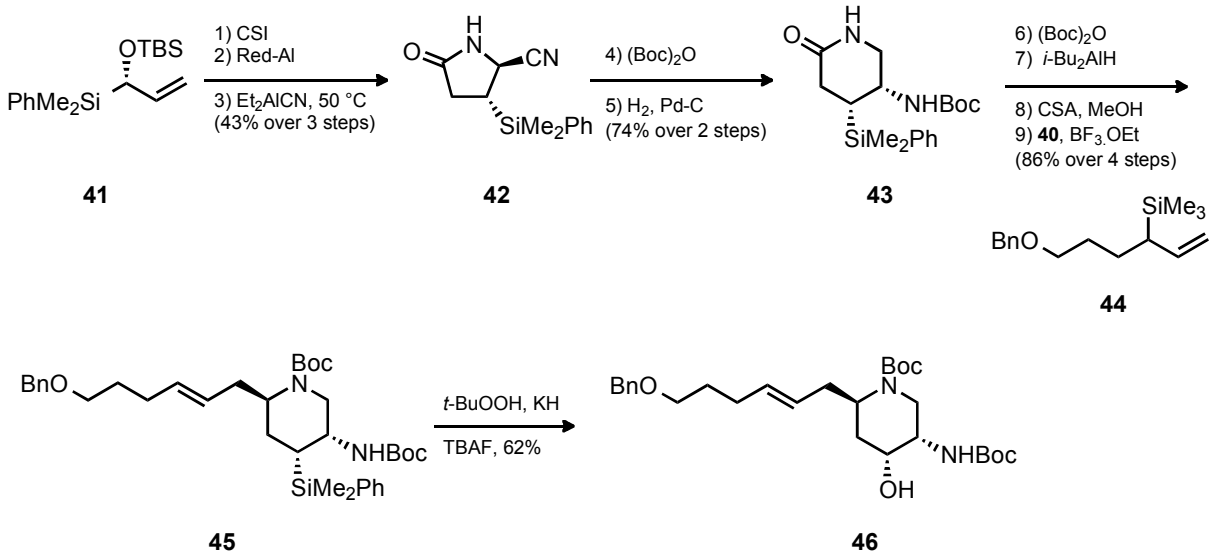
Tanaka's formal synthesis of pseudodistomin C (Scheme 6)[29] resulted in the formation of an advanced intermediate **37** from Kobayashi's total synthesis.[14] Starting from known □,□-epoxylactam[35] **38**, derived from L-pyroglutamic acid, they constructed the azido pyrrolidinone derivative **39** in six steps. Intramolecular transamidation of azido γ-lactam **39** was performed in the presence of 10% Pd-C under three atmospheres of hydrogen to afford the δ-lactam **40**. Another six steps were required to complete the formal synthesis, which included a Tebbe olefination and hydroboration to install the final stereocenter with complete diastereocontrol. Although one synthetic step longer than Kobayashi's original synthesis, eighteen steps compared to seventeen, it is a marked improvement over the original due to the higher levels of stereocontrol and overall yield of 10% compared to the original yield of 6% at the same stage. However, the real limitation of this synthesis is that relies on Kobayashi's endgame strategy, which gave very poor yields of 13% and 34% for the penultimate and final steps respectively.



38 **39** **40** **37**

Scheme 6: Tanka's formal synthesis of pseudodistomin C **7**

Recently, Woerpel has developed an annulation/ring expansion strategy that enabled access to the core structure of pseudodistomin B (Scheme 7).[31] A [3+2] annulation of □-silyloxy allylic silane **41** with chlorosulfonyl isocyanate (CSI) followed by reduction of the resulting *N*-chlorosulfonyl lactam and nitrile substitution of the silyl ether with Et_2AlCN provided the γ-lactam **42**. A similar intramolecular transamidation approach to that used by Tanaka afforded the ring expanded δ-lactam **43**. This was reduced to an *N*,*O*-acetal and subsequent nucleophilic substitution with **44** gave piperidine **45** as a single diastereomer. Oxidation of the silyl group to the corresponding hydroxyl **46** completed the synthesis, which in 15 synthetic steps and an overall yield of 16% constructed the core structure and installed a precursor to the side chain of pseudodistomin B. Unfortunately the [3+2] annulation step early on in the synthesis was not amenable to a multi-gram scale because of the use of toxic and corrosive CSI. This may limit further attempts to complete the total synthesis in the future.



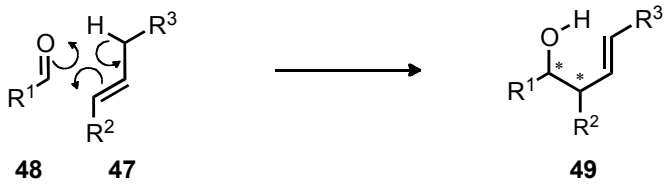
Scheme 7: Woerpel's study towards the synthesis of pseudodistomin B **5**

A number of different approaches have been presented for the synthesis of piperidines forming the core of the pseudodistomin alkaloids ranging from: amido mercuration, nitrone cycloaddition, Dieckmann condensation, reductive hydroamination and intramolecular transamidation. These reactions proceed through either C-C or C-N bond formation with concomitant creation of new stereogenic centres. Another class of reactions that have proved to be valuable in the synthesis of piperidines are the carbonyl-ene and Prins cyclisations.

1.3 Carbonyl-ene and Prins reactions

The reaction between an aldehyde or ketone and an alkene allows the formation of two contiguous stereocentres and under the correct conditions can proceed with a high degree of regio- and stereocontrol.[36,37] When the reaction occurs under thermal or Lewis acidic conditions it is usually known as the carbonyl-ene reaction,[38] whereas the same reaction in the presence of a Brønsted acid is usually known as the Prins reaction.[39] Mechanistically, both the carbonyl-ene and Prins reaction occur through the interaction of an alkene possessing an

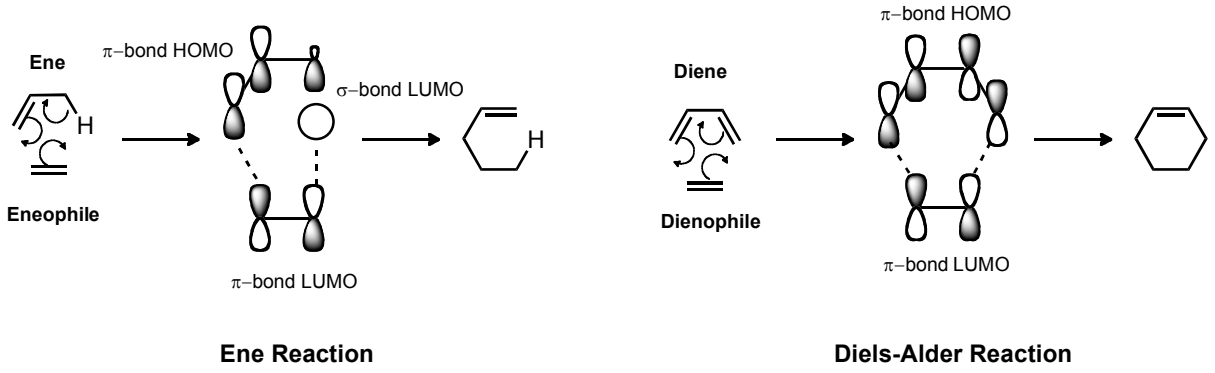
allylic hydrogen **47**, the ene component, and an electron deficient multiple bond, behaving as the enophile component, an aldehyde or ketone **48**. The process involves a [1,5]-shift of the allylic hydrogen from the ene **47** to the enophile **48** and migration of the ene π-bond to form a new -bond between the ene **47** and enophile **48**, leading to a homoallylic alcohol product **49** (Scheme 8).[40]



Scheme 8: General mechanism for a carbonyl-ene/Prins reaction

The carbonyl-ene reaction is mechanistically related to the Diels-Alder reaction as both proceed through a cyclic six electron transition state and it can be considered as a pericyclic reaction, although the ene and carbonyl-ene reactions are not necessarily concerted processes. In ene and carbonyl-ene reactions the two electrons of the allylic C-H bond replace two π-electrons in the diene of the Diels-Alder reaction. This has the consequence of raising the activation energy compared to an analogous Diels-Alder reaction and so higher reaction temperatures are required.[41] In the past, this limited its mechanistic study and synthetic use causing it to be overlooked in favour of the more renowned Diels-Alder reaction. This was until Snider *et al*. discovered that the carbonyl-ene reaction could be catalysed efficiently through the use of Lewis acids.[42-44] Complexation of a Lewis acid to the carbonyl has the effect of lowering the LUMO of the enophile, allowing facile attack by the ene. Fuki *et al.* has studied the more general case of the ene reaction, where the enophile is also an alkene, using a frontier molecular orbital approach.[45] They considered that a single orbital for the ene component has too small a coefficient at the C-H site for an effective cyclic interaction to occur. So a three orbital interaction was proposed with a *suprafacial-suprafacial* interaction

between: the HOMO of the π-bond and the LUMO of the C-H □-bond in the ene; and the LUMO of the π-bond in the enophile (Scheme 9).



Scheme 9: FMO interactions in ene and Diels-Alder reactions

Such an interaction implies that once the HOMO of the π-bond donates electrons to LUMO of the enophile, back donation occurs to the LUMO of the C-H □-bond of the ene. This would lead to an asynchronous concerted mechanism where C-C bond formation is more advanced than C-H bond formation in the transition state (Figure 4).[46]

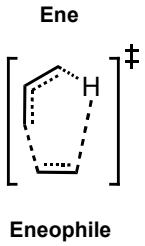
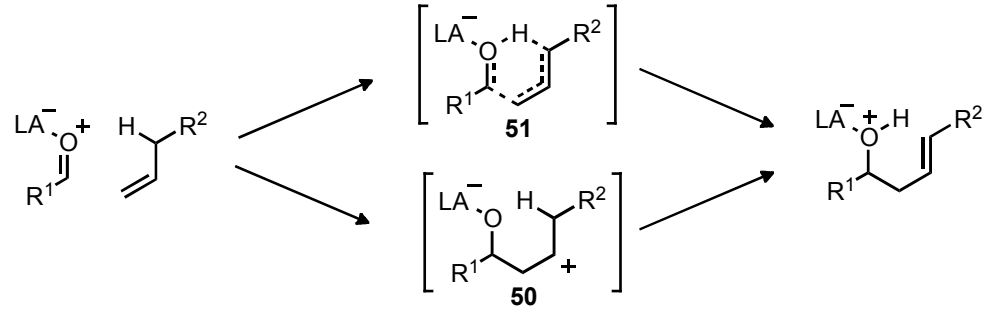


Figure 4: Ene reaction envisaged as an asynchronous concerted process

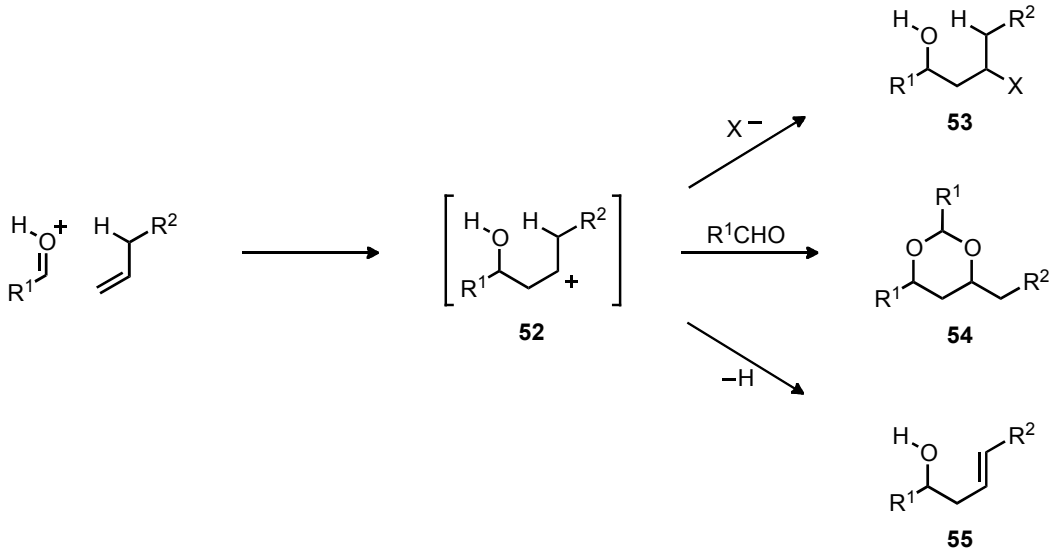
The mechanism of the carbonyl-ene reaction is not so clear-cut and different mechanisms have been suggested for different carbonyl-ene reactions. However, Lewis acid promoted ene reactions are usually considered in terms of the continuum from a concerted mechanism **51**, with a polar transition state, through to a stepwise mechanism proceeding through a

zwitterionic intermediate **50** (Scheme 10).[47,48] The energetics of the two reaction pathways have been shown to be very similar and the course of the reaction varies as a function of ene, enophile and catalyst.[49,50]



Scheme 10: Carbonyl-ene reactions proceed through either a concerted or stepwise process

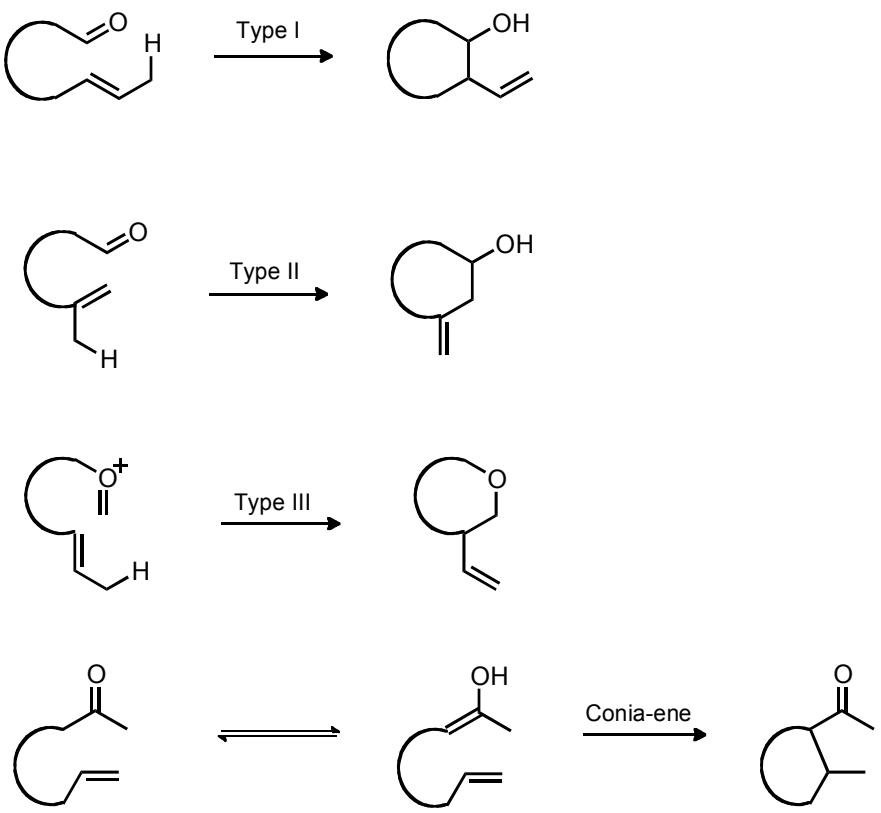
The Prins reaction is considered to proceed through a stepwise process via a cationic intermediate **52**. This carbocation can react with an external nucleophile, such as water or chloride, to give **53**, add to a second molecule of aldehyde to give **54** or lose a proton to give a homoallylic alcohol **55** (Scheme 11).[51]



Scheme 11: Mechanism of the Prins reaction

Recently, the application of organocatalytic chiral Brønsted acids has been reported that can deliver high levels of asymmetric induction.[52,53]

Intramolecular ene reactions are more facile than their intermolecular counterparts due to a lower loss of entropy in the transition state as the intermolecular reaction requires pre-organisation of two separate moieties. Intramolecular reactions have been shown to be an efficient method for ring closure, since they can proceed with high degrees of regio- and stereoselectivity through postulated six-membered chair-like transition states. Oppolzer classified intramolecular ene reactions into three distinct variants, types I, II and III, depending on the attachment position of the connecting ene and enophile.[54] Another variant is the Conia-ene reaction of unsaturated ketones, where the enol tautomer of the carbonyl serves as the ene component (Scheme 12).[55]

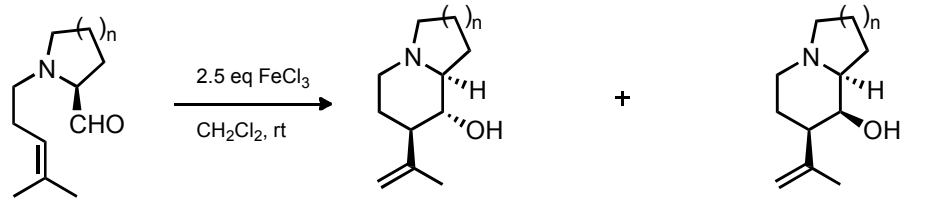


Scheme 12: Carbonyl-ene reaction variants

In type I reactions, the enophile is linked to the olefinic terminal, with C-C bond formation occurring between the carbonyl and internal carbon of the olefin. This type of reaction is most commonly encountered in the formation of five and six-membered rings.[56] The type II carbonyl-ene reaction, involves C-C bond formation to the terminal carbon of the olefin and has been employed in the construction of six and seven-membered rings. The type III reaction has the olefin side chain attached to the carbonyl oxygen with the oxocarbenium ion generated *in situ*, usually derived from acetals or hemiacetals, giving rise to cyclic ethers. The Conia-ene reaction between an activated carbonyl and an alkene or alkyne usually requires very high temperatures. The use of transition metals has been shown to catalyse the reaction effectively at ambient temperatures, though the reaction is not thought to proceed through a classical ene-type pericyclic mechanism in those cases.[57]

1.4 Piperidine synthesis via carbonyl-ene and Prins reactions

There are relatively few literature examples of piperidine synthesis and nitrogen heterocycles in general via carbonyl-ene reactions. Laschat reported the diastereoselective synthesis of indolizidine **56** and quinolizidine **57** derivatives.[58] Aldehydes **58** and **59** were treated with the Lewis acid $FeCl_3$ to afford the *cis* products **56b** and **57b** in very high diastereoselectivities (Scheme 13).

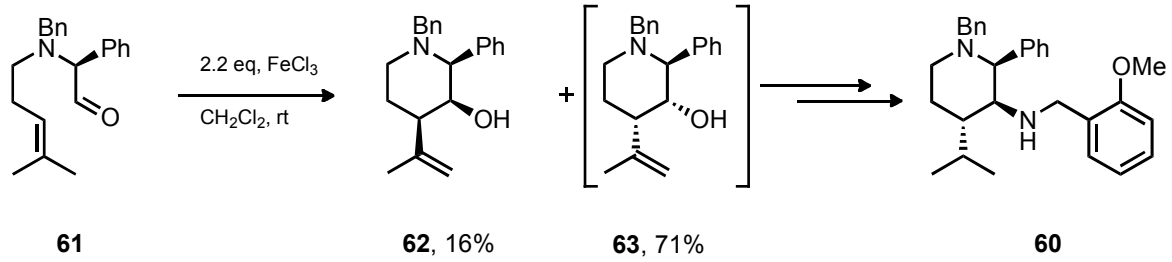


58 n = 1
59 n = 1

56a n = 1 1.6:98.4 **56b** n = 1, 65%
57a n = 2 0.2:99.8 **57b** n = 2. 59%

Scheme 13: Laschat's carbonyl-ene cyclisations

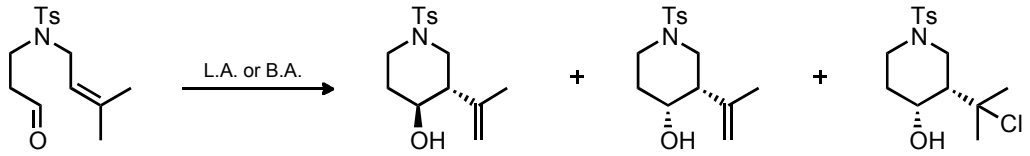
More recently, they have reported the synthesis of a non-peptidic substance P antagonist **60**.[58] Aldehyde **61**, prepared from phenylglycine, underwent a carbonyl-ene reaction to give two diastereomeric piperidines **62** and **63** in a modest diastereoselectivity of ~1:4 (Scheme 14).



61 **62**, 16% **63**, 71% **60**

Scheme 14: Laschat's synthesis of a substance P antagonist **60**

Initial work in our group focused on the synthesis of 3,4-disubstituted piperidines through the use of carbonyl-ene and Prins reactions employing aldehyde **64** as the cyclisation precursor (Scheme 15).[59,60]



64 **65** **66** **67**

Scheme 15: Initial carbonyl-ene and Prins reactions studied in the Snaith group

Extensive screening of catalysts, catalyst loadings, reaction temperatures and reaction times were conducted to assess their effects on altering the diastereoselectivity of the reaction. It was shown that the diastereoselectivity could be switched between *trans* **65** and *cis* **66** diastereomers using either Lewis or Brønsted acids (Table 2). The use of the Lewis acid $MeAlCl_2$ was found to favour the *trans* diastereomer **65** with ratios of up to 92:8 (Table 2, entry 3). The temperature effect on the carbonyl-ene reaction suggested that under these conditions the reaction is reversible and that the *cis* diastereomer **66** is the kinetic product, equilibrating to the thermodynamic *trans* product **65** upon warming. The use of concentrated

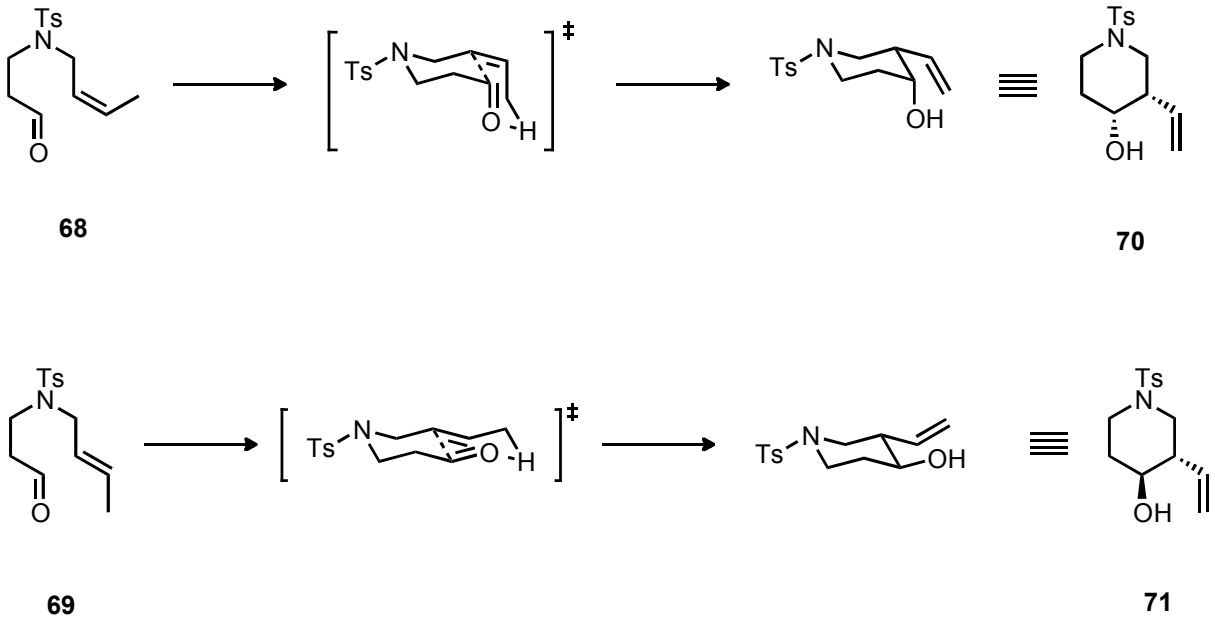
hydrochloric acid (Table 2, entry 4) was found be a very effective catalyst in the Prins reaction, favouring the *cis* piperidines of **66** and **67** with ratios up to 97:3 (**66**+**67**:**65**).

Entry	Catalyst	Temp / °C	Solvent	Time / h	Ratio 65:66:67[a]	Yield / %[b]
1	$MeAlCl_2$, 1eq	-78	CH_2Cl_2	8	33:67:0	58 (14)
2	$MeAlCl_2$, 1eq	25	CH_2Cl_2	16	67:33:0	55 (15)
3	$MeAlCl_2$, 1eq	61	$CHCl_3$	16	92:8:0	74
4	$HCl_{(aq)}$, 3eq	-78	CH_2Cl_2	16	5:90:5	86

[a] Ratio determined by ^1H NMR of crude reaction mixtures. [b] Isolated yields of major (minor in parentheses).

Table 2: Initial carbonyl-ene and Prins reaction results

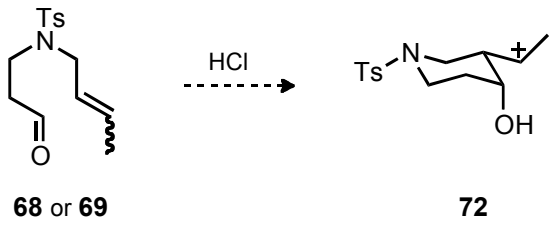
As mentioned before the carbonyl-ene reaction is highly dependent on the ene, enophile and Lewis acid used. Therefore, slight modifications of the ene component were studied. It was thought that *Z*- **68** and *E*- crotyl **69** substrates would serve as useful probes into the reaction mechanism. If, as believed, the reaction proceeded through a chair-like transition state via a concerted mechanism then the cyclisation of *Z*-crotyl aldehyde **68** would only proceed when the aldehyde is in a pseudo-axial conformation due to the more sterically demanding ene adopting a pseudo-equatorial conformation. This orientation would lead to the formation of the *cis* piperidine **70**. Adopting the same idea for the *E*-crotyl aldehyde **69** would lead to the aldehyde component adopting the pseudo-equatorial conformation in the transition state leading to the formation of the *trans* product **71** (Scheme 16).



Scheme 16: Transition states for a concerted mechanism

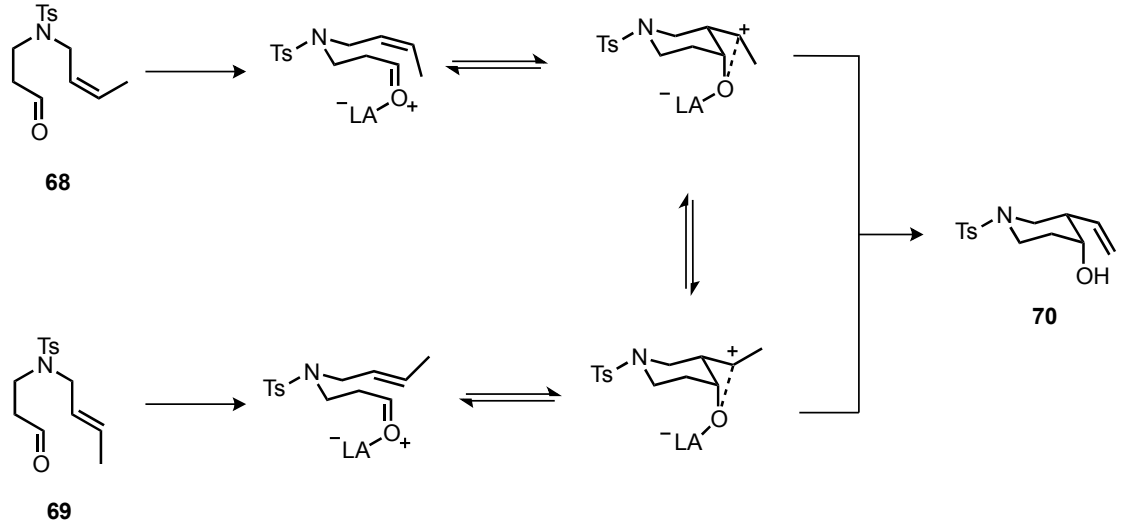
When both substrates **68** and **69** were subjected to a cyclisation reaction under Lewis acid conditions, both led to the *cis* piperidine **70** with none of *trans* diastereomer **71** observed. This result suggested that a concerted mechanism was unlikely and a reaction mechanism that proceeds with significant stepwise character was postulated.

However, under Prins reaction conditions both substrates **68** and **69** failed to cyclise. As the Prins reaction is generally thought to proceed through a stepwise mechanism via a carbocationic intermediate **72**, it would require substrates **68** and **69** to react through a less favourable secondary carbocation (Scheme 17).



Scheme 17: Prins reactions through a relatively unstable secondary carbocation

In the carbonyl-ene cyclisation it was proposed that aldehydes **68** and **69** would proceed through a common low energy pathway leading to the formation of the *cis* product **70** (Scheme 18).



Scheme 18: Proposed reaction mechanism

The pathway leading to the *cis* piperidines **65** and **70** was thought to be lowest in energy due to a stabilising interaction coming from a good overlap between the filled oxygen sp^3 orbital containing the lone pair and the vacant p-orbital of the carbocation in an intermediate or carbocationic character in a transition state. This overlap only exists when the hydroxyl group and cation occupy pseudoaxial and pseudoequatorial positions *i.e. cis* stereochemistry. This stereoelectronic stabilisation does not occur in the *trans* isomer due to poorer overlap of the orbitals. Clark has implied such a stabilizing interaction when he studied the cyclisation of citronellal.[61]

DFT calculations (B3LYP/6-31G(d)) were performed and indicated that the *cis* carbocation resulting from a stepwise cyclisation mechanism was more stable by 0.82 kcal compared to the *trans* carbocation. Calculations for the transition states resulting from a concerted

cyclisation mechanism were also performed and indicated that the *cis* transition state was more stable by 0.79 kcal (Figure 5).[62]

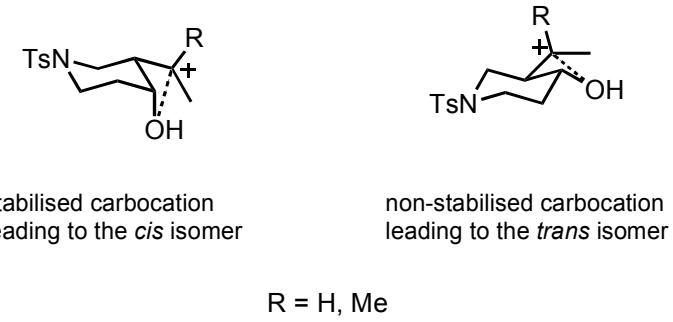
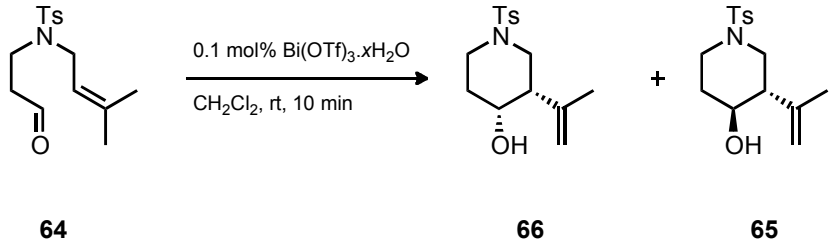


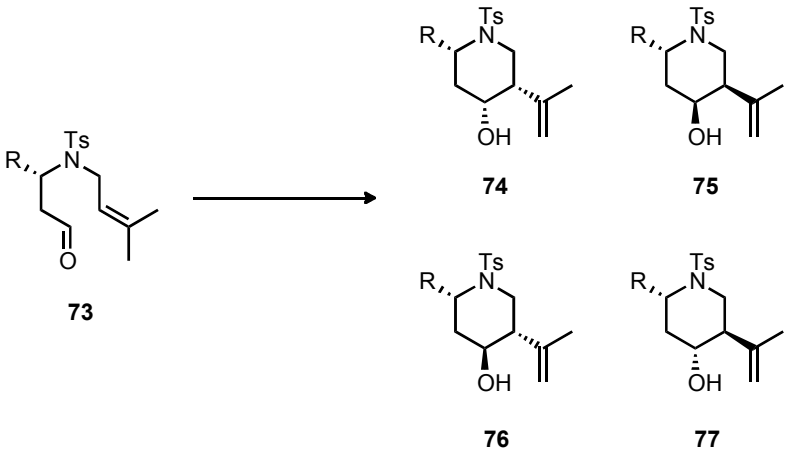
Figure 5: Stabilising interaction favouring the *cis* diastereomer

Mohan has studied the carbonyl-ene reaction between aldehyde **64** and bismuth triflate as a catalyst.[63] Impressively, the catalyst could be employed in loadings as low as 0.1 mol%. Unfortunately, they could only achieve a modest diastereoselectivity of 70:30 for piperidines **60** and **59** (Scheme 19).



Scheme 19: Carbonyl-ene reaction of aldehyde **64** with $Bi(OTf)_3$ studied by Mohan

More recent work in the group has made use of an existing stereogenic centre at the 2-position. The cyclisation of aldehyde precursors **73** could have led to four possible diastereoisomers **74-77**. It was anticipated that the existing stereogenic centre R would help to control the sense of induction at the two newly forming stereogenic centres, working in concert with the diastereocontrol model outlined above to afford 2,4,5-trisubstituted piperidines (Scheme 20).[64]



Scheme 20: Synthesis of 2,4,5-trisubstituted piperidines

The Prins cyclisation of aldehydes **73a-f** were studied using the optimised conditions of three equivalents of concentrated hydrochloric acid in CH_2Cl_2 at -78 °C. Only two out of the possible four diastereomers were observed, the major isomer was the *cis, cis* diastereoisomer **74** while the minor isomer was the trans-trans diastereoisomer **76**, summarised in (Table 3).[65]

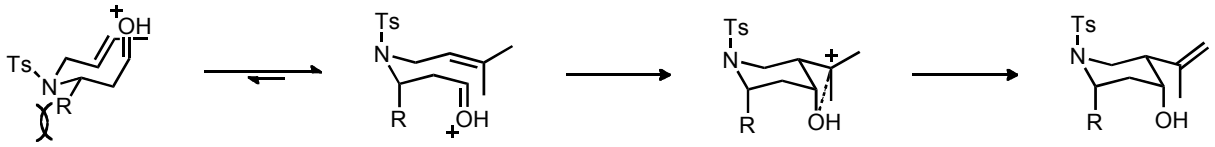
Entry	Aldehyde	R	74 : 76[a]	Yield (%)[b]
1	**73a**	Me	78 : 22	70 (22)
2	**73b**	Bn	94 : 6	70 (3)
3	**73c**	^{i}Pr	80 : 20	75 (19)
4	**73d**	^{t}Bu	47 : 53	42 (37)
5	**73e**	Ph	54 : 46	53 (40)
6	**73f**[c]	CO_2Me	100 : 0[d]	74

[a] Ratio determined by ^{1}H NMR of crude reaction mixtures. [b] Isolated yields of major (minor in parentheses) isomers following purification. [c] Reaction carried out with a saturated solution of $HCl_{(g)}$. [d] No *trans* isomer was detected due to intramolecular lactone formation .

Table 3: Prins cyclisation results

The selectivity decreases as the R group increased in size. For smaller R groups (Table 3, entries 1-3 and 6) the diastereoselectivity ranged from excellent to moderate. The reaction with the Me substituent (Table 3, entry 1) was slow to cyclise and it was believed that some

equilibration to the thermodynamic isomer occurred during the reaction. Reaction with CO_2Me substituent (Table 3, entry 6) led only to the *cis* diastereomer because of intramolecular lactone formation between the hydroxyl and ester groups preventing equilibration to the *trans* diastereomer. For the bulkiest substituents, (Table 3, entries 4-5), there was almost no selectivity. The selectivity could be rationalised by considering two factors. Firstly, there is a preference for the R group to adopt a pseudo-axial conformation in the chair-like transition state to avoid pseudo $A^{1,3}$ strain with the nitrogen protecting group.[66,67] Secondly, there is a kinetic preference for the ene group and aldehyde to adopt a *cis* relationship in order to benefit from a interaction of an oxygen lone pair stabilising any carbocationic character in the transition state (or a carbocationic intermediate, formed during a fully stepwise mechanism). The *cis* relationship is achieved by the aldehyde lying in a pseudo-axial orientation and the more sterically demanding ene component occupying the pseudo-equatorial orientation (Scheme 21). As the steric bulk of the 2-substituent increased the diastereoselectivity decreased, this was rationalised by an increased pseudo 1,3-diaxial interaction between the carbonyl and 2-substituent, which forced the aldehyde into an equatorial position.



Scheme 21: Rationale for the preferential formation of the *cis* diastereomer

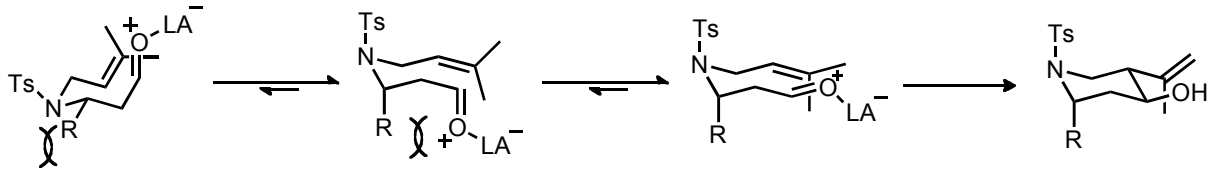
In the carbonyl ene cyclisations of aldehydes **73**, utilising the optimal Lewis acid of $MeAlCl_2$ under equilibrating conditions, the thermodynamic *trans, trans* products **76a-e** could be favoured (Table 4)

Entry	Aldehyde	R	Temp / °C[a]	74 : 76[b]	Yield (%)[c]
1	**73a**	Me	60	4 : 96	71 (4)
2	**73b**	Bn	40	5 : 95	64 (5)
3	**73c**	^{i}Pr	40	2 : 98	82 (2)
4	**73d**	^{t}Bu	60	1 : 99	88 (1)
5	**73e**	Ph	60	2 : 98	80 (2)

[a] Reactions were carried out in CH_2Cl_2 (40 °C) or $CHCl_3$ (60 °C) [b] Ratio determined by ^{1}H NMR of crude reaction mixtures. [c] Isolated yields of major (minor in parentheses) isomers following purification

Table 4: Carbonyl-ene cyclisation results

The diastereoselectivities ranged from good to excellent, with the bulkier substituents giving the highest diastereoselectivities of up to 99:1 for ^{t}Bu (Table 4, entry 4). The rationale for the observed diastereoselectivity was a large 1,3-diaxial interaction between the axial 2-substituent and the Lewis acid-coordinated aldehyde oxygen, compared to the Brønsted acid where the steric clash between the protonated oxygen of the carbonyl and the R group is less pronounced, leading to the aldehyde adopting the equatorial conformation. Such an interaction would account for the increased *trans, trans* diastereoselectivity as the 2-substituent increases in size (Scheme 22).

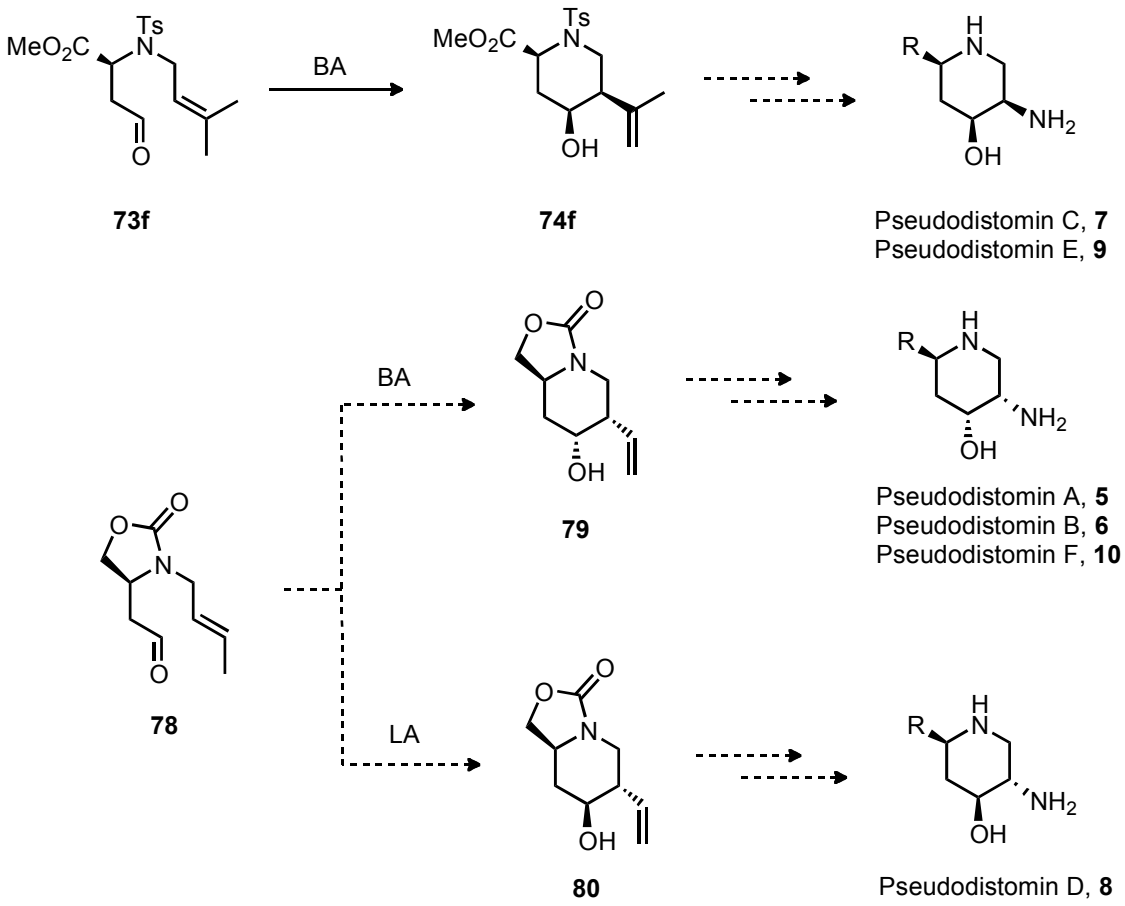


Scheme 22: Rationale for the preferential formation of the *trans*, *trans* diastereomer

1.5 Project Aims

The real test of any methodology and its establishment as a valuable chemical tool is its application in natural product synthesis. We plan to apply the carbonyl-ene/Prins methodology developed in our group to the synthesis of the pseudodistomin alkaloids. We believe the methodology is powerful enough to synthesise all the possible diastereomers of the 2,4,5-trisubstiuted piperidine core and would furnish cores with sufficient flexibility for the attachment of all possible side chains, which would make it very adept to the synthesis of new analogues in the hope of testing for improved biological activity.

Following on from previous work in the group we want to further the development of 2,4,5-trisubstituted piperidine synthesis. It has been shown that access to 2,4,5-trisubstituted piperidines possessing the *cis*, *cis* stereochemistry **74** is possible, matching the stereochemistry of pseudodistomins C **7** and E **9**. To access the previously unobtainable *trans, cis* **79** and *cis, trans* **80** diastereomers, which would lead to pseudodistomins A **5**, B **6**, F **10** and D **8** respectively, we envisaged a cyclisation precursor **78** having its 2-substituent constrained within a oxazolidinone ring linked to the nitrogen. In doing would confer several advantages. Firstly, we believed it would hold the 2-substituent in an equatorial disposition,[68,69] giving rise to a minimal interaction between the 2-substituent and either the axial or equatorial 4-substituent. Working in concert with our previously outlined stereochemical model, Prins cyclisation would lead to the *trans*, cis diastereomer **79**, while with a carbonyl-ene reaction under equilibrating condition would lead to the *cis*, *trans* diastereomer **80** (Scheme 23). Furthermore, the cyclic carbamate would be an attractive alternative to the tosyl protecting group employed in previous work as it can be cleaved under milder conditions but still provide the robustness required in the cyclisation reaction.

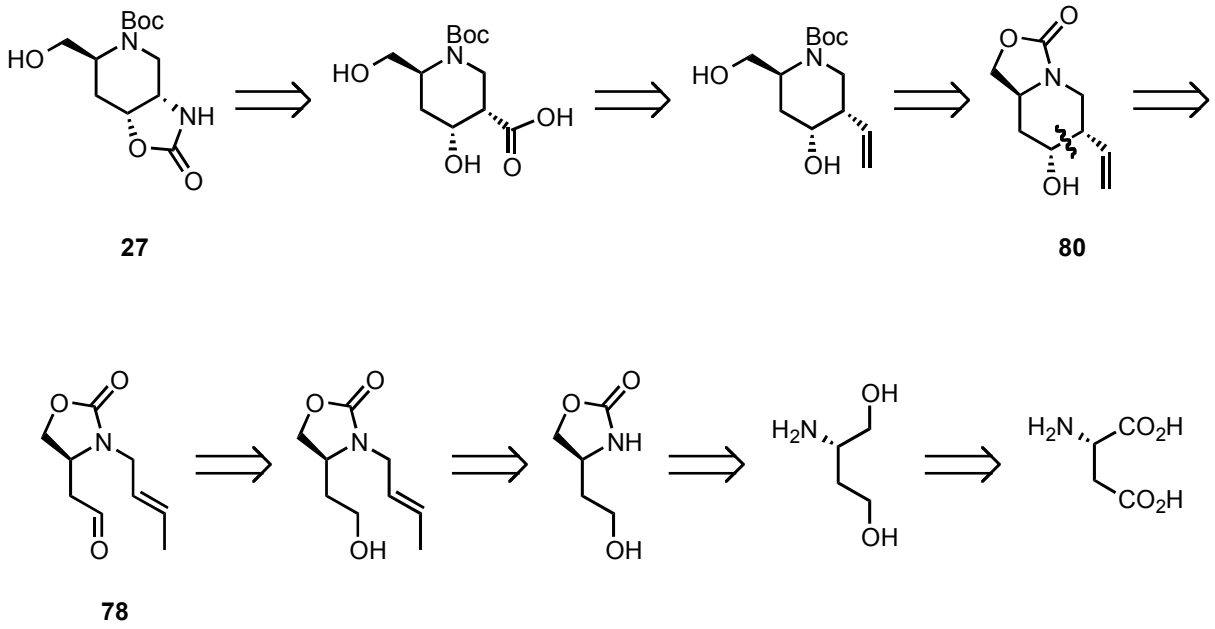


Scheme 23: Potential synthetic routes to the pseudodistomin alkaloids

To assess the viability of the proposal we wish to carry out a formal synthesis of pseudodistomin F, by synthesising an advanced intermediate **27** used in Ma and Sun's total synthesis. This intermediate was chosen as it contains the correct functionality and stereochemical arrangement of the core and with simple chemical manipulation allows appendage of the side chain. Incorporating the desired flexibility of being able to synthesise multiple pseudodistomin alkaloids or simpler side chain analogues from a common core.

A retrosynthetic analysis of Ma and Sun's advanced intermediate **27** was undertaken. The cyclic carbamate **27** could be derived from a rearrangement of a carboxylic acid, which in turn could be obtained from an oxidative cleavage of an alkene. This would lead to homo

allylic alcohol **80** derived from a Prins cyclisation of **78**. The cyclisation precursor **78** could be obtained from the amino acid L-aspartic acid in four transformations (Scheme 24).



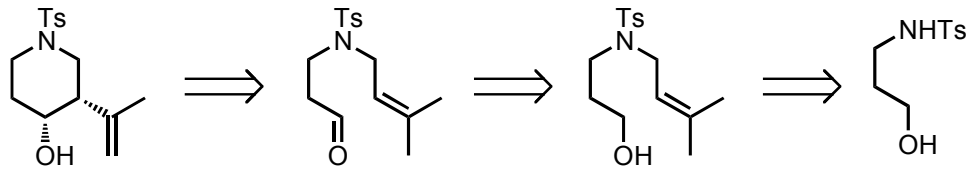
Scheme 24: Retrosynthetic analysis of the target molecule

2. Results and Discussion

2.1 Model System

Before embarking on the synthesis of the 2,4,5-trisubstituted cyclisation precursor **75**, initial work focused on the construction of a model system to evaluate Brønsted acids with weakly nucleophilic counter ions. The Brønsted acids chosen to study were perchloric acid ($HClO_4$) and chlorosulfonic acid (HSO_3Cl), which in comparison to the chloride ion of hydrochloric acid, were envisaged to reduce HX addition products that have been observed in very electron deficient ene components.

The model system chosen was the cyclisation of aldehyde **58** into the corresponding 2,4-trisubstituted piperidine **60** because the Prins reaction on this substrate has been well established allowing thorough evaluation of new reaction conditions and the synthesis is relatively simple from the *N*-tosyl amino alcohol **81** (Scheme 25).

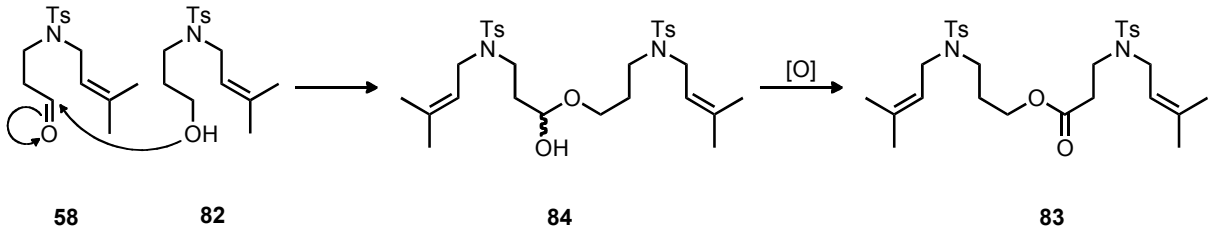


60 **58** **81**

Scheme 25: Retrosynthetic analysis of the model system

Starting from the *N*-tosyl amino alcohol **81** a regioselective *N*-alkylation with prenyl bromide gave the desired product **82** in an excellent yield. Oxidation of the alcohol **82** to the corresponding aldehyde **58** was first explored with PCC. Unfortunately, the yields of the aldehyde were only modest ~60 % and were accompanied by small amounts ~10% of ester

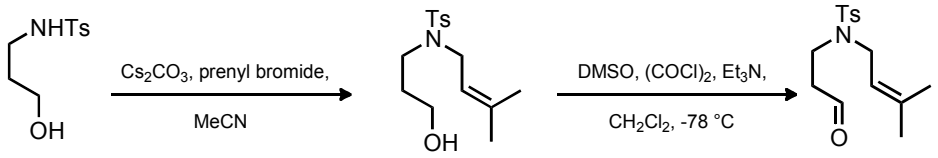
83, presumably formed from the dimerisation of alcohol starting material **82** with the aldehyde product **58** giving the hemiacetal **84** that was oxidised with PCC to the corresponding ester **83** (Scheme 26).[70]



58 **82** **84** **83**

Scheme 26: Dimerisation occurring during oxidation

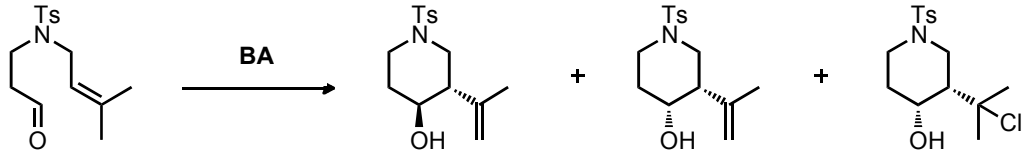
This by-product had previously been observed in the group and was known to be inseparable from the aldehyde product by chromatographic means.[60] The oxidation was completed successfully through the employment of a Swern oxidation. This gave the desired product **58** in an excellent yield with no dimerisation occurring (Scheme 27).



81 **82** 96% **58** 97%

Scheme 27: Synthesis of the cyclisation precursor

With the cyclisation precursor in hand, Prins reactions were carried out using the Brønsted acids $HClO_4$ and HSO_3Cl, with concentrated HCl used for comparison purposes (Scheme 28).



58 **59** **60** **61**

Scheme 28: Prins cyclisation

The results from the reaction are summarised below (Table 5). Although no counter ion adducts were observed for the Brønsted acids $HClO_4$ and HSO_3Cl the diastereoselectivities were low *c.f.* 4:1 and 3:1 respectively and the yields were only poor to modest, with complete decomposition of materials when $HClO_4$ was used in excess (entry 1). The use of concentrated hydrochloric acid proved to be an effective catalyst giving the *cis* product **60** in a good yield and diastereoselectivity, however a small amount of the HCl adduct **61** was detected (entry 8). As we failed to find a new Brønsted acid to catalyse the reaction, we decided to stick with the previously optimised conditions of concentrated hydrochloric acid to carry out the Prins reaction.

Entry	BA[a]	Eq	Temp / °C	59 : 60 : 61[b]	Yield (%)[c]
1	$HClO_4$	3	rt	-[d]	-
2	$HClO_4$	1	rt	35 : 65 : 0	19 (7)
3	$HClO_4$	1	-78	20 : 80 : 0	47 (14)
4	$HClO_4$	0.1	-78	25 : 75 : 0	39 (13)[e]
5	HSO_3Cl	1	rt	40 : 60 : 0	46 (27)
6	HSO_3Cl	1	-78	25 : 75 : 0	67 (22)
7	HCl	3	rt	10 : 80 : 10	76[f] (8)
8	HCl	3	-78	5 : 85 : 10	84[f] (5)

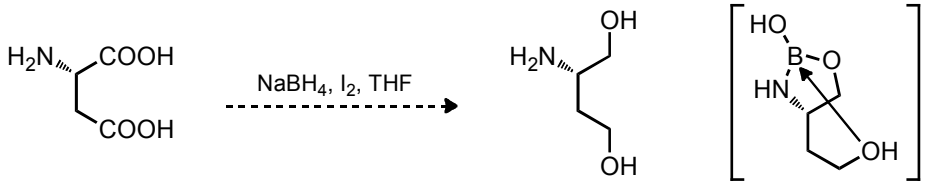
[a] Reactions were carried out in CH_2Cl_2 for 16 h [b] Ratio determined by ^1H NMR of crude reaction mixtures. [c] Isolated yields of major (minor in parentheses) isomers following purification. [d] No product formation, only a complex mixture of unidentified by-products determined by ^1H NMR of crude reaction mixture. [e] 16% unreacted starting material recovered. [f] Combined yield of **60** and **61** as they were inseparable by chromatographic methods.

Table 5: Prins cyclisation results

2.2 First Generation Synthesis

2.2.1 Synthesis of Crotyl Substrate

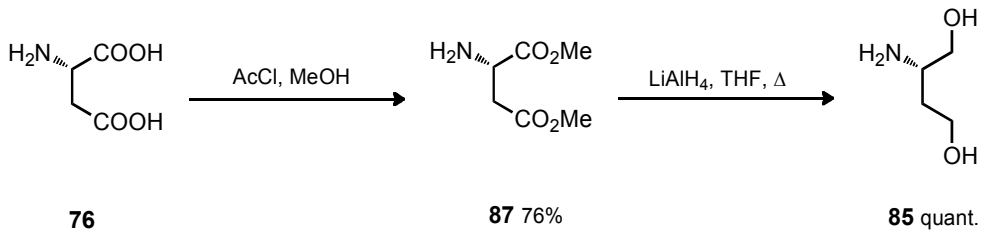
As proposed from our retrosynthetic analysis of Ma and Sun's advanced intermediate **27**, we started our synthesis from the naturally occurring amino acid, L-aspartic acid **78**. We intended to reduce the carboxylic acid functionalities to afford the corresponding diol **85**. Although there was no literature precedent for this one step reduction of L-aspartic acid we were encouraged by the work of Meyers *et al* who have shown the facile reduction of a variety of α-amino acids to the corresponding amino alcohols using $NaBH_4$ and I_2.[71] Unfortunately, this protocol failed to give any of the desired product **85**. A by-product was isolated in a 40% yield, which we believed to be the boron complex **86** based on its ^1H NMR, ^{13}C NMR, IR and mass spectra (Scheme 29).



76 **85** **86** 40%

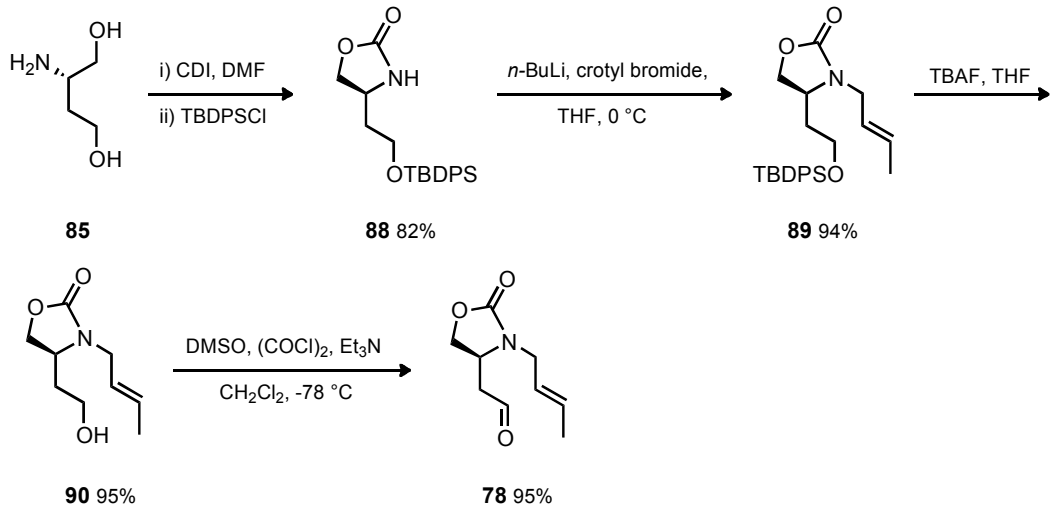
Scheme 29: Unsuccessful reduction with $NaBH_4/I_2$

Instead we employed a two-step procedure to accomplish the reduction: Firstly, esterification of aspartic acid **78** with acetyl chloride in MeOH followed by a mild basic work-up gave the corresponding methyl ester **87** in good yield of 76%.[72] Secondly, treatment of the amino ester with $LiAlH_4$ in THF and subsequent Soxhlet extraction of the aluminium salts gave the amino diol **85** in a quantitative yield (Scheme 30).[73]



Scheme 30: Esterification followed by reduction

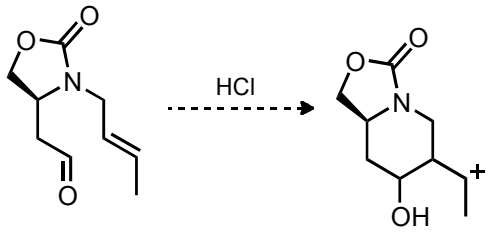
Following a modified one-pot literature procedure[73] the amino diol **85** was regioselectively cyclised to form the 5-membered cyclic carbamate with carbonyldiimidazole (CDI) followed by *in situ* protection of the β-oxygen using TBDPSCl with the imidazole by-product generated in the first step functioning both as a base and nucleophilic catalyst. This gave the silylated oxazolidinone **88** in a good yield of 82%, an improvement over the 57% yield presented in the literature. The cyclisation precursor **78** was then straightforwardly prepared in three steps. *N*-Alkylation of oxazolidinone **88** with crotyl bromide and *n*-BuLi gave **89**, which when treated with TBAF removed the silyl ether protecting group to give alcohol **90**. Finally, oxidation of the alcohol to the corresponding aldehyde using Swern conditions gave the cyclisation precursor **78** (Scheme 31).



Scheme 31: Synthesis of crotyl cyclisation precursor

The cyclisation precursor **78** was first subjected to the Prins reaction using the previously optimised Brønsted acid conditions[60] of three equivalents of concentrated HCl in CH_2Cl_2 at -

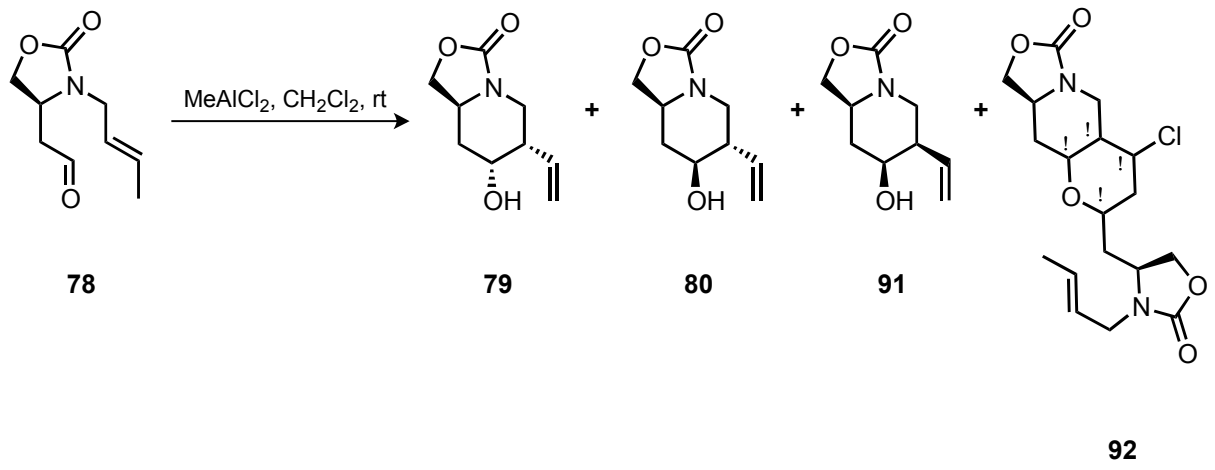
78 °C. Unfortunately this failed to catalyse the reaction and only unreacted starting material was recovered, and raising the temperature to room temperature had no effect on the outcome of the reaction. We then turned to the Brønsted acid conditions of a saturated solution of HCl gas in CH_2Cl_2 at -78 °C. This caused extensive decomposition of the starting material into multiple unidentifiable by-products with no observable product formation. The Prins reaction is usually thought of as reacting through a carbocationic intermediate. This requires the substrate to react through an unfavourable secondary carbocation, giving a possible explanation for its reluctance to form any products (Scheme 32).



78

Scheme 32: Attempted Prins reaction with HCl

The previously optimised Lewis acid-catalysed carbonyl-ene reaction conditions of two equivalents of $MeAlCl_2$ in CH_2Cl_2 at -78 °C[60] (Table 6, entry 1) failed to promote the reaction and only unreacted starting material was recovered. Raising the temperature to room temperature allowed reaction to occur, leading to a mixture of four products: the *trans*, *cis*-piperidine **79** and *cis, trans*-piperidine **80** as predicted, a new diastereomeric product *cis,-cis*-piperidine **91** and a dimerisation by-product **92** (Scheme 33).



78 **79** **80** **91** **92**

Scheme 33: Carbonyl-ene cyclisation of aldehyde **78**

The products were obtained in a ratio of 24:30:10:36 for **79**, **80**, **91** and **92** respectively (Table 6, entry 2), determined by analytical HPLC. A combination of flash column chromatography and semi-preparative HPLC afforded partial separation of the products. The dimer **92** comprises of four stereocenters allowing for a possibility of sixteen stereoisomers. Analysis of the ^{1}H NMR spectrum of **92** revealed a mixture of at least three diastereomers, from the presence of three doublets between 1.2-1.6 ppm corresponding to the methyl protons. None of the stereochemistries from the diastereomeric mixture of dimers **92** could be determined. The stereochemistry of the three piperidines **79**, **80** and **91** was tentatively assigned through analysis of coupling constants in their ^{1}H NMR spectra. The relative stereochemistry of piperidine **79** was determined to be *trans, cis*. In the ^{1}H NMR spectrum of **79** the axial proton of $^{3"}$H lies at 1.54 ppm and is split into a doublet of double doublets with coupling of 2.3, 11.7 and 13.7 Hz corresponding to a axial-equatorial, axial-axial and gem couplings. The axial proton of $^{6"}$H lies at 3.19 ppm and is split into a triplet with a large coupling constant of 12.5 Hz indicative of a axial-axial and gem couplings. The corresponding equatorial proton $^{6'}$H lies at 3.74 ppm and is split into a double doublet with couplings of 5.1 and 12.5 Hz, indicating axial-equatorial and gem couplings. The relative stereochemistry of piperidine **80** was determined to be *cis, trans*. The axial proton $^{3"}$H at 1.38 ppm is split into a quartet with a

coupling constant of 11.8 Hz coming form two diaxial and a gem coupling. The axial proton $^{6"}$H lying at 2.65 ppm is split into a double doublet with two large couplings of 11.4 and 13.4 Hz corresponding to a diaxial and a gem coupling. The relative stereochemistry of **91** was determined to be *cis, cis*. The proton assigned to the axial $^{3"}$H lies at 1.46 ppm and is split into a quartet with a coupling constant of 11.9 Hz corresponding to two diaxial a gem coupling. A doublet at 3.13 ppm corresponds to axial $^{6"}$H with coupling constants of 3.4 and 13.6 Hz equating to an axial-equatorial and gem coupling (Figure 6).

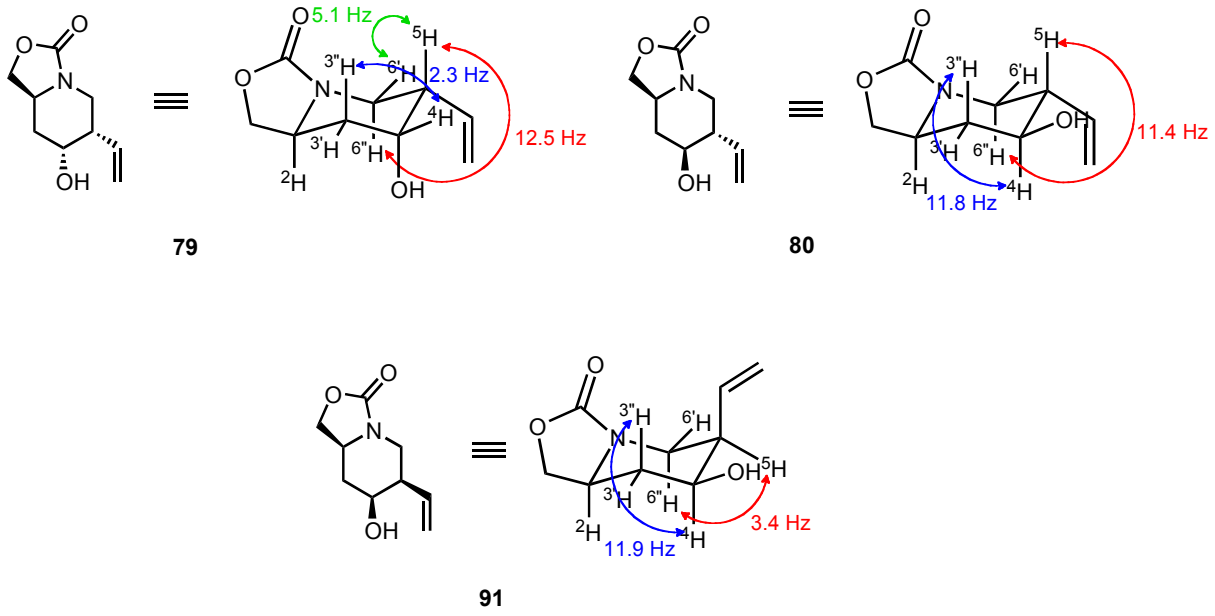


Figure 6: Selected coupling constants

Carrying out the reaction with just one equivalent of $MeAlCl_2$ for sixteen hours (Table 6, entry 3) led to significant amounts of unreacted starting material and with no noticeable decrease in dimerisation. Next, we investigated how the role of reaction concentration would affect the ratio of products. Having started with a reaction concentration of 0.1 M in CH_2Cl_2 we carried out reactions at 50 mM and 10 mM (Table 6, entries 4 & 5). Pleasingly the higher dilutions led to lower amounts of the dimerisation product **92** but also led to lower amounts of the desired *trans*, *cis* piperidine **79**. We then looked into the role that temperature played in the reaction. Noting that at very low temperatures no reaction occurred, we hoped that a

change in temperature would favour one reaction pathway over another. Carrying out the reaction at 0 °C (Table 6, entry 6) gave very similar results to the reaction at room temperature (Table 6, entry 2). Performing the reaction at an elevated temperature of 42 °C (Table 6, entry 7) resulted in less dimerisation and gave the *cis, trans* piperidine **80** as the major product. We investigated the Lewis acid TMSOTf (Table 6, entry 8) in the hope that silylation of the oxygen would occur and so preventing it from attacking another molecule of starting material **78**. Unfortunately, no reaction occurred under these conditions and only unreacted stating material was recovered.

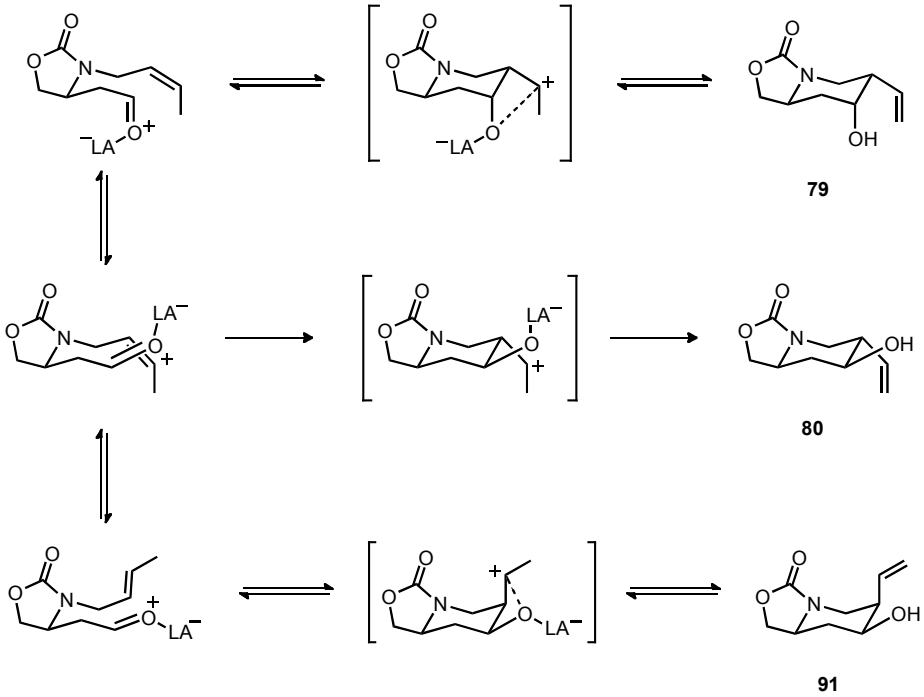
Entry	LA[a]	Eq	Temp / °C	Conc / mM	78 : 79 : 80 : 91 : 92
1	$MeAlCl_2$	2	-78	100	100 : 0 : 0 : 0 : 0[b]
2	$MeAlCl_2$	2	rt	100	0 : 24 : 30 :10: 36[c]
3	$MeAlCl_2$	1	rt	100	15 : 19 : 26 : 8 : 32[c]
4	$MeAlCl_2$	2	rt	50	0 : 18 : 32 : 31 : 19[c]
5	$MeAlCl_2$	2	rt	10	0 : 14 : 36 : 34 : 16[c]
6	$MeAlCl_2$	2	0	100	0 : 25 : 27 :10: 38[c]
7	$MeAlCl_2$	2	40	100	0 : 16 : 56 : 22 : 18[c]
8	TMSOTf	1	rt	100	100 : 0 : 0 : 0 : 0[b]

[a] Reactions were carried out in CH_2Cl_2 for 16 h. [b] Ratio determined by analysis of the ^1H NMR of the crude reaction mixture [c] Ratio determined by HPLC analysis of crude reaction mixtures.

Table 6: Carbonyl-ene cyclisation conditions

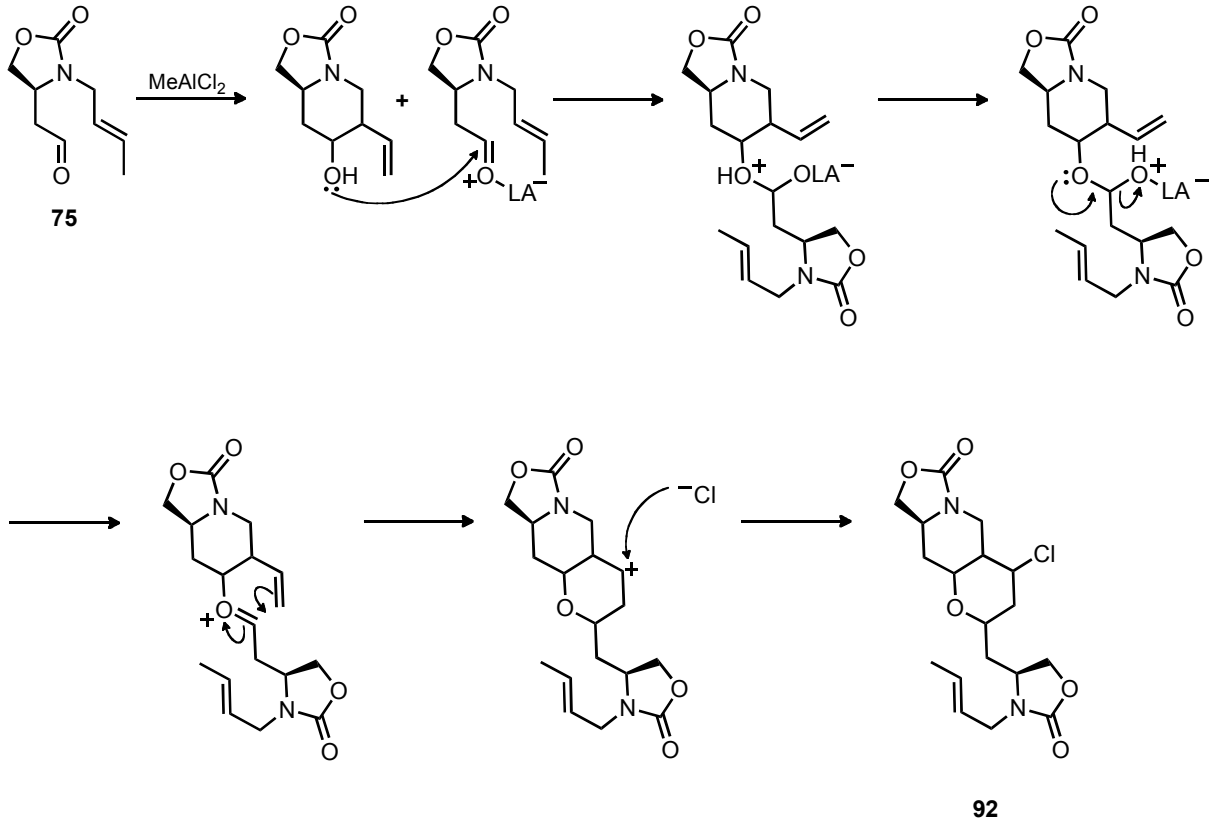
From previous studies,[60,64] we believed that the Lewis acid-promoted carbonyl-ene reaction proceeds through an asynchronous concerted mechanism with a polar transition state (or a fleeting zwitterionic intermediate). The transition state leading to the formation of *cis*, *trans* piperidine **80** has both the hydroxyl and ene component in equatorial positions; although thermodynamically favourable on steric grounds, the configuration does not allow for stabilisation of the carbocationic character in the transition state by the lone pair of the

oxygen. Regarding the piperidines that have the 4- and 5- substituents *cis* to one another **79** and **91**, we believe them to react through lower energy transition states due to the stabilising interaction of any cationic character the transition state (or carbocation in the intermediate) by the lone pair on the oxygen. Formation of either **79** or **91** would depend on the preference for either the ene component or the Lewis acid-coordinated oxygen to adopt an equatorial position. The failure to promote the reaction at cold temperatures highlights the relatively high energy transitions (or high energy secondary carbocations) involved in the reaction and the need to conduct the reaction at ambient temperatures. This has the consequence of eroding the kinetic preference to form *cis* configuration **79** and **91** in favour of the thermodynamic *trans* product **80**. However, the diastereoselectivity cannot be completely turned over completely in favour of the thermodynamic product **80** due to the significant contribution from the stabilising interactions arising in the *cis* configuration (Scheme 34).



Scheme 34: Postulated transition states leading to products

Regarding the mechanism for the formation of the dimerisation product **92**, we believe that there is a competition between the intramolecular cyclisation of aldehyde **75** and the intermolecular reaction between the aldehyde **75** and the piperidine product. After cyclisation to the piperidine product, nucleophilic attack of the hydroxyl onto another aldehyde would occur. Following breakdown of the Lewis acid-coordinated hemiacetal to reveal an oxocarbenium ion, a second cyclisation is proposed to occur, reminiscent of a type III carbonyl-ene cyclisation, followed by trapping of the resulting carbocation with a chloride ion (Scheme 35).



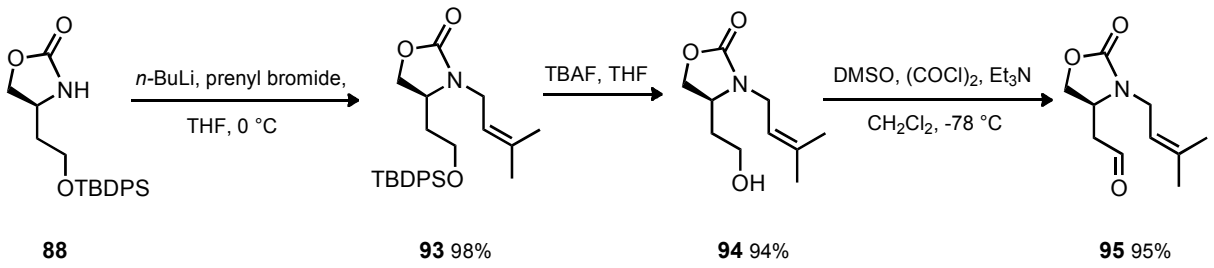
Scheme 35: Proposed mechanism for dimerisation formation

Discouraged by the lack of promising results, we decided to focus our attention on making modifications to the ene component in an attempt to improve the cyclisation reaction. The most logical modification is replacement of the distal hydrogen in the ene component by a

methyl group, which upon successful cyclisation should lead to more stable tertiary carbocation.

2.2.2 Synthesis of Prenyl Substrate

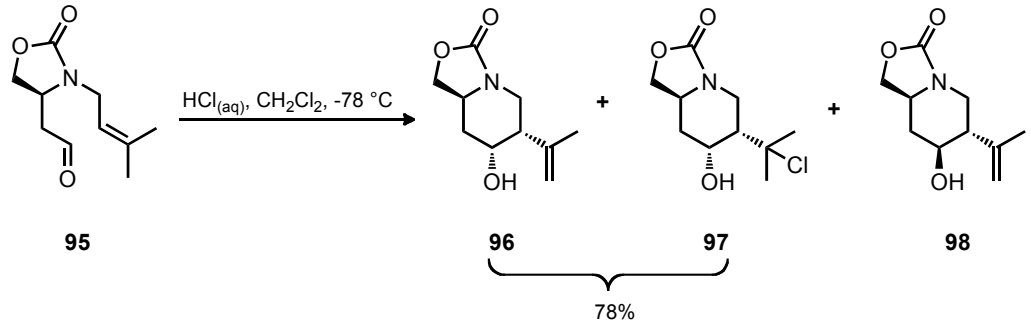
The oxazolidinone **88** was alkylated using prenyl bromide and *n*-BuLi to give the prenyl oxazolidinone **93**, deprotection of the silyl ether with TBAF gave the free alcohol **94** and finally a Swern oxidation gave the modified cyclisation precursor **95**, proceeding with excellent yields of 98, 94 and 95% respectively (Scheme 36).



Scheme 36: Synthesis of prenyl cyclisation precursor

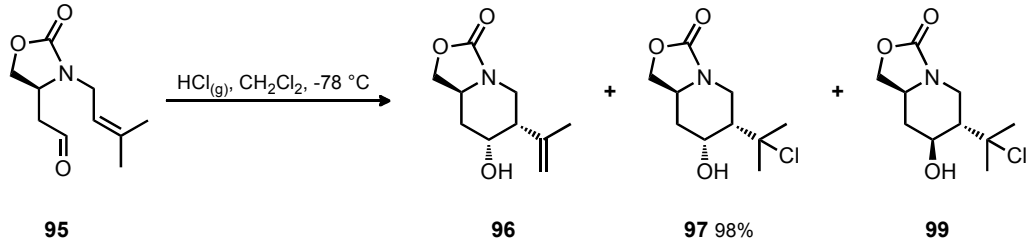
The prenyl cyclisation precursor was first subjected to a Prins reaction using three equivalents of concentrated HCl in CH_2Cl_2 at -78 °C. The cyclisation proved successful, although the reaction did not go to completion with 12% of aldehyde starting material still remaining. The reaction gave a mixture of three piperidines, **96**, **97** and **98** in ratio of 15:7:1 respectively (

Table 7, entry 1). This gave a combined c*is* to *trans* ratio of 96:4. The *cis* and *cis*-chloride were inseparable by flash column chromatography and gave a combined yield of 78% (Scheme 37).



Scheme 37: Concentrated HCl cyclisation

In an attempt to improve the efficacy of the cyclisation we performed the reaction with a saturated solution of anhydrous HCl in CH_2Cl_2 at -78 °C for 2 hours (Scheme 38).

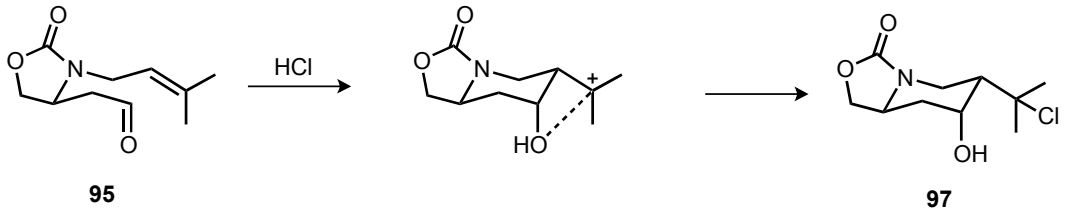


Scheme 38: Anhydrous HCl cyclisation

This resulted in complete conversion of the aldehyde starting material into products and gave an excellent diastereomeric ratio of 99.0 : 0.50 : 0.50 for **97**, **96** and **99** respectively (Table 7, entry 2) determined by HPLC analysis, giving a combined *cis* to *trans* ratio of 99.5:0.5 and isolated in an excellent yield of 98% for *cis*-chloride.

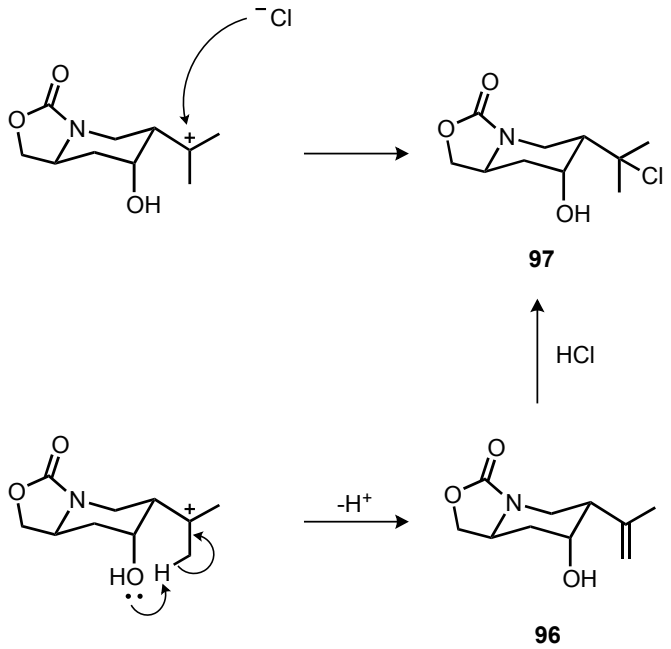
As the Prins reaction is believed to proceed through a carbocationic intermediate, the prenyl substrate would react through a stable tertiary carbocation leading to a facile route into product formation, compared to the relatively unstable secondary carbocation of the crotyl substrate. The 2-substituent and nitrogen are constrained within an oxazolidinone ring, forcing the 2-substituent to adopt an equatorial disposition leading to a minimal steric clash between itself and the hydroxyl group lying in the axial position. The isopropyl cation of the prenyl substrate is sterically more demanding than the ethyl carbocation of the crotyl substrate

Leading to the isopopyl cation having a preference to adopt an equatorial disposition to avoid $A^{1,3}$ diaxial strain. In combination with the stabilising interaction outlined before, the oxygen and carbocation to lie *cis* to one another, this gives rise to the excellent diastereoselectivity if favour of the *cis* product (Scheme 39).



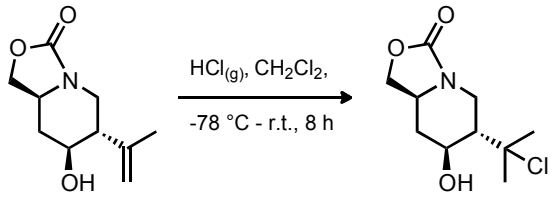
Scheme 39: Stabilised intermediate leading to product

Regarding the fate of the carbocationic intermediate, there are two possible pathways leading to the *cis* chloride **97** product; direct trapping of the carbocation intermediate with a chloride ion or loss of a hydrogen to form *cis* alkene **96** followed by HCl addition across the double bond (Scheme 40). As the reaction could never be stopped purely at the *cis* alkene **96** it suggests that either both reaction pathways are occurring or HCl addition across the alkene is a rapid process.



Scheme 40: Postulated reaction intermediates leading to products

As the quantity of *trans*-chloride **99** isolated from HPLC analysis was not sufficient for conclusive characterisation (only a mass spectrum) we decided to synthesise a sample of *trans*-chloride **99** from the HCl addition across the alkene of *trans* piperidine **98**. The *trans* piperidine isolated from the carbonyl-ene reaction (*vide infra*) was treated with a saturated solution of anhydrous HCl in CH_2Cl_2 at -78 °C for 4 hours before being warmed to room temperature and the reaction continued for a further 4 hours. The reaction time to add HCl across the *trans*-alkene of **98** was significantly longer than the analogous addition across the *cis*-alkene **96** and the *trans*-chloride **99** was only observed when using the forcing conditions of a saturated solution of anhydrous HCl in CH_2Cl_2. The long reaction times required for the *trans*-alkene **98** can be rationalised by the reaction proceeding through a higher energy *trans* carbocation leading to a slower Markovnikov addition of HCl across the alkene. Pleasingly HPLC analysis of the *trans*-chloride **99** obtained from the HCl addition of **98** reaction gave identical retention time and mass spectrum to the postulated *trans*-chloride **99** isolated from the Prins reaction of **95**.

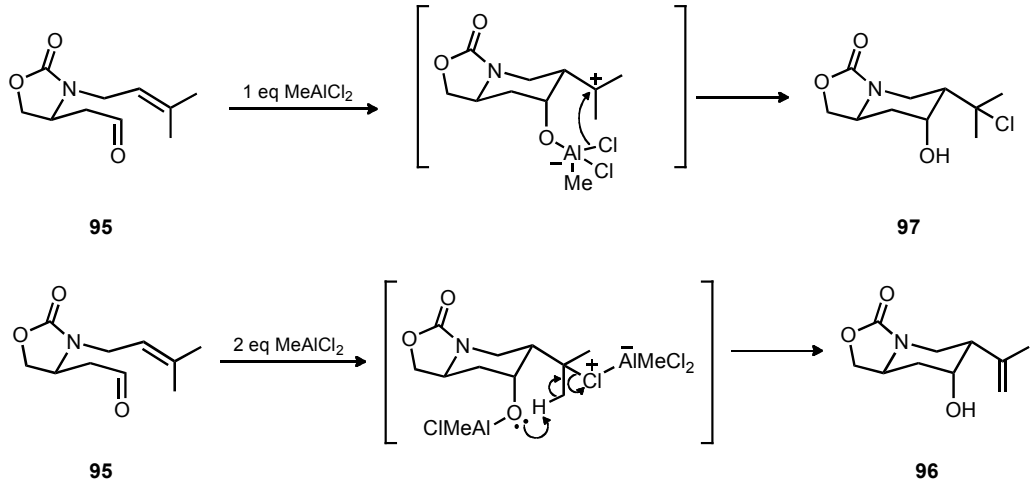


98 **99**

Scheme 41: HCl addition into *trans*-alkene **98**

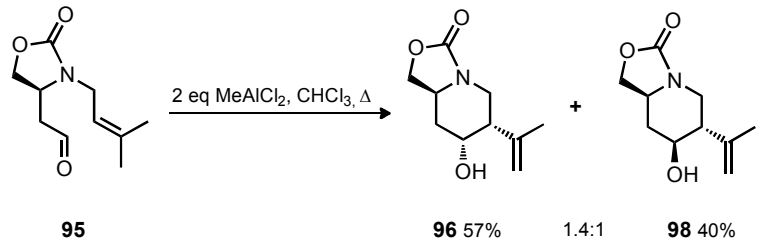
We turned our attention to the Lewis acid-promoted carbonyl-ene reaction, in the hope of favouring the thermodynamic *trans* product **98**. To compare the difference in selectivity between the Lewis acid and Brønsted acid reactions, the initial carbonyl-ene reaction was carried out with one equivalent of $MeAlCl_2$ in CH_2Cl_2 at -78 °C (Table 7, entry 3). Unsurprisingly, at low temperature, the reaction predominately favoured the kinetic *cis*

diastereomer **96** with *cis*-chloride **97** and the *trans* diastereomer **98** formed in lesser amounts in a ratio of 6:1:1.5 respectively. Surprisingly for a Lewis acid-promoted reaction there was a significant amount of the *cis*-chloride **97**. This result is not without precedent as Snider has observed that in carbonyl-ene reactions using one equivalent of an alkylaluminum chloride Lewis acid there were significant amounts of the β-hydroxy chloro product. It was proposed that the reaction proceeds through a zwitterionic intermediate and a chloride from the alcohol-Lewis acid complex adds intramolecularly to the carbocation through a [1,5] shift occurring across the same face of the molecule, *i.e.* **95** to **97** in Scheme 42. However, Snider observed that performing the reaction with two equivalents of a Lewis acid rendered the chloro-alkoxide intermediate unstable, even at -78 °C, leading to elimination of HCl to afford the homoallylic alcohol product,[49] *i.e.* **95** to **96** in Scheme 42. We repeated the reaction with two equivalents of $MeAlCl_2$ at -78 °C (Table 7, entry 4), which pleasingly gave the *cis* **96** and *trans* **98** piperidines in a ratio of 6:1, with only a trace amount of the *cis*-chloride **97** present (The observation of chloro alcohol product **97** leads us to believe that the carbonyl-ene reaction of aldehyde **95** also proceeds through a transient zwitterionic intermediate.



Scheme 42: Mechanism for the formation of chloro alcohol **97** and its breakdown to form alkene **96**

In an attempt to favour the thermodynamic product we began by raising the temperature of the reaction. Performing the reaction at room temperature with two equivalents of $MeAlCl_2$ in CH_2Cl_2 (Table 7, entry 5) gave the *cis* **96** and *trans* **98** diastereomers in a ratio of 2:1, with none of the *cis*-chloride **97** observed. Raising the temperature further to 40 °C (Table 7, entry 6) surprisingly still gave rise to the *cis* **96** diastereomer as the major component over the *trans* **98** diastereomer, in a ratio of 1.5:1. In a final attempt to favour the thermodynamic *trans* product **97** we changed the solvent to $CHCl_3$ and carried out the reaction at 61 °C (Table 7, entry 7), unfortunately the ratio was hardly improved with 1.4:1 in favour of the *cis* **96** over the *trans* **98** (Scheme 43).



Scheme 43: Cyclisation under Lewis acid conditions

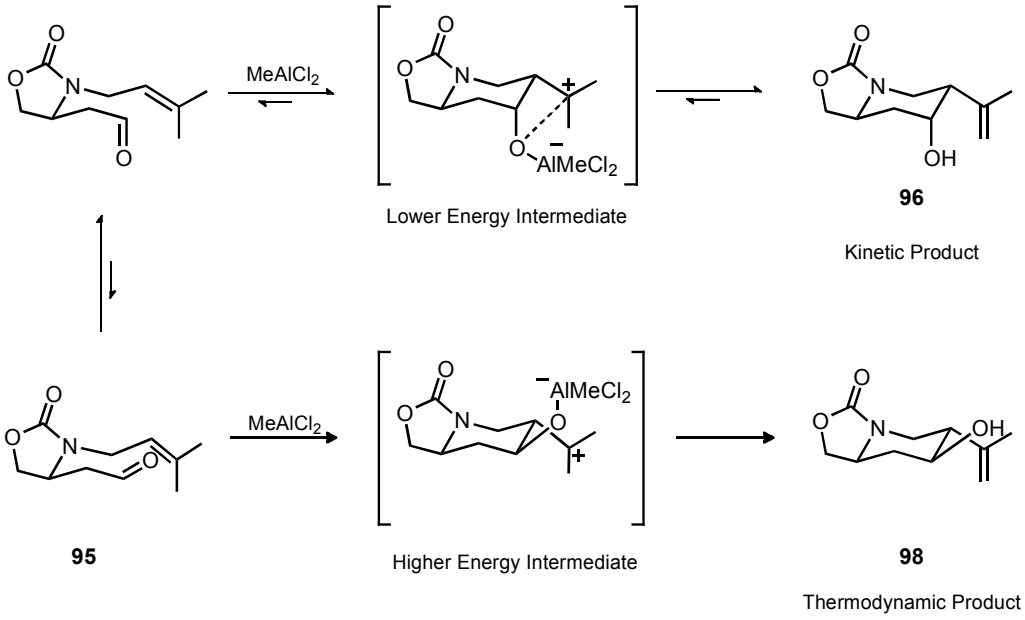
The results from both the Prins and carbonyl-ene cyclisations are summarised in the table below (Table 7).

Entry	Catalyst[a]	Eq	Temp / °C	Time / h	96 : 97 : 98 : 99[b]	Yield (%)[c]
1	$HCl_{(aq)}$	3	-78	16	15 : 7 : 1 : 0	76[d]
2	$HCl_{(g)}$	-[e]	-78	2	0.5 : 99.0 : 0 : 0.5[f]	98
3	$MeAlCl_2$	1	-78	16	6 : 1 : 1.5 : 0	82[d] (17)
4	$MeAlCl_2$	2	-78	16	6 : trace : 1 : 0	85 (14)
5	$MeAlCl_2$	2	rt	16	2 : 0 : 1 : 0	63 (30)
6	$MeAlCl_2$	2	40	16	1.5 : 0 : 1 : 0	58 (37)
7	$MeAlCl_2$	2	61[g]	16	1.4 : 0 : 1 : 0	55 (39)

[a] Reactions were carried out in CH_2Cl_2 unless otherwise stated. [b] Ratio determined by ^1H NMR analysis of crude reaction mixtures unless stated otherwise. [c] Isolated yields of major (minor in parentheses) isomers following purification. [d] Combined yield of **96** and **97**. [e] Reaction performed with a saturated solution of anhydrous HCl. [e] 16% unreacted starting material recovered. [f] Ratio determined by HPLC analysis of crude reaction mixture. [g] Reaction carried out in $CHCl_3$

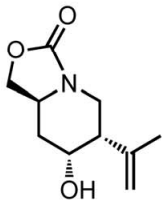
Table 7: Prins and carbonyl-ene reaction conditions and outcomes

Surprisingly for a Lewis acid cyclisation there was a continued preference for the formation of the kinetic *cis* diastereomer **96**, even at elevated temperatures. To rationalise this observation we believed that the oxazolidinone ring exerted a strong electron-withdrawing effect on the system. Resulting in destabilisation of the carbocationic charge in the intermediate, making the stabilising interaction from an oxygen lone more significant. This stabilising interaction is only possible when both hydroxyl and ene groups are *cis* to one another and offers an explanation for the preferential formation of the *cis* diastereomer **96** under both Prins and carbonyl-ene conditions (Scheme 44).



Scheme 44: Carbonyl-ene reaction intermediates leading to products

The structures of cis-alkene **96**, cis-chloride **97** and trans-alkene **98** piperidines were determined by X-ray crystallography (Figures 7, 8 & 9).



96

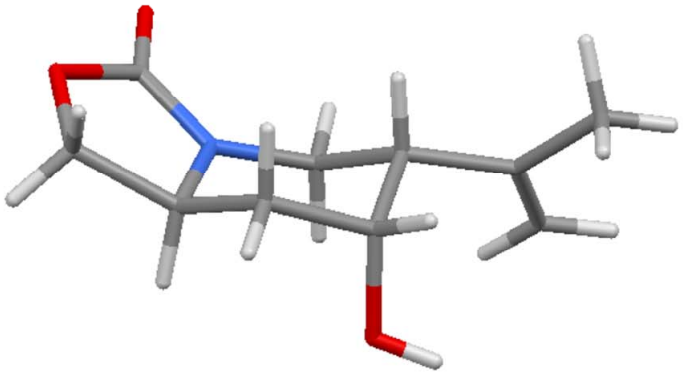
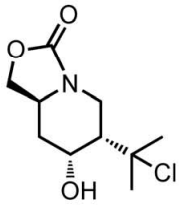


Figure 7: Crystal structure of piperidine **96**



97

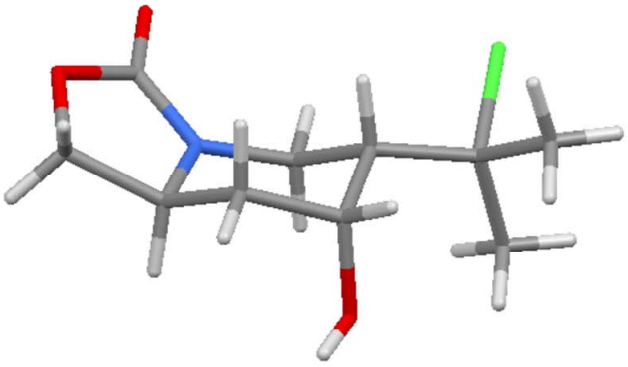
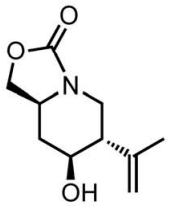


Figure 8: Crystal structure of piperidine **97**



98

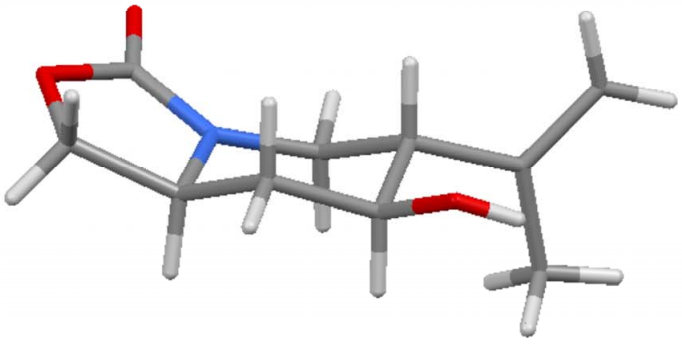
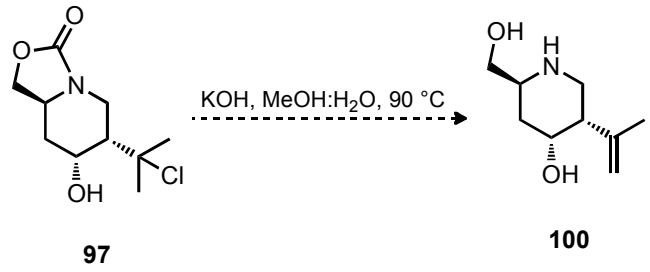


Figure 9: Crystal structure of piperidine **98**

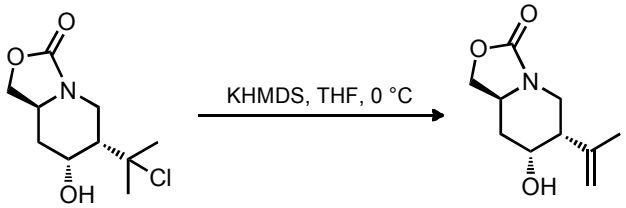
The Prins reaction using anhydrous HCl (entry 2) gave the highest *cis* to *trans* ratio. Unfortunately, the product from this reaction was the HCl adduct **97**. In order to make progress towards the target **27** we needed to eliminate HCl to access the more synthetically useful *cis*-alkene **96**. The initial reaction was carried out with aqueous KOH in MeOH in the hope of facilitating two steps in one: first, elimination of HCl to give *cis*-alkene **97** and secondly, hydrolysis of the oxazolidinone ring to give the amino diol **100**. Sadly, the reaction failed to afford any of the desired product and instead gave a complex mixture of unidentifiable products (Scheme 45).



97 **100**

Scheme 45: Failed elimination with KOH

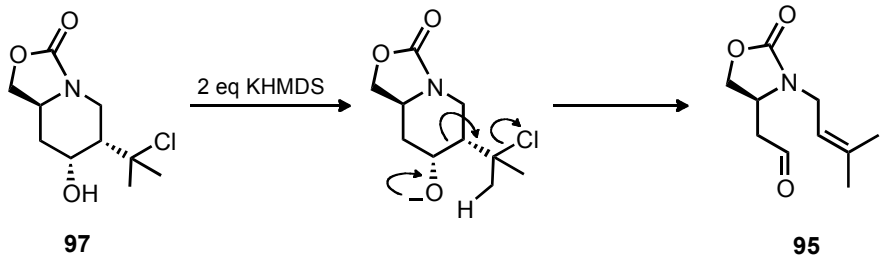
We then turned our attention to the strong non-nucleophilic base KHMDS. Employing one equivalent in THF at 0 °C resulted in successful elimination but the results were not reproducible, with yields ranging from 50-95% (Scheme 46), and decreasing appreciably above the 100 mg scale. Using a crown ether, 18-crown-6, in the hope of increasing the basicity of the anion failed to furnish any improvement in yield.



97 **96** 50-90%

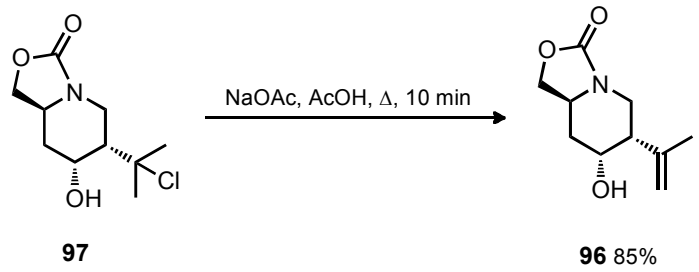
Scheme 46: Elimination with KHMDS

Employing two equivalents of KHMDS still did not afford complete elimination and led to significant amounts ~20% of aldehyde **95** resulting from an E_1cB elimination (Scheme 47).



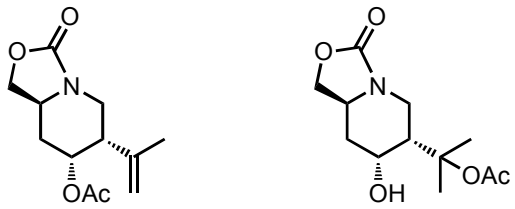
Scheme 47: Retro-ene reaction with 2eq KHMDS

The elimination was successfully accomplished in a reproducible manner by using 1 equivalent of NaOAc in refluxing AcOH[74,75] for 10 minutes to give the alkene **96** in a good yield of 85% after chromatography with none of the *cis*-chloride **97** starting material remaining (Scheme 48).



Scheme 48: Elimination with NaOAc in AcOH

Short reaction times were key to the success of this reaction, as extended reaction times led to the formation of two by-products increasing in amount as time progressed; acylation of the hydroxyl to give **101** and an AcOH adduct **102**, both of which were tentatively identified from analysis of their ^{1}H NMR and m/z spectra (Figure 10).



101 **102**

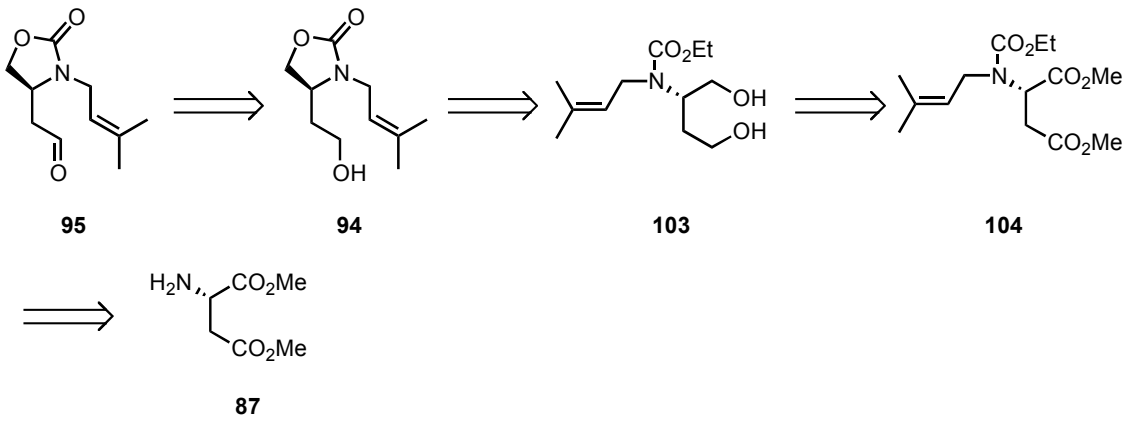
Figure 10: By-products from NaOAc/AcOH elimination

Although the synthetic route enabled access to the *cis* piperidine **97** in excellent yields and diastereoselectivities, it suffered from a few shortcomings. Firstly, the use of a TBDPS protecting group incorporated two redundant steps into the synthesis. A more expedient route would utilise functional group reactivity rather than mask it. Secondly, and most importantly, it was not amenable to a multigram scale required to complete the formal synthesis, due to the poor scalability of the $LiAlH_4$ reduction of ester **87** to diol **85**.

2.3 Second Generation Synthesis

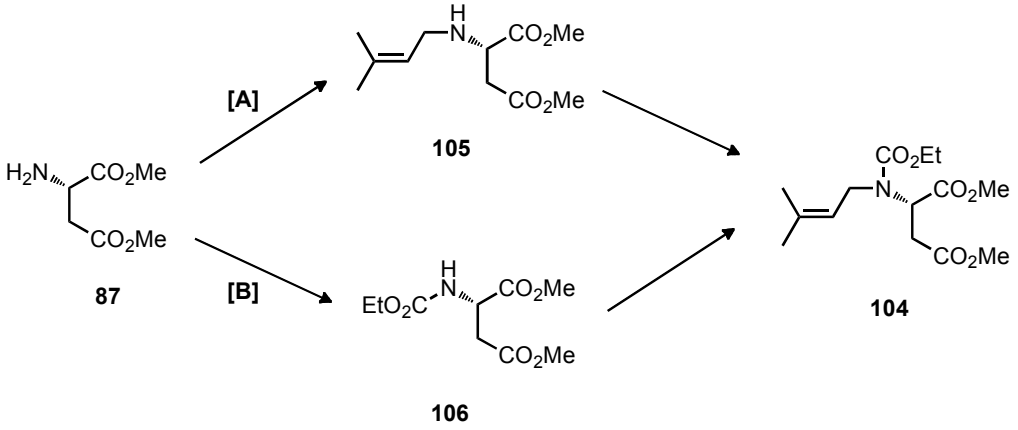
2.3.1 Introduction

Our new retrosynthetic approach to the cyclisation precursor **95** utilised the alcohol **94** which could be obtained from a regioselective cyclisation of diol **103**, derived from ester **104**. The tertiary aminoester **104** could be formed from monoalkylation and carbamation of aspartic ester **87**, which can be obtained from aspartic ester **87** as shown in the previous synthesis (Scheme 49).



Scheme 49: New retrosynthetic approach to cyclisation precursor **95**

Two potential routes for the synthesis of **104** were devised. Firstly, monoalkylation of aspartic ester **87** to give the secondary amine **105** followed by carbamation giving **104** (Route **[A]**). Alternatively, the tertiary carbamate **104** could be prepared from carbamation of **87** to afford the secondary carbamate **106** followed by alkylation (Route **[B]**), shown in Scheme 50.

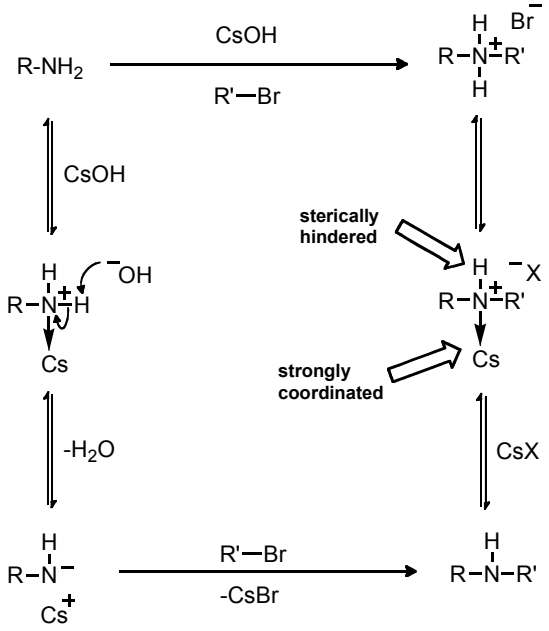


Scheme 50: Two potential routes for the synthesis of tertiary carbamate **104**

2.3.2 Primary Amine Alkylation

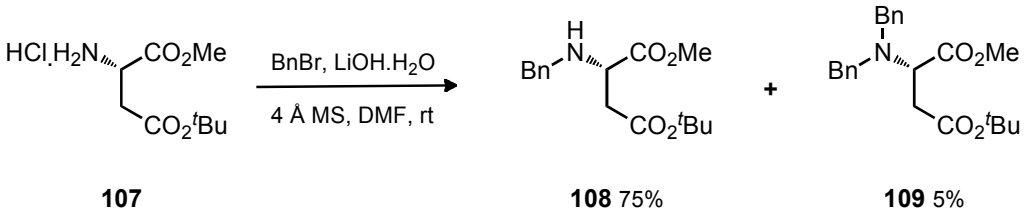
Initial research focused on the synthesis of **104** *via* route **[A]**, as it was reasoned that carbamate alkylation would require harsher conditions. The synthesis of secondary amines by

direct *N*-alkylation of primary amines is known as the Hoffmann alkylation;[76] it is usually an inefficient procedure due to over-alkylation, leading to mixtures of primary, secondary and tertiary amines, as well as quaternary ammonium salts.[77] The problem arises because upon each successive alkylation the products are more reactive than their starting materials. To circumvent this problem it is common to employ the amine in large excess relative to the alkylating agent.[78] This is an expensive and wasteful process, especially when the amine is not commercially available. However, owing to the straightforward nature of this transformation a number of researchers have studied it in the hope of imparting selectivity to the reaction.[79] Jung *et al.* have reported the chemoselective mono-*N*-alkylation of primary amines using cesium bases in DMF in the presence activated 4 Å molecular sieves.[80,81] They attribute the chemoselectivity to the formation of a strong coordinate bond between the alkylated secondary amine and a cesium ion. This has the affect of reducing the nucleophilicity of the secondary amine and inhibiting proton abstraction because of the increased sterics, which in combination helps to suppress further alkylation (Scheme 53).



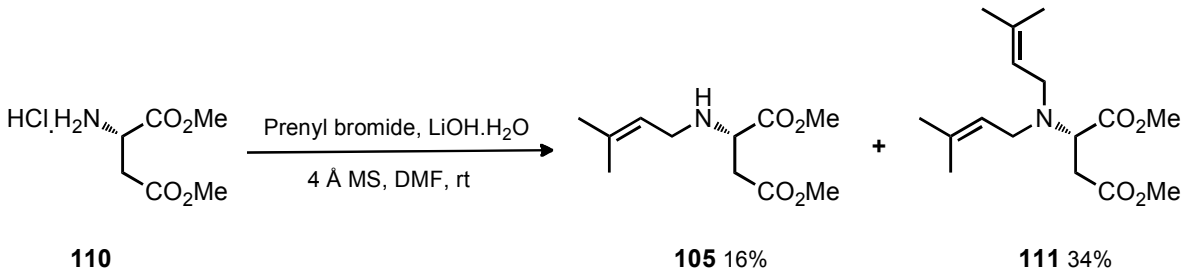
Scheme 51: Jung's rationale for the observed chemoselectivity

In parallel, Srivstava *et al*. have reported the selective *N*-alkylation of primary amines using K_2CO_3 as the base in polar aprotic solvents.[82] The selectivity could be switched between mono- and di-*N*-alkylation by varying the nature of the electrophile used in the reactions. More recently, Cho and Kim studying the selective mono-*N*-alkylation of α-amino esters observed poor selectivity when using Jung's conditions. They observed that the reaction could proceed effectively by employing LiOH and DMF in the presence of 4 Å molecular sieves, and in one example they alkylated aspartic acid *tert*-butyl methylester **107** with benzyl bromide and achieved a ratio of 15:1 of mono- **108** over dialkylated product **109 (**Scheme 52).[83]



Scheme 52: Alkylation presented by Cho and Kim

In an attempt to afford a similar transformation the aspartic ester hydrochloride salt **110** was allowed to react with two equivalents of LiOH, one equivalent of prenyl bromide in DMF in the presence of 4 Å molecular sieves. Unfortunately, the reaction favoured the formation of the di-alkylated amine **111** over the mono-alkylated amine **105** in a ratio of 2:1 respectively (Scheme 53).



Scheme 53: Alkylation of 1° amine

In an attempt to improve the selectivity in favour of the mono-alkylated product **105**, we screened a variety of bases such as CsOH, Cs_2CO_3 and K_2CO_3 but to no avail as they offered no improvement over the original attempt with LiOH (Table 8).

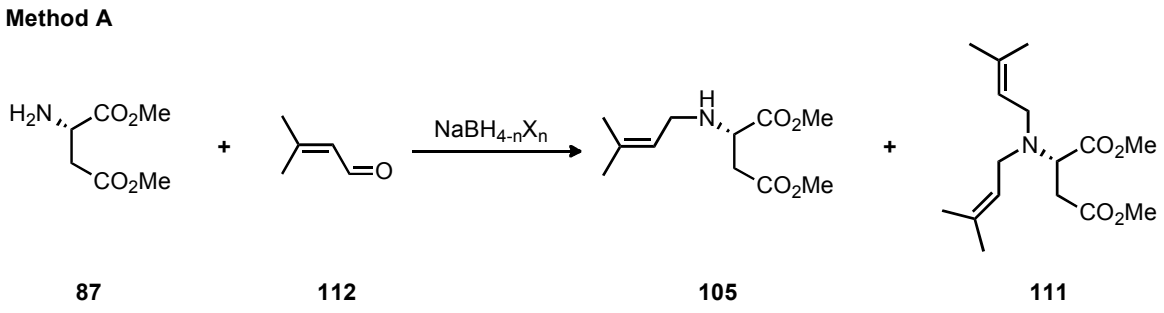
Entry	Base[a]	105 : 111[b]	Yield (%)[c]
1	$LiOH.H_2O$	1 : 2	34 (16)
2	$CsOH.H_2O$	1 : 3	30 (9)
3	Cs_2CO_3	1 : 3	32 (10)
4	K_2CO_3[d]	1 : 10	48 (3)

[a] All reactions were conducted with 1.2 eq of base and 1 eq of prenyl bromide dissolved DMF in the presence of 4 Å MS at rt for 16 h. [b] Ratio of products determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yields of major (minor in parentheses) isomers following purification. [d] An extra 0.5 eq of prenyl bromide added after 8 h.

Table 8: Alkylation of 1° amine with a variety of bases

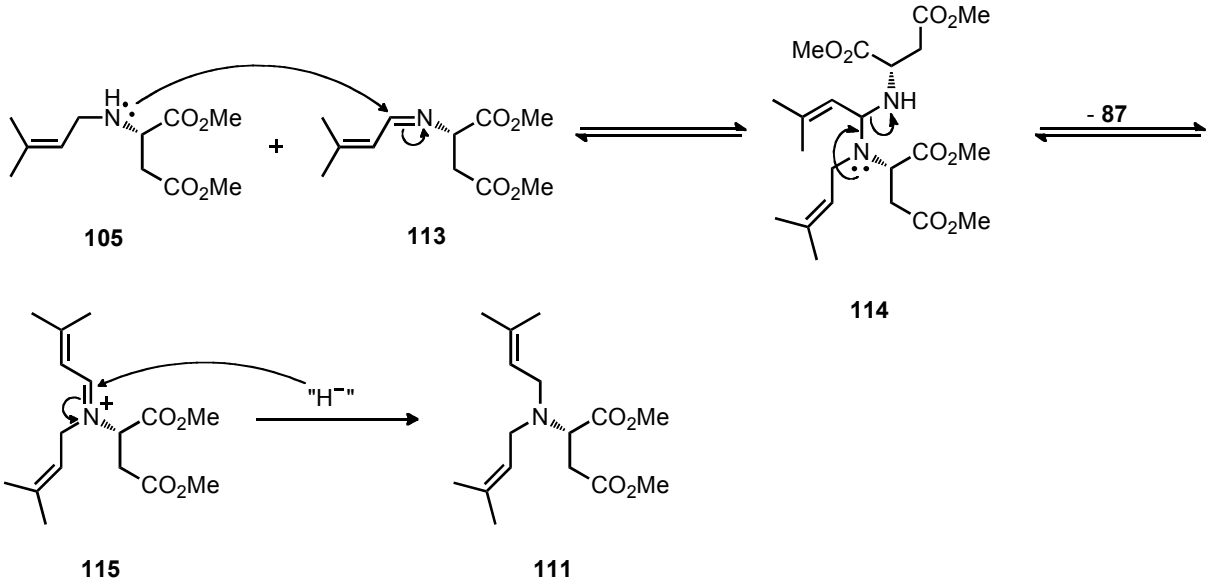
2.3.3 Reductive Amination

As the alkylation gave poor yields of the secondary amine, we decided to investigate a reductive amination approach. We began by attempting a one-pot procedure of preformation of the imine followed by subsequent reduction (shown as a general method in Scheme 54), using aspartic ester **87**, prenal **112** and $NaBH(OAc)_3$[84] dissolved in DCE at a concentration of 300 mM (Table 9, entry 1).



Scheme 54: General method A for a one-pot reductive amination

Surprisingly there was a mixture of mono-alkylated **105** and di-alkylated **111** products in a 1.2:1 ratio respectively. The significant amount of di-alkylated product can be rationalised by a molecule of the mono-alkylated product **105** attacking a molecule of the intermediate imine **113** to give aminal **114**. Breakdown of the aminal to generate a reactive iminium species **115**, followed by its reduction would yield the di-alkylated product **111** (Scheme 55).

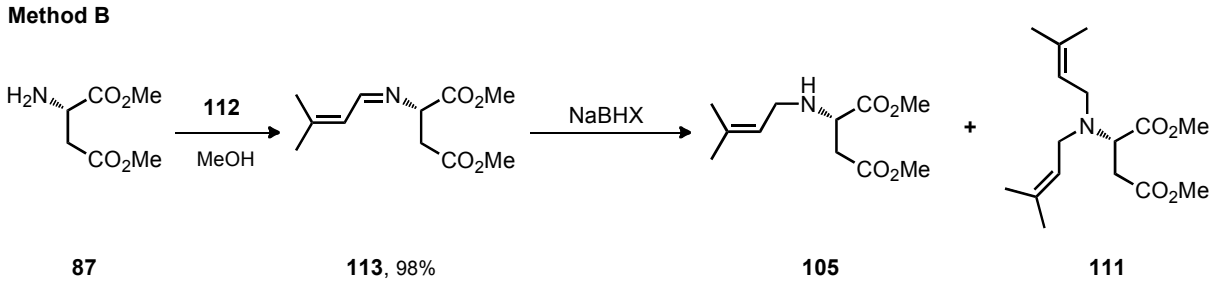


Scheme 55: Mechanism for the formation of **111** during reductive amination

To prevent over-alkylation, we employed the more reactive reducing agent $NaBH_4$ (Table 9 , entry 2) in the hope of reducing the intermediate imine **113** faster than the rate of attack by the secondary amine **105**. Although this method gave lower amounts of the over alkylated product, the overall yield of **105** was significantly lower due to a complex mixture of unidentifiable by-products, most likely formed from the reduction of the ester functionality and subsequent side reactions.

In the one-pot reductive amination procedure it was ambiguous whether preformation of the imine was complete before addition of the reducing agent, if not side reactions are possible

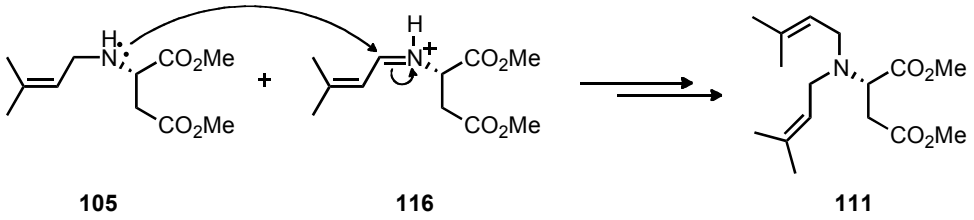
i.e. the reduced product **105** reacting with the aldehyde. A two-step method of imine formation followed by reduction was undertaken (shown as a general method in Scheme 56) to avoid such a problem. The reaction of aspartic ester **87** and prenal **112** dissolved in MeOH gave the crude imine **113** in a 98% yield, which was sufficiently pure to be used in the next step without purification. Confident that we had complete imine formation we could concentrate our efforts on the reduction, although whether imine formation is reversible in the reduction step remained unknown.



Scheme 56: General method B for a two step reductive amination

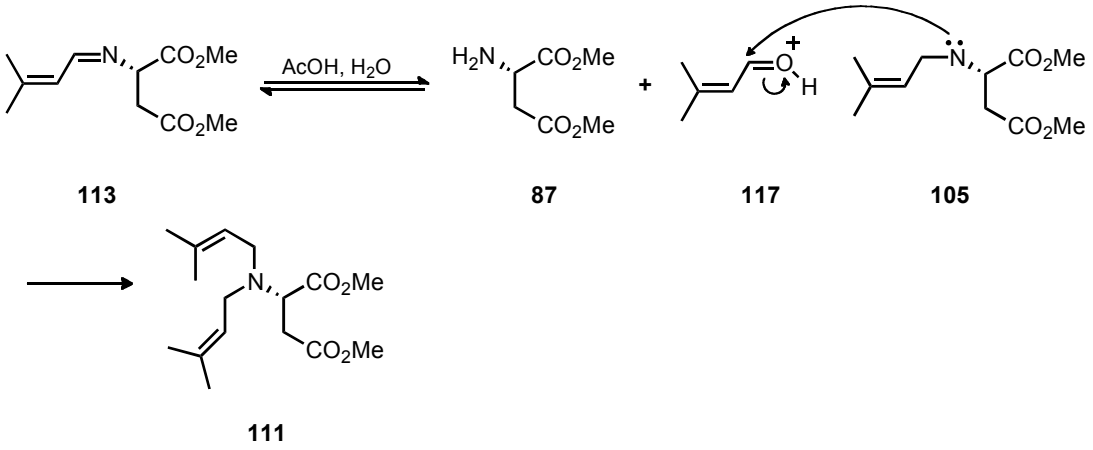
The reaction of imine **113** with $NaBH(OAc)_3$ in DCE at a concentration of 300 mM for 16 hours (Table 9, entry 3) led to significant over alkylation. We believed the over alkylation was an issue of concentration. Carrying out the reaction in a higher dilution of 0.1 M (Table 9, entry 4) pleasingly led to smaller amounts of over alkylation <10% and the gave secondary amine in a good yield of 70% but led to an increased reaction time of 72 hours. Diluting the reaction further to 50 mM (Table 9, entry 5) gave <5% over alkylation but the reaction time increased dramatically to 120 hours, with trace amounts of starting material still present. It was deemed impractical to carry out reactions on a multigram scale at concentrations of 50 mM because it would require ~100 mL of solvent per gram of reactant. Further efforts concentrated on improving the efficiency of the reaction at a concentration of 0.1 M. Additives were investigated; 4 Å molecular sieves and 2,6-lutidine had no effect on outcome

of the reaction (Table 9, entries 6 & 7); however, AcOH led to large amounts of over alkylation (Table 9, entry 8). One explanation to account for the over alkylation is the facile reaction between protonated imine **116** and secondary amine **105** leading to the formation of **111** (Scheme 57).



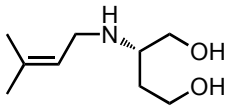
Scheme 57: Over alkylation resulting from protonation of the imine

Another possible explanation is the acid-catalysed hydrolysis of the imine with trace amounts of water leading to amine **87** and aldehyde **112**. Capture of the protonated aldehyde **117** with **105** would also lead to tertiary amine **111** (Scheme 58).



Scheme 58: Over alkylation resulting from acid catalysed hydrolysis of the imine

Changing the reducing agent to $NaBH_4$ in solvent mixture of DCE:MeOH (Table 9, entry 9) led to no observable over but instead gave significant amounts of diol **118** resulting from reduction of the esters (Figure 11).



118

Figure 11: Diol resulting from ester reduction

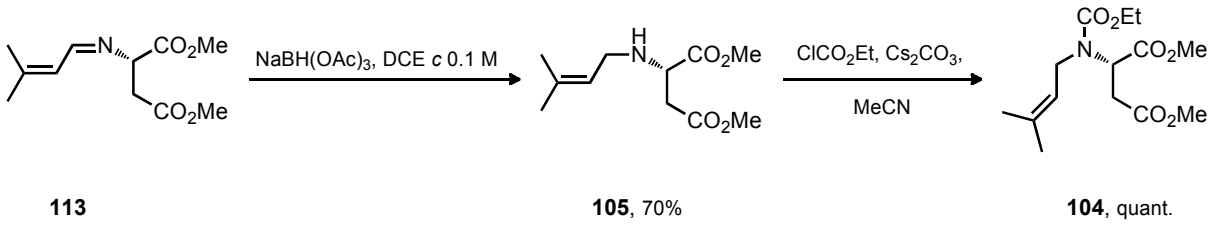
Changing the reaction solvent to a mixture of DCE:MeOH (Table 9, entry 10) and just MeOH (Table 9, entry 11) gave a complex mixtures of unidentifiable by products in both cases. From the experiments carried out the optimal conditions to carry out the reaction was *via* a two step procedure of imine formation followed by reduction with $NaBH(OAc)_3$ in DCE at a concentration of 0.1 M (Table 9, entry 4).

Entry	Method	Reducing Agent[a]	Solvent	Conc. / mM	Time / h	Additive[b]	105 :111[c]	Yield (%)[d]
1	A	$NaBH(OAc)_3$	DCE	300	16	none	1.2 : 1	31 (24)
2	A	$NaBH_4$[e]	MeOH	300	16	none	-[f]	15
3	B	$NaBH(OAc)_3$	DCE	300	16	none	1.5 : 1	39 (13)
4	B	$NaBH(OAc)_3$	DCE	100	72	none	20 : 1	70
5	B	$NaBH(OAc)_3$	DCE	50	120	none	>20 : 1	73
6	B	$NaBH(OAc)_3$	DCE	100	72	4 Å MS	20 : 1	68
7	B	$NaBH(OAc)_3$	DCE	100	72	2,6 -lutidine	20 : 1	69
8	B	$NaBH(OAc)_3$	DCE	100	72	AcOH	1 : 1	26 (23)
9	B	$NaBH_4$[g]	DCE:MeOH	100	16	none	>20 :1	22[h]
10	B	$NaBH(OAc)_3$	DCE:MeOH	100	16	none	-[i]	-
11	B	$NaBH(OAc)_3$	MeOH	100	16	none	-	-

[a] Reactions were carried out at rt with 1.5-2 eq of reducing agent unless stated otherwise. [b] 1 eq of additive used. [c] Ratio determined by ^{1}H NMR analysis of crude reaction mixtures unless stated otherwise. [d] Isolated yields of major (minor in parentheses) products following purification. [e] $NaBH_4$ added after 3 h to allow preformation of the imine [f] Many overlapping signals in the ^{1}H NMR of the crude reaction mixture made accurate integration impossible. [g] Reaction carried out at rt with 1 eq of reducing agent. [h] Purification gave diol **118** in a 31% yield. [i] Reaction gave a

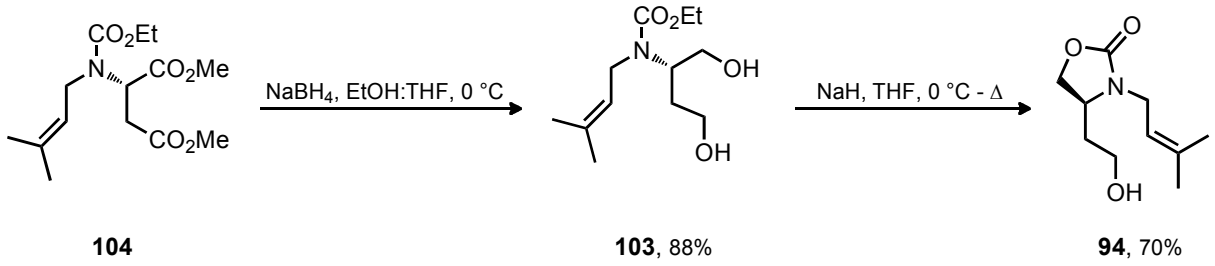
Table 9: Reductive amination results

Reaction of amine **105** with ethyl chloroformate and Cs_2CO_3 afforded the carbamate **104** in a quantitative yield (Scheme 59).



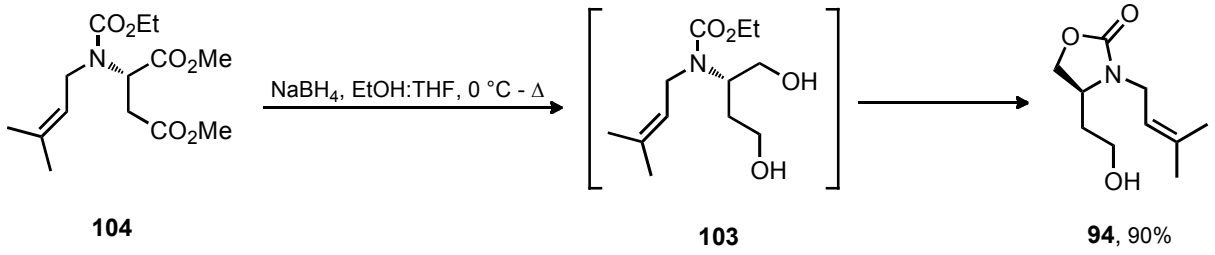
Scheme 59: Imine reduction and carbamate formation

Reduction of the esters with $NaBH_4$ in THF:EtOH at 0 °C gave the diol **103** and treatment with NaH in THF resulted in cyclisation to furnish the oxazolidinone **94** (Scheme 60).



Scheme 60: $NaBH_4$ reduction and NaH cyclisation

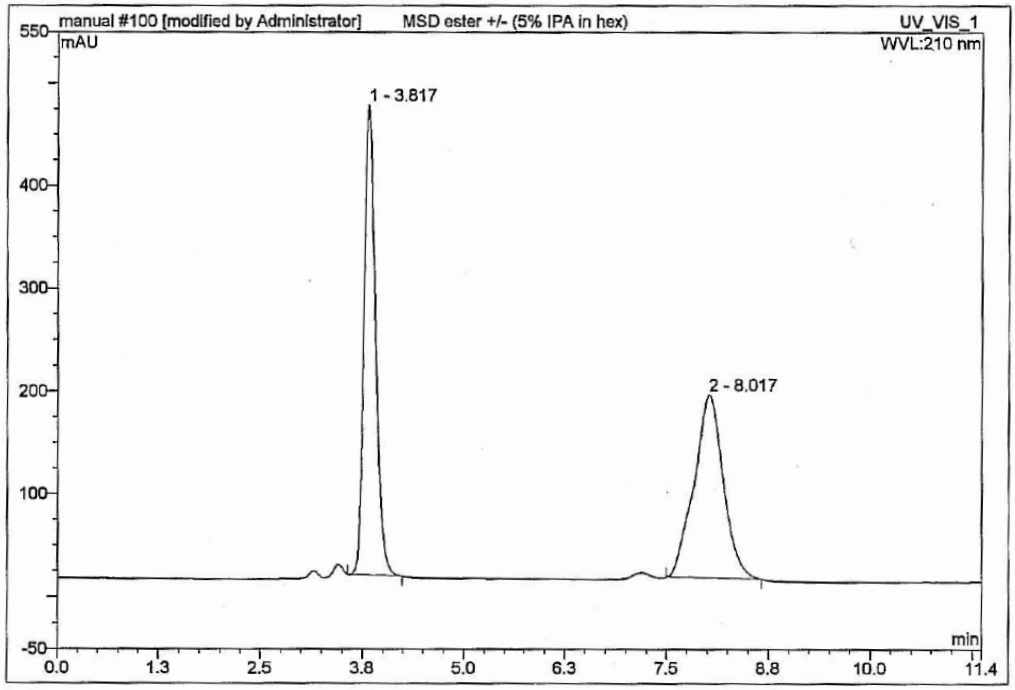
Alternatively, raising the temperature of the $NaBH_4$ reduction reaction to reflux smoothly transformed ester **104** into oxazolidinone **94** in an excellent yield of 90%, with none of the 6-membered oxazinanone regioisomer observed (Scheme 61).



Scheme 61: One-pot reduction and cyclisation

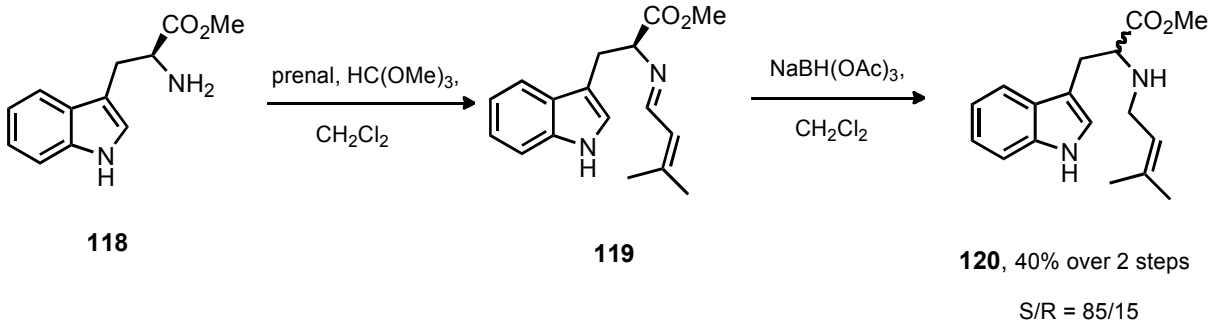
The characterisation for compound **94** synthesised by this route was consistent with the data for the compound synthesised in the first generation synthesis except for the optical rotation. The recorded optical rotation from the first generation synthesis was -14.0 while the compound obtained from the second generation synthesis recorded a null value. Suspicious of the null values obtained for the optical rotations of compounds **103**-**105** we suspected racemisation had occurred. Chiral HPLC analysis of compounds **94**, **103**, **104** and **105** was conducted. Only in compound **104** could the enantiomers be successfully resolved into two separate peaks with retention times of 3.8 min and 8.0 min in hexane:isopropanol, 95:5. Integration of the peak areas revealed a 50/50 mixture of enantiomers, confirming complete racemisation had occurred (Figure 12).

Figure 12: Chiral HPLC trace of racemic **104**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.82	n.a.	457.644	74.881	50.00	n.a.	BMB*
2	8.02	n.a.	178.488	74.878	50.00	n.a.	BMB*
Total:			636.132	149.759	100.00	0.000	

To elucidate in which step racemisation occurred compound **105** obtained from the alkylation of aspartic ester **87** with prenyl bromide (Scheme 53) was allowed to react with ethyl chloroformate and Cs_2CO_3 to give carbamate **104**. Chiral HPLC indicated no observable racemisation in this substrate. Subjecting **(*S*)-104** to the reduction and cyclisation reaction with $NaBH_4$ to afford oxazolidinone **94**, which gave an identical optical rotation to compound **94** made in the first generation synthesis. These observations pinpointed that racemisation occurred during the reductive amination step. Ganesan *et al*. observed a similar result when studying the reductive amination of L-tryptophan methylester **118** with a variety of aldehydes and $NaBH(OAc)_3$.[85] They discovered that partial racemisation only occurred when they employed prenal **112** as the aldehyde (Scheme 62). They attributed this racemisation to the lower reactivity of the α,β-unsaturated imine **119** in the reduction to secondary amine **120**; although no mechanism is specified, they observed a similar result with D-tryptophan methylester.

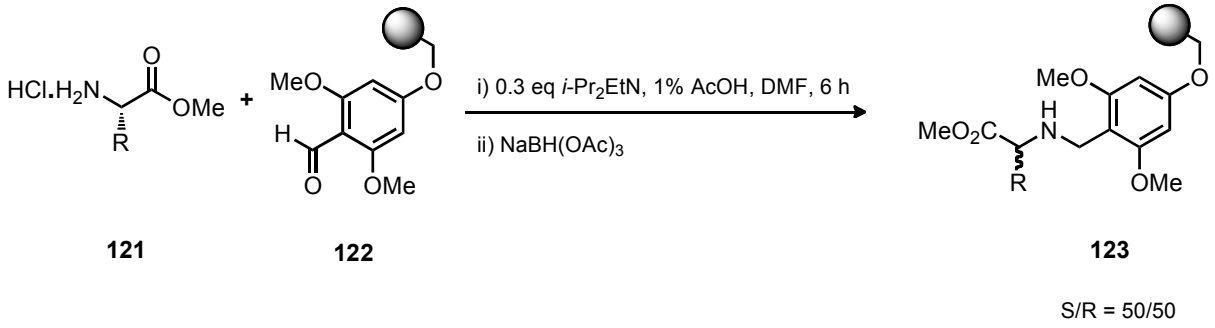


118 **119** **120**, 40% over 2 steps S/R = 85/15

Scheme 62: Racemisation of L-tryptophan methylester observed by Ganesan

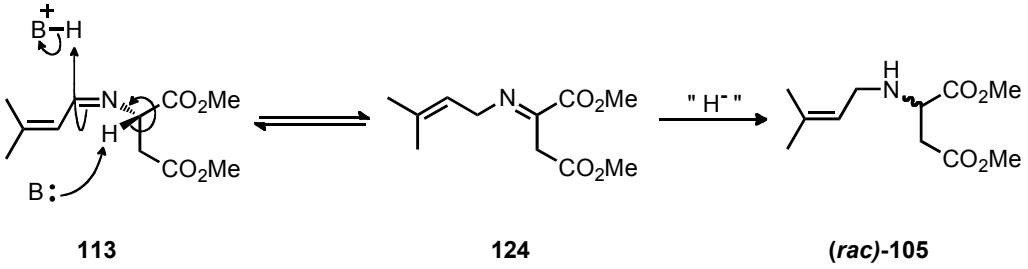
Ellman *et al.* have purposely sought to induce racemisation during the reductive amination of a variety of amino esters **121** with a resin bound aldehyde **122** in order to access the unnatural D-enantiomer.[86] They postulate that complete racemisation can be achieved through imine tautomerisation, by pre-equilibrating the amino ester hydrochloride salt, 0.3 equivalents of

Hünig's base and the resin bound aldehyde **122** for six hours before addition of the reducing agent to afford the secondary amine **123** (Scheme 63).



Scheme 63: Racemisation of amino esters studied by Ellman

We believe that a similar process occurs during the imine reduction of **113**. Facile equilibration between chiral imine **113** and the achiral imine tautomer **124** leads to the complete erosion of stereochemistry before the slow reduction of the imine can occur leading to ***(rac)*-105** (Scheme 64). Although imine **113** recorded an optical rotation of -8.8 the possibility of potential racemization occurring during its formation cannot be ruled out.

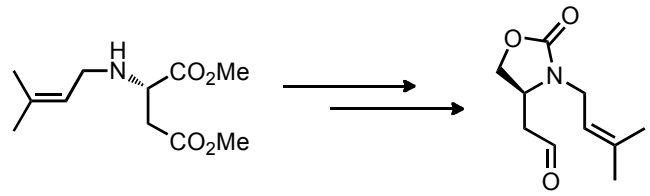


Scheme 64: Mechanism leading to racemisation

2.3.4 Conjugate Addition

The synthetic route of the second generation synthesis allowed efficient access to the cyclisation precursor **95** from the secondary amine **105** (Scheme 65). The major drawback, though, is the synthesis of amine **105** as previous attempts have suffered from poor yields

(**2.3.2**, alkylation) or racemisation accompanied with high dilutions and long reaction times (**2.3.3**, reductive amination).



105 **95**

Scheme 65: Facile synthesis of **95** from **105**

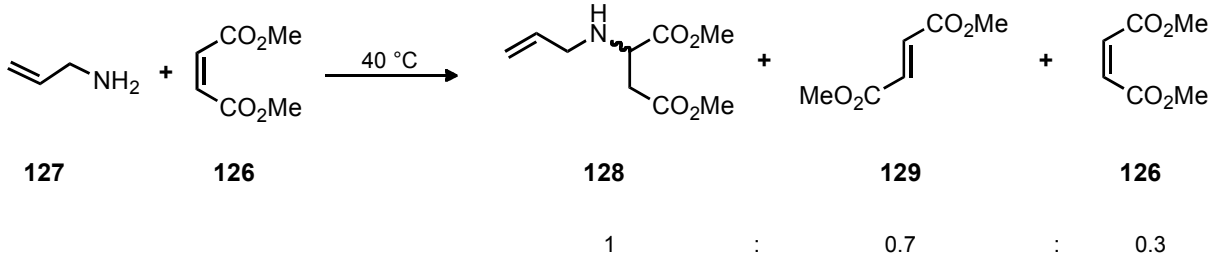
We envisaged that the conjugate addition between prenyl amine **125** and dimethylmaleate **126** would give **(*rac*)-105** (Scheme 66) and hopefully fulfil the premise of the second generation synthesis of allowing rapid access to the cyclisation precursor **95** on a multi-gram scale. This would provide the required synthetic material to enable the exploration of many possible synthetic pathways leading to a successful route to the target molecule **27**. Upon discovery of a successful racemic pathway we planned to follow up with an enantiomerically synthesis of **27** using the first generation synthesis, which was conducted on a smaller scale.

125 **126** **(*rac*)-105**

Scheme 66: Potential conjugate addition between amine **125** and α,β-unsaturated ester **126**

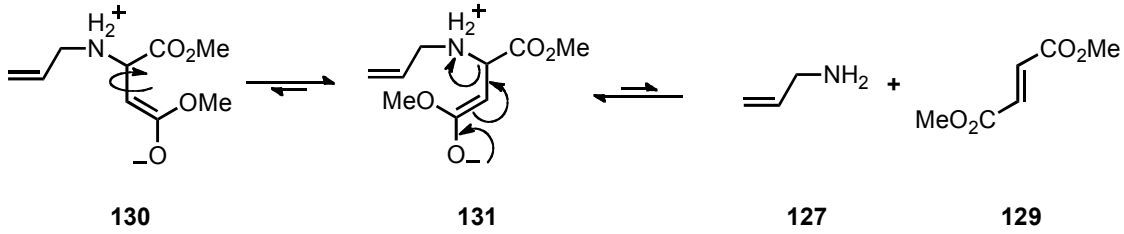
Surprisingly for a seemingly simple reaction there are only a few literature examples of the conjugate addition between a primary allyl amine and a α,β-unsaturated dicarbonyl.[87,88] As prenyl amine **125** is not commerically available we decided to study a model system using allyl amine **127** instead. Using one equivalent of allyamine and dimethylmaleate and heating them together neat at 40 °C for ten minutes (

Table 10, entry 1) led to 1:0.7:0.3 mixture of secondary amine **128**, dimethylfumarate **129** and dimethylmaleate **126** respectively (Scheme 67).



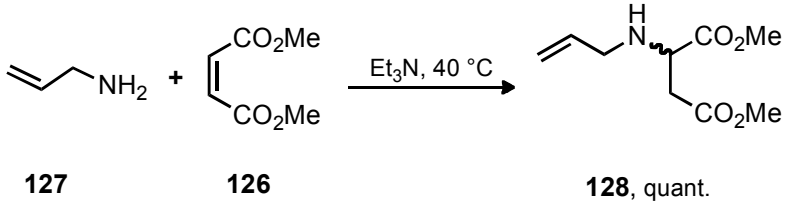
Scheme 67: Conjugate addition between allyl amine **127** and dimethylmaleate **126**

Isomerisation of maleate **126** to the more thermodynamically favourable fumerate **129** presumably arises from conjugate addition followed by retro-conjugate addition (Scheme 68).



Scheme 68: Formation of fumerate **129**

In the hope of favouring an intermolecular proton transfer we carried out the reaction with one equivalent of dimethylmaleate and two equivalents of allyl amine (Table 10, entry 2), which pleasingly gave the product **128** in a quantitative yield. Wishing to employ the allyl amine as a limiting reagent, we explored the use of another external base. Reaction with one equivalent of dimethylmaleate, allylamine and triethylamine (Table 10, entry3) gave the secondary amine **128** in a quantitative yield (Scheme 69).



Scheme 69: Conjugate addition employing Et_3N as an external base

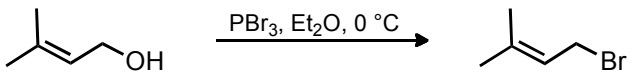
The table below summarises the results from the conjugate addition reactions with allyl amine and dimethylmaleate.

Entry	Conditions[a]	126 : 128 : 129[b]	Yield (%)
1	1 eq allyl amine	15 : 50 : 35	-[c]
2	2 eq allyl amine	0 : 100 : 0	quant.
3	1 eq allyl amine, 1 eq Et_3N	0 : 100 : 0	quant.

[a] Reactions were carried out with 1 eq of dimethylmaleate, neat at 40 °C for 10 min. [b] Ratios determined by ^1H NMR analysis of the crude reaction mixture. [c] Products not isolated

Table 10: Results of conjugate addition with allyl amine

Off the back of the success of the model system, we embarked on the synthesis of prenyl amine. A number of different methods have been described in the literature for the preparation of primary amines. Direct alkylation of ammonia usually results in poor yields of the primary amine due to the competing over alkylation, therefore a number of ammonia synthons have been developed that reduce or prevent over alkylation. One such method is the alkylation of trityl amine, the steric bulk of the trityl group affords only monoalkylation and it can be subsequently removed under mild conditions.[89] We first prepared prenyl bromide ourselves, due to the variable quality of commercial product, according to a literature procedure from prenol and PBr_3 to give prenyl bromide in a good yield of 83% (Scheme 70).[90]

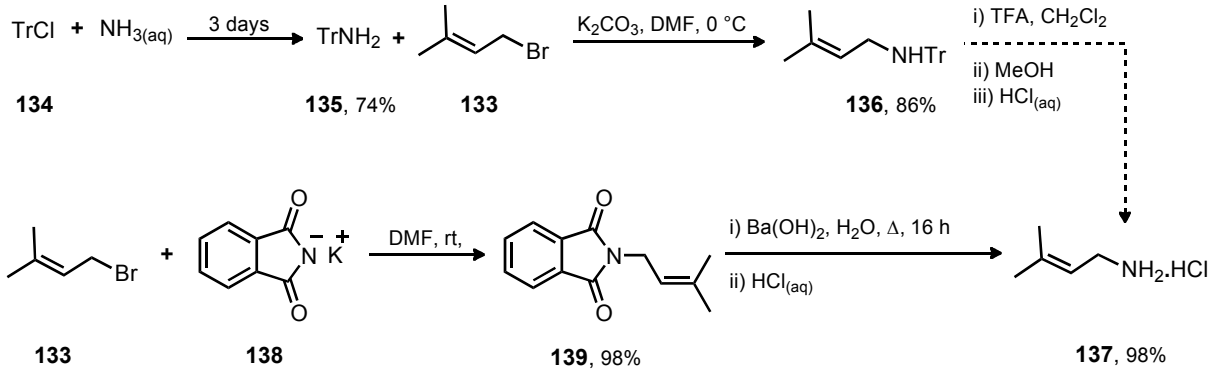


132 **133**, 83%

Scheme 70: Bromination of prenol **132**

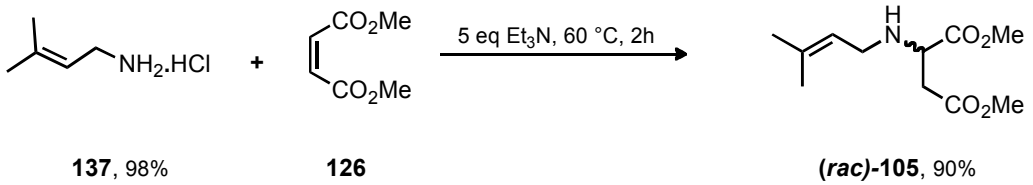
Amination of trityl chloride **134** with aqueous ammonia afforded the trityl amine **135** in a good yield of 74%. Alkylation of trityl amine **135** with prenyl bromide and K_2CO_3 gave the

secondary amine **136** in a good yield of 86%. Removal of the trityl group with TFA, trapping of the trityl cation with MeOH and displacement of the TFA salt with aqueous HCl gave the prenyl amine hydrochloride salt **137** in an excellent yield of 94%. The trityl cleavage step could only be preformed successfully on the milligram scale; scaling to the gram scale led to poor yields due to HCl addition across the alkene. An alternative was approach was a Gabriel synthesis, alkylation of potassium phthalimide **138** with prenyl bromide **133** according to a modified literature procedure[91] to give the alkylated product **139** in an excellent yield of 98%. Hydrolysis of phthalimide **139** with $Ba(OH)_2$ in water afforded the primary amine which was extracted *via* steam distillation and acidified with $HCl_{(aq)}$ to give the prenyl amine hydrochloride salt **137** in a excellent yield of 98%.[92] This approach could be successfully carried out on the multi-gram scale (Scheme 71).



Scheme 71: Synthesis of prenyl amine

Conjugate addition between prenyl amine hydrochloride salt **137** and dimethylmaleate **126** gave the secondary amine **(*rac*)-105** in an excellent yield of 90% (Scheme 72) and could be carried out on a 30 g scale. One equivalent of Et_3N was required to form the free base and because the prenyl amine suffered from greater steric hindrance than allyl amine the reaction required extra equivalents of external base as well as higher temperatures and longer reactions times to effect the reaction.



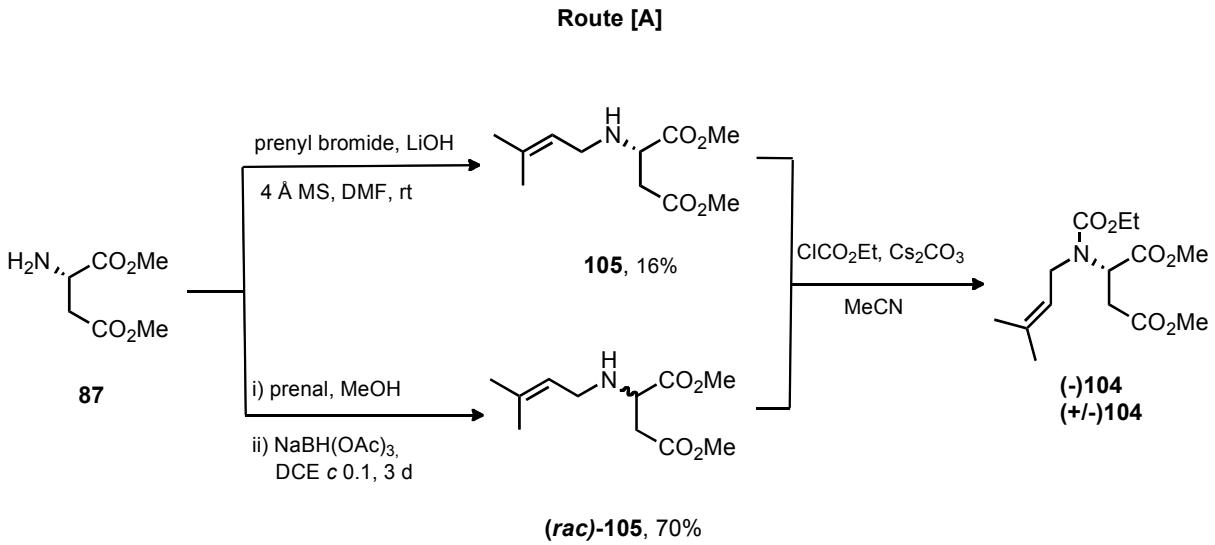
137, 98% **126** **(*rac*)-105**, 90%

Scheme 72: Conjugate addition between prenyl amine and dimethylmaleate

From the secondary amine (***rac***)-**105** the synthesis of the cyclisation precursor was carried out on a 20 g scale. This gave enough material to test out a variety of synthetic routes that eventually led to a successful racemic synthesis of the target molecule **27**, outlined *vide infra* as an asymmetric synthesis.

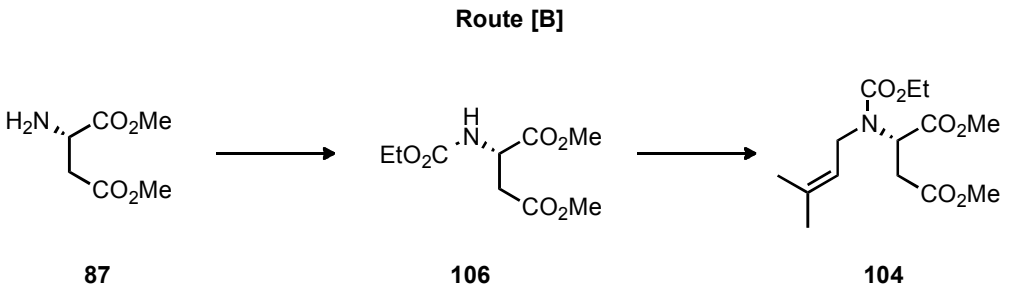
2.3.5 Carbamate Alkylation

In order to synthesise the tertiary carbamate **104** in an asymmetric fashion we explored two methods *via* route A, alkylation followed by acylation. In our initial attempt, we attempted the chemoselective mono-alkylation of **87** with prenyl bromide and variety of bases to afford the secondary amine **105**. Unfortunately, attempts to favour mono-alkylation failed, LiOH employed as the base gave the highest selectivity but still gave a poor yield of 16% for **105**. Exploring a reductive amination approach, by performing an imine from amine **87** and prenal **112** and subsequent reduction with $NaBH(OAc)_3$ afforded the secondary amine in a good yield of 70% but unfortunately led to complete racemisation to give **(rac)-105** (Scheme 73).



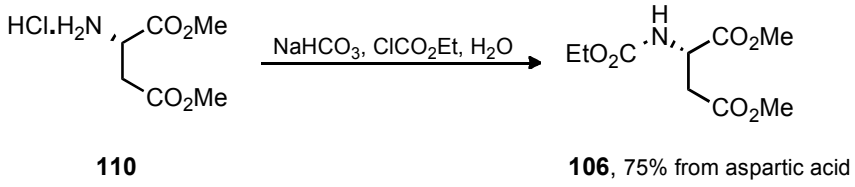
Scheme 73: Summary of tertiary carbamate synthesis *via* route A

In light of these failures, we turned our attention to the synthesis of **104** *via* route B. This entailed the carbamation of amino ester **87** followed by carbamate alkylation (Scheme 74).



Scheme 74: Proposed synthesis of tertiary carbamate *via* route B

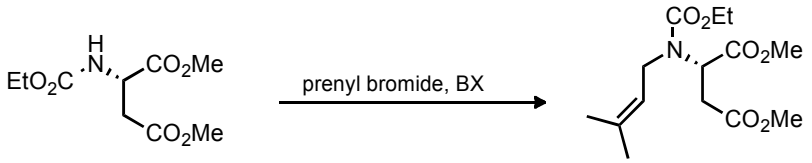
Carbamation of the crude amino ester hydrochloride salt **110** was carried out with an excess of $NaHCO_3$ and ethyl chloroformate in water to give the carbamate **106** in a good yield of 75% over two synthetic steps from L-aspartic acid. (Scheme 75).



110 **106**, 75% from aspartic acid

Scheme 75: Carbamation of aspartic ester

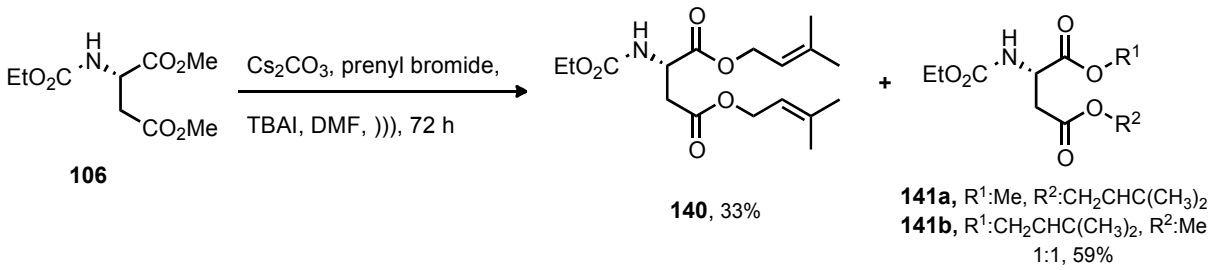
Alkylation of carbamate **106** with prenyl bromide was attempted with a variety of bases (Scheme 76).



106 **104**

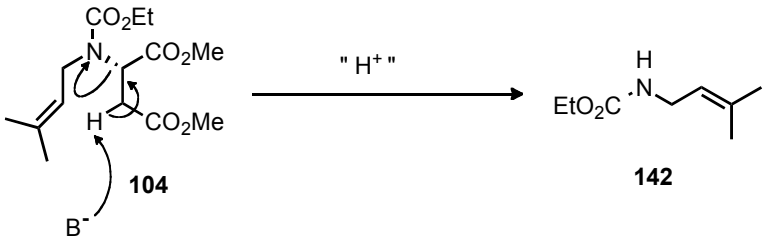
Scheme 76: General scheme for carbamate alkylation

Initial reactions employing Cs_2CO_3 (Table 11, entry1) as the base in MeCN, conducting the reaction at room temperature and with the addition of TBAI (Table 11, entry 2) failed to facilitate the reaction, with only unreacted starting material being recovered. Raising the temperature of the reaction to reflux resulted in a complex mixture of unidentified by-products. Changing the solvent to DMF and carrying out the reaction at room temperature and 60 °C (Table 11, entries 4 & 5) gave only unreacted starting material. Performing the reaction with TBAI and 4 Å molecular sieves as additives and sonicating for extended periods of time (Table 11, entry 6) also failed to convert starting material into product. However, carrying out the reaction without the inclusion of molecular sieves (Table 11, entry 7) resulted in *O*-alkylation. A di-*O*-alkylated product **140** was isolated in a 33% yield and two regioisomeric mono-*O*-alkylated products, **141a** and **141b**, were isolated as an inseparable 1:1 mixture in a combined yield of 59% (Scheme 77). Presumably an ingress of moisture led to basic hydrolysis of the esters followed by carboxylate alkylation.



Scheme 77: Alkylation resulting in *O*-alkylation

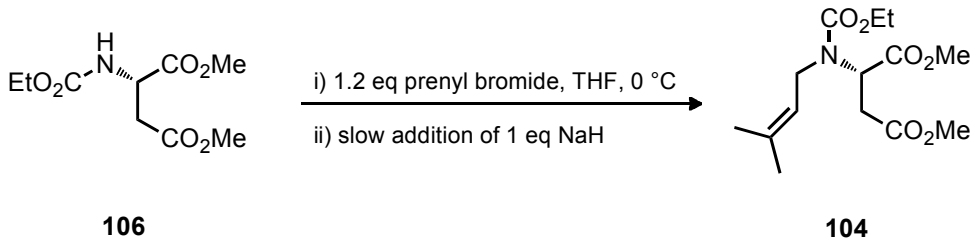
The use of stronger bases such as LiOH and KHMDS (Table 11, entries 8 & 9) failed to promote the reaction. Employing BuLi (Table 11, entry 10) gave extensive decomposition resulting in a complex mixture of unidentified by-products. The use of NaH (Table 11, entry 11) resulted in the formation of the tertiary carbamate **104** product, albeit in a low yield of 30%, along with the secondary carbamate **142** in a 45% yield, identified by its ^{1}H NMR, ^{13}C NMR and infrared spectra, resulting from the elimination of **104** (Scheme 78).



Scheme 78: NaH promoted elimination

In all of the previous reactions deprotonation of the carbamate hydrogen was performed prior to the addition of the alkylating agent, making the alkylated product **104** vulnerable to elimination. We envisaged that slow addition of NaH to a solution of carbamate **106** and prenyl bromide would hinder elimination because generation of the sodium carbamate would be followed by rapid trapping by the alkylating agent before elimination can take place. NaH was slowly added over two hours *via* a solid addition funnel to a solution of secondary carbamate **106** and prenyl bromide in THF cooled to 0 °C (Table 11, entry 12) to give the

tertiary carbamate **104** in a good yield of 81% and was successfully conducted on a 50 g scale (Scheme 79).



106 **104**

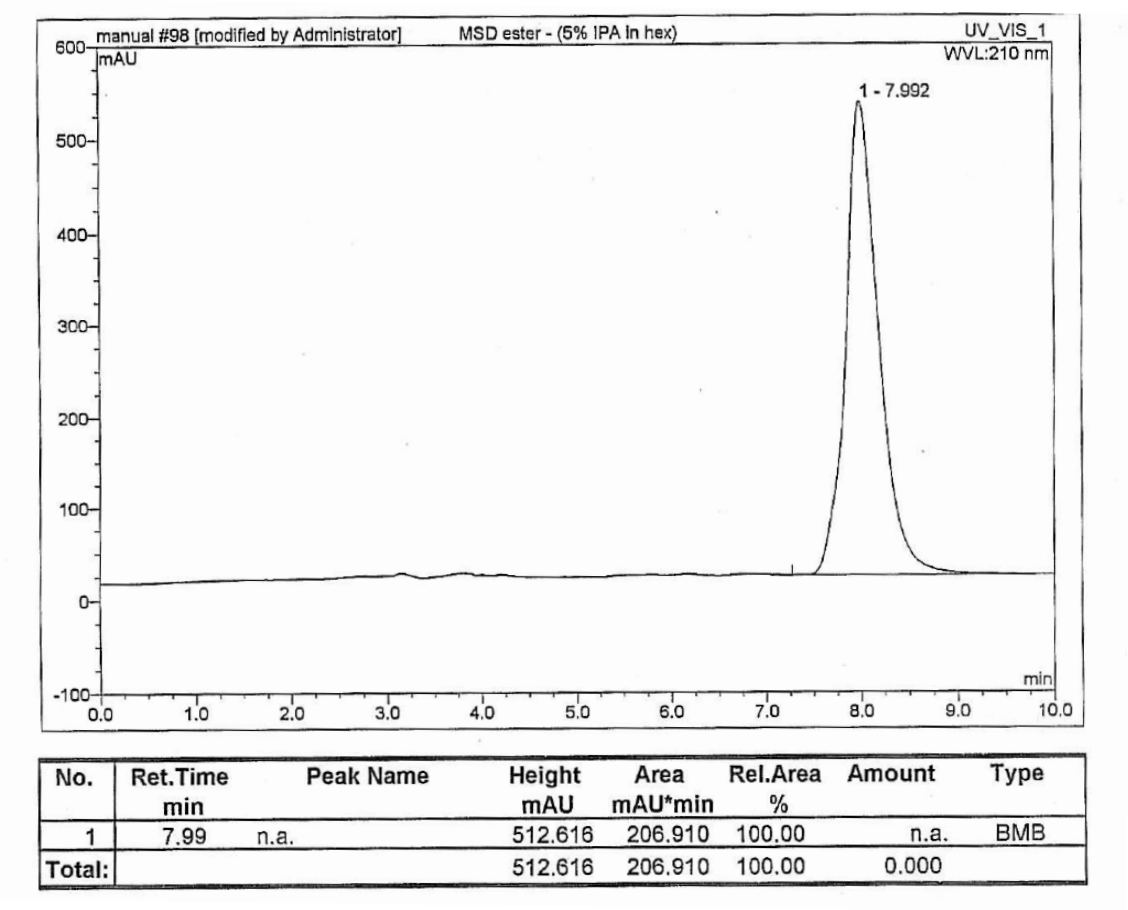
Scheme 79: Carbamate alkylation with NaH

Entry	Conditions[a]	Solvent	Temp. / °C	Time / h	Additive[b]	Product (% Yield)[b]
1	Cs_2CO_3	MeCN	rt	16	none	no reaction
2	Cs_2CO_3	MeCN	rt	16	TBAI	no reaction
3	Cs_2CO_3	MeCN	85	16	TBAI	decomposition
4	Cs_2CO_3	DMF	rt	8	none	no reaction
5	Cs_2CO_3	DMF	60	16	none	no reaction
6	Cs_2CO_3,)))[c]	DMF	rt	72	TBAI, 4 Å MS	no reaction
7	Cs_2CO_3,)))[c]	DMF	rt	72	TBAI	**140** (33%) : **141a+b** (59%)
8	LiOH	DMF	rt	16	TBAI	no reaction
9	KHMDS	THF	0	8	none	no reaction
10	BuLi	THF	0	8	none	decomposition
11	NaH	THF	0	8	none	**105** (30%) : **142** (45%)
12	NaH[d]	THF	0	4	none	**104** (81%)

[a] Reactions were carried out by the addition of 1-1.5 eq of base followed by the addition of 1-1.2 eq of prenyl bromide unless stated otherwise and. [b] Isolated yields of major products following purification. [c] Reactions were carried out with 3 eq of prenyl bromide. [d] Reaction was carried out by the addition of 1.2 eq of prenyl bromide followed by the slow addition of 1 eq of NaH.

Table 11: Carbamate alkylation conditions

The tertiary carbamate **104** was prepared with no observable erosion of enantiopurity as determined by chiral HPLC (Figure 13).

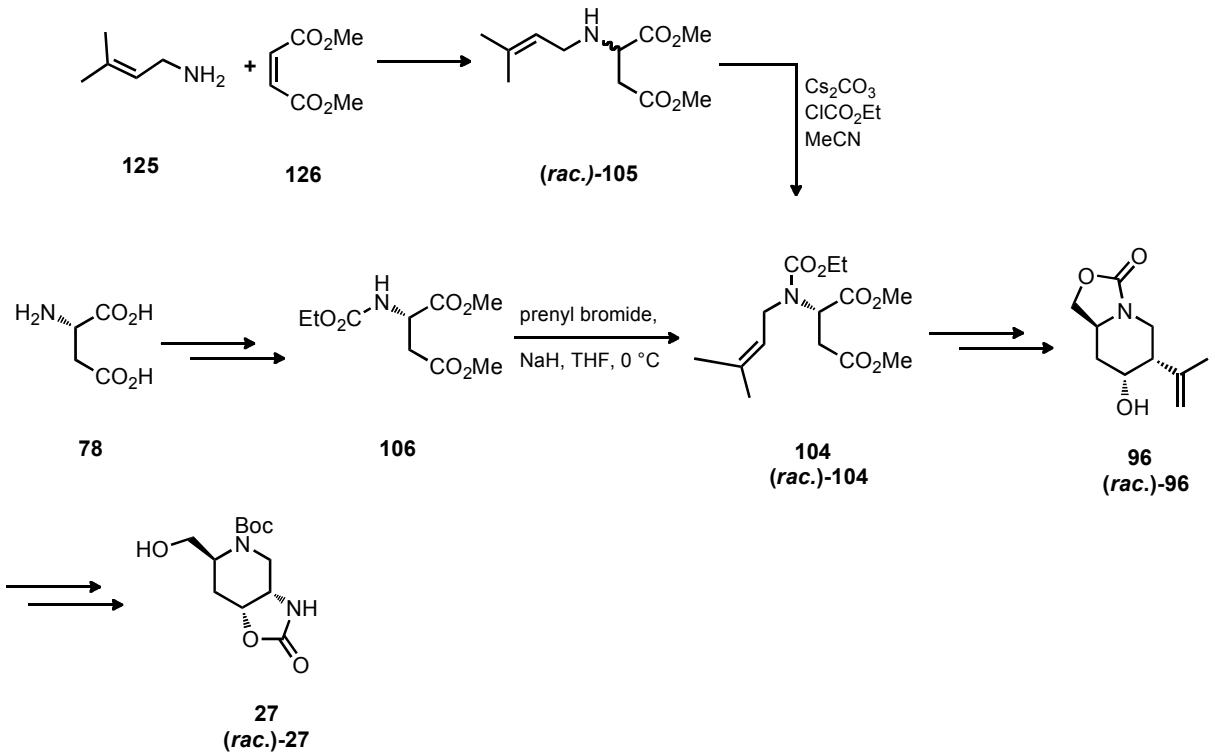


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.99	n.a.	512.616	206.910	100.00	n.a.	BMB
Total:			512.616	206.910	100.00	0.000	

Figure 13: Chiral HPLC trace of **104**

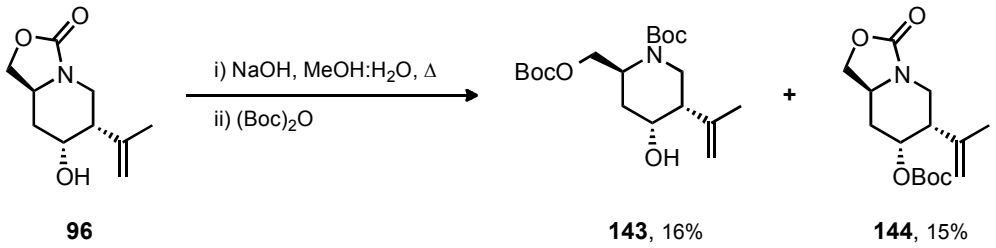
2.3.6 Oxidative Cleavage of the Methylene Bond

Two routes have been presented that gave access to the cyclisation product **96** on a multigram scale: a racemic route from the conjugate addition between prenyl amine **125** and dimethylmaleate **126** and an asymmetric route from L-aspartic acid **78** that utilised a NaH promoted alkylation of carbamate **106**. In the following sections, we will discuss the transformation of the cyclisation product **96** into the target molecule **27** (Scheme 80).



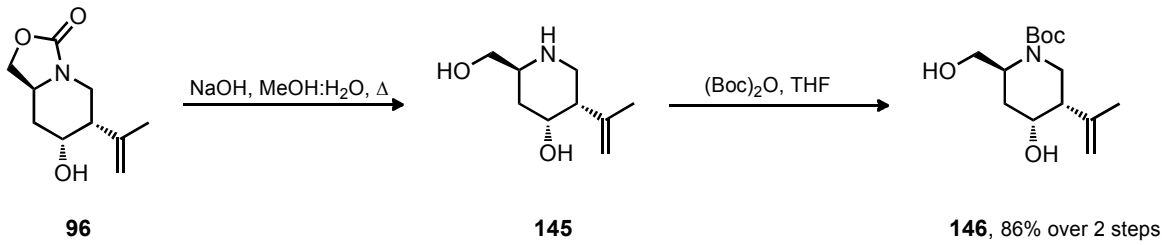
Scheme 80: Two routes to the cyclisation product **96**

Hydrolysis of the oxazolidone ring and Boc protection of the amine was attempted in one-pot with a large excess of NaOH in MeOH and water heated to reflux followed by the addition of $(Boc)_2O$. Two products were isolated from the reaction (Scheme 81). The piperidine **143** resulted from successful hydrolysis of the cyclic carbamate followed by Boc protection of the nitrogen and Boc protection the primary hydroxyl. The piperidine **144** formed from the Boc protection of the secondary hydroxyl in **96**; however, as TLC analysis indicated complete consumption of the starting material upon hydrolysis, Boc protection of the nitrogen must have occurred followed by reformation of the oxazolidone ring by attack from the primary hydroxyl under the strong basic conditions.



Scheme 81: Hydrolysis and protection in one-pot

A two step procedure was employed instead: cleavage of the oxazolidinone ring with NaOH in MeOH and water gave the amino diol **145**, which was isolated from the reaction mixture, and allowed to react with $(Boc)_2O$ in THF to give the Boc protected piperidine **146** in a very good yield of 86% over the two synthetic steps (Scheme 82).



Scheme 82: Hydrolysis and protection in two separate steps

An X-ray crystal structure of amino diol **145** was obtained (Figure 14).

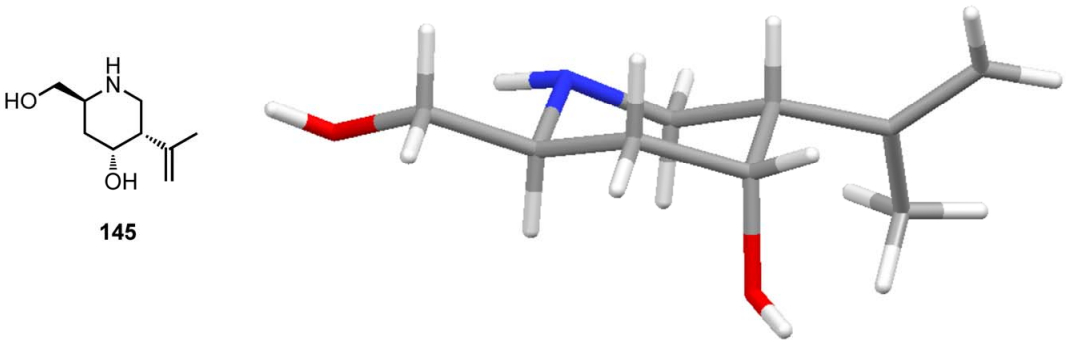
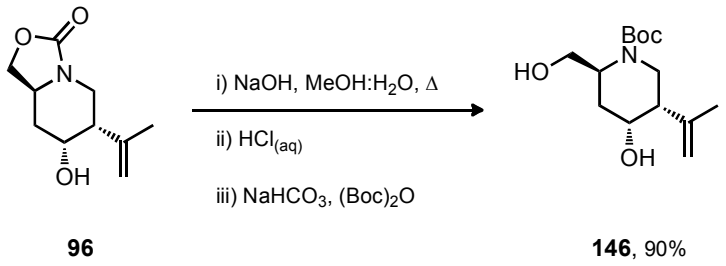


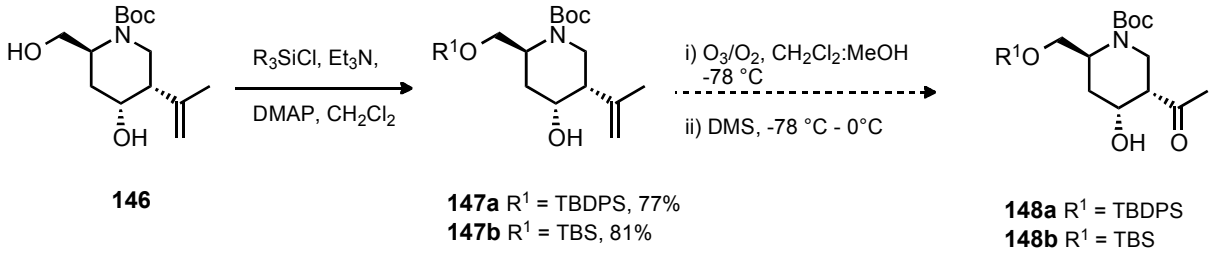
Figure 14: X-ray crystal structure of amino diol **145**

A chemoselective one-pot procedure was developed that involved basic hydrolysis followed by neutralisation with $HCl_{(aq)}$ and then addition of the mild base $NaHCO_3$ and $(Boc)_2O$ to give the protected piperidine **146** in an excellent yield of 90% (Scheme 83).



Scheme 83: Successful hydrolysis and protection in one-pot

Protection of the primary hydroxyl as a TBDPS ether gave **147a** in a good yield of 77%. Oxidative cleavage of alkene **147a** with ozone failed to yield any of the desired ketone **148a** and instead led to complex mixture of uncharacterised by-products (Scheme 84).

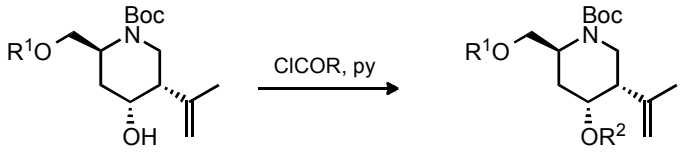


Scheme 84: Silyl ether protection of primary hydroxyl followed by failed ozonolysis

Unsure whether oxidation of the aromatic ring[93] in the TBDPS was the problem, alcohol **146** was instead protected as its TBS ether **147b** in a very good yield of 81%. Ozonolysis of **147b** also failed to result in product formation **148b** and again led to a complex mixture of products. It has been reported that ozonolysis of sterically hindered substrates have led to unexpected side product formation,[94,95, 96] therefore ozonolysis of the unprotected alkene **146** was attempted but no unfortunately none of the ketone **149** was detected.

Uncertain whether there is interference from the β-hydroxyl or how susceptible the α,β-hydroxy ketone product would be to a retro-aldol reaction, we masked the reactivity of the

secondary hydroxyl using an orthogonal protecting group strategy. The secondary hydroxyl of the TBDPS **147a** and TBS **147b** silyl ethers were protected as their acetyl and benzoyl esters **150a**-**150d** in very good to excellent yields (Scheme 85).

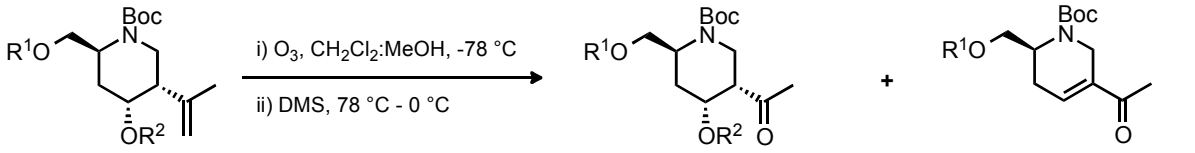


147a R^1 = TBDPS, 77%
147b R^1 = TBS, 81%

150a R^1 = TBDPS, R^2 = Ac, quant.
150b R^1 = TBDPS, R^2 = Bz, quant.
150c R^1 = TBS, R^2 = Ac, 86%
150d R^1 = TBS, R^2 = Bz, 83%

Scheme 85: Orthogonal protection of the two hydroxyl groups

Ozonolysis of **150a**, where R^1 = TBDPS and R^2 = Ac, gave the desired ketone **151a** but in quite a poor yield of 42%. Changing R^2 from Ac to Bz in the case **150b** gave the ketone **151b** in a very poor yield of 10% and the enone **152b** in a yield of 61%, resulting from the elimination of benzoate. Presumably the greater steric bulk of the benzoyl group gives greater driving force for elimination under the ozonolysis reaction conditions. Changing R^1 from TBDPS to TBS the expected ketone **151ci** in a very poor yield of 5% and ketone **151cii** where TBS removal has occurred in a good yield of 73%. To our knowledge, this is first example of TBS removal under ozonolysis conditions. Finally ozonolysis of **150d**, where R^1 = TBS and R^2 = Bz, resulted in both TBS deprotection and benzoate elimination to give enone **152d** in a poor yield of 29% (Scheme 86).

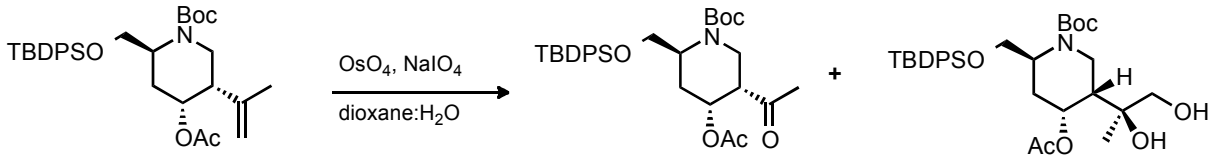


146 R^1 = H, R^2 = H
147a R^1 = TBDPS, R^2 = H
147b R^1 = TBS, R^2 = H
150a R^1 = TBDPS, R^2 = Ac
150b R^1 = TBDPS, R^2 = Bz
150c R^1 = TBS, R^2 = Ac
150d R^1 = TBS, R^2 = Bz

149 R^1 = H, R^2 = H, -
148a R^1 = TBDPS, R^2 = H, -
148b R^1 = TBS, R^2 = H, -
151a R^1 = TBDPS, R^2 = Ac, 42%
151b R^1 = TBDPS, R^2 = Bz, 10% : **152b** R^1 = TBDPS, 61%
151ci R^1 = TBS, R^2 = Ac, 5%
151cii R^1 = H, R^2 = Ac, 73%
151d R^1 = TBS R^2 = Bz, - : **152d** R^1 = H, 29%

Scheme 86: Oxidative cleavage of isoprenyl group by ozonolysis

Due to the lack of promising results from the oxidative cleavage using ozone we decided to try an alternative method using OsO_4 and $NaIO_4$. Subjecting **150a** to the dihydroxylation and oxidative cleavage reaction gave the desired ketone **151a** in a moderate yield of 65% as well as the intermediate diol **153**, where oxidative cleavage has yet to take place, in a 19% yield (Scheme 87).



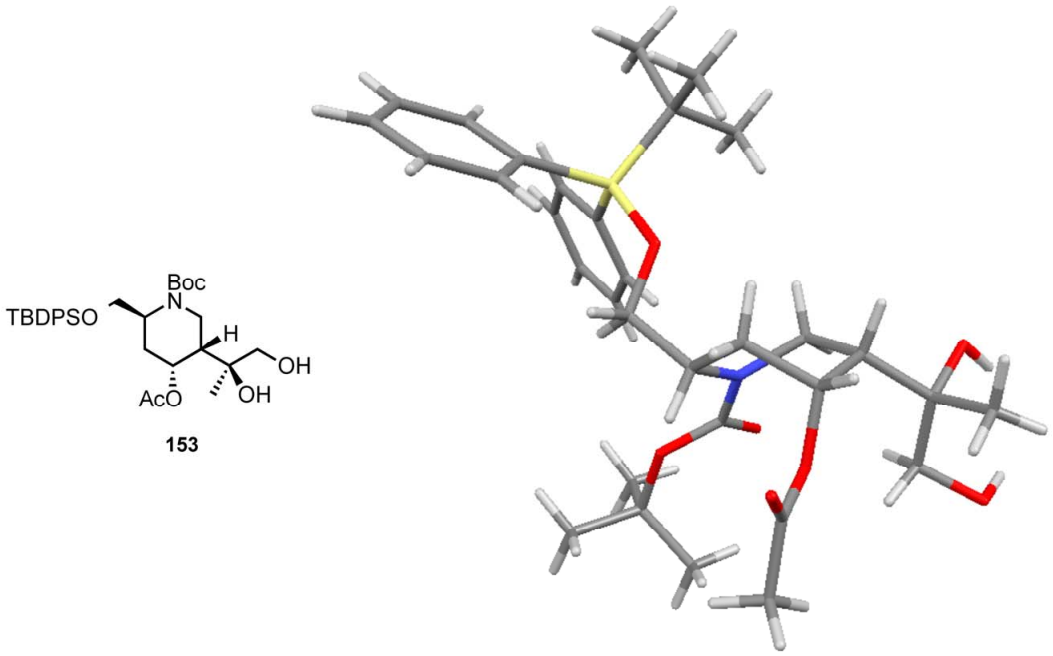
150a

151a, 65%

153, 19%

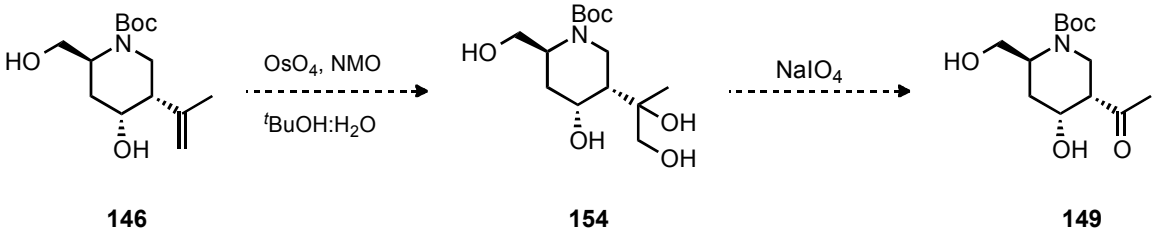
Scheme 87: Oxidative cleavage of **150a** using OsO_4/$NaIO_4$

The structure of diol **153** was determined by X-ray crystallography (Scheme 88).



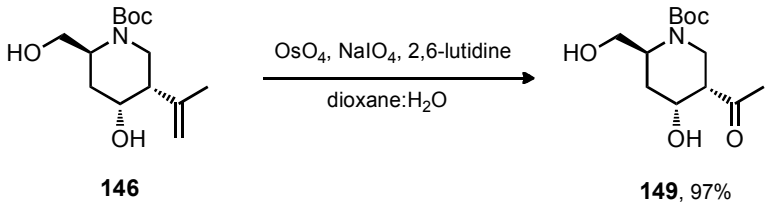
Scheme 88: X-ray crystal structure of diol **153**

The oxidative cleavage of the unprotected alkene **146** was preformed with OsO_4 and $NaIO_4$ in dioxane and water to give the ketone **149** in a poor yield of 33% (Table 12, entry 1). A two-step procedure of dihydroxylation with OsO_4 and NMO (Table 12, entry 2) followed by oxidative cleavage with $NaIO_4$ was attempted in the hope of avoiding side reactions, however no product could be isolated from the dihydroxylation step presumably due to the appreciable aqueous solubility of the tetraol **154** (Scheme 89).



Scheme 89: Attempted two step dihydroxylation/oxidative cleavage

A high-yielding one-pot dihydroxylation/oxidative cleavage procedure was performed using OsO_4 and $NaIO_4$ with 2,6-lutidine as an additive (entry 3),[97] giving the ketone **149** in an excellent yield of 97% (Scheme 90).



146 **149**, 97%

Scheme 90: $OsO_4/NaIO_4$ oxidative cleavage with 2,6-luidine as an additive

The vast improvement in yield by the addition of 2,6-lutidine is a likely a confirmation of the known ligand acceleration of OsO_4-mediated dihydroxylations of alkenes by tertiary amines[98] or more simply a buffering effect of the amine suppressing the acid-induced formation of side products.

Entry	Reagents[a]	Solvents	Yield (%)
1	OsO_4, $NaIO_4$	dioxane:H_2O	33
2	OsO_4, NMO	*t*-BuOH:H_2O	-[b]
3	OsO_4, $NaIO_4$, 2,6-lutidine[c]	dioxane:H_2O	97

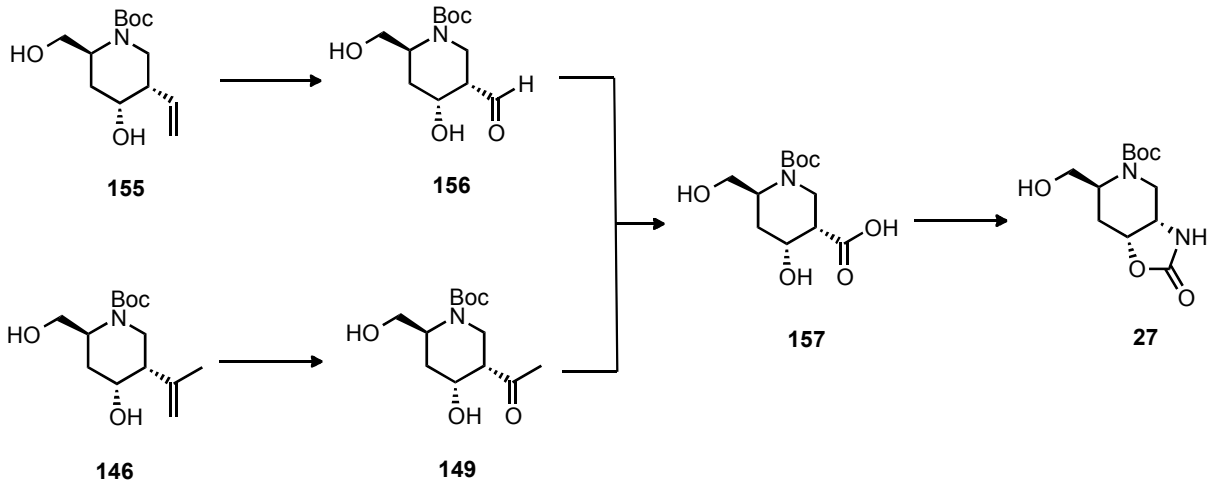
[a] Reactions were carried out with 0.1 mol% of OsO_4 and 2-2.5 eq of reoxidant. [b] Product not isolated from aqueous phase. [c] 2.5 eq or 2,6-lutidine.

Table 12: Dihydroxylation/oxidative cleavage results of ketone **146**

2.3.7 Methyl Ketone Cleavage

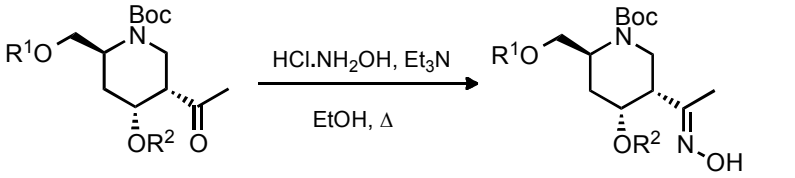
In our initial retrosynthetic analysis, we envisaged a cyclisation product that would have led to compound **155** containing a vinyl group. Oxidative cleavage of the alkene would have given aldehyde **156** followed by a relatively simple conversion to carboxylic acid **157**, which could undergo a rearrangement reaction to afford the target molecule **27**. Unfortunately, an

extra methyl group had to be incorporated to deliver high yields in the Prins cyclisation. Subsequent synthetic steps gave the compound **146** containing an isoprenyl group, and oxidative cleavage of the isoprenyl group gave the methyl ketone **149**. Conversion of the methyl ketone **149** to the carboxylic acid **157** and/or amine of **27** is now not such a straightforward process (Scheme 91). The following section details how we achieved this transformation.



Scheme 91: Proposed alkene to amine functional group interconversions

An attractive method for the direct conversion of a ketone to an amine is the Beckmann rearrangement. Formation of an oxime followed by suitable activation results in alkyl migration *anti* to the leaving group. Ketone **149** was allowed to react with hydroxylamine hydrochloride and Et_3N in refluxing EtOH to give oxime **158** in a quantitative yield. Reaction of ketone **151a** led to a complex mixture of products (Scheme 92).

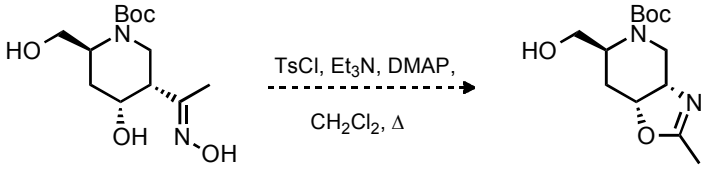


149 R^1 = H, R^2 =H
151a R^1 = TBDPS, R^2 = Ac

158 R^1 = H, R^2 =H, quant.
159 R^1 = TBDPS, R^2 = Ac, -

Scheme 92: Oxime formation

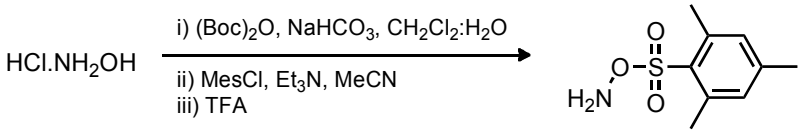
Beckmann rearrangement of oxime **158** was attempted by tosylation of the oxime using TsCl, Et_3N and DMAP in refluxing CH_2Cl_2. The reaction failed to afford the expected product **160** and instead led to decomposition of starting materials (Scheme 93).



158 **160**

Scheme 93: Beckmann rearrangement with TsCl

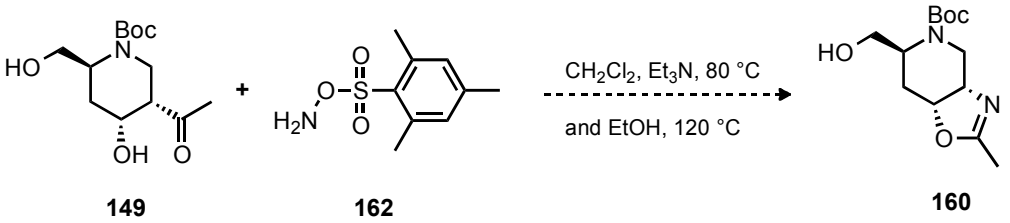
The failure to effect the Beckmann rearrangement might be due to the unsuccessful attachment of a leaving group to the oxime, and so we decided to synthesise a hydroxylamine with a preinstalled leaving group. The activated hydroxylamine was prepared in three synthetic steps from hydroxylamine hydrochloride **161** according to a literature procedure to give O-mesitylenesulfonylhydroxylamine **162** in a moderate yield of 64% over three synthetic steps (Scheme 94).[99]



161 **162**, 64% over 3 steps

Scheme 94: Synthesis of activated hydroxylamine

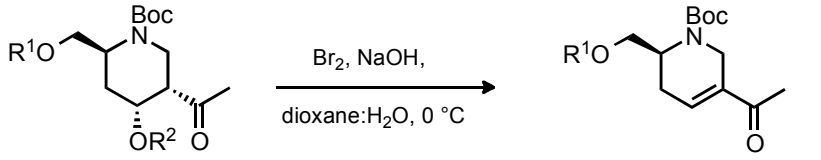
The one-pot oxime formation and Beckmann rearrangement of ketone **149** was carried out with the activated hydroxylamine **162**. Performing the reaction in CH_2Cl_2 with Et_3N and in EtOH heated in sealed tubes to 80 °C and 120 °C respectively resulted in the recovery of unreacted starting materials with no product formation observed (Scheme 95).



149 **162** **160**

Scheme 95: Attempted Beckmann rearrangement with an activated hydroxylamine

One method for the direct conversion of a methyl ketone to its corresponding carboxylic acid is the Lieben haloform reaction. The reaction involves exhaustive halogenation of a methyl ketone, followed by nucleophilic substitution of hydroxide for the haloform anion. The reaction of **149** and **151a** with Br_2 and NaOH in dioxane and water at 0 °C failed to convert the methyl ketones into carboxylic acids and instead, under the strong basic conditions, led to elimination to afford enones **152d** and **152b** in yields of 53% and 52% respectively (Scheme 96).



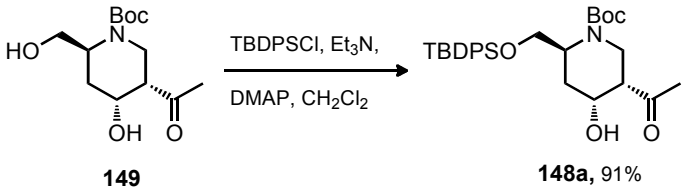
149 R^1 = H, R^2 =H
151a R^1 = TBDPS, R^2 = Ac

152d R^1 = H, 53%
152b R^1 = TBDPS, 52%

Scheme 96: Haloform reaction

Another method to convert the methyl ketone to a carboxylic acid is formation of the kinetic silyl enol ether followed by its oxidative cleavage. A rearrangement reaction of the carboxylic acid was envisaged to proceed through an isocyanate intermediate; trapping by the secondary

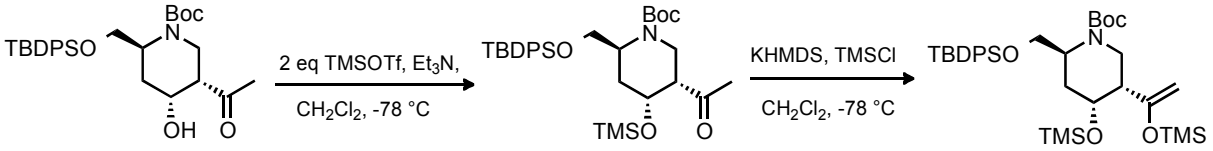
hydroxyl would form the corresponding oxazolidinone. To avoid any regioselectivity issues during the rearrangement step the primary hydroxyl of ketodiol **149** was protected as its TBDPS ether in an excellent yield of 91%.



149 **148a,** 91%

Scheme 97: TBDPS protection of ketone **149**

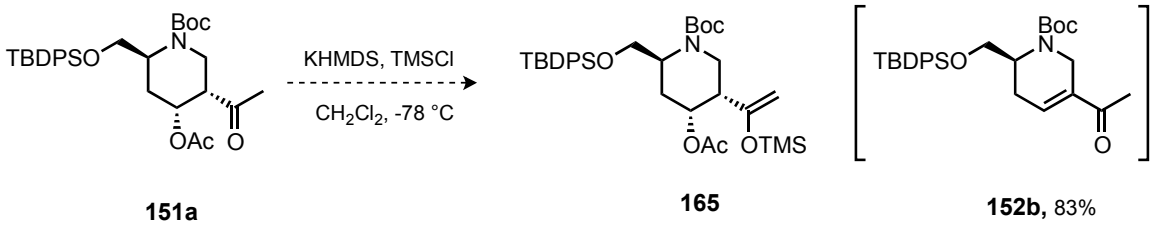
Treatment of ketone **148a** with two equivalents of TMSOTf and Et_3N in CH_2Cl_2 cooled to -78 °C did not furnish the expected silyl enol ether but gave silyl ether **163** instead in a good yield of 82%. However, utilising the stronger base KHMDS and TMSCl in CH_2Cl_2 cooled to -78 °C pleasingly gave the silyl enol ether **164** in a good yield of 79% (Scheme 98). A TMS group was employed because of the extremely mild conditions needed for its deprotection and low propensity to act as a good leaving group, thereby minimising elimination.



148a **163**, 82% **164**, 79%

Scheme 98: Silyl enol ether formation of **148a**

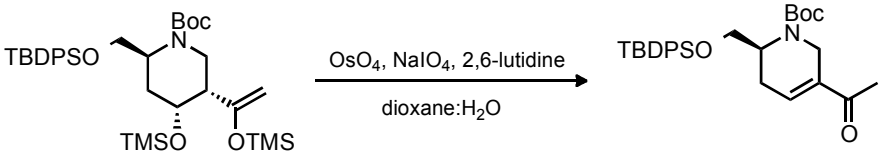
Unsurprising in the light of earlier results the reaction between ketone **151a**, KHMDS and TMSCl failed to yield the silyl enol ether **165** and instead led to the enone **157b** in a 83% yield. Further reactions utilising compounds with acyl protection of the secondary hydroxyl were abandoned due to their susceptibility to undergo elimination.



151a **165** **152b,** 83%

Scheme 99: Attempted silyl enol ether formation of **156a**

Attempted oxidative cleavage of silyl enol ether **164** using OsO_4, $NaIO_4$ and 2,6-lutidine in dioxane and water resulted in the formation of enone **152b**, where under the mildly acidic reactions conditions hydrolysis and elimination of the silyl enol ether occurred at a faster rate than the desired dihydroxylation/oxidative cleavage (Scheme 100).



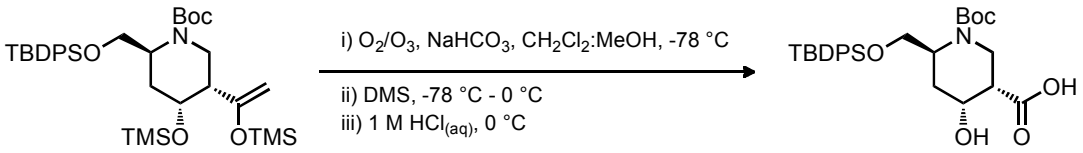
164 **152b**, 82%

Scheme 100: Silyl enol ether oxidative cleavage using OsO_4/$NaIO_4$

Ozonolysis of **164** was then attempted in CH_2Cl_2 (Table 13, entry 1) and in combination with the participating solvent MeOH (Table 13, entry 2) followed by reduction of the intermediate peroxides with dimethylsulfide. No carboxylic acid product was detected and instead both reactions resulted in conversion of starting materials to ketone **148a**. We believed that latent acidity associated with the ozonolysis conditions was causing breakdown of the silyl enol ether and cleavage of the TMS ether and so we planned to perform the reaction in the presence of a variety of bases.

Tertiary amines are often used as additives to improve yields in ozonolysis reactions. The use of triethylamine has been reported to directly reduce the secondary ozonide[100] or by its *N*-

oxide, generated *in situ*, to reduce intermediate carbonyl oxide *via* a Grob fragmentation.[101] The role pyridine in the reduction of the intermediate carbonyl oxides *via* its *N*-oxide has been reported and later refuted.[102,103] Performing the reactions with pyridine and triethylamine (Table 13, entries 3 & 4) present resulted in only ketone **148a** being isolated from the reaction. However, using the inorganic base $NaHCO_3$[104] (Table 13, entry 5) gave the desired carboxylic acid **166** in a quantitative yield, following acidification of the carboxylate salt (Scheme 101). The synthesis of **166** constituted a formal synthesis of pseudodistomin-F, however as Ma and Sun report no characterisation for this compound we needed to synthesise the next intermediate with characterisation *i.e*. **27**.



164 **166**, quant.

Scheme 101: Ozonolysis of the silyl enol ether

Entry	Solvent[a]	Additive	Yield of 171 (%)
1	CH_2Cl_2	none	-[b]
2	CH_2Cl_2:MeOH	none	-[b]
3	CH_2Cl_2:MeOH	1 eq py	-[b]
4	CH_2Cl_2:MeOH	1 eq Et_3N	-[b]
5	CH_2Cl_2:MeOH	10 eq $NaHCO_3$	quant.

[a] Reactions were carried out by bubbling O_2/O_3 into the solution cooled to -78 °C before being quenched with DMS 2-10 eq and being allowed to warm to 0 °C. [b] Product isolated from reaction was ketone **148a** in a 90%-quant. yield.

Table 13: Conditions tested for the ozonolysis of silyl enol ether **164**

A Curtius rearrangement of the carboxylic acid **166** followed by trapping of the intermediate isocyanate by the secondary hydroxyl gave the oxazolidinone **167** in a very good yield of

83%. The structure of oxazolidinone **167** was confirmed by X-ray crystallography (Figure 15).

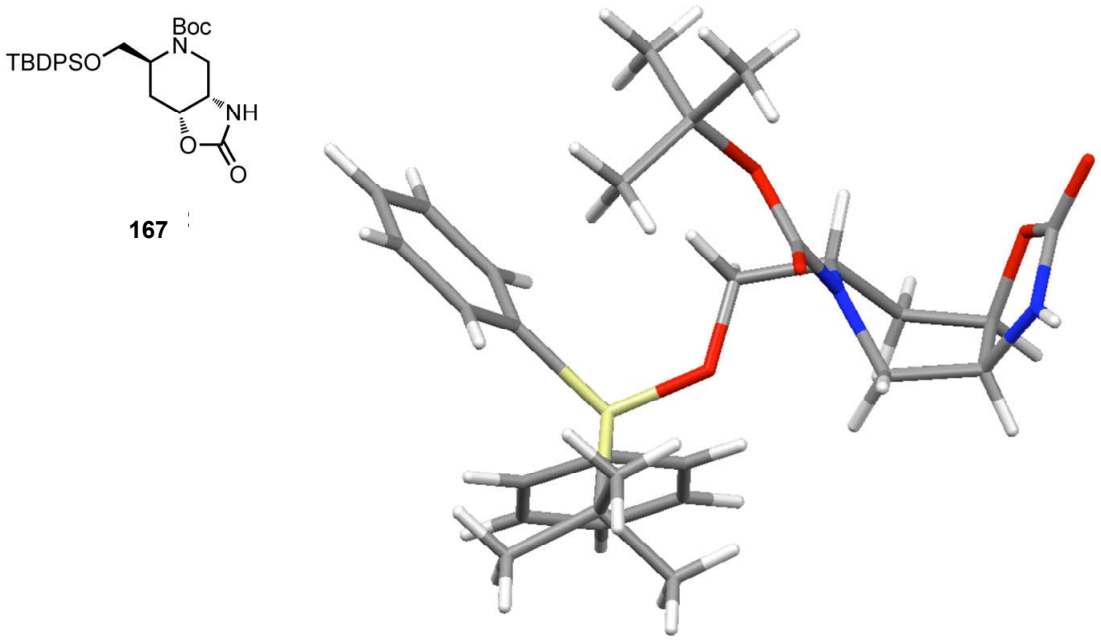
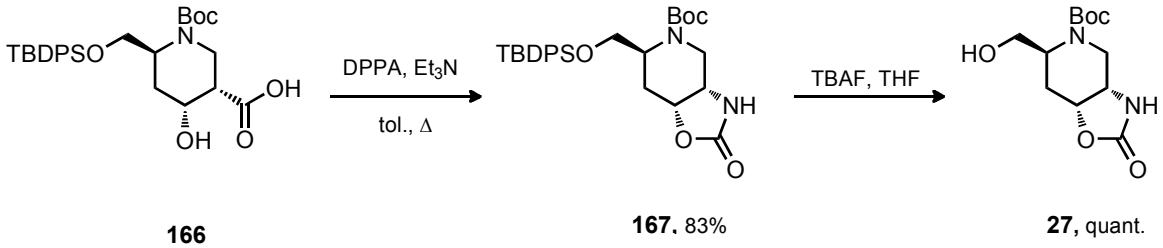


Figure 15: X-ray crystal structure of **167**

Removal of the TBDPS protecting group with TBAF gave the unprotected oxazolidinone **27** in a quantitative yield and completed the formal synthesis of pseudodistomin F (Scheme 102).



Scheme 102: Curtius rearrangement followed by deprotection

The structure of oxazolidinone **27** was confirmed by X-ray crystallography, showing that it adopted a twist boat conformation in the crystal phase (Figure 16).

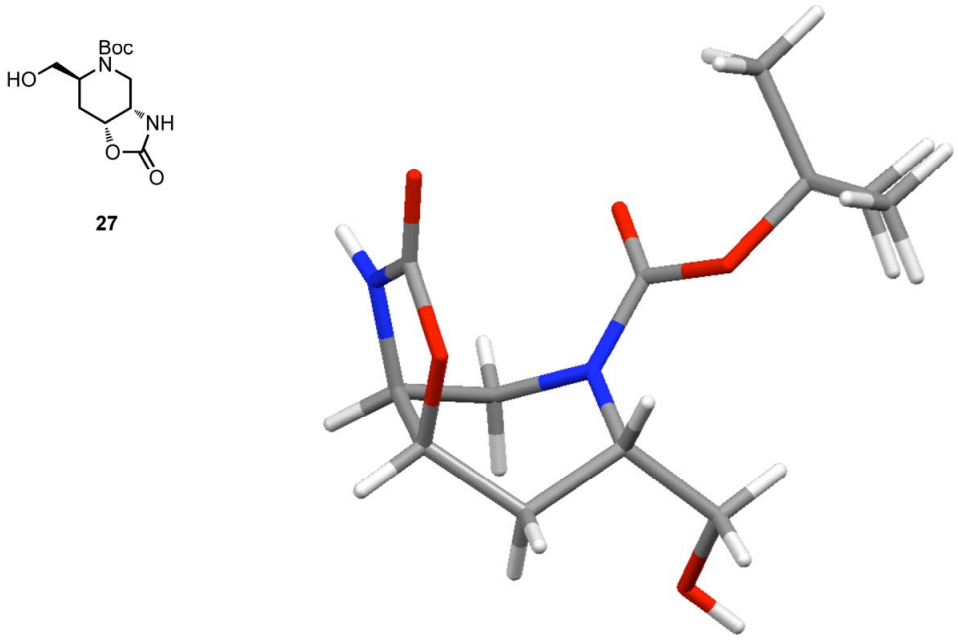
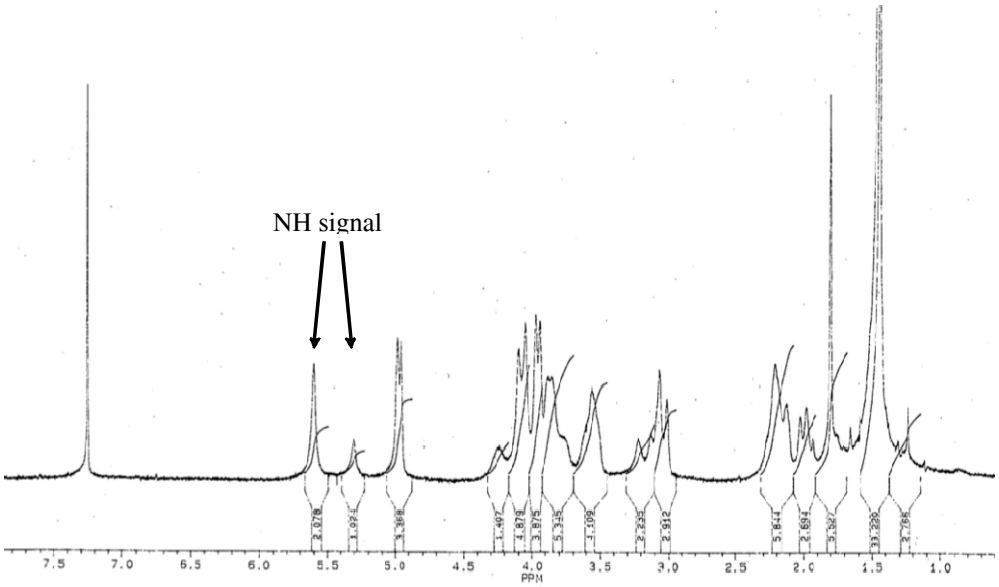


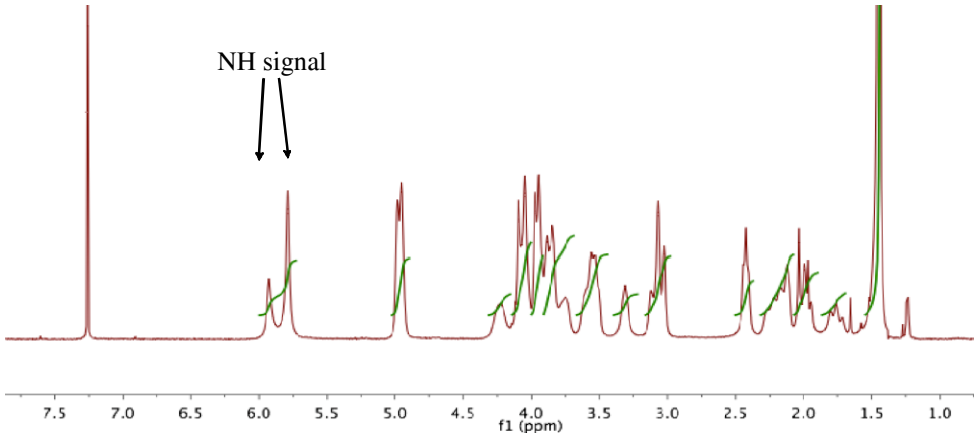
Figure 16: X-ray crystal structure of **27**

The ^{I}H NMR spectrum of the oxazolidinone **27** synthesised by Ma and Sun is in good agreement with ^{I}H NMR spectrum of **27** synthesised by ourselves. The ^{I}H NMR spectra are complicated by the presence of rotamers in a ~2:1 ratio, presumably from restricted rotation of the Boc group. This has the effect of causing line broadening and splitting of the peaks into separate signals, most obvious in the splitting of the oxazolidinone NH proton into 2 separate singlets at ~5.6-6.0 ppm. The peaks in the ^{1}H NMR spectrum can be sharpened by employing MeOD as the solvent (Figure 17). Unfortunately, Ma and Sun did not report the ^{13}C NMR, melting point, elemental analysis and X-ray crystal structure and so comparisons could not be made with our own results. The recorded optical rotation of $[\alpha]^{21}_{D}$ -107.4 (*c* 1, MeOH) was in good agreement with the literature value of $[\alpha]^{21}_{D}$ -111.4 (*c* 0.92, MeOH),[24] and chiral HPLC confirmed the existence of only one enantiomer (Figure 18).

^{1}H NMR spectrum **27** synthesised by Ma and Sun in $CDCl_3$



^{1}H NMR spectrum **27** synthesised by ourselves in $CDCl_3$



^{1}H NMR spectrum of **27** synthesised by ourselves in MeOD

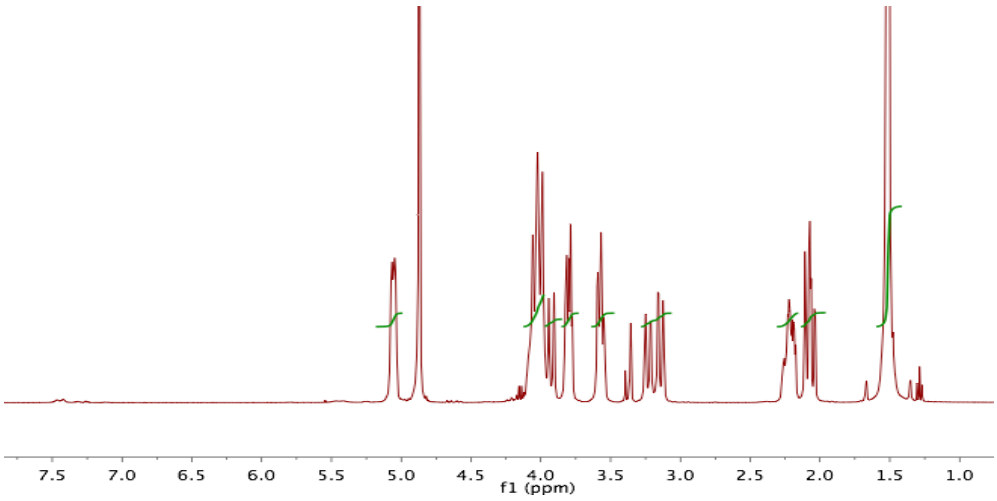
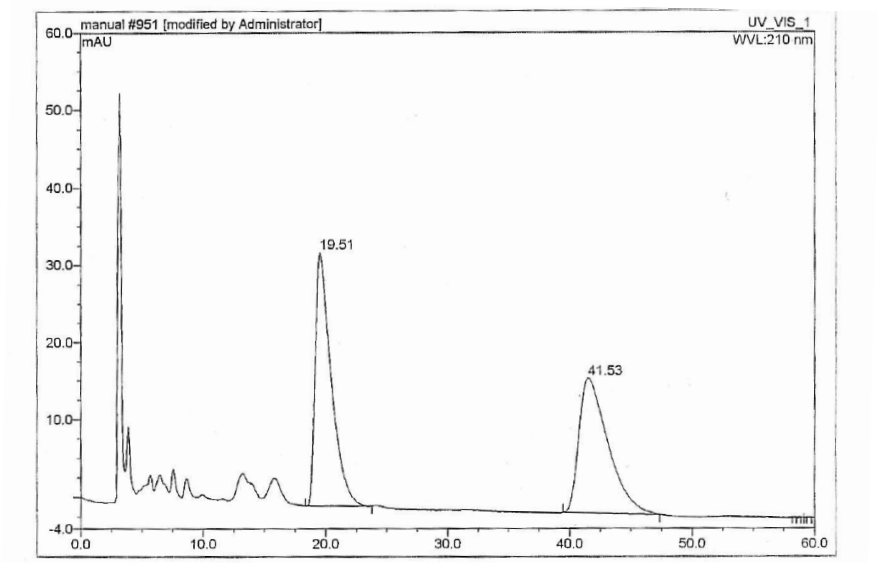


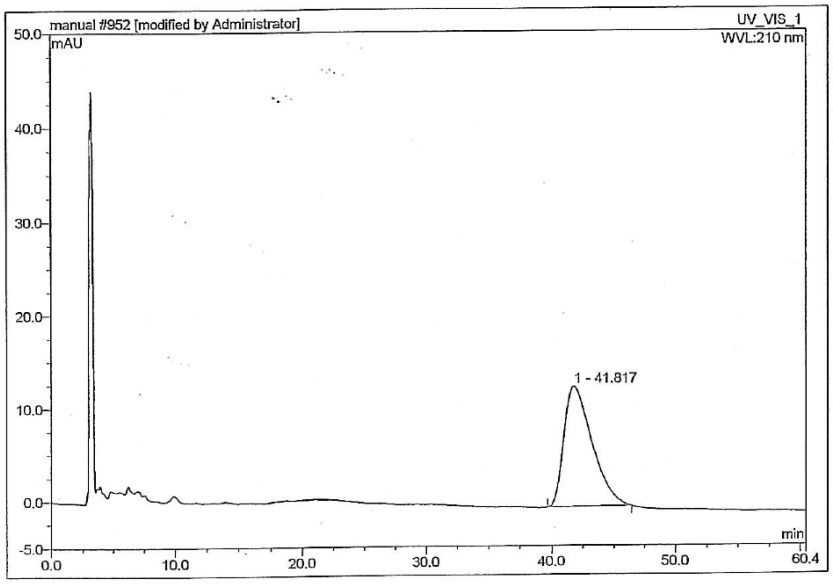
Figure 17: Comparisons of the ^{1}H NMR spectra of **27**

- Chiral HPLC trace of racemic target molecule **27**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.51	n.a.	32.692	48.914	50.66	n.a.	BMB*
2	41.53	n.a.	17.331	47.637	49.34	n.a.	BMB*
Total:			50.023	96.550	100.00	0.000	

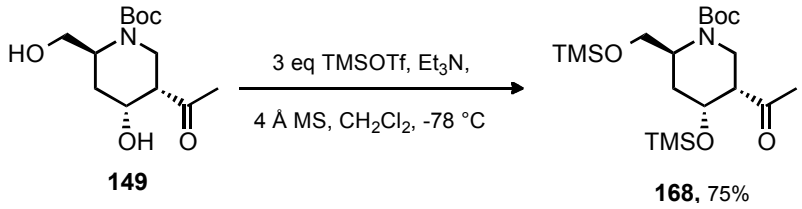
- Chiral HPLC trace of enantiopure target molecule **27**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	41.82	n.a.	12.930	33.908	100.00	n.a.	BMB*
Total:			12.930	33.908	100.00	0.000	

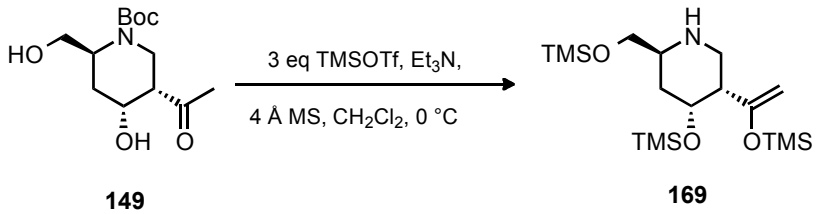
Figure 18: Racemic and enantiopure chiral HPLC traces of **27**

Having completed the formal synthesis of pseudodistomin F we looked to improve the efficiency of the synthetic route. Protection of the primary alcohol as a TBDPS ether introduced two additional steps into the synthesis (protection & deprotection). We speculated whether it was possible to carry out the Curtius rearrangement without protection of the primary hydroxyl, as there is a potential regioselectivity issue of the primary alcohol reacting with the isocyanate intermediate in an intermolecular fashion. Therefore, ketone **149** was allowed to react with three equivalents of TMSOTf at -78 °C in the hope of forming the corresponding silyl ether enol but instead gave the bis-protected TMS silyl ether **168** (Scheme 103).



Scheme 103: Silyl enol formation with TMSOTf at -78 °C

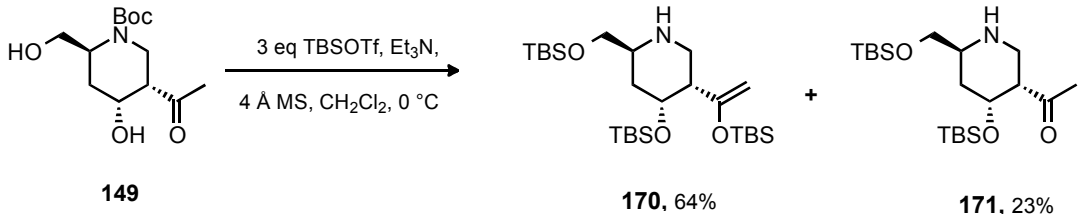
Raising the temperature of the reaction to 0 °C resulted in successful silyl ether formation but unfortunately removed the Boc protecting group,[105] as confirmed by analysis of the ^{1}H NMR of the crude reaction. Unfortunately, attempts to purify **169** led to decomposition (Scheme 104).



Scheme 104: Silyl enol formation with TMSOTf at 0 °C

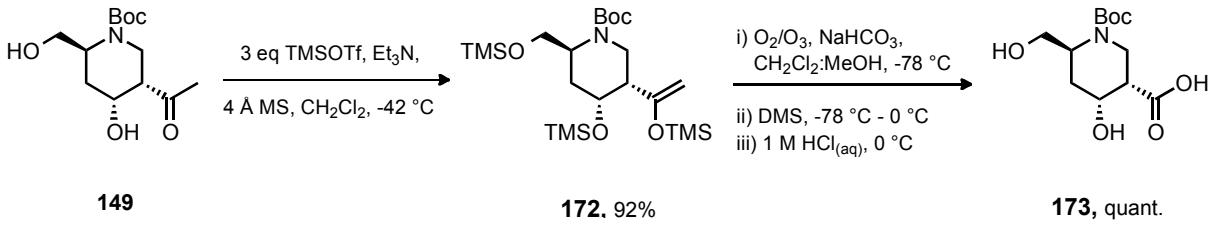
In the hope of preserving the Boc protecting group we employed the bulkier silyl triflate, TBSOTf, but regrettably the Boc group was not retained under these conditions which gave

silyl enol ether **170** and ketone **171** that were sufficiently stable to be purified by flash column chromatography (Scheme 105).



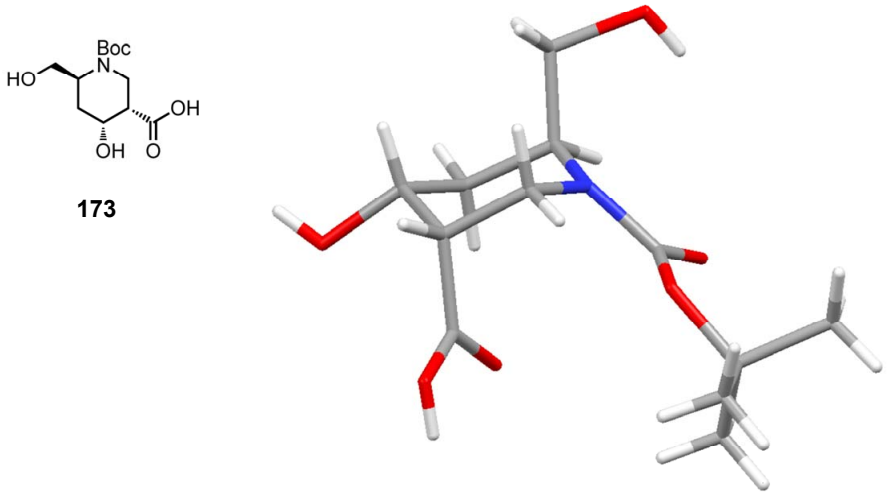
Scheme 105: Silyl enol ether formation with TBSOTf

Performing the reaction at an intermediate temperature of -42 °C with 3 equivalents of TMSOTf preserved the Boc and gave the silyl enol ether **172** in an excellent yield of 92% . Attempts to purify the crude silyl enol ether on neutralised silica by flash column chromatography resulted in poor yields ~30% due to breakdown of the silyl enol ether to the corresponding ketone. The key to high reaction yields of the pure silyl enol was to flood the crude reaction mixture with diethylether, rendering the triethylammonium triflate by-product insoluble and allowing for simple separation of the diethylether layer containing the silyl enol ether product **173**. Ozonolysis of the silyl enol ether gave the carboxylic acid in an quantitative yield (Scheme 106).



Scheme 106: Silyl enol formation and ozonolysis

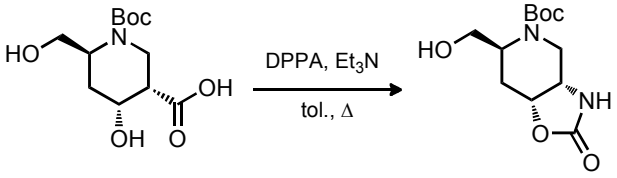
The structure of carboxylic acid **173** was determined by X-ray crystallography (Figure 19).



173

Figure 19: X-ray crystal structure of carboxylic acid **173**

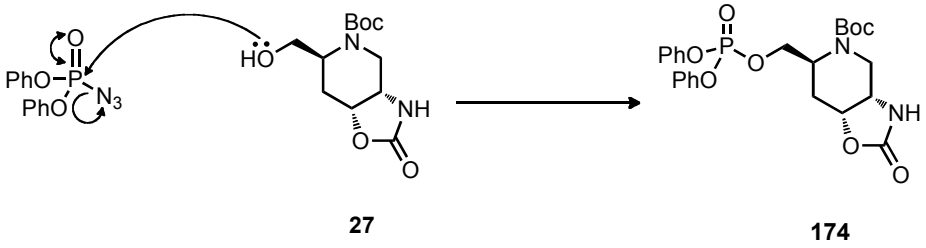
Curtius rearrangement of the carboxylic acid **173** gave the desired oxazolidinone **27** in a good yield of 75%, and completed the formal synthesis (Scheme 107).



173 **27**, 75%

Scheme 107: Curtius rearrangement of carboxylic acid **173**

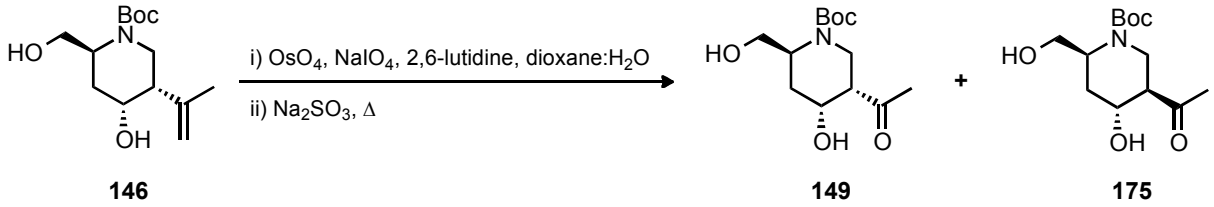
High reaction yields were dependent on prior heating of the carboxylic acid and Et_3N together before the addition of DPPA, due to formation of a phosphate ester by-product **174**, tentatively assigned from its ^1H NMR and mass spectra. Its formation presumably occurs due to the poor solubility of the carboxylic acid in toluene at room temperature compared to the corresponding oxazolidinone, which further reacted with reacted with DPPA.



Scheme 108: Mechanism for the formation of the phosphate ester by-product **174**

2.3.8 Ketone Epimerisation

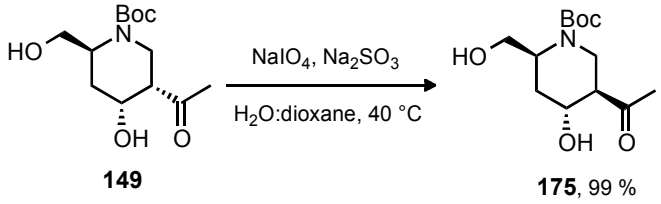
While investigating the oxidative cleavage of alkene **146** using $OsO_4/NaIO_4$ (Table 12, entry 3) it was observed that after quenching of the reaction with Na_2SO_3 and heating to remove the solvents *in vacuo* epimerisation occurred at the ketone stereocentre to afford a mixture of *cis*-ketone **149** and *trans*-ketone **175** (Scheme 109).



146 **149** **175**

Scheme 109: Epimerisation during oxidative cleavage

In an attempt to isolate the species responsible for the epimerisation of **149**, we looked at each reagent in turn. The reactions between *cis*-ketone **149** and 2,6-lutidine (Table 14, entry 1), $NaIO_4$ (Table 14, entry 2) and a saturated aqueous solution of Na_2SO_3 (Table 14, entry 3) in dioxane and water heated to 40 °C for twenty-four hours resulted in no epimerisation. However, treating *cis*-ketone **149** with $NaIO_4$ and a saturated aqueous solution of Na_2SO_3 together in dioxane led to complete epimerisation in one hour (Table 14, entry 4) (Scheme 110).



Scheme 110: Epimerisation with a combination of $NaIO_4$ and Na_2SO_3

We rationalised that the likely products generated from the reaction between $NaIO_4$ and Na_2SO_3 were $NaIO_3$ and Na_2SO_4. Performing the reaction individually with $NaIO_3$ and Na_2SO_4 (Table 14, entries 5 & 6) and in combination of the two reagents (Table 14, entry 7) failed to furnish the epimerisation.

Entry	Reagent[a]	Solvent[b]	Temp. / °C	Time / h	149 : 175[c]	Yield of 175 (%)[d]
1	2,6-lutidine	H_2O:dioxane	40	24	100 : 0	-[e]
2	$NaIO_4$	H_2O:dioxane	40	24	100 : 0	-[e]
3	$Na_2SO_{3\,(aq)}$[f]	dioxane	40	24	100 : 0	-[e]
4	$NaIO_4/Na_2SO_{3\,(aq)}$[f]	dioxane	40	1	0 :100	99
5	$NaIO_3$	H_2O:dioxane	40	24	100 : 0	-[e]
6	Na_zSO_4	H_2O:dioxane	40	24	100 : 0	-[e]
7	$NaIO_3/Na_2SO_4$	H_2O:dioxane	40	24	100 : 0	-[e]
8	DBU	CH_2Cl_2	rt	4	0 : 100	98
9	Et_3N[g]	CH_2Cl_2	rt	168	100 : 0	-[e]
10	Et_3N	CH_2Cl_2	40	8	75 : 25	-[h]

[a] Two equivalents of reagent used unless stated otherwise. [b] Reactions carried out at a total *c* of 0.1 M, in the case of mixed solvents a 1:1 ratio was used. [c] Ratio of products determined by analysis of the ^1H NMR of the crude reaction mixture. [d] Isolated yield following purification. [e] No reaction had taken place. [f] An equivalent volume of a saturated aqueous solution of Na_2SO_3 to reaction solvent was added. [g] Ten equivalents of reagent used. [h] Products not isolated from crude reaction mixture.

Table 14: Results from the epimerisation of ketone **149**

To gain an insight into the reaction mechanism we performed the reaction using conditions normally employed to affect the epimerisation of carbonyls with α-stereogenic centres. The strong organic base DBU in CH_2Cl_2 in 4 hours at room temperature (Table 14, entry 8)

afforded complete epimerisation. Using the weaker base triethylamine in CH_2Cl_2 for 1 week at room temperature (Table 14, entry 9) failed to effect epimerisation, however heating the to 40 °C over eight hours resulted in partial epimerisation (Table 14, entry 10). Unfortunately, we were not able to determine the active species responsible for the epimerisation, generated from the reaction between $NaIO_4$ and Na_2SO_3, although it would appear not to occur from a simple oxidation/reduction reaction.

The stereochemistry of *trans*-ketone **175** was determined by a NOESY experiment and was compared to the NOESY spectrum of the *cis*-ketone **149**. The important interactions of H^5 are shown below (Figure 20). In the NOESY spectrum of *trans*-ketone **175** there are nOes between H^5 the axial $H^{3'}$ and a single H^6 proton. In addition, the doublet of double doublets (ddd) corresponding to H^5 has coupling constants of 4.1, 10.1, and 12.2 Hz indicative of two diaxial couplings. The nOe interactions supported by the coupling constants are consistent with H^5 being axial within the chair conformation. In comparison, H^5 of *cis*-ketone **149** exhibits nOes between the two H^6 protons and H^4 but crucially there is no nOe between H^5 and any of the H^3 protons. The quartet corresponding to H^5 has a relatively small coupling constant of 3.4 Hz indicating no diaxial couplings. The nOe interactions and coupling constants imply that H^5 lies equatorial within the chair conformation.

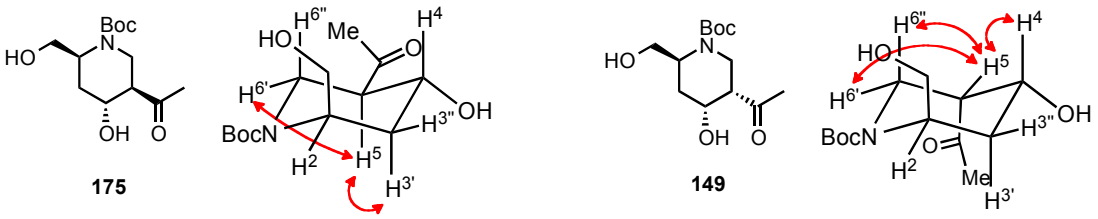
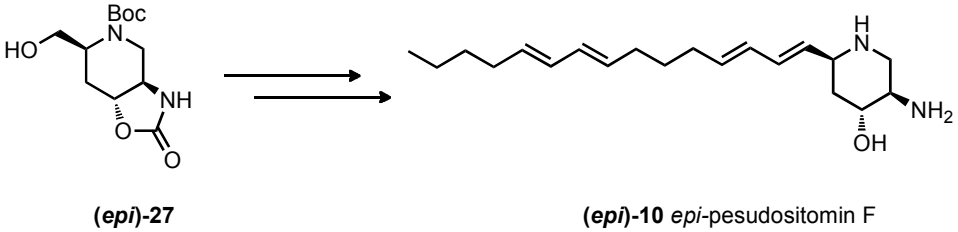


Figure 20: Comparison of H^5 nOe interactions between *trans*-ketone 175 and *cis*-ketone **149**

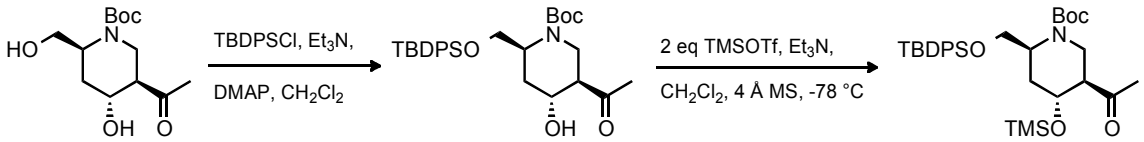
We decided to utilise this transformation for the synthesis of an unnatural core structure of the pseudodistomin family. Assuming the chemistry to transform **27** into **10** would work for (***epi*)-*27*** this would allow access to the unnatural diastereomer *epi*-pseudodistomin F ***(epi*)-10** (Scheme 111).



(*epi*)-27 (*epi*)-10 *epi*-pesudositomin F

Scheme 111: Potential synthesis of *epi*-pseudodistomin F

The formation of a strained *trans* oxazolidinone in the Curtius rearrangement might present a greater regioselectivity issue than before. Capture of the isocyanate intermediate by the *trans*-secondary hydroxyl was predicted to be slower than the in *cis* compound, therefore capture by the primary hydroxyl was of greater concern. Protection of the primary hydroxyl in **175** was accomplished with TBDPSCl to give the protected ketone **176** in an excellent yield of 96%. The hydrogens in the methyl group of the *trans*-ketone are predicted to be more accessible than the corresponding hydrogens in the *cis*-ketone, therefore silyl enol ether formation was attempted with two equivalents of TMSOTf at -78 °C but as in the previous case only the formation of a silyl ether **177** was observed (Scheme 112).

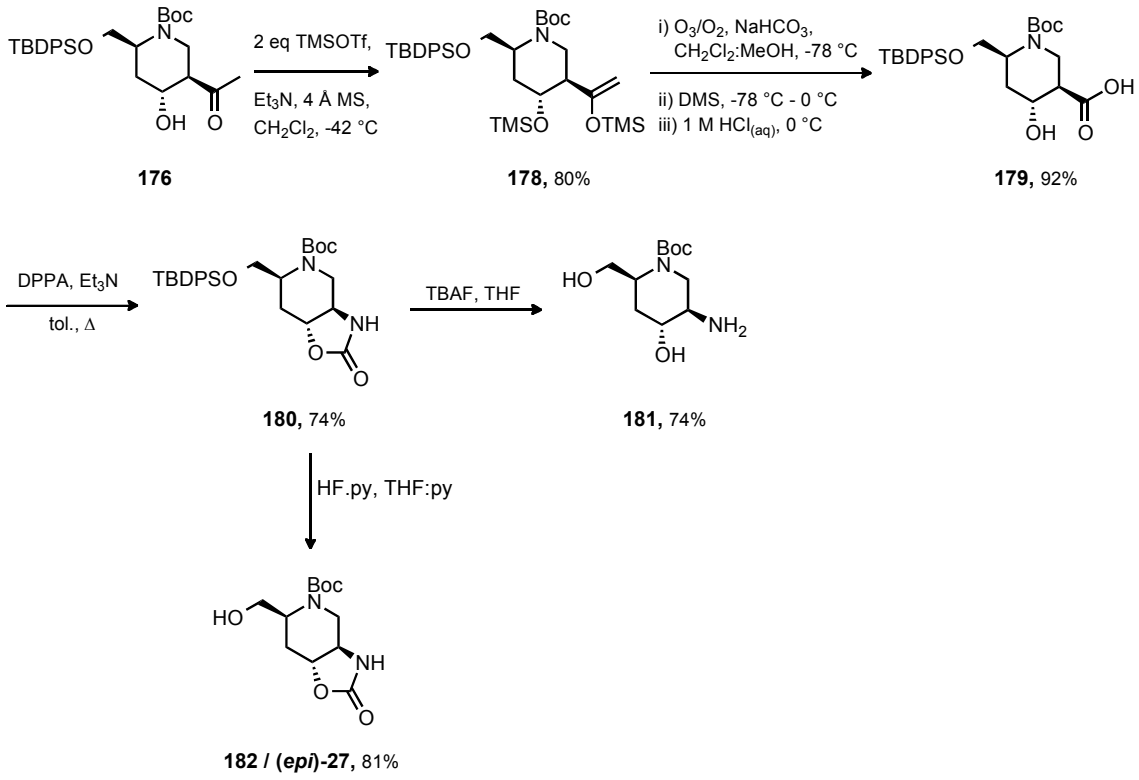


175 **176,** 96% **177,** 78%

Scheme 112: Primary and secondary hydroxyl protection

Silyl enol ether was successfully accomplished by raising the temperature to -42 °C, giving **178** in a very good yield of 80%. Ozonolysis of the silyl enol ether gave the carboxylic acid

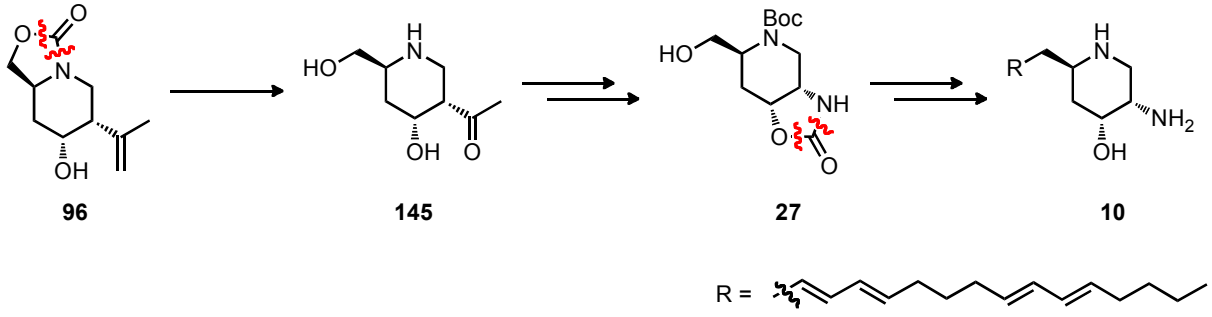
179 in an excellent yield of 92% and a Curtius rearrangement of the carboxylic acid with DPPA gave the *trans*-oxazolidinone **180** in a good yield of 74%. Deprotection of the TBDPS silyl ether with TBAF was successful but also resulted in cleavage of the oxazolidinone, giving amino diol **181** in a good yield of 74%. The commercial TBAF sold in a solution of THF is wet and basic, resulting in hydrolysis of the strained *trans*-oxazolidinone, which is susceptible to ring opening under these mild conditions. Deprotection of the silyl ether and retainment of the oxazolidinone ring was accomplished by employing HF in pyridine gave the oxazolidinone **182/(*epi*)-27** in a very good yield of 81% (Scheme 113).



Scheme 113: Silyl enol ether formation, ozonolysis, Curtius rearrangement and deprotection

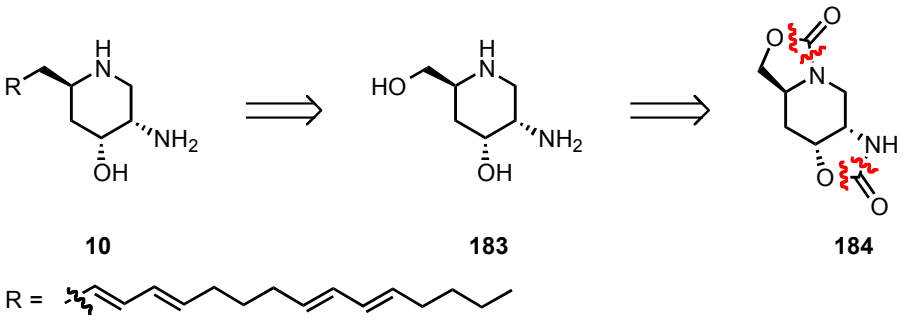
2.4 Third Generation Synthesis

In parallel with our studies towards the formal synthesis of pseudodistomin F **10** we envisaged a more expedient route to the total synthesis of this natural product. Our synthetic route to the synthesis of pseudodistomin F *via* the 'formal synthesis' pathway requires the construction of two oxazolidinone rings and their cleavage in two separate steps (Scheme 114).



Scheme 114: Current synthetic route for the total synthesis of pseudodistomin F

A more logical approach to the total synthesis of pseudodistomin F **10** would be the cleavage of both oxazolidinones in one step, therefore an alternative retrosynthetic approach to **10** was proposed. Installation of the alkyl side-chain in **10** occur from an olefination reaction of diamino diol **183**, which in turn can be formed the hydrolysis of bis-oxazolidinone **184** (Scheme 115).



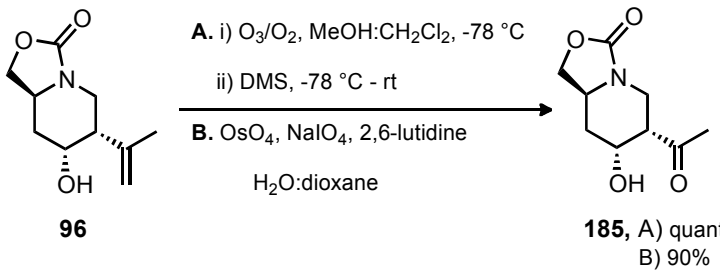
Scheme 115: Alternative retrosynthetic approach

Oxidative cleavage of alkene **96**, initially performed with ozone in CH_2Cl_2 at -78 °C with PPh_3 as the reducing agent (Table 15, entry 1), gave a poor yield of 26% for the ketone **185**. Changing the solvent to a mixture of CH_2Cl_2 and MeOH (Table 15, entry 2) resulted in smooth conversion into products, but problematic purification of the product and triphenylphosphine oxide by-product decreased the yield to 60% yield. Changing the reducing agent to DMS (Table 15, entry 3) yielded DMSO as the by-product, which cold be removed *in vacuo* gave the ketone **185** in a quantitative yield.

Entry	Solvent	Reducing agent	Time / min	Yield of 185 (%)
1	CH_2Cl_2	PPh_3	30	26
2	CH_2Cl_2 : MeOH	PPh_3	15	60
3	CH_2Cl_2 : MeOH	DMS	15	quant.

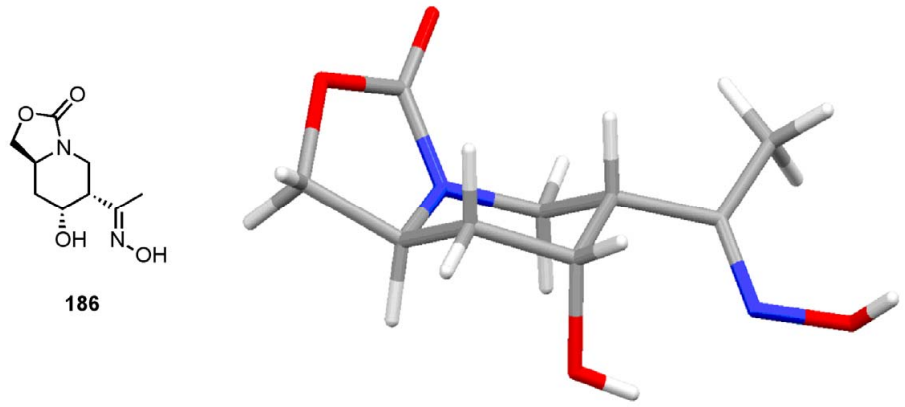
Table 15: Ozonolysis conditions

The oxidative cleavage was also carried out successfully using OsO_4 and $NaIO_4$, giving the ketone **189** in a 90% yield (Scheme 116).



Scheme 116: Oxidative cleavage of alkene **96** with either ozone or OsO_4/$NaIO_4$

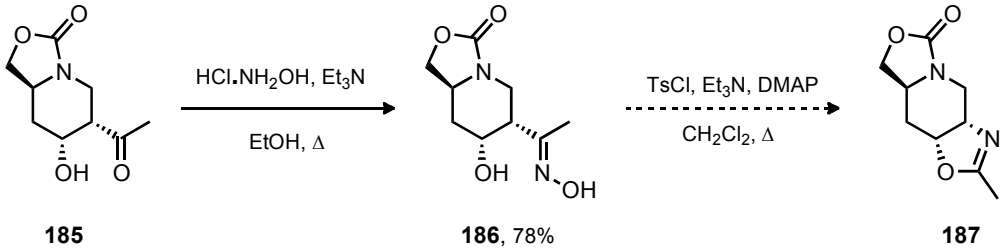
Ketone **185** could be transformed to oxime **186** in a good yield of 78%. The structure of the oxime was determined by X-ray crystallography (Figure 21).



186

Figure 21: X-ray crystal structure of oxime **186**

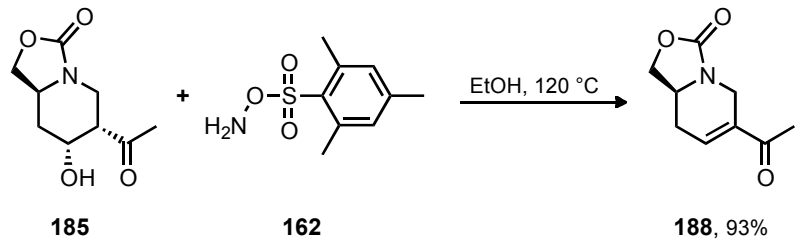
The Beckmann rearrangement of oxime **186** was attempted with TsCl, but unfortunately the oxazoline derivative **187** was not formed and only unreacted starting materials were recovered from the reaction (Scheme 117).



185 **186**, 78% **187**

Scheme 117: Oxime formation and attempted Beckmann rearrangement

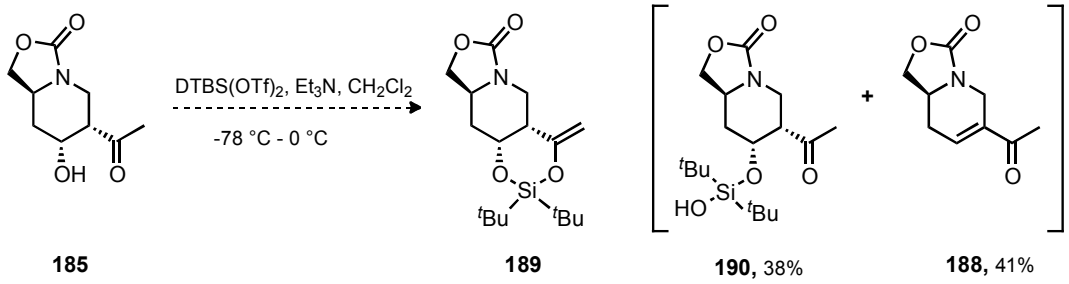
The one-pot oxime formation and Beckmann rearrangement between ketone **185** and the activated hydroxylamine **162** was attempted. Reaction with Et_3N in CH_2Cl_2 heated to 80 °C in sealed tube only gave unreacted starting materials. The same result was obtained when heating **185** and **162** together in EtOH at reflux. Performing the reaction in a sealed tube heated to 120 °C resulted in elimination to give enone **188** (Scheme 118).



185 **162** **188**, 93%

Scheme 118: Attempted Beckmann rearrangement with activated hydroxylamine

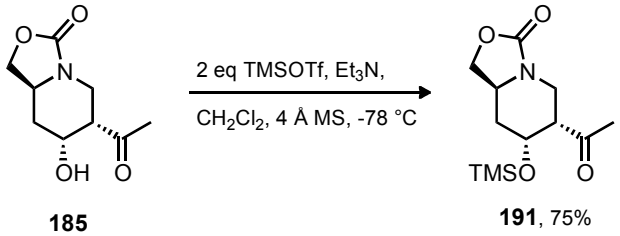
The TMS enol ethers synthesised previously have been relatively unstable; we believed the stability could be increased by the formation of a tethered silyl ether/silyl enol ether **189**. Ketone **185** was allowed to react with $DTBS(OTf)_2$ and Et_3N at -78 °C before warming to 0 °C. The formation of the tethered silyl enol ether **189** was not observed and only silyl ether **190** and the elimination product **188** were recovered in yields of 38% and 41% respectively (Scheme 119).



185 **189** **190,** 38% **188,** 41%

Scheme 119: Attempted tethered silyl ether/silyl enol ether formation

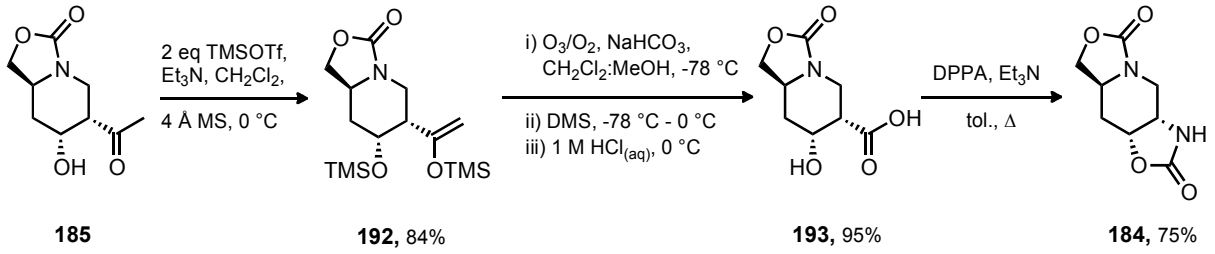
The reaction between ketone **185** and two equivalents of TMSOTf at -78 °C failed to afford the desired silyl enol ether and instead gave silyl ether **191** in a yield of 75% (Scheme 120).



185 **191**, 75%

Scheme 120: Attempted silyl enol ether formation at -78 °C

The reaction between ketone **185** and two equivalents of TMSOTf in CH_2Cl_2 at 0 °C gave the silyl enol ether **192** in a very good yield of 84%. Ozonolysis of the silyl enol ether **192** gave the carboxylic acid **193** in an excellent yield of 95% followed by a Curtius rearrangement to give the bis-oxazolidinone **184** in a good yield of 75%.



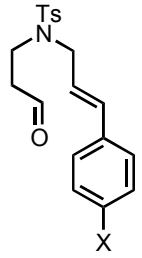
185 **192,** 84% **193,** 95% **184,** 75%

Scheme 121: Synthesis of bis-oxazolidinone 184

Unfortunately, time constraints prevented further attempts towards the total synthesis of pseudodistomin F **10**, *via* this synthetic route.

2.5 Modifying the Stereoelectronics of the Prins Reaction

Due to our ongoing interest in the Prins cyclisation methodology, we wanted to probe the mechanistic details of the reaction by studying whether varying the electronics of the ene component could alter the diastereoselectivity. The cyclisation precursor **194** bearing various substituents on the phenyl ring was chosen for study. This substrate was chosen because substituents could be installed relatively easily, enabling the electronics of the system to be finely tuned (Figure 22).



194

Figure 22: Substituted phenyl cyclisation precursor **194**

We reasoned that as the electron withdrawing ability of the substituent X increases the carbocation becomes destabilised, leading to a greater preference for the proposed electrostatic interaction of the oxygen lone and carbocation to occur which in turn would lead to higher *cis* diastereoselectivities (Figure 23).

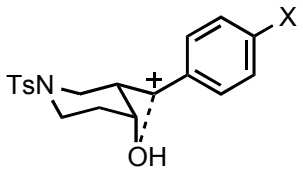
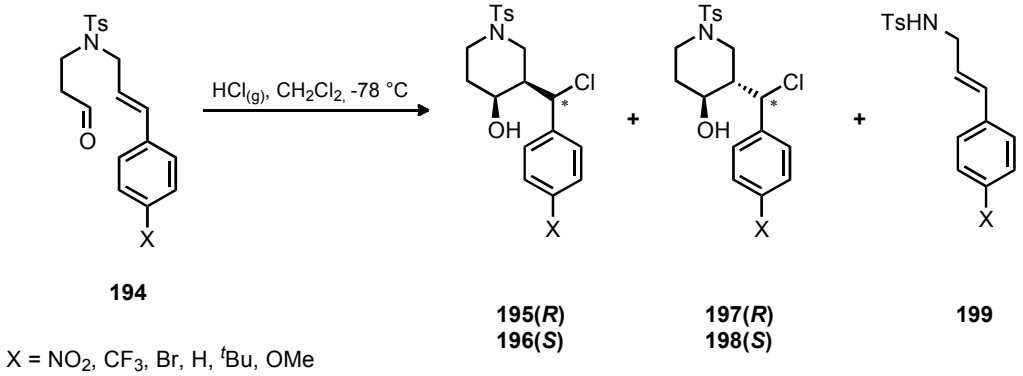


Figure 23: Stabilising interaction of an oxygen lone pair

Previous work in the group has looked at the Prins cyclisation between the Brønsted acid $HCl_{(g)}$ and the cyclisation precursor **194** with substituents NO_2, CF_3, Br, H, ^{t}Bu and OMe (Scheme 122).[64]



194

X = NO_2, CF_3, Br, H, ^{t}Bu, OMe

195(*R*)
196(*S*)

197(*R*)
198(*S*)

199

Scheme 122: Previously studied Brønsted acid cyclisations

The results from the reaction are summarised below in Table 16. The stereoselectivities for all substrates are poor, with *cis*:*trans* ratios ranging from 1:2.20 to 1:1.14 for CF_3 and OMe substrates respectively (entries 2 & 6). Substituting the phenyl ring with a very electron withdrawing group (entries 1 & 2) led to significant amounts of the elimination by-product **199**.

Entry	**194**	Reaction time / h	**195(*R*)**	**196(*S*)**	**197(*R*)**	**198(*S*)**	**199**	*cis:trans* ratio
1	NO_2	16[a]	0	0	traces		42%	-
2	CF_3	120[b]	24	7	5	64	18%	1:2.20[c]
3	Br	16	33	14	24	29	0	1:1.13[c]
4	H	16	26	11	29	34	0	1:1.70[c]
5	^{t}Bu	16	28	15	37	20	0	1:1.33[c]
6	OMe	16	-	-	-	-	0	1:1.14[d]

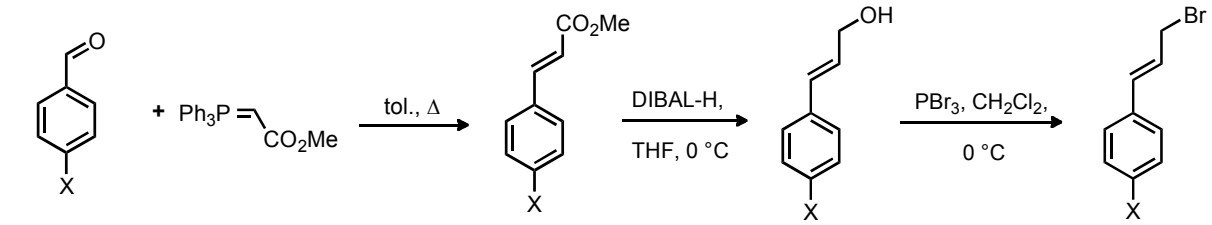
[a] 10% of aldehyde remained. [b] Traces of aldehyde remained. [c] Ratio determined by integration of ^{1}H NMR of crude reaction mixtures. [d] Ratio determined by the relative areas from the HPLC of the crude reaction mixture.

Table 16: Previously studied Brønsted acid cyclisations[62]

The relative stereochemistries of the reaction products were determined by X-ray crystallography of the piperidines with phenyl substrate X = H. The stereoselectivities countered the proposed stereochemical outcome of the reaction, as the *trans* diastereomer was isolated as the major component. It would appear that the postulated stabilising interaction is not as significant in this system compared to previous systems studied.

We wished to study the Lewis acid-promoted Prins cyclisation in the hope of improving the diastereoselectivity. We chose to study a similar substrate range of electron-withdrawing to electron-donating groups NO_2, CF_3, Br, H, Me and OMe to allow us to make comparisons

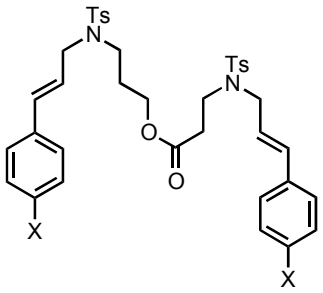
with the previously studied Brønsted acid cyclisations.[62] The cyclisation precursors **194** were synthesised in five steps from commerically available *para*-substituted benzaldehydes **200a-e**. The aldehydes **200a-e** were subjected to a Wittig reaction with phosphorous ylide **201** to afford the methyl cinnamates **202a-e**, with stereoselectivities in favour of the *E*-isomer with ratios ranging from 7:1 to >40:1. Reduction of the esters **202a-e** to the corresponding alcohols **203a-e** was achieved with DIBAL-H, before bromination of alcohols, **203a-d** with PBr_3 gave the desired bromides **204a-d** (Scheme 123).



200a X = NO_2 **201** **202a**, 80% **203a**, 63% **204a**, 84%
b X = CF_3 **b**, 90% **b**, 96% **b**, 99%
c X = Br **c**, 90% **c**, 97% **c**, 99%
d X = Me **d**, 90% **d**, 94% **d**, 83%
e X = OMe **e**, 81% **e**, 94%

Scheme 123: Synthesis of allylic bromides

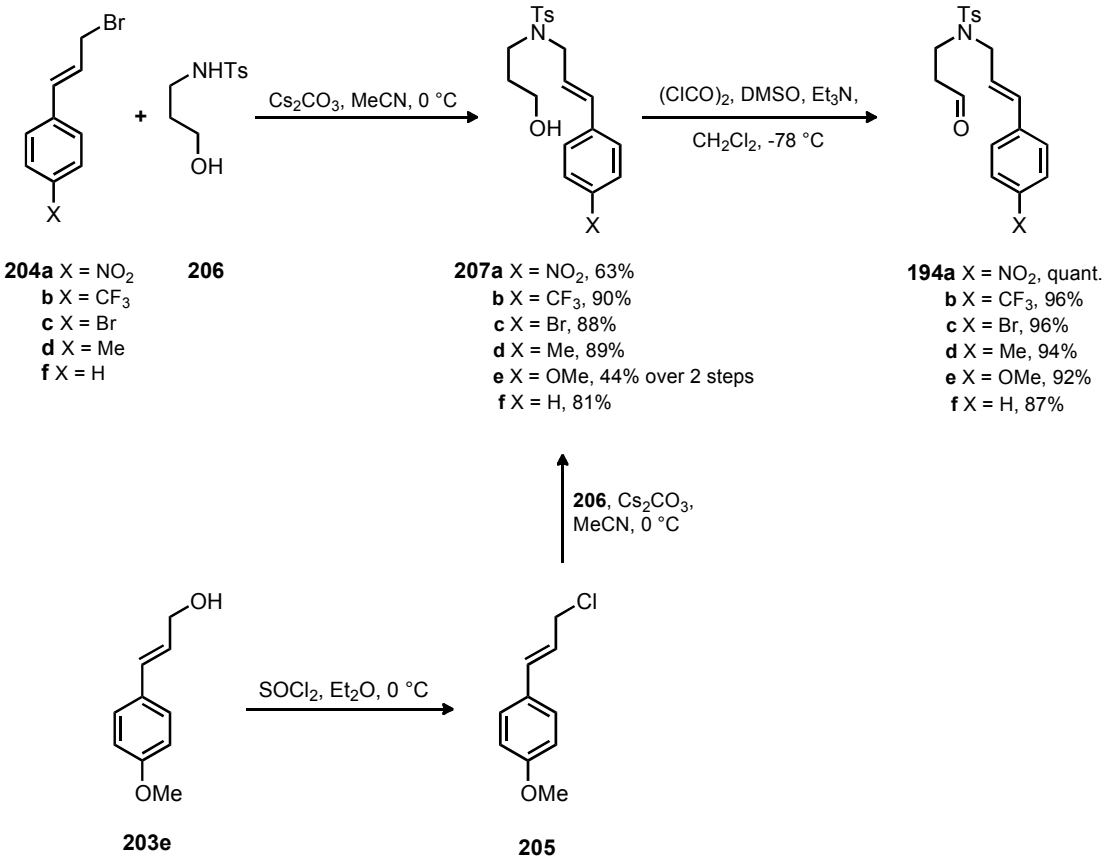
Attempted bromination of the *para*-methoxy alcohol **203e** led to decomposition, so the less reactive chloride **205** was synthesised from $SOCl_2$. Alkylation of the amino alcohol **206** with the synthesised alkylating agents **204a-d**, **205** and the commercially available cinnamyl bromide **204f** gave the alkylated amino alcohols **207a-f**. Oxidation of the alcohols **207a-f** with PCC, DMP and TPAP led to significant amounts ~20-50% of ester **208** (Figure 24) resulting from hemiacetal formation/oxidation.



208

Figure 24: Ester by-product from oxidation reactions

However, oxidation using Swern conditions gave the aldehydes **194a-f** in very good to excellent yields with no ester by-product occurring (Scheme 124).



204a X = NO_2
b X = CF_3
c X = Br
d X = Me
f X = H

206

207a X = NO_2, 63%
b X = CF_3, 90%
c X = Br, 88%
d X = Me, 89%
e X = OMe, 44% over 2 steps
f X = H, 81%

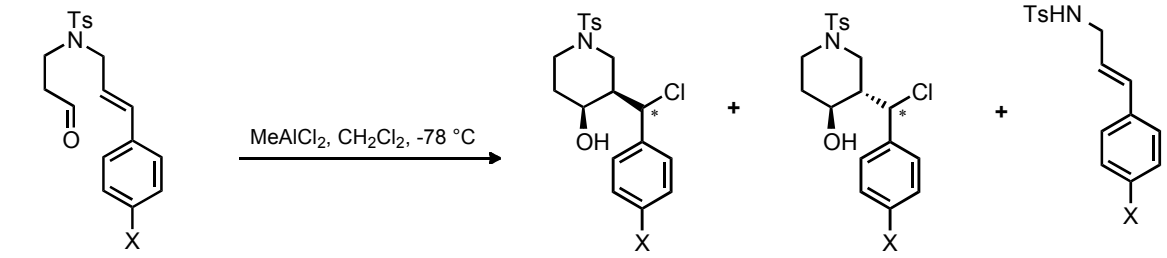
194a X = NO_2, quant.
b X = CF_3, 96%
c X = Br, 96%
d X = Me, 94%
e X = OMe, 92%
f X = H, 87%

203e

205

Scheme 124: Synthesis of the cyclisation precursor

With the cyclisation precursors **194a**-**f** in hand we subjected them to a Prins reaction using the Lewis acid $MeAlCl_2$ (Scheme 125). The results of the cyclisations are summarised below (Table 17).



194a X = NO_2, quant.
b X = CF_3, 96%
c X = Br, 96%
d X = Me, 94%
e X = OMe, 92%
f X = H, 87%

195(*R*)a, 196(*S*)a
195(*R*)b, 196(*S*)b
195(*R*)c, 196(*S*)c
195(*R*)d, 196(*S*)d
195(*R*)e, 196(*S*)e
195(*R*)f, 196(*S*)f

197(*R*)a, 198(*S*)a
197(*R*)b, 198(*S*)b
197(*R*)c, 198(*S*)c
197(*R*)d, 198(*S*)d
197(*R*)e, 198(*S*)e
197(*R*)f, 198(*S*)f

199

Scheme 125: Prins cyclisation with the Lewis acid $MeAlCl_2$

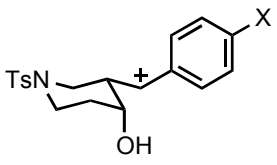
Entry	**194**[a]	Temp / °C	**195(*R*)**	**196(*S*)**	**197(*R*)**	**198(*S*)**	**199**	*tans* : *cis* ratio[b]	Yield / %[c]
1	NO_2	-78	5	5	69	11	10	8 : 1	45
2	CF_3	-78	5	5	25	15	50	4 : 1	-[d]
3	Br	-78	trace[e]		86	14	0	>25 : 1	77
4	H	-78	5	5	78	12	0	9 : 1	71
5	Me	-78	23[e]		50	27	0	3.3 : 1	32
6	OMe	-78	-	-	-	-	-	-	-[f]

[a] All reactions carried out with 2 eq of $MeAlCl_2$ in CH_2Cl_2 unless stated otherwise. [b] Ratios determined by integration of the ^1H NMR of the crude reaction mixture. [c] Yield of isolated major component following purification. [d] Purification of the crude reaction mixture was unsuccessful. [e] Combined ratio of products determined by the ^1H NMR of the crude reaction mixture. [f] Reaction led to a complex mixture of unidentified by products unidentified by-products.

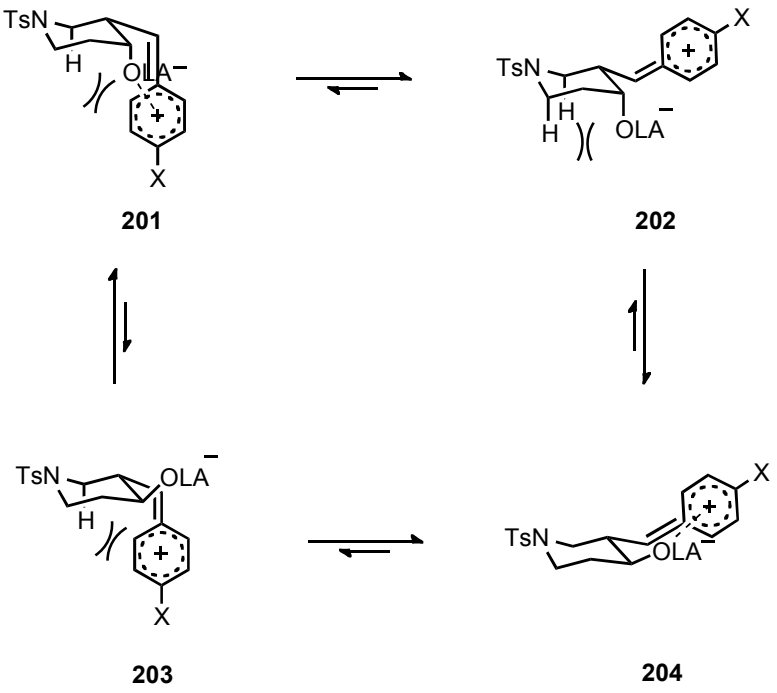
Table 17: $MeAlCl_2$ promoted cyclisations of aldehydes **194**

The stereochemical assignments were made by comparison ^1H NMR spectra of the crude reaction mixtures to the known phenyl piperidines determined by X-ray crystallography, in particular the shifts of the C*H*-Cl hydrogen between 4.7-5.5 ppm were diagnostic of the

stereochemistry. The Lewis acid-promoted Prins reaction favoured the *trans* diastereomer as seen previously with the Brønsted acid but generally with higher diastereoselectivities ranging from to >25:1 to 3.3:1 for *trans*:*cis*. Interpretation of the diastereoselectivities for the most electron withdrawing substituents, (Table 17, entries 1 & 2), are complicated by significant amounts of the elimination product **199**. However, for the substrates where no elimination occurs the trend is for an increase in *trans* selectivity as the X substituent becomes more electron withdrawing (Table 17, entries 3-5). Cyclisation of the most electron rich substrate, OMe, led to complex mixture of unidentified by-products, with none of the desired products detected in the ^{1}H NMR of the crude reaction mixture (Table 17, entry 6). Tentatively we can account for the observed selectivities favouring the *trans* products it was envisaged that the initial benzyl carbocation **200** becomes delocalised over the phenyl ring. A stabilising electrostatic interaction of the delocalised carbocation resulting from the negative charge on the oxygen-Lewis acid complex could only occur in intermediates **201** and **204**. A 1,3 diaxial interaction between the phenyl ring and an axial hydrogen, might favour **202** over **201**. The coordination of a bulkier Lewis acid to the oxygen, in comparison to a proton for the Brønsted acid, would lead to greater 1,3 diaxial interactions helping to reinforce the selectivity for the *trans* diastereomer (Scheme 126).



200



Scheme 126: Postulated intermediates to account for the observed diastereoselectivities

Alternatively, the observed diastereoselectivity can be rationalised by the steric preference for the bulky Lewis acid-coordinated oxygen to adopt an equatorial conformation. The reaction can be envisaged to proceed through either: an asynchronous concerted process **205**, or through a zwitterionic intermediate with intramolecular chloride transfer **206** (Figure 25).

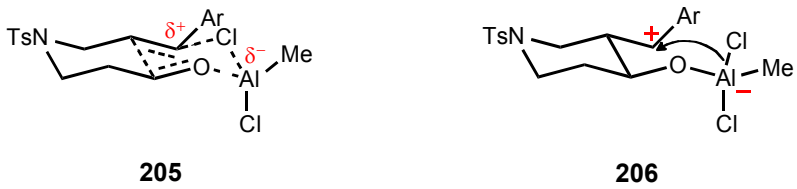
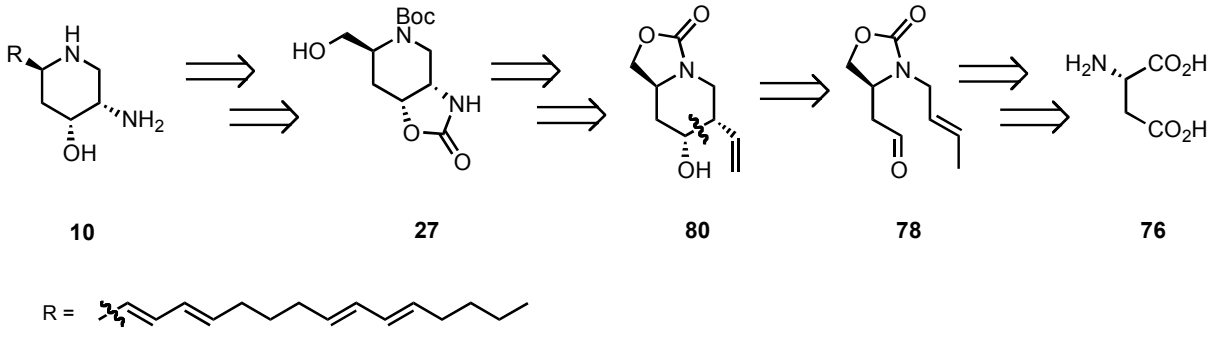


Figure 25: Alternative explanation for the observed diastereoselectivity

3. Conclusions and Future Work

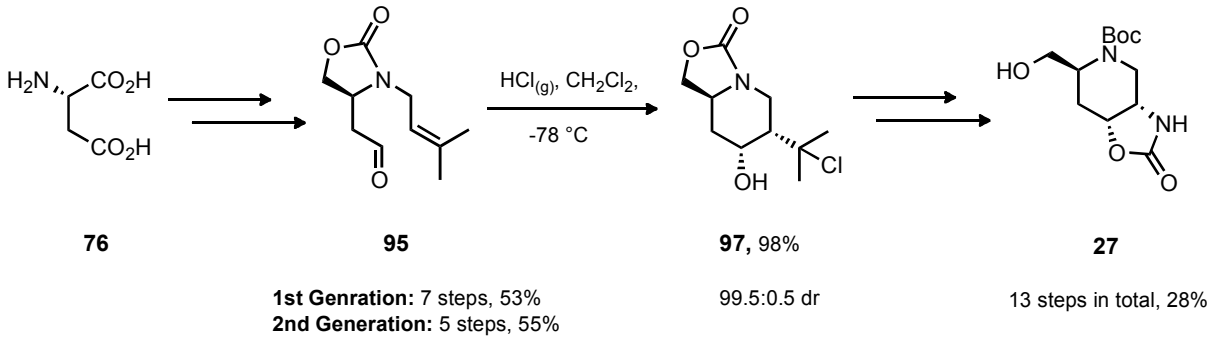
This work describes the successful application of the carbonyl-ene/Prins reaction in total synthesis. The aim was to synthesise an advanced intermediate **27** used in Ma and Sun's total synthesis of pseudodistomin F **10**. Our initial retrosynthetic approach to the target molecule **27** was a carbonyl-ene/Prins reaction of the crotyl-ene cyclisation precursor **78** to form piperidine **80** (Scheme 127).



Scheme 127: Initial retrosynthetic approach to the target molecule

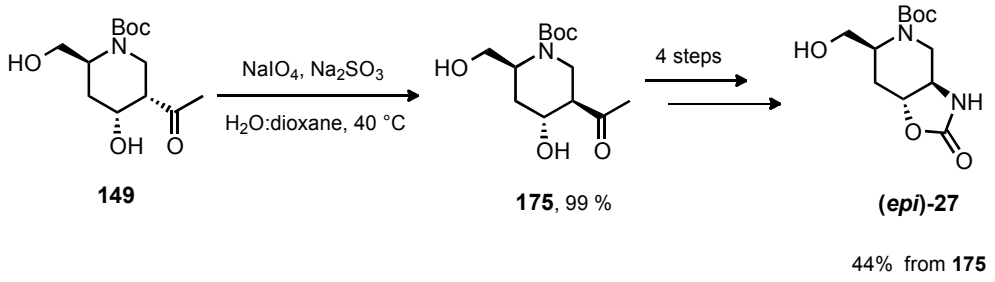
Subjecting the cyclisation precursor **78** to a carbonyl-ene reaction gave the desired piperidine **80** in a very poor yield of 25% due to the formation of three out of the possible four diastereomers and a dimerisation by-product. The poor selectivity in the reaction was thought to be a consequence of the reaction proceeding through an unfavourable secondary carbocation. Changing the cyclisation precursor to a prenyl-ene substrate **95**, resulted in successful Prins cyclisation giving excellent diastereoselectivities of up to 200:1 in favour of *cis* over *trans*. Two successive generations were developed that gave access to the cyclisation precursor **95**. Although both generations gave similar yields 53% to 55% for the first and second generations respectively, only the second generation synthesis gave access to the cyclisation precursor on a multigram scale and required fewer synthetic transformations to complete. Using the second generation synthesis we were able to complete the formal

synthesis **27** of pseudodistomin F in a total of thirteen synthetic steps and in an overall yield of 28% from aspartic acid **76**, a noticeable improvement over the original synthesis of **27** presented by Ma & Sun, which required fifteen steps and with a overall yield of 12% from commerically available starting materials.



Scheme 128: 1st and 2nd generation syntheses

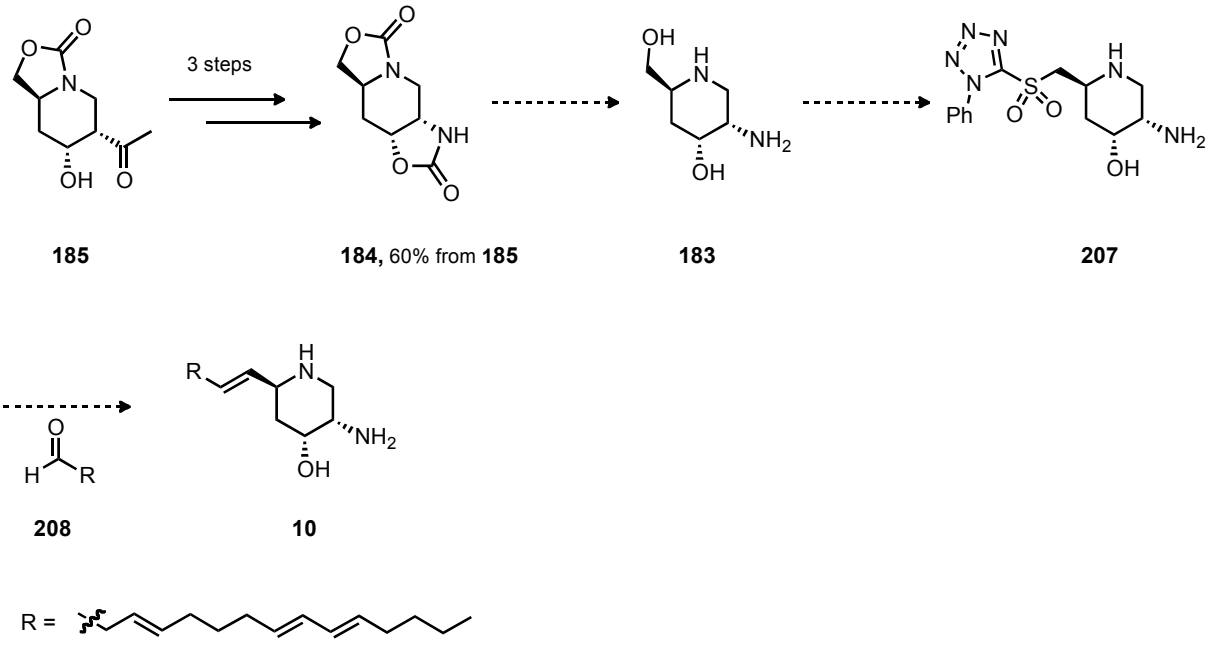
We serendipitously discovered a facile method to epimerise the ketone stereocentre of **149** to give its epimer **175** using a combination of $NaIO_4$ and Na_2SO_3, although the active species that causes epimerisation remains unresolved. We utilised this reaction and synthesised **(*epi*)-27**, which possess an unnatural core stereochemistry of the pseudodistomin alkaloids.



Scheme 129: Epimerisation and synthesis of **(*epi*)-27**

Having completed the formal synthesis of pseudodistomin F we turned our attention towards its total synthesis. From ketone **185** the *bis*-oxazolidinone **184** was prepared in three steps, this would potentially allow the cleavage of both oxazolidinone groups in one step instead of two steps as in the second generation synthesis. Future work could involve the formation of

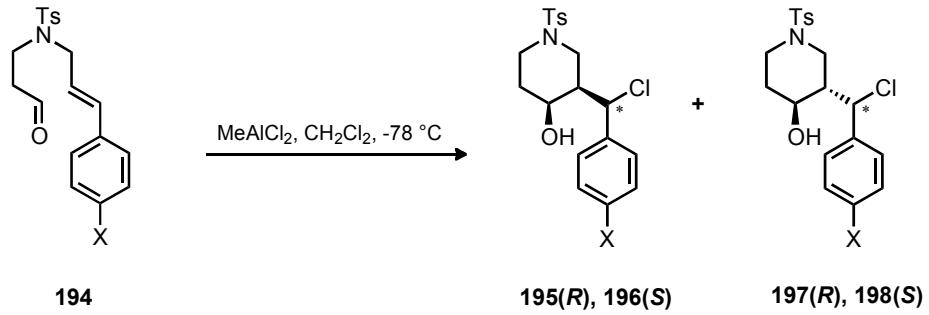
sulfone **207** from amino diol **183**. The sulfone **207** would allow efficient installation of the side chain through a Kocienski-modified Julia olefination with aldehyde **208** to give pseudodistomin F (Scheme 130).



Scheme 130: Towards the total synthesis of pseudodistomin F **10**

It would be interesting to conduct an SAR study to test for improved biological activities *in vitro*. In particular olefination reactions with aldehydes of varying chain lengths would quickly and easily build up diversity.

We also conducted a study into how changing the electronics of the ene component would alter the diastereoselectivity of the reaction. The results indicated that the diastereoselectivity favoured the *trans* products **197** and **198** as the electron withdrawing power of the substituent X increased in the cyclisation precursor **194** (Scheme 131).



Scheme 131: Prins cyclisation of the substituted cinnamyl substrate **194**

Considering the cinnamyl substrates **194** (Figure 26), it would be interesting to expand the substituent range and screen a variety of Lewis acids in order to gain a greater understanding of the reaction mechanism.

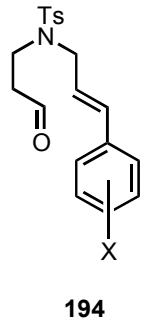


Figure 26: Various substituted cyclisation precursors

4. Experimental

^{1}H and ^{13}C spectra were recorded on either a Bruker AC 300 (300 and 75 MHz), a Bruker AV 300 (300 and 75 MHz), a Bruker AVIII300 (300 MHz), a Bruker AVIII400 (400 and 101 MHz), a Bruker AMX 400 (400 and 100 MHz) or a Bruker DRX500 (500 and 125 MHz respectively). Chemical shifts (□) are expressed in parts per million (ppm) Coupling constants (*J*) are reported in Hz. Multiplicity of signals of ^{1}H NMR are expressed as follows: s = singlet, d = doublet, t = triplet q = quartet, the term "stack" is used to describe a region where resonance arising from non-equivalent nuclei are coincident, and multiplet, m, is used to describe a region where resonance arising from a single nucleus (or equivalent nuclei) are coincident, but coupling constants cannot be readily assigned. ^{13}C NMR spectra were measured using the pendant technique. Multiplicity of signals and coupling constants are reported as observed after off-line processing (WinNMR or MestRe Nova).

Mass spectra were recorded on a Micromass ZABspec spectrometer utilizing electrospray ionisation (and a methanol mobile phase), and a Micromass Zabspec spectrometer utilising *m*-nitrobenzoylalcohol (3-NOBA) as the matrix, EI mass spectra were recorded on either a VG ProSpec or VG Zabspec instrument at 70 eV, and are reported as (*m/z* (%)).

Elemental analyses were recorded on a CARLO ERBA EA110 CHNS elemental analyser.

Infrared spectra were recorded as thin films (neat) or with nujol between sodium chloride plates on a Perkin Elmer 1600 FTIR spectrometer. The intensity of each band is described as s (strong), m (medium) or w (weak).

Optical rotations were measured using an Optical Activity PolAAr 2001 automatic polarimeter in 0.25 dm length cells. Concentrations used are expressed in grams of solute per 100 mL. $[\alpha]_D$ values are reported in units of 10^{-1} deg cm^2 g^{-1}.

Melting points were determined in open-ended glass capillaries using a Stuart Scientific SMP1 apparatus.

X-ray crystallography: Suitable crystals were selected and datasets were measured on a Bruker SMART 6000 diffractometer ($\lambda_{Cu\text{-}K\alpha}$ = 1.54178 Å) at 120 K. The data collections were driven by SMART and processed by SAINT. Or, suitable crystals were selected and datasets were measured by the EPSRC National Crystallography Service on a Bruker KappaCCD diffractometer at the window of a Bruker FR591 rotating anode ($\lambda_{Mo\text{-}K\alpha}$ = 0.71073 Å) at 120 K. The data collections were driven by COLLECT and processed by DENZO. Absorption corrections for all four datasets were applied using SADABS. The structures were solved in SHELXS-97 and were refined by a full-matrix least-squares procedure on F in SHELXL-97. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. Figures were produced using ORTEP3 for Windows.

All reactions were carried out under a nitrogen or argon atmosphere in flame-dried glassware. Molecular sieves (3 and 4 Å) were activated by flame-heating under high vacuum during 15 min and used immediately. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile (MeCN) and dimethylformamide (DMF) were distilled from CaH_2. Toluene was distilled from sodium and used immediately. Triethylamine was distilled from KOH and stored over 4 Å M.S. Other chemicals were used as purchased, unless otherwise stated. Aqueous solutions are saturated unless otherwise stated.

Flash column chromatography was carried out using Fluka 60 (40-60 μm mesh) silica gel. Analytical thin layer chromatography (TLC) was performed on Machery-Nagel SIL G-25 UV_{254} pre coated glass-backed plates and visualised by UV (254 nm) and potassium manganate(VII) solution. Evaporation and concentration under reduced pressure was done at (50-500mBar). Residual solvent was removed under high vacuum (1 mBar).

HPLC was performed on Dionex Summit HPLC systems using helium degassed HPLC grade solvents. Data were collected, recorded and processed using the Dionex Chromeleon 6.11 software package.

Analytical HPLC:

Pump: Summit P580 Quaternary Low Pressure Gradient Pump with built in vaccum degasser.

Detector: Summit UVD 170s UV/Vis Multi-Channel Detector with analytical flow cell.

Column: Phenomenex Luna 10µ C18 (250 mm x 4.6 mm).

Chiral analytical HPLC:

Pump: Summit P580 Quaternary Low Pressure Gradient Pump with built in vaccum degasser.

Detector: Summit UVD 170s UV/Vis Multi-Channel Detector with analytical flow cell.

Column: Daicel Chiral Pak AD (250 mm x 4.6 mm).

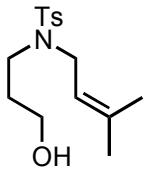
Semi-preparative HPLC:

Pump: Summit P580 Quaternary Low Pressure Gradient Pump with built in vaccum degasser.

Detector: Summit UVD 170s UV/Vis Multi-Channel Detector with Prep flow cell.

Column: Phenomenex Luna 10µ C18 (250 mm x 10 mm).

***N*-(3-Hydroxypropyl)-4-methyl-*N*-(3-methylbut-2-enyl)benzenesulfonamide (82)**



Cesium carbonate (1.85 g, 5.67 mmol) was added to a solution of *N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (1.00 g, 4.36 mmol) in MeCN (25 mL) at 0 °C. The resulting mixture was stirred for 15 min before 1-bromo-3-methylbut-2-ene (0.50 mL, 4.36 mmol) was added dropwise over 30 s. The resulting solution was allowed to warm to room temperature and stirred for a further 2 h. The solvent was removed *in vacuo* and the resulting white solid was dissolved in water (50 mL). The aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and evaporated *in vacuo* to leave a yellow crystalline solid, which was purified by flash column chromatography (R_f = 0.28, hexane:EtOAc, 2:1) to afford the *N*-alkylated sulfonamide **82** as a white crystalline solid (1.25 g, 96%).

mp: 41-42 °C (from hexane:EtOAc)

ν_{max}: (film)/cm^{-1} 3429 (OH), 2936 (CH), 1333 (SO_2), 1156 (SO_2)

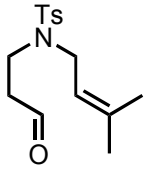
δ_H: (300 MHz, $CDCl_3$) 1.60 (3H, s, C*H*$_3$), 1.63 (3H, s, C*H*$_3$), 1.70-1.78 (2H, m, C*H*$_2$CH$_2$OH), 2.41 (3H, s, C*H*$_3$), 2.47 (1H, br s, O*H*), 3.20 (2H, t, *J* 6.5, CH$_2$C*H*$_2$N), 3.72 (2H, t, *J* 5.7, C*H*$_2$OH), 3.79 (2H, d, *J* 7.0, CHC*H*$_2$N), 4.95 (1H, t, *J* 7.0, =C*H*), 7.29 (2H, d, *J* 8.0 Ar C*H*), 7.67 (2H, d, *J* 8.0, Ar C*H*)

δ_C: (125 MHz), 18.8 (*C*H$_3$), 22.6 (*C*H$_3$), 26.8 (*C*H$_3$), 32.1 (*C*H$_2$CH$_2$OH), 44.8 (CH$_2$*C*H$_2$N), 46.9 (CH*C*H$_2$N), 59.9 (*C*H$_2$OH), 119.9 (*C*H=), 128.2 (Ar *C*H), 130.7 (Ar *C*H), 137. 3 (C_q), 138.1 (C_q), 144.3 (C_q)

m/z: (ES^+) 320.0 (100 %, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 320.1289. $C_{15}H_{23}NO_3S$ requires *M*, 320.1296]

4-Methyl-*N*-(3-methyl-but-2-enyl)-*N*-(3-oxopropyl)benzenesulfonamide (58)



PCC Oxidation

Celite (1.0 g) was added to a suspension of PCC (0.56 g, 2.56 mmol) in CH_2Cl_2 (15 mL). The resultant slurry was stirred vigorously for 5 min before being cooled to 0 °C. A solution of *N*-alkylated sulfonamide **82** (0.52 g, 1.72 mmol) in CH_2Cl_2 (5 mL) was then added in one portion. The resulting solution was allowed to warm to room temperature and stirred for a further 4 h. $NaHSO_4$ (1.0 g) and Et_2O (20 mL) were added and the mixture was stirred vigorously for 15 min before being filtered through a silica plug, washed with diethyl ether (100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield the crude product as a yellow oil, which was purified by flash column chromatography (R_f = 0.27, hexane:EtOAc, 3:1) to afford the aldehyde **58** as a colourless oil (0.31 g, 61%).

Swern Oxidation

Anhydrous DMSO (0.32 mL, 4.56 mmol) was added at a rapid rate to a solution of oxalyl chloride (0.24 mL, 2.28 mmol) in CH_2Cl_2 (25 mL) at -78 °C. The resulting mixture was stirred for 5 min before a solution of the alcohol **82** (0.57 g, 1.90 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 10 min. After 30 min Et_3N (1.32 mL, 9.50 mmol) was added dropwise over 30 s and the resulting solution was stirred for a further 3 h at -78 °C before being allowed to warm to room temperature. Water (50 mL) was added and the aqueous phase was further extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with 1 M HCl (100 mL), water (100 mL) and finally with brine (100 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to give the crude aldehyde as a pale yellow oil, which

was purified by flash column chromatography (R_f = 0.27, hexane:EtOAc, 3:1) to give the aldehyde **58** as a colourless oil (0.54 g, 97%).

ν_{max}: (film)/cm^{-1} 2973 (CH), 2926 (CH), 1724 (C=O), 1339 (SO_2), 1159 (SO_2)

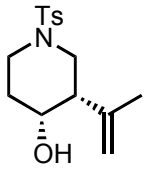
δ_H: (300 MHz, $CDCl_3$) 1.60 (3H, s, CH_3), 1.64 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.79 (2H, t, *J* 6.9 CH_2CHO) 3.35 (2H, t, *J* 6.9, CH_2CH_2N), 3.75 (2H, d, *J* 7.0, CHCH_2N), 4.96 (1H, t, *J* 7.0, =C*H*), 7.29 (2H, d, *J* 8.0 Ar C*H*), 7.67 (2H, d, *J* 8.0, Ar C*H*) 9.74 (1H, s, C*H*O)

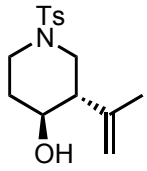
δ_C: (125 MHz), 16.1 (CH_3), 19.8 (CH_3), 24.0 (CH_3), 39.3 (CH_2CHO), 42.2 (CH_2CH_2N), 44.8 (CHCH_2N), 117.0 (*C*H=), 125.7 (Ar *C*H), 128.0 (Ar *C*H), 134.7 (C_q), 135.9 (C_q), 141.7 (C_q), 198.8 (*C*HO)

m/z: (ES^+) 318.1 (100 %, $[M+Na]^+$), 350.2 (20, $[M+Na+MeOH]^+$)

HRMS: [Found: $(M+Na)^+$ 318.1145. $C_{15}H_{21}NO_3S$ requires *M*, 318.1140]

(3*R, 4*S**)-3-Isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (59)** and **(3*S**, 4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (59)**





Prins Cyclisation

Concentrated HCl (37 %, 0.10 mL, 1.02 mmol) was added to a solution of aldehyde **58** (100 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at -78 °C. The resulting solution was stirred at -78 °C for 16 h, before being quenched by the addition of water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid, which was purified by flash column chromatography (R_f = 0.23, hexane:EtOAc, 2:1) to give or piperidine **59** as a white crystalline solid (79 mg, 79%).

mp: 91-92 °C (from hexane:EtOAc)

ν_{max}: (film)/cm^{-1} 3366 (OH), 2925 (CH) 2867 (CH), 1341 (SO_2), 1164 (SO_2)

δ_H: (300 MHz, $CDCl_3$) 1.48 (1 H, br s, O*H*), 1.77 (3 H, s, CH_3), 1.83-1.93 (2H, m, CH_2CH_2N), 2.36-2.40 (1H, m, C*H*CH_2N), 2.42 (3 H, s, CH_3), 2.52-2.63 (2 H, stack, CHC*H*HN and CH_2C*H*HN), 3.54-3.59 (2 H, stack, CHCH*H*N and CH_2CH*H*N), 3.96 (1H, d, *J* 2.6, C*H*OH), 4.58 (1H, s, C=CH*H*), 4.97 (1H, s, C=C*H*H), 7.31 (2H, d, *J* 8.1 Ar C*H*), 7.64 (2H, d, *J* 8.1, Ar C*H*)

δ_C: (125 MHz), 21.4 (*C*H_3), 22.7 (*C*H_3), 32.1 (*C*H_2CH_2NH), 40.5 (CH_2*C*H_2N), 43.4 (CH*C*H_2N), 46.6 (*C*HCH_2NH), 62.9 (*C*HOH), 112.2 (=*C*H_2), 127.5 (Ar *C*H), 129.6 (Ar *C*H), 133.2 (C_q), 143.4 (C_q), 143.7 (C_q)

m/z: (ES^+) 318.1 (100 %, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 318.1128. $C_{15}H_{23}NO_3S$ requires *M*, 318.1140]

Further elution (R_f = 0.15) afforded piperidine **60** as a white crystalline solid (4 mg, 4 %). Data *vide infra*.

Carbonyl-Ene Cyclisation

$MeAlCl_2$ (1 M soln. in hexanes, 0.34 mL, 0.34 mmol) was added to a solution of aldehyde **58** (100 mg, 0.34 mmol) in $CHCl_3$ (10 mL). The resulting mixture has heated to reflux for 16 h, before being quenched by the addition of water (10 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid, which was purified by flash column chromatography (R_f = 0.23, hexane:EtOAc, 2:1) to give piperidine **60** as a white

crystalline solid (6 mg, 6%), data *vide supra*. Further elution (R_f = 0.15) afforded piperidine **59** as a white crystalline solid (74 mg, 74%).

mp: 149-150 °C (from hexane:EtOAc)

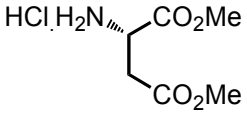
ν_{max}: (film)/cm^{-1} 3364 (OH), 2928 (CH) 2855 (CH), 1341 (SO_2), 1165 (SO_2)

δ_H: (300 MHz, $CDCl_3$) 1.58-1.68 (1H, m, CH*H*CH_2N), 1.71 (3 H, s, C*H*$_3$), 1.85 (1 H, br s, OH), 2.01-2.07 (1H, m, C*H*CH_2N), 2.17-2.27 (2 H, stack, C*H*C_2N and CHC*H*HN), 2.35 (1 H, dt, *J* 12.5 and 2.8, CH_2C*H*HN), 2.44 (3H, s, *CH*$_3$), 3.44 (1H, dt, *J* 10.3 and 4.5, C*H*OH), 3.73-3.77 (1 H, m, CHCH*H*N), 3.81-3.86 (1H, m, CH_2C*H*HN), 4.89 (1H, s, C=CH*H*), 5.01 (1H, s, C=C*H*H), 7.32 (2 H, d, *J* 8.1 Ar C*H*), 7.64 (2 H, d, *J* 8.1, Ar C*H*)

δ_C: (125 MHz), 20.5 (*C*H_3), 21.5 (*C*H_3), 32.4 (*C*H_2CH_2NH), 45.0 (CH_2*C*H_2N), 48.7 (CH*C*H_2N), 51.5 (*C*HCH_2NH), 69.2 (*C*HOH), 114.6 (=*C*H_2), 127.5 (Ar *C*H), 129.7 (Ar *C*H), 133.2 (C_q), 143.3 (C_q), 143.6 (C_q)

m/z: (ES^+) 318.1 (100 %, $[M+Na]^+$)

L-Aspartic acid dimethyl ester hydrochloride (110)



Acetyl chloride (85.9 mL, 1.20 mol) was added dropwise over 20 min *via* a dropping funnel to a stirred solution of MeOH (93 mL) cooled to 0 °C. L-aspartic acid (50.0 g, 0.376 mol) was added to the solution and the resulting mixture was warmed to rt and stirred overnight. The solvent was removed *in vacuo* to afford 76.5 g of the crude aspartic ester hydrochloride salt **110** as a colourless viscous oil, which was used without further purification.

$[\alpha]_D^{20}$: +11.4 (*c* 1.0 in H_2O) (lit.[106] $[\alpha]_D^{20}$: +10.2 (*c* 0.65 in H_2O))

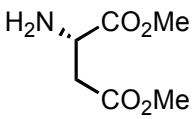
ν_{max}: (film)/cm^{-1} 3384 (NH), 3020 (CH), 2955 (CH), 1736 (C=O)

δ_H: (300 MHz, D_2O) 3.14 (2H, t, *J* 5.9, CH_2), 3.71 (3H, s, CH_3), 3.81 (3H, s, CH_3), 4.47 (1H, t, *J* 5.9 C*H*)

δ_C: (75 MHz, D_2O) 32.1 (*C*H_2), 47.7 (*C*H), 51.6 (*C*H_3), 52.5 (*C*H_3), 167.8 (*C*=O), 170.0 (*C*=O)

m/z: (ES^+) 162.0 (100%, $[M+H-Cl]^+$)

L-Aspartic acid dimethyl ester (87)



Acetyl chloride (17.1 mL 240 mmol) was added dropwise over 10 min to a solution of MeOH (93 mL) cooled to 0 °C. L-aspartic acid (10.0 g, 75.1 mmol) was added to the solution and the resulting mixture was slowly warmed to reflux for 3 h. The solvent was removed *in vacuo* to afford the hydrochloride salt as a colourless viscous oil, which was dissolved in water (50 mL) and cooled to 0 °C before a saturated aqueous solution of $NaHCO_3$ (50 mL) was added slowly to the stirred solution. The aqueous solution was extracted with EtOAc (5 x 100 ml) and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product **87** as a colourless oil (9.16 g, 76 %).

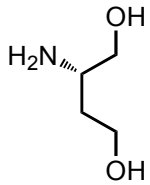
$[\alpha]_D^{20}$: +17.4 (*c* 1.0 in MeOH) (lit.[107] $[\alpha]_D^{14}$: +16.8)

ν_{max}: (film)/cm^{-1} 3384 (NH), 3020 (CH), 2955 (CH), 1736 (C=O)

δ_H: (300 MHz, $CDCl_3$) 1.72 (2H, s, NH_2), 2.66 (1H, dd *J* 16.5 and 7.3, C*H*H), 2.77 (1H, dd *J* 16.5 and 4.7, C*H*H), 3.65 (3H, s, CH_3), 3.69 (3H, s, CH_3), 3.78 (1H, dd, *J* 4.7 and 7.3, C*H*)

δ_C: (75 MHz, $CDCl_3$) 38.6 (*C*H_2), 51.0 (*C*H), 51.9 (*C*H_3), 52.2 (*C*H_3), 171.4 (*C*=O), 174.5 (*C*=O); m/z (ES^+) 159.0 (5%), 102.0 (100), 88.0 (32), 70.0 (45), 60.0 (28), 43.0 (40.0)

(2*S*)-Aminobutan-1,4-diol (85)



A solution of L-aspartic acid dimethyl ester **87** (4.77 g, 29.58 mmol) in THF (20 mL) was added dropwise over 20 min to a stirred slurry of $LiAlH_4$ (3.37 g, 88.75 mmol) in THF (25 mL) cooled to 0 °C. The solution was heated to reflux for 30 min before being cooled to room temperature and then to 0 °C. Propan-2-ol (35 mL) was then added as fast as effervescence would allow, followed by water (10 mL). The resulting mixture was stirred vigorously for 15 min before the solvents were removed *in vacuo* to give a white salt. The salt was added into a cellulose thimble and continuously extracted with a Soxhlet extractor using propan-2-ol overnight. The propan-2-ol filtrate was evaporated *in vacuo* to give the product **85** as a pale yellow oil (3.10 g, quant).

$[\alpha]_D^{20}$: -4.0 (*c* 1.0 in H_2O) (lit.[108] $[\alpha]_D^{22}$: -2.0 (*c* 2.0 in H_2O))

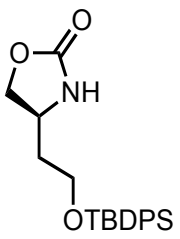
ν_{max}: (film)/cm^{-1} 3341 (OH, NH), 2940 (CH), 1054 (CO)

δ_H: (300 MHz, D_2O) 1.38-1.49 (1H, m, CHC*H*HCH$_2$), 1.57-1.68 (1H, m, CHCH*H*CH$_2$), 2.82-2.90 (1H, m, C*H*), 3.36 (1H, dd, *J* 11.2 and 6.9, C*H*HOH), 3.53 (1H, dd, *J* 11.2 and 4.6 and, CH$_2$CH*H*), 3.63 (2H, t, *J* 6.6, CHC*H*$_2$OH)

δ_C: (75 MHz, D_2O) 37.5 (CH*C*H$_2$CH$_2$), 51.6 (*C*H), 61.5 (*C*H$_2$OH), 68.8 (*C*H$_2$OH) **m/z:** (ES^+) 128.3 (60%, $[M+Na]^+$), 106.4 (100, $[M+H]^+$)

m/z: (ES^+) 128.2 (60%, $[M+Na]^+$), 106.4 (100, $[M+H]^+$)

(4*S*)-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-oxazolidin-2-one (88)



CDI (1.64 g, 10.09 mmol) was added to a solution of amino diol **85** (1.06 g, 10.09 mmol) in DMF (30 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3 h before warming to room temperature overnight. *tert*-butyldiphenylsilyl chloride (3.15 mL, 12.12 mmol) was added dropwise over 5 min to the solution at 0 °C. The resulting solution was stirred at room temperature 8 h. Water (30 mL) was added and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic fractions were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as an orange oil. The oil was purified by flash column chromatography (R_f = 0.34, hexane:EtOAc, 1:1) to afford a white crystalline solid **88** (3.06 g, 82%).

mp: 110-111 °C (from hexane:EtOAc) (lit.[109] 113-114.5 °C)

$[\alpha]_D^{22}$: -11.2 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3263 (NH), 3071 (Ar CH), 3050 (Ar CH), 2930 (CH), 2875 (CH), 1754 (C=O)

δ_H: (300 MHz, $CDCl_3$) 1.06 (9H, s, C(CH_3)$_3$, 1.70-1.89 (2H, m, CH$CH_2$$CH_2$), 3.73-3.77 (2H, m, CH_2OSi), 4.00-4.12 (2H, stack, C*H* and C*H*HOCO), 4.46-4.53 (1H, m, CH*H*OCO), 5.51 (1H, br s, N*H*), 7.39-7.46 (6H, m, Ar C*H*), 7.62-.7.65 (4H, m Ar C*H*)

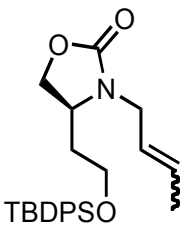
δ_C: (75 MHz, $CDCl_3$) 19.0 (Si*C*(CH_3)$_3$, 26.8 (SiC(*C*H_3)$_3$, 37.4 (CH*C*$H_2$$CH_2$), 51.3 (*C*H), 61.2 (O*C*H_2), 70.5, (O*C*H_2), 127.9 (Ar *C*H), 130.0 (C_q), 132.3 (Ar *C*H), 135.5 (Ar *C*H), 159.3 (*C*=O)

m/z: $(ES)^+$ 392.0 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 392.1655. $C_{21}H_{27}NNa\ O_3Si$ requires *M* 392.1658]

(4*S*)-3-But-2-enyl-4-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-oxazolidin-2-one (89)

(5:1 mixture of E:Z, only E reported)



n-BuLi (2.5 M soln. in hexanes, 4.29 mL, 10.72 mmol) was added dropwise over 5 min to a solution of oxazolidinone **88** (3.96 g, 10.72 mmol) in THF (50 mL) at 0 °C. The resulting solution was stirred for 15 min before crotyl bromide (1.12 mL, 10.72 mmol) was added dropwise over 1 min. The resulting solution was allowed to warm to room temperature overnight before being quenched with water (50 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with Et_2O (4 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a yellow oil, which was purified by flash column chromatography (R_f = 0.37, hexane:EtOAc, 4:1) to give the product **89** as a colourless oil (4.82 g, 94%).

$[\alpha]_D^{23}$: -5.6 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3070 (Ar CH), 3048 (Ar CH), 2930 (CH), 2857 (CH), 1756 (C=O)

δ_H: (300 MHz, $CDCl_3$) 1.05 (9H, s, C(CH_3)$_3$), 1.57-1.72 (4H, stack, =CHCH_3 and CHC*H*HCH_2) 1.97-2.07 (1H, m, CHCH*H*CH_2), 3.47 (1 H, dd, 1H, *J* 15.0 and 7.9, NC*H*H), 3.70 (2H, t, *J* 5.8, CH_2OSi), 3.87-3.96 (1H, m, CH*H*OCO), *4*.01-4.11 (2H, stack, C*H* and NC*H*H), 4.32 (1H, t, *J* 8.5, C*H*HOCO), 5.34-5.43 (1H, m, =CH), 5.59-5.70 (1H, m, =CH), 7.38-7.46 (6H, m, Ar C*H*), 7.62-7.65 (4H, m Ar C*H*)

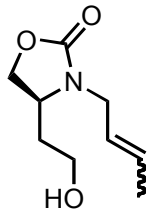
δ_C: (75 MHz, $CDCl_3$) 17.6 (=CCH_3), 19.0 SiC(CH_3)$_3$, 26.8 (SiC(CH_3)$_3$, 34.5 (CHCH_2CH_2), 44.0 (NCH_2), 53.1 (NCH), 60.1 (OCH_2Si), 67.9 (CH_2OCO), 124.7 (=CH), 127.8 (Ar *C*H), 129.9 (Ar *C*H), 130.1 (=*C*H), 132.9 (C_q) 135.4 (Ar *C*H), 137.0 (C_q), 158.0 (*C*=O)

m/z: $(ES)^+$ 446.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$446.2124. $C_{25}H_{33}NNaO_3Si$ requires *M* 466.2127]

(4*S*)-3-But-2-enyl-4-(2-hydroxyethyl)-oxazolidin-2-one (90)

(5:1 mixture of E:Z, only E reported)



TBAF (1 M soln. in THF, 8.47 mL, 8.47 mmol) was added dropwise over 5 min to a solution of **89** (3.58 g, 8.47 mmol) in THF (40 mL) cooled to 0 °C. The reaction was stirred at room temperature overnight before the solvent was removed in *vacuo*. Water (50 mL) was added and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a red oil, which was purified by flash column chromatography (R_f = 0.24, hexane:EtOAc, 1:4) to give the product **90** as a colourless oil (1.61 g, 95%).

$[\alpha]_D^{23}$: -14.0 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3417 (OH), 2921 (CH), 1732 (C=O)

δ_H: (300 MHz, $CDCl_3$) 1.62-1.68 (4H, stack, =CHC*H*$_3$ and CHC*H*HCH$_2$) 1.92-2.01 (1H, m, CHCH*H*CH$_2$), 2.41 (1H, br s, O*H*), 3.50 (1H, dd, *J* 15.3 and 7.8, NC*H*H), 3.65-3.74 (2H, m, C*H*$_2$OH), 3.83-3.92 (1H, m, CH*H*OCO), 3.99-4.09 (2H, stack, C*H* and NC*H*H), 4.39 (1H, t, *J* 8.5, C*H*HOCO), 5.30-5.38 (1H, m, =C*H*), 5.59-5.70 (1H, m, =C*H*)

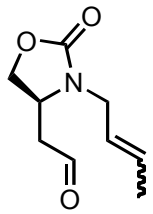
δ_C: (75 MHz, $CDCl_3$) 17.6 (=C*C*H$_3$), 34.2 (CH*C*H$_2$CH$_2$), 44.0 (N*C*H$_2$), 53.3 (N*C*H), 60.1 (*C*H$_2$OH), 68.0 (*C*H$_2$OCO), 127.8 (=*C*H), 130.1 (=*C*H), 158.3 (*C*=O)

m/z: $(ES)^+$ 208.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 208.0940. $C_9H_{15}NNaO_3$ requires *M* 208.0950]

(4*S*)-(3-But-2-enyl-2-oxo-oxazolidin-4-yl)-acetaldehyde (78)

(5:1 mixture of E:Z, only E reported)



DMSO (1.54 mL, 21.65 mmol) was added at a rapid rate to a solution of oxalyl chloride (0.93 mL, 10.39 mmol) in CH_2Cl_2 (50 mL) at -78 °C. The resulting mixture was stirred for 10 min before a solution of the alcohol **90** (1.60 g, 8.66 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 20 min. After 30 min Et_3N (6.09 mL, 43.30 mmol) was added dropwise over 2 min and the resulting solution was stirred for a further 3 h at -78 °C before being allowed to warm to room temperature. Water (50 mL) was added and the aqueous phase was further extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with HCl (1 M, 100 mL), water (100 mL) and finally with brine (100 mL) before being dried over $MgSO_4$ and evaporated *in vacuo* to give the crude aldehyde as a pale yellow oil, which was purified by flash column chromatography (R_f = 0.28, hexane:EtOAc, 1:3) to give the aldehyde **78** as a colourless oil (1.57 g, 95%).

$[\alpha]_D^{23}$: +24.8 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3011 (=CH), 2918 (CH), 2856 (CH), 1748 (2 x C=O)

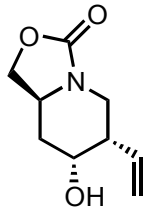
δ_H: (400 MHz, $CDCl_3$) 1.65 (3H, d, *J* 6.4, =CHC*H*$_3$), 2.62 (1H, dd, *J* 18.6 and 9.1, CHC*H*HCHO) 3.02 (1H, dd, *J* 18.6 and 3.9, CHCH*H*CHO), 3.48 (1H, dd, *J* 15.4 and 7.6, NC*H*H), 3.84 (1H, dd *J* 8.8 and 6.3, C*H*HOCO), 3.94-3.99 (1H, m, NCH*H*), 4.10-4.19 (1H, m, NC*H*), 4.50 (1H, t, *J* 8.8, CH*H*OCO), 5.28-5.38 (1H, m, CH_2C*H*=), 5.63-5.72 (1H, m, =C*H*CH_3), 9.73 (1H, s, C*H*O)

δ_C: (75 MHz, $CDCl_3$) 17.6 (=C*C*H_3), 44.4 (N*C*H_2), 46.8 (CH*C*H_2CHO), 49.8 (N*C*H), 67.7 (*C*H_2OCO), 124.6 (CH_2*C*H=), 130.5 (=*C*HCH_3), 157.6 (N*C*OO), 198.6 (*C*HO);

m/z: $(ES)^+$ 238.0 (100%, $[M+MeOH+Na]^+$)

HRMS: [Found: $(M+MeOH+Na)^+$ 238.1052. $C_{10}H_{17}NNaO_4$ requires *M* 238.1055]

(6*S*,7*R*,8a*S*)-7-hydroxy-6-vinyltetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (79)



$MeAlCl_2$ (1 M soln. in hexanes, 1.14 mL, 1.14 mmol) was added to a solution of aldehyde **78** (106 mg, 0.57 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 16 h, before being quenched by the addition of water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a yellow oil, which was purified by flash column chromatography (R_f = 0.30, EtOAc) to give piperidine **79** as a colourless oil (9 mg, 16%).

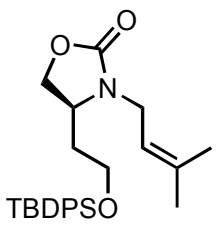
ν_{max}: (film)/cm^{-1} 3362 (OH), 2928 (CH) 2855 (CH), 1729 (C=O), 1341 (SO_2), 1165 (SO_2)

δ_H: (400 MHz, $CDCl_3$) 1.54 (1H, ddd, *J* 13.7, 11.7 and 2.3, NCHC*H*H), 2.05 (1H, dt, *J* 13.7 and 3.6, NCHCH*H*), 2.34-2.38 (1H, m, NCH_2C*H*), 3.19 (1H, t, *J*, 12.5, NC*H*H), 3.74 (1H, dd, *J* 5.1 and 2.5, NCH*H*), 3.88 (1H, dd, *J* 8.4 and 5.1, C*H*HO), 4.04-4.14 (2H, stack, C*H*OH and C*H*NH), 4.41 (1H, t, *J* 8.4, CH*H*O)

m/z: (EI^+) 183.1 (50 %, $[M]^+$), 116.0 (100), 86.0 (95)

HRMS: [Found: $(M)^+$ 183.0893. $C_9H_{13}NO_3$ requires *M* 183.0895]

(4*S*)-[2-(tert-Butyldiphenylsilanyloxy)etyl]-3-(3-methylbut-2-enyl)oxazolidin-2-one (93)



n-BuLi (1.37 M soln. in hexanes, 15.56 mL, 21.32 mmol) was added dropwise over 10 min to a solution of oxazolidinone **88** (7.16 g, 19.38 mmol) in THF (50 mL) at 0 °C. The resulting solution was stirred for 15 min before 1-bromo-3-methylbut-2-ene (1.32 mL, 11.38 mmol) was added dropwise over 1 min. The resulting solution was allowed to warm to room temperature overnight before being quenched with water (50 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with Et_2O (4 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a yellow oil, which was purified by flash column chromatography (R_f = 0.33, 4:1, hexane:EtOAc) to give the product **93** as a colourless oil (8.46 g, 98%).

$[\alpha]_D^{22}$: +3.6 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3071 (Ar CH), 3049 (Ar CH), 2931 (CH), 2878 CH) 1756 (C=O);

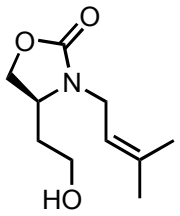
δ_H: (300 MHz, $CDCl_3$) 1.05 (9H, s, C(C*H*$_3$)$_3$, 1.57-1.72 (7H, stack, =C(C*H*$_3$)$_2$ and CHC*H*HCH$_2$) 1.97-2.07 (1H, m, CHCH*H*CH$_2$), 3.61 (1H, dd, *J* 15.4 and 8.3, NC*H*H), 3.70 (2H, t, *J* 5.8 C*H*$_2$OSi), 3.85-3.93 (1H, m C*H*HOCO) 4.00-4.08 (2H, stack, C*H* and NCH*H*), 4.31 (1H, t, *J* 8.5, C*H*HOCO), 5.51 (1H, m, =C*H*), 7.37-7.46 (6H, m, Ar C*H*), 7.61-7.64 (4H, m Ar C*H*)

δ_C: (75 MHz, $CDCl_3$) 17.9 (=C*C*H$_3$), 19.0 (Si*C*(CH$_3$)$_3$, 25.7 (=C*C*H$_3$), 26.7 (SiC(*C*H$_3$)$_3$, 34.6 (CH*C*H$_2$CH$_2$), 39.8 (N*C*H$_2$), 51.2 (N*C*H), 60.2 (O*C*H$_2$Si), 67.9 (*C*H$_2$OCO), 118.3 (=*C*H), 127.8 (Ar *C*H), 129.9 (Ar *C*H), 132.9 (*C*$_q$) 135.4 (Ar *C*H), 137.0 (*C*$_q$), 158.1 (*C*=O)

m/z: $(ES)^+$ 460.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 460.2297. $C_{26}H_{35}NNaO_3Si$ requires *M* 460.2284]

(4*S*)-(2-Hydroxy-ethyl)-3-(3-methylbut-2-enyl)oxazolidin-2-one (94)



TBAF Deprotection

TBAF (1 M soln. in THF, 5.81 mL, 5.81 mmol) was added dropwise over 2 min to a solution of **93** (2.54 g, 5.81 mmol) in THF (60 mL) cooled to 0 °C. The reaction was allowed to warm to room temperature and stirred overnight before the solvent was removed *in vacuo*. Water (50 mL) was added and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a red oil, which was purified by flash column chromatography (R_f = 0.29, hexane:EtOAc, 1:4) to give the product **94** as a colourless oil (1.08 g, 94%).

NaH Cyclisation

NaH (60 % dispersed in mineral oil, 8 mg, 0.39 mmol) was added to a solution of diol **103** (48 mg, 0.20 mmol) in THF (4 mL) cooled to 0 °C. The solution was slowly warmed to reflux and stirred for a further 2 h. The solution was allowed to cool to room temperature before being quenched by the addition of water (4 mL). The solvent was removed *in vacuo* and the aqueous phase extracted with EtOAc (4 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a yellow oil, which was purified by flash column chromatography (R_f = 0.29, hexane:EtOAc, 1:4) to give the product as a colourless oil **94** (28 mg, 70%).

$NaBH_4$ Reduction and Cyclisation

Powdered $NaBH_4$ (9.8 g, 0.318 mol) was added in portions over 30 min to a stirred solution of ester **104** (47.9 g, 0.159 mol) in THF:EtOH (3:1, 400 mL) cooled to 0 °C, which resulted in gas evolution. The resulting solution was allowed to warm to room temperature and stirred for 2 h before being warmed to reflux for a further 4 h. The solution was allowed to cool to room temperature before being cooled to 0 °C and quenched by the addition of saturated aqueous solution of NH_4Cl (200 mL), which generated a white precipitate. The reaction mixture was filtered and the filter cake washed with EtOH (3 x 50 mL). The combined filtrates were concentrated to 1/5 in volume *in vacuo* and then diluted with EtOAc (300 mL) and water (300 mL). The organic phase was separated and the aqueous phase was further extracted with EtOAc (4 x 300 mL). The combined organic phases were washed with water (400 mL) and brine (400 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to afford the product **94** as a colourless oil (28.4 g, 90%).

$[\alpha]_D^{22}$: -23.2 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3415 (OH), 2929 (CH), 1729 (C=O), 1026 (C-O)

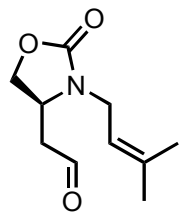
δ_H: (300 MHz, $CDCl_3$) 1.60-1.73 (7H, stack, =C(CH_3)$_2$ and CHC*H*HCH_2) 1.91-2.02 (1H, m, CHCH*H*CH_2), 2.63 (1H, br s, O*H*), 3.60-3.76 (3H, stack, C*H*HOH, NC*H*H and NC*H*), 3.82-3.91 (1H, m, CHC*H*HOH), 3.97-4.01 (1H, m, NC*H*H), 4.07 (1H, m, C*H*HOCO), 4.39 (1H, t, *J* 8.8 CH*H*OCO) 5.08-5.13 (1H, m, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 17.9 (=CCH_3), 25.6 =CCH_3), 34.4 CHCH_2CH_2), 39.8 (NCH_2), 53.4 (N*C*H), 58.6 (*C*H_2OH), 68.0 (*C*H_2OCO), 118.1 (=*C*H), 137.2 (C_q), 158.5 (C=O)

m/z: $(ES)^+$ 222.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 222.1102. $C_{10}H_{17}NNaO_3$ requires *M* 222.1106]

(4*S*)-(2-Oxoethyl)-*N*-(3-methylbut-2-enyl)-2-oxazolidinone (95)



A solution of DMSO (30.5 mL, 0.429 mol) in CH_2Cl_2 (43 mL) was added dropwise over 20 min via a dropping funnel to a solution of oxalyl chloride (18.7 mL, 0.214 mol) in CH_2Cl_2 (240 mL) cooled to -78 °C resulting in considerable gas evolution. The resulting mixture was stirred for a further 5 min before a solution of alcohol **94** (28.4 g, 0.143 mol) in CH_2Cl_2 (240 mL) was added dropwise over 30 min via a dropping funnel equipped with a cold jacket cooled to -78 °C. The dropping funnel was washed with extra portions of CH_2Cl_2 (3 x 5 mL) to complete the transfer. The solution was stirred for a further 15 min before Et_3N (100 mL, 0.715 mol) was added dropwise over 15 min via a dropping funnel and the resulting solution was stirred for a further 20 min at -78 °C before being allowed to warm 0 °C, which resulted in gas evolution. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (250 mL). The organic phase was separated and the aqueous phase further extracted with CH_2Cl_2 (3 x 250 mL). The combined organic phases were washed with water (250 mL) and brine (250 mL) before being dried over $MgSO_4$ and in concentrated *in vacuo* to give the aldehyde **95** as a colourless oil (26.8 g, 95%).

R_f : 0.49 (hexane:EtOAc, 1:3)

$[\alpha]_D^{22}$:-25.2 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3019 (=CH), 2972 (CH), 2927 (CH), 1742 (C=O)

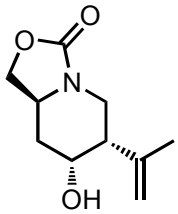
δ_H: (300 MHz, $CDCl_3$) 1.61 (3H, s, CH_3), 1.66 (3H, s, CH_3), 2.65 (1H, dd, *J* 18.6 and 9.1, C*H*HCHO), 2.98 (1H, dd, *J* 18.6 and 3.8, CH*H*CHO), 3.58 (1H, dd, *J* 15.5 and 7.7, NC*H*H), 3.82 (1H, dd, *J* 8.8 and 6.4, C*H*HO), 3.93 (1H, dd, *J* 15.5 and 6.3, NCH*H*), 4.06-4.16 (1H, m, NC*H*), 4.47 (1H, t, *J* 8.8, CH*H*O), 5.02-5.08 (1H, m, =C*H*), 9.71 (1H, s, C*H*O)

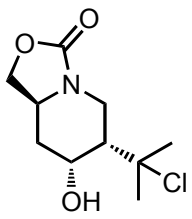
δ_C: (75 MHz, $CDCl_3$) 17.7 (*C*H_3), 25.5 (*C*H_3), 40.0 (N*C*H_2), 46.6 (C*H*$_2$CHO), 49.7 (N*C*H), 67.4 (*C*H_2OCO), 117.9 (=*C*H), 137.2 (C_q), 157.5 (O*C*=O), 198.7 (H*C*O);

m/z: $(ES)^+$ 252.2 (100%, $[M+MeOH+Na]^+$), 220.1 (40, $[M+Na]^+$).

HRMS: [Found: $(M+Na)^+$ 220.0945. $C_{10}H_{15}NNaO_3$ requires *M* 220.0950]

(6*S*, 7*R*, 8a*S*)-7-Hydroxy-6-(prop-1-en-2-yl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (96) and **(6*S*, 7*R*, 8a*S*)-6-(2-Chloropropan-2-yl)-7-hydroxytetrahydro-1*H*-oxazolo [3,4-*a*] pyridin-3(5*H*)-one (97)**





Concentrated HCl cyclisation

Concentrated HCl (37 %, 0.13 mL, 1.52 mmol) was added to a solution of aldehyde **95** (100 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) at -78 ^oC. The resulting mixture was stirred at -78 ^oC for 16 h, before being quenched by the addition of water (10 mL). The organic layer was separated was the aqueous phase further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a white crystalline solid, which was purified by flash column chromatography (R_f = 0.28, 1:3, hexane:EtOAc) to afford piperidines *cis*-alkene **96** and *cis*-chloride **97** as an inseparable mixture in a 2:1 ratio as a white crystalline solid (70 mg, 76 %).

ν_{max}: (film)/cm^{-1} 3445 (OH), 3028 (=CH), 2972 (CH), 2913 (CH), 1735 (C=O), 760 (C-Cl)

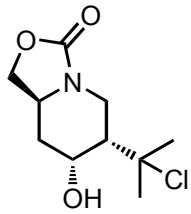
δ_H: (300 MHz, $CDCl_3$) 1.41-1.51 (1H from *cis-Cl*, m, C*H*HCHOH), 1.56 (1H from *cis*, t, *J* 12.5, C*H*HCHOH), 1.67 (3H from *cis-Cl*, s, C*H*$_3$), 1.69 (3H from *cis-Cl*, s, C*H*$_3$), 1.72-1.75 (1H from *cis-Cl,* m, NCH$_2$C*H*), 1.78 (3H from *cis*, s, C*H*$_3$), 1.92 (1H from *cis,* s, O*H*), 2.00-

2.05 (1H from *cis-Cl,* m, C*H*HCHOH), 2.11 (1H from *cis,* dt, *J* 12.5 and 3.7, C*H*HCHOH), 2.18 (1H from *cis*, dd, 12.4 and 4.5, NCH_2CH), 2.92 (1H from *cis-Cl*, br s, O*H*), 3.25 (1H from *cis*, t, *J* 12.6, NC*H*H), 3.40-3.42 (1H from *cis*-Cl, m, NC*H*H), 3.67 (1H from *cis*, dd, *J* 12.6 and 4.7, NCH*H*), 3.85-3.95 (1H from *cis* and 2H from *cis-Cl*, stack, C*H*HO from *cis*, C*H*HO from *cis-Cl* and NC*H*H from *cis-Cl*), 4.03-4.20 (2H from *cis* and 1H from *cis-Cl*, stack, NC*H* and C*H*OH from *cis,* NC*H cis-Cl*), 4.37-4.43 (1H from *cis* and 1H from *cis-Cl*, stack, CH*H*O from both), 4.42 (1H from *cis-Cl*, t, *J* 8.2 CH*H*O), 4.45 (1H from *cis-Cl*, br s, C*H*OH), 4.75 (1H from *cis*, s, =C*H*H), 5.02 (1H from *cis*, s, =CH*H*)

C: (75 MHz, $CDCl_3$) 22.8 (*C*H_3 from *cis*), 31.6 (*C*H_3 from *cis-Cl*), 31.9 (*C*H_3 from *cis-Cl*), 36.0 (*C*H_2CHOH from *cis*), 37.6 (NCH*C*H_2 from *cis-Cl*), 37.9 (N*C*H_2 from *cis-Cl*), 38.6 (N*C*H_2 from *cis*), 45.8 (NCH_2CH from *cis*), 48.7 (N*C*H from *cis-Cl*), 48.8 (N*C*H from *cis*), 50.1 (NCH_2CH from *cis-Cl*), 64.1 (C*H*OH from *cis*), 65.0 (C*H*OH from *cis-Cl*), 67.4 (*C*H_2OCO from *cis*), 67.5 (*C*H_2OCO from *cis-Cl*), 71.3 (*C*Cl), 112.5 (=*C*H_2), 143.1 (*C*=CH_2), 157.1 (O*C*O)

m/z: $(ES)^+$ 258.1 (12%, $[M(^{37}Cl)+Na]^+$ for *cis-Cl*), 256.1 (100%, $[M(^{35}Cl)+Na]^+$ for *cis-Cl*), 256.1 (50%, $[M+Na]^+$ for *cis*)

(6*S*, 7*R*, 8a*S*)-6-(2-Chloropropan-2-yl)-7-hydroxytetrahydro-1*H*-oxazolo[3,4-*a*] pyridin-3(5*H*)-one (97)



Anhydrous HCl cyclisation

Anhydrous HCl gas was bubbled through a gas dispersion tube and into a solution of aldehyde **95** (26.8 g, 0.136 mol) in CH_2Cl_2 (500 mL) cooled to -78 °C, before passing through a gas scrubber containing water, for 10 min. The solution was

stirred at -78 °C for 2 h before being allowed to warm slowly to 0 °C. The reaction was quenched by the addition of water (500 mL) and the organic layer was separated. The aqueous phase was further extracted with EtOAc (3 x 500 mL) and the combined organic phases were washed with brine (500 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product that was recrystallised from hexane:EtOAc, filtered and the filter cake washed with portions of ice cold EtOAc (3 x 20 mL) to give the product as a white crystalline solid (31.1 g, 98%).

R_f : 0.29 (hexane:EtOAc, 1:3)

$[\alpha]_D^{20}$: -24.4 (*c* 1.0 in $CHCl_3$)

mp: 124-125 °C (from hexane:EtOAc)

μ: (Found: C, 51.71; H, 7.09; N, 5.87. $C_{10}H_{16}ClNO_3$ requires C, 51.40; H, 6.90; N, 5.99%)

ν_{max}: (film)/cm^{-1} 3431 (OH), 2974 (CH), 1748 (C=O), 1088 (C-O), 758 (C-Cl)

δ_H: (300 MHz, $CDCl_3$) 1.36-1.53 (1 H, m, NCHC*H*HCH), 1.63-1.74 (7 H, stack, $(CH_3)_2$ and NCH_2CH), 2.03 (1 H, dt, *J* 13.4 and 3.9, NCHC*H*HCH), 2.72 (1 H, br s, O*H*), 3.40 (1 H, t, *J* 12.5, NC*H*H), 3.80-3.99 (2 H, stack, C*H*HO and NC*H*H), 4.07-4.22 (1 H, m, NC*H*),), 4.40 (1 H, t, *J* 8.2, C*H*HO), 4.56 (1H, br s, C*H*OH)

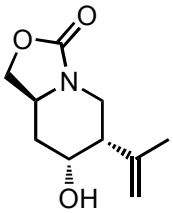
δ_C: (75 MHz, $CDCl_3$) 31.8 (CH_3), 32.1 (CH_3), 37.8 (NCH_2), 38.1 ($NCHCH_2CH$), 48.9 (NCH), 50.3 (NCH_2CH), 65.2 (CHOH), 67.72 (CH_2O), 71.5 (CCl), 157.4 (C=O)

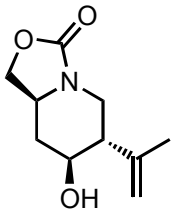
m/z: $(ES)^+$ 258.0 (10%, $[M(^{37}Cl)+Na]^+$), 256.0 (100, $[M(^{35}Cl)+Na]^+$), 220.1 (40)

HRMS: [Found: $(M+Na)^+$ 256.0719 $C_{10}H_{16}ClNNaO_3$ requires *M* 256.0716]

X-ray: See *Appendix*

(6*S*, 7*R*, 8a*S*)-7-Hydroxy-6-(prop-1-en-2-yl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (96) and **(6*S*, 7*S*, 8a*S*)-7-Hydroxy-6-(prop-1-en-2-yl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (98)**





$MeAlCl_2$ Cyclisation

$MeAlCl_2$ (1 M in hexanes, 1.12 mL, 1.12 mmol) was added dropwise over 30 s to a solution of aldehyde **95** (110 mg, 0.56 mmol) in CH_2Cl_2 (20 mL) cooled to -78 °C. The reaction was stirred for a further 16 h at -78 °C before being quenched with water (20 mL). After warming to room temperature the organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a white crystalline solid, which was purified by flash column chromatography (R_f = 0.28, hexane:EtOAc, 1:3) to afford *cis* piperidine **96** as a white crystalline solid (94 mg, 85%), data *vide infra*. Further elution (R_f = 0.14) afforded *trans* piperidine **98** as a white crystalline solid (15 mg, 14%).

$[\alpha]_D^{22}$: +4.8 (*c* 1.0 in $CHCl_3$)

mp: 112-113 °C (from hexane:EtOAc)

µ: (Found: C, 60.96; H, 7.77; N, 7.33. $C_{10}H_{15}NO_3$ requires C, 60.90; H, 7.67; N, 7.10%)

ν_{max}: (film)/cm^{-1} 3431 (OH), 3018 (=CH), 2974 (CH), 1748 (C=O), 1095 (C-O)

δ_H: (300 MHz, $CDCl_3$) 1.38 (1H, q, *J* 11.7, C*H*HCHOH), 1.73 (3H, s, CH_3), 2.03-2.19 (2H, stack, CH*H*CHOH and NCH_2CH), 2.74 (1H, dd, *J* 13.6 and 11.7, NC*H*H), 3.67 (1H, td, *J* 10.7 and 4.2, C*H*OH), 3.73-3.80 (1H, m, NC*H*), 3.84 (1H, dd, *J* 13.6 and 4.9, NCH*H*), 3.93 (1H,

dd, *J* 8.6 and 5.1, C*H*HO), 4.37 (1H, t, *J* 8.6, CH*H*O), 4.91 (1H, s, =C*H*H), 5.01 (1H, s, =CH*H*)

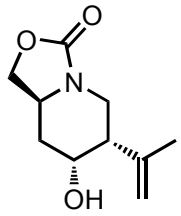
δ_C: (75 MHz, $CDCl_3$) 20.3 (*C*H_3), 37.8 (*C*H_2COH), 43.4 (N*C*H_2), 51.4 (NCH_2*C*H), 53.0 (N*C*H), 67.0 (*C*H_2O), 68.2 (*C*HOH), 115.0 (=*C*H_2), 141.9 (*C*=CH_2), 156.8 (*C*=O)

m/z: $(ES)^+$ 220.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 220.0955 $C_{10}H_{15}NNaO_3$ requires *M* 220.0950]

X-ray: See *Appendix*

(6*S*, 7*R*, 8a*S*)-7-Hydroxy-6-(prop-1-en-2-yl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (96)



HCl Elimination

Chloride **97** (15.01 g, 64.3 mmol) was added to a stirred solution of NaOAc (5.28 g, 64.3 mmol) in AcOH (215 mL). The resulting solution was heated at reflux for 10 min, which resulted in a white precipitate. The reaction mixture was poured into water (200 mL) and the aqueous phase extracted with EtOAc (4 x 200 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (200 mL), water (200 mL) and brine (200 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as an orange solid. The crude product was purified by flash column chromatography (R_f = 0.28, hexane:EtOAc, 1:3) to afford cis piperidine **96** as a white crystalline solid (10.29 g, 85%).

$[\alpha]_D^{22}$: -85.2 (*c* 1.0 in $CHCl_3$)

mp: 121-122 °C (from hexane:EtOAc)

µ: (Found: C, 60.91; H, 7.64; N, 7.20. $C_{10}H_{15}NO_3$ requires C, 60.90; H, 7.67; N, 7.10%)

ν_{max}: (film)/cm^{-1} 3445 (OH), 3082 (=CH), 2972 (CH), 1730 (C=O), 1098 (C-O)

δ_H: (300 MHz, $CDCl_3$) 1.52-1.68 (1H, m, NCHC*H*H), 1.79 (3H, s, CH_3), 1.84 (1H, br s, O*H*), 2.12 (1H, dt *J* 13.2 and 3.7, NCHC*H*H), 2.20 (1H, dd, *J* 12.5 and 4.8, NCH_2CH), 3.26 (1H, t, *J* 12.5, NC*H*H), 3.68 (1H, dd, *J* 12.5 and 4.8, NC*H*H), 3.90 (1H, dd, *J* 8.5 and 5.5, C*H*HO), 4.03-4.14 (2H, stack, NC*H* and C*H*OH), 4.41 (1H, t, *J* 8.5, C*H*HO), 4.75 (1H, s, =C*H*H), 5.02 (1H, s, =C*H*H)

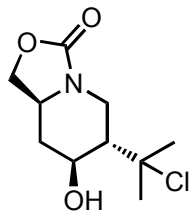
δ_C: (75 MHz, $CDCl_3$) 22.6 (CH_3), 35.9 (CH_2COH), 48.6 (NCH_2), 45.8 (NCH_2CH), 58.8 (NCH), 64.3 (CHOH), 67.6 (CH_2O), 112.9 ($=CH_2$), 143.7 ($C=CH_2$), 157.8 (C=O)

m/z: $(ES)^+$ 252.1 (10%, $[M+MeOH+Na]^+$), 220.1 (100, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 220.0947. $C_{10}H_{15}NNaO_3$ requires *M* 220.0950]

X-ray: *See Appendix*

(6*S*, 7*S*, 8a*S*)-6-(2-Chloropropan-2-yl)-7-hydroxytetrahydro-1*H*-oxazolo[3,4-*a*] pyridin-3(5*H*)-one (99)



Anhydrous HCl gas was bubbled through a solution of piperidine **98** (132 mg, 0.67 mmol) in CH_2Cl_2 (7 mL) cooled to -78 °C for 15 min. The reaction was stirred at -78 °C for 4 h before being allowed to warm to room temperature and stirred for a further 4 h. The reaction was quenched by the addition of water (10 mL) and the organic layer was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the product **99** as a white crystalline solid (156 mg, quant.).

R_f : 0.26 (hexane:EtOAc, 3:1)

[α]$_D^{20}$: +22.4 (*c* 1.0 in $CHCl_3$)

mp: 91-92 °C (from hexane:EtOAc)

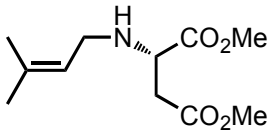
δ_H: (300 MHz, $CDCl_3$) 1.52 (1 H, q, *J* 12.0, NCHC*H*HCH), 1.70 (3H, s, C*H*$_3$), 1.82-1.75 (4 H, stack, C*H*$_3$ and NCH_2CH), 2.13 (1 H, dt, *J* 12.0 and 3.8, NCHC*H*HCH) 2.65 (1 H, br s, O*H*), 2.75 (1 H, dd, *J* 13.6 and 11.5, NC*H*H), 3.71-3.83 (1 H, m, NC*H*), 3.90-4.03 (2 H, stack, C*H*HO and C*H*OH), 4.10 (1 H, dd, *J* 13.6 and 5.0, NC*H*H), 4.39 (1 H, t, *J* 8.3, C*H*HO)

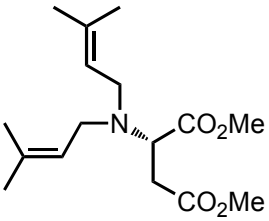
δ_C: (75 MHz, $CDCl_3$) 32.2 (*C*H_3), 33.1 (*C*H_3), 39.8 (N*C*H_2), 41.5 (NCH*C*H_2CH), 52.2 (N*C*H), 52.8 (NCH_2*C*H), 67.1 (*C*H_2O), 70.2(*C*HOH), 71.9 (*C*Cl), 157.1 (*C*=O)

m/z: $(ES)^+$ 256.1 (100, $[M(^{35}Cl)+Na]^+$), 220.1 (37)

HRMS: [Found: $(M+Na)^+$ 256.0721. $C_{10}H_{16}ClNNaO_3$ requires *M* 256.0716]

(*S*)-*N*-(3-methylbut-2-enyl)aspartic acid dimethyl ester (105) and **(*S*)-bis(3-methylbut-2-en-1-yl)aspartic acid dimethyl ester (111)**





LiOH (144 mg, 6.03 mmol) was added to a solution of dimethyl L-asparticester hydrochloride **110** (567 mg, 2.87 mmol) in DMF (15 mL) containing activated 4 Å MS (1.6 g) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for a further 30 min. Prenyl bromide (0.33 mL, 2.87 mmol) was added and the resulting mixture was stirred for a further 5 h before being quenched with water (30 mL). The reaction was filtered and washed with Et_2O (3 x 5 mL). The organic layer was separated and the aqueous phase was further extracted with Et_2O (3 x 15 mL). The combined organic phases

were washed with brine (30 mL) and dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a pale yellow oil, which was purified by flash column chromatography (R_f = 0.65, hexane:EtOAc, 4:1) to give the tertiary amine **111** as a colourless oil (295 mg, 34%).

$[\alpha]_D^{25}$: -74.4 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 2951 (C-H), 2915 (C-H), 2855 C-H), 1735 (C=O), 1436, 1164 (C-O)

δ_H: (300 MHz, $CDCl_3$) 1.36 (6H, s, =C(CH_3)), 1.52 (6H, s, =C(CH_3)), 2.54 (1H, dd, *J* 12.0 and 6.8, C*H*HCO_2), 2.83 (1H, dd, *J* 12.0 and 6.8, C*H*HCO_2), 3.15 (4H, d, *J* 6.0, CH_2N), 3.60 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.98 (1H, t, *J* 6.8, NC*H*), 5.10-5.20 (2H, m, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 20.3 (=C(*C*H_3)), 28.2 (=C(*C*H_3)), 36.7 (*C*H_2CO_2), 45.2 (=C*C*H_2), 53.6 (O*C*H_3), 53.9 (O*C*H_3), 60.6 (NH*C*H), 124.5 (=*C*H), 137.5 (=*C*$(CH_3)_2$), 171.4 (*C*=O), 174.6 (C=O)

m/z: $(ES)^+$ 320.1 (100%, $[M+Na]^+$)

HRMS: [HRMS Found: $(M+Na)^+$ 320.1844. $C_{16}H_{27}NNaO_4$ requires *M* 320.1838]

Further elution (R_f = 0.20) gave the secondary amine **105** as a colourless oil (105 mg, 16%).

$[\alpha]_D^{24}$: +55.6 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3560 (NH), 2983 (CH), 2956 (CH), 1740 (C=O)

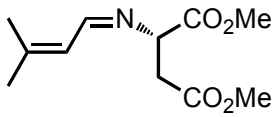
δ_H: (300 MHz, $CDCl_3$) 1.56 (3H, s, =C(CH_3)), 1.64 (3H, s, =C(CH_3)), 2.01 (1H, br s, NH), 2.63 (2H, t, *J* 6.5 CH_2N), 3.07 (1H, dd, *J* 12.8 and 7.0, C*H*HCO_2), 3.19 (1H, dd, *J* 12.8 and 7.0, C*H*HCO_2), 3.57 (1H, t, *J* 7.0, NHC*H*), 3.61 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 5.10-5.16 (1H, m, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 17.6 (=C(CH3)), 25.5 (=C(CH3)), 37.6 (CH2COO), 45.2 (=CCH2), 51.6 (OCH3), 51.9 (OCH3), 56.7 (NHCH), 121.9 (=CH), 135.1 (=C(CH3)2), 171.1 (*C*=O), 174.0 (*C*=O)

m/z: $(ES)^+$ 252.1 (100%, $[M+Na]^+$)

HRMS: [HRMS Found: $(M+Na)^+$ 252.1205. $C_{11}H_{19}NNaO_4$ requires *M* 252.1212]

(*S*)-*N*-3-Methyl-but-2-enylidene-aspartic acid dimethyl ester (113)



3-methyl-but-2-enal (13.1 mL, 0.136 mol) was dropwise over 5 min to a solution of L-aspartic acid dimethyl ester **87** (20.0 g, 0.124 mol) in MeOH (400 mL). The resulting solution was stirred at room temperature overnight. The solvent was removed *in vacuo* to give the imine product **113** as a red oil (98% yield).

$[\alpha]_D^{20}$: -8.8 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 2955 (CH), 1740 (C=O), 1676 (C=N), 1438

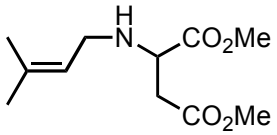
δ_H: (300 MHz, $CDCl_3$) 1.87 (3H, s, CC*H*$_3$), 1.93 (3H, s, CC*H*$_3$), 2.76 (1H, dd, *J* 16.7 and 7.7, CHC*H*H), 3.05 (1H, dd, *J* 16.7 and 5.9, CHCH*H*), 3.65 (3H, s, OC*H*$_3$), 3.72 (3H, s, OC*H*$_3$), 4.27 (1H, dd, *J* 7.7 and 5.9, C*H*CH_2), 6.00 (1H, d, *J* 9.5, $(CH_3)_2$C=C*H*), 8.25 (1H, d, *J* 9.5, N=C*H*)

δ_C: (75 MHz, $CDCl_3$) 18.8 (C*C*H_3), 26.6 (C*C*H_3), 37.5 (CH*C*H_2), 51.7 (O*C*H_3), 52.4 (O*C*H_3), 68.9 (*C*HCH_2), 125.0 ($(CH_3)_2$C=*C*H), 149.7 ($(CH_3)_2$*C*=CH), 163.5 (N=*C*H), 171.2 (*C*=O), 171.3 (*C*=O)

m/z: $(ES)^+$ 250.1 (100%, $[M+Na]^+$), 228.1 (12, $[M+H]^+$)

HRMS: [Found: $(M+Na)^+$ 250.1045. $C_{11}H_{17}NNaO_4$ requires *M* 250.1055]

***N*-(3-methylbut-2-enyl)aspartic acid dimethyl ester (*rac*-105)**



Imine Reduction

Imine **113** (23.6 g, 0.104 mol) in $C_2H_4Cl_2$ (500 mL) was added via cannula to a solution $NaBH(OAc)_3$ (44.1 g, 0.208 mol) in $C_2H_4Cl_2$ (500 mL) cooled to 0 °C. The resulting solution was stirred for a further 1 h at 0 °C before being allowed to warm to room temperature and stirred for 3 days. The reaction was cooled to 0 °C before being quenched with a saturated aqueous solution of $NaHCO_3$ (500 mL). The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 500 mL). The combined organic phases were washed with brine (500 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to afford the crude product as a yellow oil, which was purified by flash column chromatography (R_f = 0.20, 4:1, hexane:EtOAc) to afford the product **(*rac*)-105** as a colourless oil (70%).

Conjugate Addition

Et_3N (191 mL, 1.37 mol) was added over 10 min to a stirred solution prenyl amine hydrochloride **137** (33.2 g, 0.273 mol) cooled to 0 °C. The resulting solution allowed to warm to room temperature before dimethyl maleate (34.1 mL, 0.273 mol) was added and the reaction mixture was heated to 60 °C for 2 h. The reaction was allowed to cool to room temperature and quenched with water (500 mL). The aqueous phase was extracted with EtOAc (3 x 500 mL). The combined organic phases were washed with water (500 mL), brine (500 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to afford the product **(*rac*)-105** as a colourless oil (56.3 g, 90%).

ν_{max}**:** (film)/cm^{-1} 3560 (NH), 2983 (CH), 2956 (CH), 1740 (C=O)

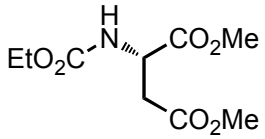
δ_H**:** (300 MHz, $CDCl_3$) 1.56 (3H, s, =C(CH_3)), 1.64 (3H, s, =C(CH_3)), 2.01 (1H, br s, NH), 2.63 (2H, t, *J* 6.5 CH_2N), 3.07 (1H, dd, *J* 12.8 and 7.0, $CHHCO_2$), 3.19 (1H, dd, *J* 12.8 and 7.0, $CHHCO_2$), 3.57 (1H, t, *J* 7.0, NHC*H*), 3.61 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 5.10-5.16 (1H, m, =C*H*)

δ_C**:** (75 MHz, $CDCl_3$) 17.6 (=C(CH3)), 25.5 (=C(CH3)), 37.6 (CH2COO), 45.2 (=CCH2), 51.6 (OCH3), 51.9 (OCH3), 56.7 (NHCH), 121.9 (=CH), 135.1 (=C(CH3)2), 171.1 (*C*=O), 174.0 (*C*=O)

m/z: $(ES)^+$ 252.1 (100%, $[M+Na]^+$)

HRMS: [HRMS Found: $(M+Na)^+$ 252.1205. $C_{11}H_{19}NNaO_4$ requires *M* 252.1212]

(*S*)-*N*-Ethoxycarbonylaspartic acid dimethyl ester (106)



$NaHCO_3$ (158 g, 1.88 mol) was added in portions over 20 min to a stirred solution of the crude aspartic ester **110** (76.5 g) in water (700 mL) cooled to 0 °C. Ethyl chloroformate (43 mL, 0.45 mol) was added over 20 min and the solution was allowed to warm to room temperature and stirred for a further 4 h, this produced a colourless oil that pooled at the bottom of the flask. The oil was separated and the aqueous phase was further extracted with EtOAc (4 x 500 mL). The combined organic phases were washed with brine (500 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to afford the product **106** as a colourless oil (65.9 g, 75% over 2 synthetic steps).

$\mathbf{R_f}$**:** 0.61 (hexane:EtOAc, 1:1)

$[\alpha]_D^{23}$: +38.4 (*c* 1.0 in $CHCl_3$) (Lit.[72] $[\alpha]_D^{24}$ +41.5 (*c* 4.65 in $CHCl_3$))

ν_{max}: (film)/cm^{-1} 3358 (NH), 2983 (CH), 2956 (CH), 1736 (C=O)

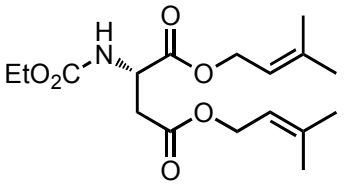
δ_H: (300 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.1, CH_2CH_3), 2.80 (1H, dd, *J* 17.1 and 4.6, CHC*H*H), 2.98 (1H, dd, *J* 17.1 and 4.6, CHCH*H*), 3.65 (3H, s, OC*H*$_3$), 3.72 (3H, s, OC*H*$_3$), 4.08 (2H, q, *J* 7.1, CH_3CH_2), 4.58 (1H, m, C*H*) 5.65 (1H, d, *J* 8.2, N*H*)

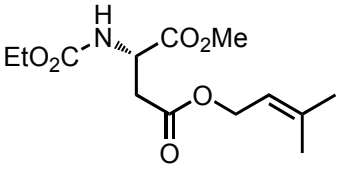
δ_C: (75 MHz, $CDCl_3$) 14.4 (CH_3CH_2), 36.7 ($CHCH_2$), 50.1 (N*C*H), 51.9 (O*C*H_3), 52.7 (O*C*H_3), 61.2 (O*C*H_2), 156.0 (N*C*O_2Et), 172.0 (*C*O_2Me)

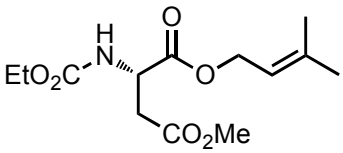
m/z: $(ES)^+$ 256.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 256.0799. $C_9H_{15}NNaO_6$ requires *M* 256.0797]

(*S*)-*N*-Ethoxycarbonyl-aspartic acid bis(3-methylbut-2-enyl) ester (140) and **(*S*)-*N*-Ethoxycarbonyl-aspartic acid 1-methyl 4-(3-methylbut-2-enyl) ester (141a)** and **(*S*)-*N*-Ethoxycarbonyl-aspartic acid 1-(3-methylbut-2-enyl) 4-methyl ester (141b)**







Cs_2CO_3 (425 mg, 1.30 mmol) was added in one portion to a stirred solution of carbamate **106** (101 mg, 0.43 mmol) and TBAI (483 mg, 1.30 mmol) in DMF (4 mL). The resulting mixture was stirred for 15 min before prenyl bromide (0.15 mL, 1.30 mmol) was added to the solution. The reaction mixture was sonicated for 2 h before being stirred at rt for 48 h. The reaction was quenched by the addition of water (20 mL) and diluted with Et_2O (10 mL) the

organic phase was separated and the aqueous phase further extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (R_f = 0.40, hexane:EtOAc, 4:1) to give the bis-*O*-alkylated product **140** as a colourless oil (48 mg, 33%).

ν_{max}: (film)/cm^{-1} 3366 (NH), 2980 (CH), 1734 (C=O), 1517, 1212

δ_H: (300 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.0, CH_2CH_3), 1.68 (6H, s, CH=CCH_3) 1.79 (6H, s =CCH_3) 2.74 (1H, dd, *J* 17.0 and 4.4, CHC*H*H), 2.90 (1H, dd, *J* 17.0 and 4.4, CHCH*H*), 4.18 (2H, q, *J* 7.0, C$H_2$$CH_3$), 4.52-4.63 (5H, stack, OCH_2 and NC*H*), 5.35 (2H, t, *J* 7.4, C*H*=CCH_3), 5.60 (1H, m, N*H*)

δ_C: (75 MHz, $CDCl_3$) 13.8 (CH_2*C*H_3), 17.3 (CH=C*C*H_3), 26.0 (CH=C*C*H_3), 36.2 (CH*C*H_2), 59.7 (N*C*H), 60.5 (*C*$H_2$$CH_3$), 61.2 (O*C*$H_2$), 61.9 (O*C*$H_2$), 117.3 (*C*H=$CCH_3$), 117.4 (*C*H=$CCH_3$), 139.2 (CH=*C*$CH_3$), 139.3 (CH=*C*$CH_3$), 156.2 (N*C*$O_2$Et), 170.1 (*C*$O_2$Me)

m/z: $(ES)^+$ 364.2 (100%, $[M+Na]^+$)

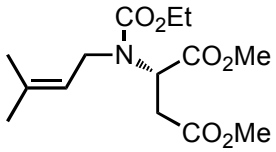
Further elution (R_f= 0.31) gave the mono-*O*-alkylated products **141a** and **141b** as a colourless oil (73 mg, 59%) in a 1:1 mixture. (NMR data reported on the mixture).

ν_{max}: (film)/cm^{-1} 3364 (NH), 2977 (CH), 2934 (CH) 1734 (C=O), 1511, 1209

δ_H: (300 MHz, $CDCl_3$) 1.20 (6H, stack, CH_2CH_3), 1.67 (6H, stack, CH=CCH_3) 1.78 (6H, stack, CH=CCH_3) 2.75-2.92 (4H, stack, CHCH*H*), 3.62 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.20 (4H, stack, C$H_2$$CH_3$), 4.85-4.72 (6H, stack OCH_2 and NC*H*), 5.35 (2H, stack, C*H*=CCH_3), 5.60 (2H, stack, N*H*)

m/z: $(ES)^+$ 310.1 (100%, $[M+Na]^+$), 242.1(48, $[M+Na-C_5H_8]^+$

(*S*)-*N*-Ethoxycarbonyl-3-methylbut-2-enyl aspartic acid dimethyl ester (104)



Carbamation of 2° amino-ester

Cs_2CO_3 (523 mg, 1.60 mmol) was added to a solution of secondary amine **105** (184 mg, 0.80 mmol) in MeCN (8 mL) cooled to 0 °C. The solution was stirred for 30 min before ethyl chloroformate (750 μL, 0.80 mmol) was added to the solution at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for a further 4 h. The solvent was removed *in vacuo* and the resulting white solid was dissolved in water (10 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in *vacuo* to leave the product **104** as a colourless oil (242 mg, quant.).

Carbamate Alkylation

Prenyl bromide **133** (36.0 mL, 0.310 mol) was added to a solution of carbamate **106** (60.1 g, 0.258 mol) in DMF (650 mL) cooled to 0 °C. NaH (60% dispersion in mineral oil, 8.67 g, 0.258 mol) was added in small portions over 2 h *via* a solid addition funnel to the stirred solution, gas evolution followed and a white precipitate fell out of solution as the reaction progressed. The reaction was stirred at 0 °C for a further 2 h before being quenched by the addition of water (600 mL). The solution was diluted with Et_2O (300 mL) and the organic phase separated. The aqueous phase was further extracted with Et_2O (3 x 300 mL) and the combined organic phases were washed with water (2 x 500 mL), brine (500 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give the crude product as a yellow oil. The crude product was split in half and purified in two portions by flash column chromatography (R_f = 0.35, hexane:EtOAc, 4:1) to give as a colourless oil (62.9 g, 81%).

$[\alpha]_D^{21}$: -76.8 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 2980 (CH), 2953 (CH), 1740 (C=O), 1704 (C=O)

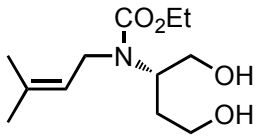
δ_H: (400 MHz, $C_2H_2Cl_4$ at 100 °C) 1.20 (3H, t, *J* 7.1, C*H*$_3$CH$_2$), 1.65 (3H, s, =C(C*H*$_3$)), 1.70 (3H, s, =C(C*H*$_3$)), 2.69 (1H, dd, *J* 16.4 and 6.8, CHC*H*HCO), 3.11 (1H, dd, *J* 16.4 and 6.8, CHCH*H*CO), 3.66 (3H, s, OC*H*$_3$), 3.67 (3H, s, OC*H*$_3$), 3.86 (1H, dd, *J* 15.4 and 6.7, NC*H*H), 3.95 (1H, dd, *J* 15.4 and 6.7, NCH*H*), 4.10 (2H, q, *J* 7.1, CH$_3$C*H*$_2$), 4.52 (1H, t, *J* 6.8, NC*H*), 5.17 (1H, t, *J* 6.7, =C*H*)

δ_C: (100 MHz, $C_2H_2Cl_4$ at 100 °C); 14.2 (*C*H$_3$CH$_2$), 17.4 (=C*C*H$_3$), 25.2 (=C*C*H$_3$), 35.4 (N*C*H$_2$), 45.6 (CH*C*H$_2$CO), 51.3 (O*C*H$_3$), 51.9 (O*C*H$_3$), 56.3 (N*C*H), 61.3 (CH$_3$*C*H$_2$), 120.2 (=*C*H), 135.3 (=*C*(CH$_3$)$_2$), 155.5 (O*C*ON), 170.6 (*C*O$_2$CH$_3$), 170.9 (*C*O$_2$CH$_3$)

m/z: (ES)$^+$ 324.2 (100%, [M+Na]$^+$)

HRMS: [Found: (M+Na)$^+$ 324.1430. $C_{14}H_{23}NNaO_6$ requires *M* 324.1423]

(*S*)-2-(Ethoxycarbonyl-3-methylbut-2-enylamino)-butan-1,4-diol (103)



$NaBH_4$ (59 mg, 1.56 mmol) was added in small portions over 5 min to a solution of carbamate ester **104** (100 mg, 0.31 mmol) in EtOH:THF (3:1, 4 mL) cooled to 0 °C. The reaction was allowed to warm to room temperature and stirred for a further 5 h, before being quenched with water (5 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (4 x 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and evaporated *in vacuo* to afford a yellow oil, which was purified by flash column chromatography (R_f = 0.29, hexane:EtOAc, 1:4), to give the product **103** as a colourless oil (32 mg, 88%).

$[\alpha]_D^{23}$: +8.0 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3418 (OH), 2965 (CH), 2927 (CH), 1742 (C=O), 1736 (C=O)

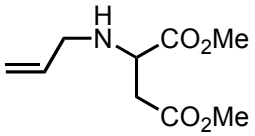
δ_H: (300 MHz, $CHCl_3$) 1.23 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.64 (3H, s, =CC*H*$_3$), 1.71 (3H, s, =CC*H*$_3$), 1.71-1.86 (1H, m, CHC*H*HCO), 2.84-2.91 (1H, m, CHCH*H*CO), 3.45-3.75 (6H, stack, CHC*H*$_2$OH, CH$_2$C*H*$_2$OH and NC*H*$_2$), 4.01-4.07 (1H, m, NC*H*), 4.12 (2H, q, *J* 7.0, CH$_3$C*H*$_2$), 5.17 (1H, br s, =C*H*)

δ_C: (75 MHz, $CHCl_3$); 14.6 (*C*H$_3$CH$_2$), 17.8 (=C*C*H$_3$), 25.7 (=C*C*H$_3$), 29.7 (N*C*H$_2$), 31.5 (N*C*H$_2$), 42.4 (CH*C*H$_2$CH$_2$), 55.9 (N*C*H), 58.9 (*C*H$_2$OH), 61.8 (*C*H$_2$OH), 64.0 (CH$_3$*C*H$_2$), 121.2 (=*C*H), 134.9 (=*C*(CH$_3$)$_2$), 158.1 (*C*=O)

m/z: $(ES)^+$ 268.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 268.1522. $C_{12}H_{23}NNaO_4$ requires *M* 268.1525]

***N*-(Allyl)aspartic acid dimethyl ester (128)**



Allyl amine (40 μL, 1.00 mmol) was added to a solution of dimethyl maleate (125 μL, 1.00 mmol) in Et_3N (139 μL, 1.00 mmol). The resulting mixture was heated to 40 °C for 10 min before being concentrated *in vacuo* to give the product **128** as a colourless oil (201 mg, quant.).

ν_{max}: (film)/cm^{-1} 3340 (N-H), 3079 (=C-H)), 2954 (C-H), 1738 (C=O), 1438, 1169 (C-O)

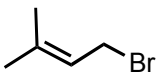
δ_H: (300 MHz, $CDCl_3$) 1.84 (1H, br s, N*H*), 2.64 (2H, t, *J* 6.3, C*H*$_2$NH), 3.12 (1H, dd, *J* 13.9 and 6.0 , C*H*$_2$CO), 3.26 (1H, dd, *J* 13.9 and 6.0, C*H*$_2$CO), 3.55-3.66 (4H, stack, C*H*$_3$ and C*H*CH$_2$), 3.68 (3H, s, C*H*$_3$), 5.04 (1H, d, *J* 10.2, *H*HC=), 5.12 (1H, d, *J* 15.2, *H*HC=), 5.58-6.06 (1H, m, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 37.9 (*C*H_2CH), 50.6 (*C*H_2NH), 51.8 (*C*H_3), 52.1 (*C*H_3), 56.7 (*C*HNH), 116.5 (=*C*H_2), 136.1 (=*C*H), 171.2 (*C*=O), 174.1 (*C*=O)

m/z: $(ES)^+$ 224.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$224.0891. $C_9H_{15}NNaO_4$ requires *M* 224.0899]

Prenyl bromide (133)



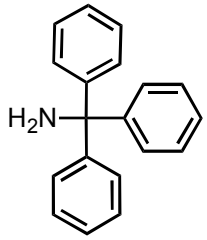
PBr_3 (43 mL, 0.24 mol) was added to a stirred solution of prenol (60 mL, 0.59 mol) in Et_2O (200 mL) cooled to 0 °C. The resulting solution was stirred for a further 30 min before being quenched with a saturated aqueous solution containing $NaHCO_3$ (200 mL) and diluted with Et_2O (100 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$ before the solvent was removed *in vacuo* at 20 °C to give prenyl bromide **133** as a colourless oil (72 g, 83%). This was used straight away or stored in the dark over silver wire under Ar at -25 °C for up to week before being used in the next step.

ν_{max}: (film)/cm^{-1} 2970, 2910, 2855, 1664, 1443, 1150, 980, 845, 760

δ_H: (300 MHz, $CDCl_3$) 1.73 (3H, s, C*H*$_3$), 1.78 (3H, s, C*H*$_3$), 4.02 (2H, d, *J* 8.2, C*H*$_2$), 5.58 (1H, t, *J* 8.2, C*H*)

δ_C: (75 MHz, $CDCl_3$) 17.0 (*C*H_3), 25.2 (*C*H_3), 29.1 (*C*H_2), 120.2 (=*C*H), 139.4 (=C_q)

Trityl amine (135)



Aqueous ammonia (35% soln., 350 mL, 5.25 mol) was added in 4 portions over 10 min to a mechanically stirred solution of trityl chloride (97.5 g, 0.35 mol) in CH_2Cl_2 (350 mL) cooled to 0 °C. The solution was allowed to warm to room temperature and stirred for a further 3 days. The organic layer was separated and the aqueous phase further extracted with CH_2Cl_2 (2x 200 mL). The combined organic layers were washed with water (300 mL) and brine (300 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product as a pale yellow solid. The crude product was recrystallised from EtOH to give the pure product **135** as a white crystalline solid (67.2 g, 74%).

mp: 98-100 °C (from ethanol) (Lit.[110] 100-102 °C (from H_2O))

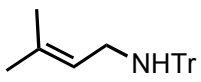
ν_{max}: (film)/cm^{-1} 2970, 2910, 2855, 1664, 1443, 1150, 980, 845, 760

δ_H: (300 MHz, $CDCl_3$) 2.48 (2H, br s, N*H*$_2$), 7.25- 7.43 (15H, m, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 62.8 (*C*NH_2), 125.5 (Ar*C*H), 126.9 (Ar*C*H), 127.1 (Ar*C*H), 147.5 (ArC_q)

m/z: (EI)$^+$ 259 (20%, $[M]^+$), 243 (40, $[M\text{-}NH_2]^+$), 182 (100, $[M\text{-}C_6H_5]^+$)

3-methyl-*N*-tritylbut-2-en-1-amine (136)



K_2CO_3 (110 g, 0.798 mol) was added in 4 portions over 10 min to a stirred solution of trityl amine **136** (69 g, 0.266 mol) in DMF (670 mL) cooled to 0 °C. Prenyl bromide (46 mL, 0.399 mol) was added over 10 min to the stirred suspension. The resulting solution was stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred for a further 6 h. The reaction was quenched with H_2O (1 L) and the

aqueous layer was extracted with Et_2O (3 x 600 mL). The combined organic layers were washed with H_2O (2 x 500 mL) and brine (500 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product **136** as a pale yellow oil (87 g), which was used in the next step without further purification.

ν_{max}: (film)/cm^{-1} 3365 (NH), 3047, 3018, 2855, 1596, 1575, 1448, 1444, 1212, 844, 766, 696

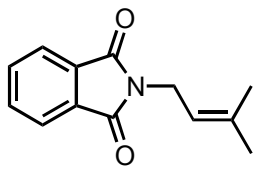
δ_H: (300 MHz, $CDCl_3$) 1.53 (3H, s, C*H*$_3$), 1.75 (3H, s, C*H*$_3$), 2.78 (2H, d, *J* 8.0, C*H*$_2$), 5.42 (1H, t, *J* 8.0, C*H*), 7.15-7.23 (3H, ArC*H*), 7.24-7.31 (6H, m, ArC*H*), 7.48-7.55 (6H, m, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 22.4 (*C*H$_3$), 30.2 (*C*H$_3$), 48.1 (*C*H$_2$), 119.4 (*C*H=), 135.2 (Ar*C*H), 135.3 (Ar*C*H), 144.3 (C_q), 148.5 (C_q)

m/z: $(ES)^+$ 350.2 (81%, $[M+Na]^+$), 243.1 (100)

HRMS: [Found: $(M+Na)^+$ 350.1879. $C_{24}H_{25}NNa$ requires *M* 350.1885]

2-(3-methylbut-2-enyl)isoindoline-1,3-dione (138)



Prenyl bromide **133** (50.0 g, 0.335 mol) was added over 2 min to a stirred solution of potassium phthalimide (68.4 g, 0.369 mol) in DMF (250 mL) cooled to 0 °C, this resulted in the generation of a white precipitate. The solution was allowed to warm to room temperature and stirred for a further 30 min. The reaction was diluted with water (500 mL) and the aqueous phase extracted with Et_2O (4 x 250 mL). The combined organic phases were washed with 1 M NaOH (250 mL), water (250 mL) and brine (250 mL) before being dried over $MgSO_4$ and the solvent removed *in vacuo* to give the product **138** as a white crystalline solid (70.7 g, 98%).

R_f: 0.44 (hexane:EtOAc, 3:1)

mp: 96-98 °C (from $CHCl_3$) (Lit.[111] 100 °C (from MeOH))

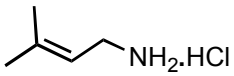
ν_{max}: (film)/cm^{-1} 2978 (CH), 2941 (CH), 2923 (CH), 1767 (C=O), 1699, 1425, 1096, 943, 718

δ_H: (300 MHz, $CDCl_3$) 1.61 (3H, s, CH_3), 1.73 (3H, s, CH_3), 4.25 (2H, d, *J* 7.9, CH_2), 5.22 (1H, t, *J* 7.9, C*H*), 7.58-7.67 (2H, ArC*H*), 7.71-7.79 (2H, m, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 18.2 (*C*H_3), 25.9 (*C*H_3), 36.1 (*C*H_2), 118.6 (*C*H=), 123.4 (Ar*C*H), 132.8 (C_q), 134.1 (Ar*C*H), 137.5 (C_q), 166.9 (C=O)

m/z: (ES)$^+$ 238.0 (100%, $[M+Na]^+$), 182.2 (27)

Prenyl amine hydrochloride (137)



Phthalimide Cleavage

$Ba(OH)_2.8H_2O$ (234 g, 0.743 mol) was added in portions over 15 min to a stirred suspension of alkylated phthalimide **139** (64.0 g, 0.297 mol) in water (600 mL). The resulting solution was heated to reflux and the free amine extracted *via* steam distillation for 16 h until the pH of the distillate was no longer alkaline, while the still pot is topped up with water equal to the volume of distillate removed. The alkaline distillate is then neutralised to pH 7 with 1M HCl and the distillate is then concentrated *in vacuo* to 1/10 th volume before MeOH (100 mL) is added and the solvent removed *in vacuo* to give the product **137** as a white amorphous solid upon standing (35.4 g, 98%).

Trityl Cleavage

Trifluoroacetic acid (3 mL) was added over 2 min to a stirred solution of alkylated trityl amine **136** (240 mg, 0.73 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C, resulting in a colour change from colourless to bright yellow. The solution was stirred for 10 min at 0 °C before

MeOH (10 mL) was added to the resulting solution over 10 min, resulting in a colour change from bright yellow to colourless. The solvent was removed *in vacuo* to give a yellow solid that was treated with concentrated HCl (2 mL, 2.19 mmol) in MeOH (8 mL) before the solvent removed *in vacuo*. The resulting residue was washed Et_2O to precipitate a white solid, which was filtered from the mother liquid and washed with further portions of Et_2O to give the product as a white amorphous solid **137** (83 mg, 94%).

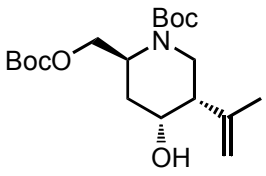
mp: 196-197 °C (from MeOH) (lit.[112] 200 °C (from EtOH))

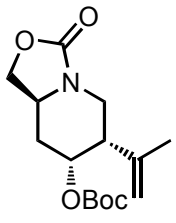
ν_{max}: (film)/cm^{-1} 3424 (NH), 2977 (CH), 1671, 1596, 1449, 756, 706

δ_H: (300 MHz, CD_3OD) 1.71 (3H, s, CH_3), 1.78 (3H, s, CH_3), 3.53 (2H, d, *J* 8.2, CH_2), 5.31 (1H, t, *J* 8.2, C*H*)

δ_C: (75 MHz, CD_3OD) 17.4 (*C*H_3), 25.2 (*C*H_3), 37.5 (*C*H_2), 116.1 (*C*H=), 141.4 (=C_q)

(6*S*, 7*S*, 9*S*)-4-*tert*-Butoxycarbonyloxy-2-hydroxymethyl-5-isopropenylpiperidine-1-carboxylic acid tert-butyl ester (143) and **(6*S*, 7*S*, 9*S*)-7-Carbonic acid *tert*-butyl ester-6-isopropenyl-hexahydro-oxazolo[3,4-*a*]pyridine-3-one (144)**





A solution of aqueous NaOH (6 M, 3 mL) was added to a solution of piperidine **96** (58 mg, 0.29 mmol) in MeOH (6 mL). The reaction was heated to 95 °C for 16 h before the solvent was removed *in vacuo*. The resulting solid was dissolved in THF (6 mL) and cooled to 0 °C. $(Boc)_2O$ (128 mg, 0.59 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for a further 4 h before the solvent was removed *in vacuo.* The

aqueous phase was extracted with EtOAc (4 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (R_f = 0.38, hexane:EtOAc, 2:1) to afford piperidine **143** as colourless oil (17 mg, 16%).

ν_{max}: (film)/cm^{-1} 3447 (OH), 2979 (CH), 2931 (CH), 1743 (C=O), 1670 (C=O), 1424, 1366, 1287, 1255, 1161, 1066 (C-O)

δ_H: (400 MHz, $CDCl_3$) 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.62 (1H, dt, *J* 14.1 and 6.3, C*H*HCHOH), 1.75 (3H, s, =CC*H*$_3$), 2.04 (1H, ddd, *J* 14.1, 6.3 and 3.8, CH*H*CHOH), 2.16-2.19 (1H, m, CHOHC*H*), 3.50 (1H, dd, *J* 14.1 and 5.0, NC*H*H), 3.70 (1H, dd, *J* 14.1 and 3.8, NCH*H*), 3.95 (1H, td, *J* 6.3 and 3.8, C*H*OH), 4.12 (1H, quin., *J* 6.3, NC*H*), 4.30 (2H, d, *J* 6.3, OC*H*$_2$), 4.85 (1H, s, =C*H*H), 4.88 (1H, s, =C*H*H)

δ_C: (75 MHz, $CDCl_3$) 20.0 (=C*C*H$_3$), 27.8 (C(*C*H$_3$)$_3$), 28.4 (C(*C*H$_3$)$_3$), 30.4 (*C*H$_2$CHOH), 40.7 (N*C*H$_2$) 49.2 (NCH$_2$*C*H), 50.1 (N*C*H), 67.1 (*C*H$_2$O), 67.2 (*C*HOH), 80.0 (*C*(CH$_3$)$_3$), 82.2 (*C*(CH$_3$)$_3$), 112.9 (=*C*H$_2$), 143.9 (*C*=CH$_2$), 153.6 (*C*=O), 154.8 (*C*=O)

m/z: $(ES)^+$ 394.2 (100%, $[M+Na]^+$).

HRMS: [Found: $(M+Na)^+$ 394.2215. $C_{19}H_{33}NNaO_6$ requires *M* 394.2206]

Further elution, R_f = 0.29, afforded piperidine **144** as a white crystalline solid (13 mg, 15%).

mp: 171-173 °C (from hexane:EtOAc)

ν_{max}: (film)/cm^{-1} 2954 (CH), 2923 (CH), 2853 (CH), 1743 (C=O)

δ_H: (400 MHz, $CDCl_3$) 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.53 (1H, q, *J* 11.8, NCHC*H*H), 1.74 (3H, s, =CC*H*$_3$), 2.25 (1H, dt, *J* 11.8 and 3.8, NCHCH*H*), 2.35 (1H, dt, *J* 11.8 and 5.1, NCH$_2$C*H*), 2.83 (1H, dd, *J* 13.6 and 11.8, NC*H*H), 3.80-3.87 (1H, m, NC*H*), 3.92 (1H, dd, *J* 13.6 and 5.1,

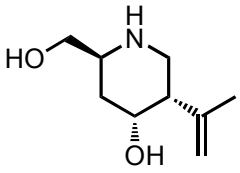
NCH*H*), 3.96 (1H, dd, *J* 8.7 and 4.9, C*H*HO), 4.40 (1H, t, *J* 8.7, CH*H*HO), 4.77 (1H, dt, *J* 11.8 and 3.8, C*H*O), 4.88 (1H, s, =C*H*H), 4.94 (1H, s, =CH*H*)

δ_C: (75 MHz, $CDCl_3$) 20.5 (=C*C*H_3), 27.7 (C(*C*H_3)$_3$, 35.7 (NCH*C*H_2), 43.9 (N*C*H_2), 58.3 (NCH_2*C*H), 52.8 (N*C*H), 66.8 (*C*H_2O), 63.6 (*C*HO), 82.6 (*C*(CH_3)$_3$, 114.6 (=*C*H_2), 141.0 (*C*=CH_2), 152.8 (*C*=O), 156.6 (*C*=O)

m/z: $(ES)^+$ 320 (100%, $[M+Na]^+$), 264.1 (40, $[M+Na-C_4H_8]$)

HRMS: [Found: $(M+Na)^+$ 320.1479. $C_{15}H_{23}NNaO_5$ requires *M* 320.1474]

(2*S*, 4*R*, 5*S*)-2-(hydroxymethyl)-5-isopropenylpiperidin-4-ol (145)



NaOH (4.79 g, 0.120 mol) in water (15 mL) was added dropwise over 30 s to a solution of piperidine **96** (2.36 g, 11.98 mmol) in MeOH (45 mL) cooled to 0 °C. The solution was allowed to warm to room temperature and then heated to 95 °C for 5 h. After cooling to room temperature the solvent was removed *in vacuo* and the resulting white solid was extracted with CH_2Cl_2 (20 mL), filtered and washed with further portions of CH_2Cl_2 (3 x 10 mL) before the solvent was removed *in vacuo* to afford the product **145** as hygroscopic white crystalline solid (2.05 g) which was used in the next step without any further purification.

R_f: 0.20 (8:2, $CHCl_3$:MeOH + 1% $NH_{3(aq)}$)

$[\alpha]_D^{20}$: -20.0 (*c* 1 in $CHCl_3$)

mp: 106-107 °C (from EtOAc)

ν_{max}: (film)/cm^{-1} 3386 (OH), 3309 (NH), 2925 (CH), 1645 (C=C), 1446, 1216, 754

δ_H: (300 MHz, $CDCl_3$) 1.44-1.54 (1H, m, NCHC*H*HCH), 1.78 (3H, s, C*H*$_3$) 1.85 (1H, dt, *J* 14.0 and 2.9, NCHC*H*HCH), 2.23 (1H, br d, *J* 11.8, NCH_2C*H*), 2.90 (1H, dd, *J* 12.1 and 4.0,

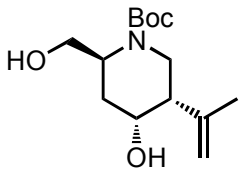
NC*H*H), 3.07 (1H, dd, *J* 12.1 and 11.8, NC*H*H), 3.12-3.18 (1H, m, NC*H*), 3.31 (3H, br s, 2 x O*H* and N*H*), 3.43 (1H, dd, *J* 11.0 and 7.4, C*H*HOH), 3.65 (1H, dd, *J* 11.0 and 3.3, C*H*HOH) 4.10 (1H, br s, C*H*OH), 4.68 (1H, s, =C*H*H), 4.97 (1H, s, =C*H*H)

C: (75 MHz, $CDCl_3$) 22.9 (=C*C*H_3), 34.2 (NCH*C*H_2CH), 43.2 (N*C*H_2), 47.8 (NCH_2*C*H), 51.8 (N*C*H), 64.3 (*C*HOH), 65.6 (*C*H_2O), 112.6 (C=*C*H_2), 144.8 (*C*=CH_2)

m/z: $(ES)^+$ 194.4 (20%, $[M+Na]^+$), 172.4 (90, $[M+H]^+$), 154.4 (100)

X-ray: See *Appendix*

(2*S*, 4*R*, 5*S*)-4-hydroxy-2-(hydroxymethyl)-5-isopropenylpiperidine-1-carboxylic acid tertbutyl ester (146)



Boc Protection

$(Boc)_2O$ (2.62 g, 11.98 mmol) was added in one portion to a stirred solution of piperidine **145** (2.05 g) in THF (60 mL) cooled to 0 °C. The solution was allowed to warm to room temperature and stirred for a further 5 h before the solvent was removed *in vacuo.* The resulting residue was diluted with water and the aqueous phase was extracted with EtOAc (4 x 40 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (R_f = 0.25, hexane:EtOAc, 1:3) to afford piperidine **146** as colourless oil (2.77 g, 86% over 2 synthetic steps).

NaOH ring opening and BOC protection *in situ*

NaOH (12.5 g, 312 mmol) in water (60 mL) was added over 2 min to a solution of piperidine **96** (10.1 g, 52.0 mmol) in MeOH (120 mL) cooled to 0 °C. The solution was allowed to warm

to room temperature and then heated to 95 °C for 5 h. The solution was allowed to cool to room temperature before being cooled to 0 °C. The solution was neutralised to pH 7 with concentrated HCl. $NaHCO_3$ (8.74 g, 104 mmol) was added to the stirred solution followed by $(Boc)_2O$ (13.6 g, 62.4 mmol) and the reaction allowed to warm to room temperature before being stirred overnight. The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (4 x 80 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (R_f = 0.25, hexane:EtOAc, 1:3) to afford piperidine **146** as colourless oil (12.7 g, 90%).

$[\alpha]_D^{20}$: -78.8 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3420 (OH), 2974 (CH), 2930 (CH), 1668 (C=O), 1424, 1366, 1170

δ_H: (300 MHz, $CDCl_3$) 1.40 (9 H, s, $C(CH_3)_3$), 1.73-1.82 (5 H, stack, $=CCH_3$ and $NCHCH_2CH$), 2.06-2.26 (2H, stack, NCH_2CH and OH), 3.32 (1H, dd, *J* 13.4 and 9.7, NCHH), 3.60-3.74 (3H, stack, CH_2OH and NCHH), 3.75-3.87 (1H, m, CHOH), 4.04-4.13 (1H, m, CHN), 4.24 (1H, br s, OH), 4.69 (1H, s, =CHH), 4.96 (1H, s, =CHH)

δ_C: (75 MHz, $CDCl_3$) 23.2 ($=CCH_3$), 28.4 ($C(CH_3)_3$), 33.3 ($NCHCH_2CH$), 44.8 (NCH_2), 46.8 (NCH_2CH), 54.9 (NCH), 63.5 (CH_2O), 64.8 (CHOH), 80.4 ($C(CH_3)_3$) 112.9 ($C=CH_2$), 144.0 ($C=CH_2$) 155.4 (C=O)

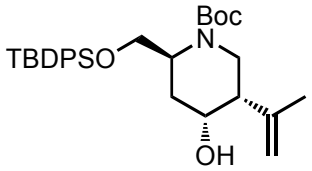
m/z: $(ES)^+$ 294.0 (100%, $[M+Na]^+$), 238.0 (8, $[M+Na-^tBu]^+$)

HRMS: [Found: $(M+Na)^+$ 294.1677. $C_{14}H_{25}NNaO_4$ requires *M* 294.1681]

General Procedure 1: TBDPS/TBS Protection of 1° Hydroxyl

Et_3N (l.2-2.5 eq) followed by DMAP (0.2 eq) were added to a stirred solution of the alcohol (1 eq) in CH_2Cl_2 (0.3-0.5 M). TBDPSCl/TBSCl (1-1.5 eq) was added dropwise over 1 min to the solution and stirred for a further 2 h before the reaction was quenched by the addition of water (10 mL). The organic layer was separated and the aqueous layer was further extracted with 3 x CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the crude silyl ether product.

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxy-5(prop-1-en-2-yl)piperidine-1-carboxylate (147a)



Silyl ether **147a** was prepared from: alcohol **146** (140 mg, 0.52 mmol), Et_3N (86 μL, 0.62 mmol), DMAP (13 mg, 0.10 mmol), TBDPSCl (161 μL, 0.62 mmol); in CH_2Cl_2 (2 mL) according to general procedure 1. Purification by flash column chromatography (R_f = 0.34, hexane:EtOAc, 5:1) gave the product as a colourless oil (202 mg, 77%).

$[\alpha]_D^{19}$: -45.6 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3454 (OH), 3072 (=CH), 2961 (CH), 2932 (CH), 2858 (CH), 2363 (ArCH), 1676 (C=O), 1590 (Ar C=C), 1428 (CH_2-C=C), 1113 (C-O)

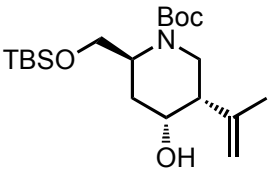
δ_H: (500 MHz, $CDCl_3$) 1.06 (9H, s, SiC(CH_3)$_3$), 1.40 (9H, s, OC(CH_3)$_3$), 1.75 (1H, br s, O*H*), 1.83 (3H, s, =CCH_3), 1.86-2.08 (2H, m, CHCH_2CH), 2.46 (1H, q, *J* 4.4, NCH_2C*H*), 3.23 (1H, dd, *J* 14.0 and 4.4, NC*H*H), 3.66-3.82 (2H, m, CH_2O), 4.00 (1H, dd, *J* 14.0 and 4.4, NC*H*H), 4.04-4.10 (1H, m, C*H*OH), 4.27-4.38 (1H, m, NC*H*), 4.93 (1H, s, =C*H*H), 5.04 (1H, s, =C*H*H), 7.31-7.47 (6H, m, ArC*H*), 7.67 (4H, dd, *J* 1.7 and 7.4, ArC*H*)

δ_C**:** (125 MHz, $CDCl_3$) 19.3 (Si*C*$(CH_3)_3$), 24.1 (=C*C*H_3), 27.0 (SiC(*C*$H_3)_3$), 28.5 (OC(*C*$H_3)_3$), 30.8 (NCH*C*H_2CH), 42.7 (N*C*H_2), 46.0 (NCH_2*C*H), 52.1 (N*C*H), 64.1 (*C*H_2O), 65.5 (*C*HOH), 79.8 (O*C*$(CH_3)_3$) 114.7 (C=*C*H_2), 127.8 (Ar*C*H), 129.82 (Ar*C*H), 133.4 (ArC_q), 133.5 (ArC_q), 143.8 (*C*=CH_2) 155.0 (C=O)

m/z: $(ES)^+$ 532.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 532.2867. $C_{30}H_{43}NNaO_4Si$ requires *M* 532.2859]

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-5-(prop-1-en-2-yl)piperidine-1-carboxylate (147b)



Silyl ether **147b** was prepared from: alcohol **146** (130 mg, 0.48 mmol), Et_3N (80 μL, 0.58 mmol), DMAP (12 mg, 0.10 mmol) and TBSCl (87 mg, 0.58 mmol); in CH_2Cl_2 (2 mL) according to general procedure 1. Purification by flash column chromatography (R_f = 0.36, hexane:EtOAc, 5:1) gave the product as a colourless oil (150 mg, 81%).

ν_{max}**:** (film)/cm^{-1} 2955 (CH), 2930 (CH), 2858 (CH), 1678 (C=O), 1419 (CH_2-C=C), 1366, 1253, 1120, 838

δ_H**:** (300 MHz, $CDCl_3$) 0.03 (6H, s, Si(C*H*$_3)_2$), 0.87 (9H, s, SiC(C*H*$_3)_3$), 1.41 (9H H, s, OC(C*H*$_3)_3$), 1.65 (1H, br s, O*H*), 1.83 (3H, s, =CC*H*$_3$), 1.86-2.01 (2H, m, C*H*$_2$CHOH), 2.49 (1H, q, *J* 4.4, NCH_2C*H*), 3.28 (1H, dd, *J* 14.0 and 4.4, NC*H*H), 3.62-3.80 (2 H, m, C*H*$_2$O), 3.95 (1H, dd, *J* 14.0 and 4.4, NC*H*H), 4.07-4.22 (2H, stack, C*H*OH and NC*H*), 4.90 (1H, s, =C*H*H), 5.02 (1H, s, =C*H*H)

δ_C: (125 MHz, $CDCl_3$) -5.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 24.0 ($=CCH_3$), 25.9 ($SiC(CH_3)_3$), 28.4 ($OC(CH_3)_3$), 30.8 (CH_2CHOH), 42.9 (NCH_2), 45.8 (NCH_2CH), 52.1 (NCH), 63.5 (CH_2O), 65.4 (CHOH), 79.6 ($OC(CH_3)_3$) 114.5 ($C=CH_2$), 143.8 ($C=CH_2$) 154.9 (C=O)

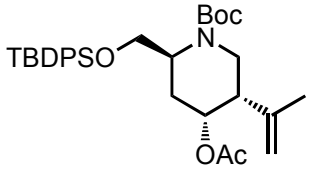
m/z: $(ES)^+$ 408.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 408.2549. $C_{20}H_{39}NNaO_4Si$ requires *M* 408.2546]

General procedure 2: Acylation of 2° hydroxyl

An acyl chloride (1 eq) was added dropwise over 10 s to a solution of an alcohol (1 eq) in pyridine (0.2 M) cooled to 0 °C. The solution was allowed to warm to room temperature and stirred for a further 2 h before being quenched with a saturated aqueous solution of $NaHCO_3$. The solution was extracted with 4 x CH_2Cl_2 before the combined organic fractions were washed with a solution of 0.1 M HCl, water, brine and dried over $MgSO_4$.

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-acetoxy-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(prop-1-en-2-yl)piperidine-1-carboxylate (150a)



Acetyl ester **150a** was prepared from: alcohol **147a** (90 mg, 0.18 mmol), and acetyl chloride (13 μL, 0.18 mmol); in pyridine (1 mL) according to general procedure 2. Purification by flash column chromatography (R_f = 0.34, hexane:EtOAc, 6:1) gave the product as a white crystalline solid (98 mg, quant).

$[\alpha]_D^{20}$: -4.4 (*c* 1 in $CHCl_3$)

mp: 73-75 °C (from hexane:EtOAc)

μ: (Found: C, 69.66; H, 8.32; N, 2.83 $C_{32}H_{45}NO_5Si$ requires C, 69.65; H, 8.22; N, 2.54%)

ν_{max}: (film)/cm^{-1} 3075 (=CH), 2972 (CH), 2932 (CH), 2862 (CH), 1737 (C=O), 1695, (C=O), 1423 (CH_2-C=C), 1113 (C-O), 1040, 700

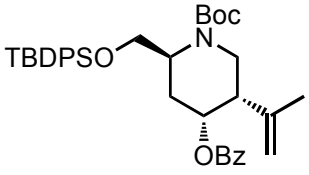
δ_H: (300 MHz, $CDCl_3$) 1.01 (9H, s, SiC(CH_3)$_3$), 1.38 (9H, s, OC(CH_3)$_3$), 1.75 (3H, s, =CCH_3), 1.83-1.91 (1H, dt, *J* 14.0 and 2.9, C*H*HCHO), 2.01 (3H, s, OC(O)CH_3) 2.02-2.13 (1H, m, C*H*HCHO), 2.56 (1H, q, *J* 4.0, NCH_2CH), 3.37 (1H, dd, *J* 14.0 and 4.0, NC*H*H), 3.61-3.75 (2H, m, CH_2O), 4.02 (1H, dd, *J* 14.0 and 4.0, NC*H*H), 4.36-4.45 (1H, m, NC*H*), 4.82 (1H, s, =C*H*H), 4.90 (1H, s, =C*H*H), 5.15-5.24 (1H, m, C*H*O), 7.30-7.46 (6H, m, ArC*H*), 7.48-7.52 (4H, m, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 19.8 (Si*C*(CH_3)$_3$), 21.5 (=C*C*H_3), 24.5 (OC(O)*C*H_3) 27.3 (SiC(*C*H_3)$_3$), 27.9 (NCH*C*H_2CH), 39.8 (OC(*C*H_3)$_3$), 43.4 (NCH_2*C*H), 43.7 (N*C*H_2), 52.0 (N*C*H), 64.7 (*C*H_2O), 70.4 (*C*HO), 80.1 (O*C*(CH_3)$_3$) 112.3 (C=*C*H_2), 128.4 (Ar*C*H), 129.5 (Ar*C*H), 133.0 (ArC_q), 135.1 (Ar*C*H), 142.2 (*C*=CH_2), 155.0 (N*C*=O), 169.9 (CH_3*C*=O)

m/z: $(ES)^+$ 574.2 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 574.2971. $C_{32}H_{45}NNaO_5$ Si requires *M* 547.2965]

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-(benzoyloxy)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(prop-1-en-2-yl)piperidine-1-carboxylate (150b)



Benzoyl ester **150b** was prepared from: alcohol **147a** (84 mg, 0.17 mmol), and benzoyl chloride (19 μL, 0.17 mmol); in pyridine (1 mL) according to general procedure 2. Purification by flash column

chromatography (R_f = 0.33, hexane:EtOAc, 9:1) gave the product as a colourless oil (101 mg, quant).

ν_{max}: (film)/cm^{-1} 3072 (=CH), 2961 (CH), 2932 (CH), 2858 (CH), 2363 (ArCH), 1678 (C=O), 1590 (Ar C=C), 1428 (CH_2-C=C), 1113 (C-O)

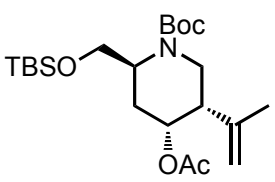
δ_H: (300 MHz, $CDCl_3$) 1.08 (9H, s, SiC(CH_3)$_3$), 1.41 (9H H, s, OC(CH_3)$_3$), 1.80 (3H, s, =CCH_3), 2.02-2.10 (1H, m, CHC*H*HCH), 2.20-2.33 (1H, m, CHC*H*HCH), 2.72 (1H, q, *J* 4.0, NCH_2CH), 3.35 (1H, dd, *J* 14.0 and 4.0, NC*H*H), 3.60-3.88 (2H, m, CH_2O), 4.13 (1H, dd, *J* 14.0 and 4.0, NC*H*H), 4.31-4.42 (1H, m, NC*H*), 4.93 (1H, s, =C*H*H), 4.97 (1H, s, =C*H*H), 5.48-5.59 (1H, m, C*H*O), 7.31-7.47 (8H, m, ArC*H*), 7.49-7.53 (3H, m, ArC*H*), 7.62-7.70 (4H, m, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 21.8 (Si*C*(CH_3)$_3$), 26.7 (=C*C*H_3), 29.5 (SiC(*C*H_3)$_3$), 30.3 (NCH*C*H_2CH), 31.0 (OC(*C*H_3)$_3$), 45.7 (N*C*H_2), 46.1 (NCH_2*C*H), 54.6 (N*C*H), 66.7 (*C*H_2O), 72.5 (*C*HO), 82.4 (O*C*(CH_3)$_3$) 116.5 (C=*C*H_2), 130.4 (Ar*C*H), 131.0 (Ar*C*H), 131.6 (Ar*C*H), 132.3 (Ar*C*H), 133.0 (ArC_q), 133.3 (Ar*C*H), 135.9 (ArC_q), 138.2 (Ar*C*H), 145.7 (*C*=CH_2), 155.0 (*C*=O), 167.0 (*C*=O)

m/z: $(ES)^+$ 636.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 636.3138. $C_{37}H_{47}NNaO_5Si$ requires *M* 636.3121]

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-acetoxy-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(prop-1-en-2-yl)piperidine-1-carboxylate (150c)



Acetyl ester **150c** was prepared from: alcohol **147b** (115 mg, 0.30 mmol), and acetyl chloride (17 μL, 0.30 mmol); in pyridine (1.5 mL)

according to general procedure 2. Purification by flash column chromatography (R_f = 0.49, hexane:EtOAc, 6:1) gave the product as a colourless oil (106 mg, 83%).

$[\alpha]_D^{20}$: -18.8 (*c* 1 in $CHCl_3$)

ν_{max}: (neat)/cm^{-1} 2955 (CH), 2930 (CH), 2897 (CH), 2857 (CH), 1741 (C=), 1697, (C=O), 1417, 1367, 1242, 1045, 837, 777

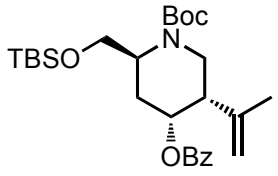
δ_H: (300 MHz, $CDCl_3$) 0.03 (6H, s, SiCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 1.45 (9H, s, OC(CH_3)$_3$), 1.73 (3H, s, =CCH_3), 1.85 (1H, dt, *J* 13.5 and 4.5, C*H*HCHO), 2.00-2.12 (4H, stack, C*H*HCHO and C(O)CH_3) 2.54-2.63 (1H, m, NCH$_2$C*H*), 3.26 (1H, dd, *J* 14.0 and 4.2, NC*H*H), 3.62 (1H, dd, *J* 10.5 and 4.8, C*H*HO), 3.80 (1H, dd, *J* 10.5 and 6.8, C*H*HO), 4.03 (1H, dd, *J* 14.0 and 4.2, NC*H*H), 4.13-4.24 (1H, m, NC*H*), 4.81 (1H, s, =C*H*H), 4.90 (1H, s, =C*H*H), 5.25-5.34 (1H, m, C*H*O)

δ_C: (75 MHz, $CDCl_3$) -5.4 (Si(*C*H$_3$)$_2$), 18.1 (Si*C*(CH$_3$)$_3$), 21.2 (=C*C*H$_3$), 24.0 (C(O)*C*H$_3$), 26.1 (SiC(*C*H$_3$)$_3$), 28.5 (*C*H$_2$CHO), 29.3 (OC(*C*H$_3$)$_3$), 43.2 (NCH$_2$*C*H), 43.8 (N*C*H$_2$), 51.4 (N*C*H), 63.2 (*C*H$_2$O), 69.1 (*C*HO), 79.0 (O*C*(CH$_3$)$_3$) 113.7 (C=*C*H$_2$), 142.5 (*C*=CH$_2$), 153.3 (NC=O), 169.7 (C=O)

m/z: $(ES)^+$ 450.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 450.2657. $C_{22}H_{41}NNaO_5Si$ requires *M* 450.2652]

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-(benzoyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(prop-1-en-2-yl)piperidine-1-carboxylate (150d)



Benzoyl ester **150d** was prepared from: alcohol **147b** (439 mg, 1.14 mmol), and benzoyl chloride (103 μL, 1.14 mmol); in pyridine (7 mL)

according to general procedure 2. Purification by flash column chromatography (R_f = 0.54, hexane:EtOAc, 6:1) gave the product as a white crystalline solid (482 mg, 86%).

$[\alpha]_D^{20}$: -25.2 (*c* 1 in $CHCl_3$)

mp: 70-71 °C (from hexane:EtOAc)

ν_{max}: (neat)/cm^{-1} 2955 (CH), 2930 (CH), 2857 (CH), 1720 (C=O), 1694 (C=O), 1273, 1112, 838

δ_H: (400 MHz, $CDCl_3$) 0.03 (3H, s, SiCH_3) 0.04 (3H, s, SiCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 1.44 (9H, s, OC(CH_3)$_3$), 1.76 (3H, s, =CCH_3), 2.01 (1H, dt, *J* 13.5 and 4.2, C*H*HCHO), 2.19 (1H, ddd, *J* 13.5, 9.8 and 6.6, C*H*HCHO) 2.71 (1H, q, *J* 4.2, NCH_2CH), 3.38 (1H, dd, *J* 14.0 and 4.2, NC*H*H), 3.68 (1H, dd, *J* 10.1 and 4.8, C*H*HO), 3.80 (1H, dd, *J* 10.1 and 6.7, C*H*HO), 4.12 (1H, dd, *J* 14.0 and 4.2, NC*H*H), 4.19-4.27 (1H, m, NC*H*), 4.90 (1H, s, =C*H*H), 4.94 (1H, s, =C*H*H), 5.58 (1H, dt, *J* 9.8 and 4.2 , C*H*O), 7.36 (2H, t, *J* 7.4, ArC*H*), 7.48 (1H, t, *J* 7.4, ArC*H*), 8.01 (2H, d, *J* 7.4, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) -5.6 (Si(*C*H_3)$_2$), 18.0 (Si*C*(CH$_3$)$_3$), 24.0 (SiC(*C*H_3)$_3$), 25.7 (=C*C*H_3), 27.3 (*C*H_2CHO), 28.2 (OC(*C*H_3)$_3$), 43.1 (N*C*H_2), 43.2 (NCH_2*C*H), 51.8 (N*C*H), 63.4 (*C*H_2O), 69.7 (*C*HOH), 79.5 (O*C*(CH$_3$)$_3$) 113.6 (C=*C*H_2), 128.1 (Ar*C*H), 129.4 (Ar*C*H), 130.3 (ArC_q), 132.7 (Ar*C*H), 143.0 (*C*=CH_2), 154.6 (NC=O), 166.4 (C=O)

m/z: $(ES)^+$ 512.3 (100%, $[M+Na]^+$)

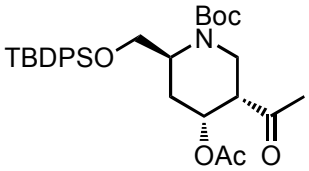
HRMS: [Found: $(M+Na)^+$ 512.2828. $C_{27}H_{43}NNaO_5Si$ requires *M* 512.2808]

General Procedure 3: Ozonolysis of an alkene

Ozone was bubbled through a solution of an alkene (1 eq) in CH_2Cl_2:MeOH (2:1, 0.1 M) at -78 °C and out into an aqueous KI scrubber. After the solution changed in colour from

colourless to clear blue, usually 10 min, O_2 was bubbled through the solution followed by argon each for 5 min, to remove excess ozone, changing the colour of from clear blue to colourless. DMS (1.2 eq) was added and the solution was allowed to warm to room temperature before the solvent was removed *in vacuo* to obtain the crude product.

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-acetoxy-5-acetyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl) piperidine-1-carboxylate (151a)



Ozone was bubbled through a solution of alkene **150a** (50 mg, 0.09 mmol) in CH_2Cl_2:MeOH (1:1, 1 mL) and quenched with DMS (7 μL, 0.10 mmol) according to general procedure3. Purification by flash column chromatography (R_f = 0.30, hexane:EtOAc, 2:1) gave ketone **151a** as a colourless oil (21 mg, 42%).

$[\alpha]_D^{20}$: +7.2 (*c* 1 in $CHCl_3$)

ν_{max}: (neat)/cm^{-1} 3186 (ArCH), 3135 (ArCH), 2995 (CH), 2961 (CH), 2931 (CH), 2858 (CH), 1736 (C=O), 1719 (C=O), 1690 (C=O), 1426, 1366, 1237, 1046, 823, 702

δ_H: (300 MHz, $CDCl_3$) 1.02 (9H, s, SiC(CH_3)$_3$), 1.43 (9H, s, OC(CH_3)$_3$), 1.82-1.91 (1H, m, C*H*HCHO), 2.01 (3H, s, OC(O)CH_3), 2.15 (3H, s, CC(O)CH_3) 2.26-2.39 (1H, m, C*H*HCHO), 3.03 (1H, q, *J* 4.2, NCH_2CH), 3.36 (1H, dd, *J* 4.2 and 14.0, NC*H*H), 3.63-3.72 (2H, m, CH_2O), 4.24-4.35 (1H, m, NC*H*H), 4.39-4.48 (1H, m, NC*H*), 5.12-5.23 (1H, m, C*H*O), 7.32-7.44 (6H, m, ArC*H*), 7.59-7.61 (4H, m, ArC*H*)

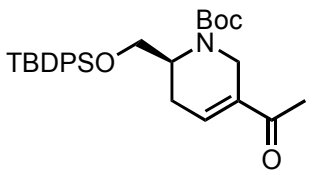
δ_C: (75 MHz, $CDCl_3$) 18.1 (Si*C*(CH_3)$_3$), 20.6 (OC(O)*C*H_3), 26.2 (SiC(*C*H_3)$_3$), 26.4 (*C*H_2CHO), 27.7 (OC(*C*H_3)$_3$), 30.2 (CC(O)*C*H_3), 39.2 (N*C*H_2), 48.0 (NCH_2*C*H), 51.3 (N*C*H),

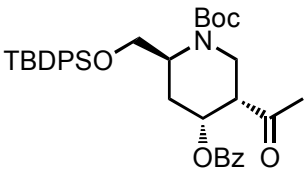
63.3 (*C*H_2O), 68.3 (*C*HO), 80.0 (O*C*(CH_3)$_3$), 127.2 (Ar*C*H), 129.4 (Ar*C*H), 132.2 (ArC_q), 135.0 (Ar*C*H), 153.2 (N*C*=OO), 169.5 (O*C*=OCH_3), 205.4 (C*C*=OCH_3)

m/z: $(ES)^+$ 576.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 576.2764. $C_{31}H_{43}NNaO_6Si$ requires *M* 576.2757]

(*S*)-*tert*-Butyl-3-acetyl-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5,6-dihydropyridine-1(2*H*) –carboxylate (152b) and **(2*S*, 4*R*, 5*S*)-*tert*-Butyl 5-acetyl-4-(benzoyloxy)-2-(((*tert*-butyldiphenyl silyl)oxy)methyl)piperidine-1-carboxylate (152a)**





Ozone was bubbled through a solution of alkene **150b** (101 mg, 0.17 mmol) in CH_2Cl_2:MeOH (2:1, 3 mL) and quenched with DMS (15 μL, 0.20 mmol) according to general procedure 3. Purification by flash column chromatography (R_f = 0.47, hexane:EtOAc, 3:1) gave enone **152b** as a colourless oil (50 mg, 61%).

ν_{max}: (film)/cm^{-1} 2961 (CH), 2929 (CH), 2857 (CH), 1697 (C=O), 1680 (C=O), 1106, 701

δ_H: (300 MHz, $CDCl_3$) 1.07 (9H, s, SiC(CH_3)$_3$), 1.44 (9H, s, OC(CH_3)$_3$), 2.23 (3H, s, (C(O)CH_3), 2.26-2.34 (1H, m, CHC*H*HCH), 2.42-2.58 (1H, m, CHC*H*HCH), 3.41-3.62 (4H, stack, NCH_2 and CH_2O), 4.32-4.52 (1H, m, NC*H*), 6.72-6.79 (1H, m, =C*H*), 7.31-7.47 (6H, m, ArC*H*), 7.56-7.64 (4H, m, ArC*H*)

m/z: $(ES)^+$ 516.3(100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 516.2550. $C_{29}H_{39}NNaO_4$ Si requires *M* 516.2546]

Further elution (R_f = 0.32) gave ketone **151b** as a colourless oil (10 mg, 10%).

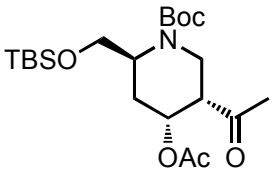
ν_{max}: (film)/cm^{-1} 3072 (ArCH), 3012 (ArCH), 2960 (CH), 2932 (CH), 2858 (CH), 1720 (C=O), 1694 (C=O), 1603, 1584, 1427, 1272, 1112, 756, 709

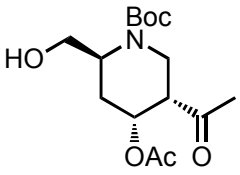
δ_H: (300 MHz, $CDCl_3$) 1.07 (9H, s, $SiC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 1.94-2.02 (1H, m, CHC*H*HCH), 2.19 (3H, s, $C(O)CH_3$), 2.42-2.55 (1H, m, CHC*H*HCH), 3.11-3.24 (2H, stack, NC*H*H and NCH_2CH), 3.64-3.82 (2H, m, CH_2O), 4.31-4.50 (2H, stack, NC*H* and NC*H*H), 5.48-5.52 (1H, m, C*H*O), 7.31-7.47 (8H, m, ArC*H*), 7.49-7.53 (3H, m, ArC*H*), 7.62-7.70 (4H, m, ArC*H*)

m/z: $(ES)^+$ 638.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 638.2904. $C_{36}H_{45}NNaO_6Si$ requires *M* 638.2914]

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-acetoxy-5-acetyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl) piperidine-1-carboxylate (151ci) and **(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-acetoxy-5-acetyl-2-(hydroxymethyl)piperidine-1-carboxylate (151cii)**





Ozone was bubbled through a solution of alkene **150c** (106 mg, 0.25 mmol) in CH_2Cl_2:MeOH (2:1, 3 mL) and quenched with DMS (23 μL, 0.30 mmol) according to general procedure 3. Purification by flash column chromatography (R_f = 0.30, hexane:EtOAc, 3:1) gave ketone **151ci** as a colourless oil (6 mg, 5%).

$[\alpha]_D^{21}$: -21.6 (*c* 0.5 in $CHCl_3$)

ν_{max}: (neat)/cm^{-1} 2955 (CH), 2930 (CH), 2857 (CH), 1739, (C=O), 1720 (C=O), 1694 (C=O), 1472, 1419, 1248, 1047, 838, 777

δ_H: (300 MHz, $CDCl_3$) 0.04 (6H, s, SiCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 1.43 (9H, s, OC(CH_3)$_3$), 1.82-1.91 (1H, m, C*H*HCHO), 2.02 (3H, s, OC(O)CH_3), 2.16 (3H, s, CC(O)CH_3), 2.25-2.69 (1H, m, C*H*HCHO), 3.06 (1H, q, *J* 4.2, NCH$_2$C*H*), 3.26 (1H, dd, *J* 14.0 and 4.2, NC*H*H), 3.63 (1H, dd, *J* 10.5 and 4.5, C*H*HO), 3.69 (1H, dd, *J* 10.5 and 6.3, C*H*HO), 4.23-4.36 (2H, stack, NC*H*H and NC*H*), 5.27-5.33 (1H, m, C*H*O)

δ_C: (75 MHz, $CDCl_3$) -4.6 (Si(*C*H$_3$)$_2$), 19.1 (Si*C*(CH$_3$)$_3$), 22.1 (OC(O)*C*H$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 28.0 (*C*H$_2$CHO), 29.3 (OC(*C*H$_3$)$_3$), 31.5 (CC(O)*C*H$_3$), 41.5 (N*C*H$_2$), 49.7 (NCH$_2$*C*H), 52.7 (N*C*H), 65.0 (*C*H$_2$O), 69.9 (*C*HO), 81.0 (O*C*(CH$_3$)$_3$) 155.6 (N*C*=O), 171.4 (O*C*=OCH$_3$), 206.5 (C*C*=OCH$_3$)

m/z: $(ES)^+$ 452.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 452.2436. $C_{21}H_{39}NNaO_6Si$ requires *M* 452.2444]

Further elution (R_f = 0.36, hexane:EtOAc, 1:3) gave ketone **151cii** as a colourless oil (57 mg, 73%).

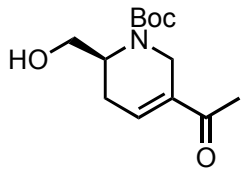
ν_{max}: (neat)/cm^{-1} 3384 (OH), 2954 (CH), 2932 (CH), 2858 (CH), 1722 (C=O), 1693 (C=O), 1472, 1248, 1046

δ_H: (300 MHz, $CDCl_3$) 1.44 (9H, s, OC(CH_3)$_3$), 1.81-1.90 (1H, m, C*H*HCHO), 2.01 (3H, s, OC(O)CH_3), 2.10-2.18 (4H, stack, CC(O)CH_3 and C*H*HCHO), 2.75-2.82 (1H, m, NCH$_2$C*H*), 3.34-3.45 (1H, m, NC*H*H), 3.63-3.70 (2H, m, CH_2O), 3.82-3.89 (1H, m, NC*H*H), 3.94-4.02 (1H, m, NC*H*), 5.28-5.31 (1H, m, C*H*O)

m/z: $(ES)^+$ 338.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 338.1585. $C_{15}H_{25}NNaO_6$ requires *M* 338.1580]

(*S*)-*tert*-Butyl 3-acetyl-6-(hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (152d)



Ozonolysis

Ozone was bubbled through a solution of alkene **150d** (96 mg, 0.20 mmol) in CH_2Cl_2:MeOH (1:1, 2 mL) and quenched with DMS (17 μL, 0.23 mmol) according to general procedure 3. Purification by flash column chromatography (R_f = 0.45, hexane:EtOAc, 1:3) gave enone **152d** as a colourless oil (15 mg, 29%).

Haloform Reaction

Bromine (27 μL, 0.53 mmol) was added to a solution of NaOH (63 mg, 1.58 mmol) in water (1 mL) cooled to 0 °C, after 5 min the dark brown colour of the solution dissipated and the solution was transferred to a solution of ketone **149** (48 mg, 0.18 mmol) in dioxane (0.5 mL) cooled to 0 °C. The solution was allowed to warm to rt and stirred overnight. The solution was acidified to a pH of 4 with an aqueous solution 1 M HCl. The reaction was concentrated *in vacuo* before the crude residue was taken up in acetone, filtered and concentrated *in vacuo* to give the crude product that was purified by semi-preparative HPLC (water/MeOH gradient + 0.01% TFA) to give the product **152d** as a colourless oil (22 mg, 53%).

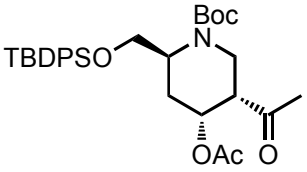
ν_{max}: (film)/cm^{-1} 3389 (OH), 2978 (CH), 2930 (CH), 2857 (CH), 1671 (C=O), 1366, 1161

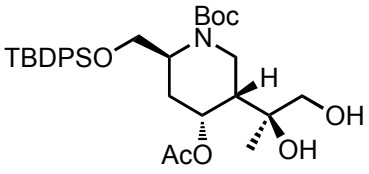
δ_H: (300 MHz, $CDCl_3$) 1.45 (9H, s, OC(C*H*$_3$)$_3$), 2.22-2.29 (4H, stack, C(O)C*H*$_3$ and NCHC*H*HCH), 2.45-2.51 (1H, m, NCHCH*H*CH), 2.65 (1H, br s, OH), 3.41-3.50 (2H, m, C*H*$_2$O), 3.68 (1H, d, *J* 13.9, NC*H*H), 4.33-4.52 (2H, stack, NCH*H* and NCH), 6.83-6.89 (1H, m, C*H*=*)*

m/z: $(ES)^+$ 278.1(100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 278.1359. $C_{13}H_{21}NNaO_4$ requires *M* 278.1368]

(2*S*, 4*R*, 5*S*)-*tert*-Butyl 4-acetoxy-5-acetyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl) piperidine-1-carboxylate (151a) and **(2*S*, 4*R*, 5*R*)-*tert*-Butyl 4-acetoxy-2-(((*tert*-butyl diphenylsilyl)oxy)methyl)-5-((*R*)-1,2-dihydroxyethyl)piperidine-1-carboxylate (153)





$NaIO_4$ (135 mg, 0.63 mmol) was added to a stirred solution of alkene **150a** (166 mg, 0.30 mmol) and 2,6-lutidine (66 μL, 0.60 mmol) in dioxane:water (2:1, 3 mL) cooled to 0 °C. A small crystal of OsO_4 was added to the solution and the resulting mixture was stirred at 0 °C for 2h before the reaction was quenched by the addition of a saturated aqueous solution of Na_2SO_3 (3 mL). The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic fractions were washed with brine (10 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the crude product which was purified by flash column chromatography (R_f = 0.33, hexane:EtOAc, 3:1) to give ketone **151a** as a colourless oil (107 mg, 65%). Data *vide supra.*

Further elution (R_f = 0.10) gave diol **153** as a white crystalline solid (34 mg, 19%).

mp: 87-88 °C (from hexane:EtOAc)

ν_{max}: (neat)/cm^{-1} 3470 (OH), 2930 (CH), 2858 (CH), 1734 (C=O), 1677 (C=O), 1427, 1244, 1113, 756

δ_H: (300 MHz, $CDCl_3$) 1.03 (9H, s, $SiC(CH_3)_3$), 1.15 (1H, br s, O*H*), 1.21 (1H, br s, O*H*), 1.37 (9H, s, $OC(CH_3)_3$), 1.39 (3H, s, CCH_3), 1.72-1.87 (1H, m, C*H*HCHO), 2.03-2.12 (4H, stack, CCH_3 and C*H*HCHO), 2.14-2.27 (1H, m, NCH_2CH), 3.35-3.41 (2H, m, NCH_2), 3.62-3.83

(2H, m, CH_2O), 3.89-4.07 (1H, m, NC*H*), 5.31-4.41 (1H, m, C*H*O), 7.32-7.43 (6H, m, ArC*H*), 7.51-7.62 (4H, m, ArC*H*)

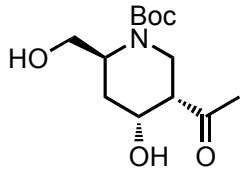
δ_C: (75 MHz, $CDCl_3$) 18.0 (Si*C*(CH_3)$_3$), 19.7 (COH*C*H_3), 21.5 (NCH_2*C*H), 22.0 (OC(O)*C*H_3), 25.2 (SiC(*C*H_3)$_3$), 27.6 (OC(*C*H_3)$_3$), 28.3 (*C*H_2CHO), 30.2 (CC(O)*C*H_3), 37.7 (N*C*H_2), 49.9 (NCH_2*C*H), 51.3 (N*C*H), 63.2 (*C*H_2OH), 66.1 (*C*H_2OSi), 67.8 (*C*HO), 71.2 (*C*$_q$OH) 78.6 (O*C*(CH_3)$_3$), 126.1 (Ar*C*H), 128.1 (Ar*C*H), 131.2 (Ar*C*$_q$), 133.8 (Ar*C*H), 153.0 (N*C*=OO), 166.7 (O*C*=OCH_3)

m/z: $(ES)^+$ 608.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 608.3018. $C_{32}H_{47}NNaO_7Si$ requires *M* 608.3020]

X-ray: See *Appendix*

(2*S*, 4*R*, 5*S*)-5-Acetyl-4-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylic acid *tert*-butyl ester (149)



2,6-Lutidine (10.2 mL, 93.4 mmol) was added to a solution of alkene **146** (11.5 g, 42.4 mmol) in dioxane:water (2:1, 210 mL) cooled to 0 °C. $NaIO_4$ (22.7 g, 106 mmol) followed by OsO_4 (10 mg, 0.1 mol%) were added to the stirred solution. After 5 min a white precipitate began to fall out of solution. The reaction was stirred at 0 °C for 30 min before being allowed to warm to room temperature and stirred for a further 5 h. The reaction was cooled to 0 °C and quenched with a saturated aqueous solution of Na_2SO_3 (100 mL). The aqueous phase was extracted with EtOAc (5 x 200 mL) before the combined organic phases were washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the product **149** as a colourless oil (11.2 g, 97%).

R_f: 0.24 (EtOAc)

$[\alpha]_D^{20}$: -104.2 (*c* 1 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3391 (OH), 2976 (CH), 2932 (CH), 1693 (C=O), 1662 (C=O), 1159, (C-O), 1051 (C-O)

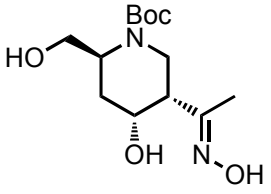
δ_H: (400 MHz, $CDCl_3$) 1.40 (9H, s, $C(CH_3)_3$), 1.76 (1H, dt, *J* 13.5 and 4.3, NCHC*H*HCH), 1.80-1.90 (1H, m, NCHC*H*HCH), 2.13 (3H, s, $CHC(O)CH_3$), 2.66 (1H, q, *J* 3.4, NCH_2CH), 3.24 (1H, dd, *J* 14.2 and 3.4, NC*H*H), 3.55 (2H, d, *J* 6.4, CH_2OH) 3.64-3.82 (2H, m, 2 x O*H*), 3.92-4.21 (3H, stack, NC*H*H, C*H*OH and C*H*N)

δ_C: (100 MHz, $CDCl_3$) 28.2 ($C(CH_3)_3$), 29.5 ($C(O)CH_3$), 31.3 ($NCHCH_2CH$), 41.2 (NCH_2), 51.8 (NCH_2CH), 53.2 (N*C*H), 61.8 (CH_2O), 66.3 (*C*HOH), 80.5 ($C(CH_3)_3$), 155.1 (OC=O), 210.9 ($CH_3C=O$)

m/z: $(ES)^+$ 296.2 (100%, $[M+Na]^+$), 240.1 (11, $[M+Na-^tBu]^+$)

HRMS: [Found: $(M+Na)^+$ 296.1469. $C_{13}H_{23}NNaO_5$ requires *M* 296.1474]

(2*S*, 4*R*, 5*R*)-*tert*-Butyl 4-hydroxy-5-((*E*)-1-(hydroxyimino)ethyl)-2-(hydroxy methyl) piperidine-1-carboxylate (158)



Et_3N (23 µL, 0.17 mmol) was added to a stirred solution of ketone **149** (15 mg, 0.06 mmol) in EtOH (0.5 mL) followed by the addition of hydroxylamine hydrochloride (6 mg, 0.08 mmol). The reaction was heated to reflux for 2 h before being allowed to cool to room temperature and quenched by the addition of water (5 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (4 x 5 mL). The combined organic fractions were washed with brine (5 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give the oxime product **158** as a colourless oil (16 mg, quant.)

R_f : 0.53 ($CHCl_3$:MeOH, 9:1)

ν_{max}: (film)/cm^{-1} 3506 (OH), 3295 (OH), 2976 (CH), 2932 (CH), 1668 (C=O, C=N), 1159, 1051, 950 (N-O)

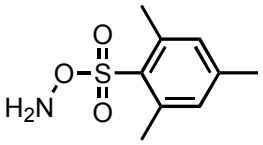
δ_H: (300 MHz, $CDCl_3$) 1.42 (9H, s, C(CH_3)$_3$), 1.62-1.70 (1H, m, NCHC*H*HCH) 1.90-2.04 (4H, stack, NCHC*H*HCH and CCH_3), 2.39-2.44 (1H, m, NCH_2CH), 3.51-3.68 (2H, m, NC*H*H), 3.60-3.71 (2H, m, CH_2OH) 3.92-4.01 (1H, m, C*H*OH), 4.14-4.25 (1H, m, C*H*N)

δ_C: (75 MHz, $CDCl_3$) 17.4 (CCH_3), 28.5 (C(CH_3)$_3$), 31.8 (NCHCH_2CH), 40.5 (NCH_2CH), 45.2 (NCH_2), 53.9 (NCH), 61.8 (CH_2O), 68.3 (CHOH), 80.2 ($C(CH_3)_3$), 155.0 (C=O), 159.4 (C=N-OH)

m/z: $(ES)^+$ 311.2 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 311.1590. $C_{13}H_{24}N_2NaO_5$ requires *M* 311.1583]

***O*-(Mesitylsulfonyl)hydroxylamine (162)**



$NaHCO_3$ (2.2 g, 25.9 mmol) was added in small portions over 5 min to a stirred solution of hydroxylamine hydrochloride (1.0 g, 14.3 mmol) in CH_2Cl_2:water (1:1 20 mL) cooled to 0 °C. After 10 min $(Boc)_2O$ (2.5 g, 11.5 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with a saturated aqueous solution of $NaHCO_3$ (25 mL) and the organic phase separated. The aqueous phases was further extracted with CH_2Cl_2 (3 x 25 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give *N*-Boc hydroxylamine as a colourless oil that solidified on standing (1.4 g).[113] Et_3N (1.8 mL, 12.7 mmol) was added to a solution of *N*-Boc hydroxylamine (1.4 g, 10.6 mmol) in MeCN (10 mL) cooled to 0 °C. MesCl (2.3 g, 10.6 mmol) in MeCN (5 mL) was added dropwise over 10

min to the solution resulting in a white precipitate. The solution was allowed to warm to room temperature and stirred for a further 4 h. The reaction mixture was filtered and washed with Et_2O (3 x 5 mL). The combined filtrates were concentrated *in vacuo* to give the crude *N*-Boc mesitylhydroxylamine as a yellow oil (3.6 g). TFA (20 mL) was added to *N*-Boc mesitylhydroxylamine (3.6 g) cooled to 0 °C. The solution was allowed to warm to room temperature and stirred for a further 30 min before being poured into ice cold water (20 mL). The solution was extracted with Et_2O (4 x 20 mL) and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the product **162** as a pale yellow solid. (2.0 g, 64% over 3 steps).

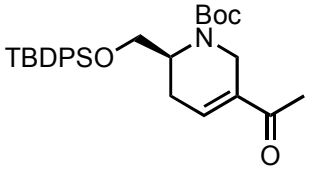
mp: 90-92 °C (from Et_2O) (Lit.[114] 90-91 °C)

ν_{max}: (neat)/cm^{-1} 3371 (NH), 3262 (NH), 2975 (CH), 2988 (CH), 1603, 1330, 1149

δ_H: (300 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 2.64 (6H, s, CH_3), 4.70 (2H, br s, NH_2), 6.93 (2H, C*H*)

δ_C: (101 MHz, $CDCl_3$) 20.9 (*C*H_3), 23.1 (*C*H_3), 131.7 (Ar*C*H), 138.2 (ArC_q), 139.5 (ArC_q), 143.0 (ArC_q)

(*S*)-*tert*-Butyl 3-acetyl-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)5,6-dihydropyridine - 1(2*H*)-carboxylate (152b)



Haloform Reaction

Bromine (6 µL, 0.13 mmol) was added to a solution of NaOH (10 mg, 0.25 mmol) in water (0.5 mL) cooled to 0 °C, after 2 min the dark brown colour of the solution dissipated and the solution was then transferred to a

solution of ketone **151a** (23 mg, 0.04 mmol) in dioxane (0.5 mL) cooled to 0 °C. The solution was stirred at 0 °C for 4 h before being quenched with a saturated aqueous solution of NH_4Cl (5 mL). The mixture was extracted was with EtOAc (4 x 5 mL) and the combined organic fractions were washed with a saturated aqueous solution of Na_2SO_3 (10 mL), water (10 mL) and brine (10 mL) before being concentrated *in vacuo* to give the crude product that was purified by flash column chromatography (R_f = 0.46, hexane:EtOAc, 3:1) to give the product **152b** as a colourless oil (10 mg, 52%).

Silyl Enol Ether Formation

KHMDS (0.5 M solution in toluene, 108 μL, 0.05 mmol) was added dropwise over 10 s to a stirred solution of ketone **151a** (30 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) containing 4 Å MS cooled to -78 °C. TMSOTf (10 μL, 0.05 mmol) was added immediately afterwards and the resulting solution was stirred at -78 °C for a further 1 h before being quenched by the addition of water (2 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (4 x 4 mL). The combined organic fractions were washed with brine (4 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (R_f = 0.46, hexane:EtOAc, 3:1) to give the product **152b** as a colourless oil (20 mg, 83%).

Oxidative Cleavage of Silyl Enol Ether

$NaIO_4$ (33 mg, 0.15 mmol) was added to a stirred solution of 2,6-lutidine (13 μL, 0.12 mmol) in dioxane:water (1:1, 1 mL) cooled to 0 °C. A small crystal of OsO_4 was added to the mixture before a solution of silyl enol ether **164** (30 mg, 0.06 mmol) in dioxane (0.5 mL) was added dropwise over 2 min. The solution was allowed to warm to rt before being stirred for a

further 20 min. The reaction was quenched by the addition of a saturated aqueous solution of $NaSO_3$ (5 mL) and diluted with EtOAc (5 mL). The organic phase was separated and the aqueous phase further extracted with EtOAc (3 x 5 mL). The combined organic fractions were washed with water (5 mL), brine (5 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give the crude product. The crude product was purified by flash column chromatography (R_f = 0.45, hexane:EtOAc, 1:3) to give the enone **152b** as a colourless oil (13 mg, 82%).

ν_{max}: (film)/cm^{-1} 3389 (OH), 2978 (CH), 2930 (CH), 1670 (C=O), 1366, 1161, 1064

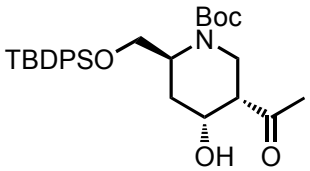
δ_H: (400 MHz, $CDCl_3$) 1.43 (9 H, s, C(C*H*$_3$)$_3$), 2.25 (3H, s, C(O)C*H*$_3$), 2.30-2.35 (1H, m, NCHC*H*HCN) 2.51-2.59 (1H, m, NCHC*H*HCH) 2.67 (1H, br, s, O*H*), 3.42-3.51 (2H, m, C*H*$_2$OH), 3.62-3.71 (1H, m, NC*H*H), 4.35-3.53 (2H, stack, NC*H*H and N*C*H), 6.84-6.89 (1H, m, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 25.1 (C(O)*C*H$_3$), 26.1 (NCH*C*H$_2$CH), 28.4 (C(*C*H$_3$)$_3$), 39.2 (N*C*H$_2$), 49.8 (N*C*H), 63.2 (*C*H$_2$O), 80.5 (*C*(CH$_3$)$_3$), 136.1 (=*C*$_q$), 136.3 (=*C*H), 155.1 (OC=O), 196.9 (CH_3C=O)

m/z: $(ES)^+$ 278.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 278.1479. $C_{13}H_{21}NNaO_4$ requires *M* 278.1471]

(2*S, 4*R**, 5*S**)-*tert*-butyl 5-acetyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxypiperidine-1-carboxylate (148a)**



Silyl ether **148a** was prepared from: piperidine **149** (0.98 g, 3.60 mmol), Et_3N (1.00 mL, 7.19 mmol), DMAP (88 mg, 0.72 mmol)

and TBDPSCl (0.94 mL, 3.60 mmol); in a solution of CH_2Cl_2 (7 mL) according to general procedure 1. The crude material was purified by flash column chromatography (R_f = 0.32, hexane:EtOAc, 2:1) to give the product **148a** as a colourless oil (1.68 g, 91%).

ν_{max}: (film)/cm^{-1} 3427 (OH), 3078 (ArCH), 3056 (ArCH), 2970 (CH), 2932 (CH), 2859 (CH), 1690 (C=O), 1671 (C=O), 1426, 1106, 1079, 701

δ_H: (300 MHz, $CDCl_3$) 1.05 (9H, s, SiC(CH_3)$_3$), 1.40 (9H, s, OC(CH_3)$_3$), 1.51-1.70 (1H, m, NCHC*H*H), 1.88-2.09 (1H, m, NCHC*H*H), 2.26 (3H, s, C(O)CH_3), 2.68-2.82 (1H, m, NCH_2CH), 3.08 (1H, dd, *J* 14.6 and 3.7, NC*H*H), 3.67 (2H, dd, *J* 6.4 and 3.0, CH_2O), 3.84-4.01 (1H, m, C*H*OH), 4.26-4.48 (1H, m, NC*H*), 4.51-4.71 (1H, m, NC*H*H), 7.32-7.49 (6H, m, ArC*H*), 7.65 (4H, dd, *J* 7.4 and 1.7, ArC*H*)

δ_C: (101 MHz, $CDCl_3$) 19.1 (Si*C*(CH_3)$_3$), 26.9 (SiC(*C*H_3)$_3$), 28.3 (OC(*C*H_3)$_3$), 29.6 (C(O)*C*H_3), 31.1 (NCH*C*H_2), 41.1 (N*C*H_2), 51.7 (NCH_2CH), 52.3 (N*C*H), 63.3 (*C*H_2O), 67.3 (*C*HOH),80.2 (O*C*(CH_3)$_3$), 127.8 (Ar*C*H), 129.8 (Ar*C*H), 133.1 (ArC_q), 135.5 (Ar*C*H), 135.6 (Ar*C*H), 154.8 O*C*=O), 212.2 (CH_3C=O)

m/z: $(ES)^+$ 534.3 (100%, $[M+Na]^+$)

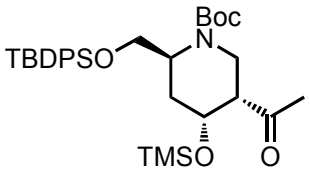
HRMS: [Found: $(M+Na)^+$ 534.2662. $C_{29}H_{41}NNaO_5Si$ requires *M* 534.2652]

General Procedure 4: TMS Ether Formation

A solution containing the ketone (1 eq) in CH_2Cl_2 (0.1-0.2 M) was transferred *via* cannula to a r.b. flask containing 4 Å MS and stirred for 5 min at room temperature. Et_3N (2-6 eq) was added to the mixture and the resulting solution was stirred for a further 5 min before being cooled to -78 °C. TMSOTf (2-3 eq) was added dropwise over 5 min and the resulting solution was stirred at -78 °C for a further 5 h. The solution was diluted with CH_2Cl_2 (0.1 M) and then

poured into a saturated aqueous solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 x 3. The combined organic fractions were washed with brine and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the crude product.

(2*S, 4*R**, 5*S**)-*tert*-butyl 5-acetyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxy piperidine-1-carboxylate (163)**



Silyl ether **163** was prepared from: alcohol **148a** (80 mg, 0.16 mmol), Et_3N (66 µL, 0.46 mmol) and TMSOTf (60 µL, 0.32 mmol); in CH_2Cl_2 (1.6 mL) according to general procedure 4. The crude product as a light brown oil which was purified by flash column chromatography (hexane:EtOAc, 6:1, R_f = 0.49) to give the pure product **163** as a colourless oil (76mg, 82%).

ν_{max}**:** (film)/cm^{-1} 3076 (ArCH), 3052 (ArCH), 2959 (CH), 2935 (CH), 2858 (CH), 1713 (C=O), 1693 (C=O), 1427, 1251, 1161, 1099, 840, 701

δ_H**:** (300 MHz, $CDCl_3$) 0.11 (9H, s, Si(C*H*$_3$)$_3$), 1.05 (9H, s, SiC(C*H*$_3$)$_3$), 1.41 (9H, s, OC(C*H*$_3$)$_3$), 1.85-1.95 (1H, m, NCHC*H*H), 2.02-2.15 (1H, m, NCHC*H*H), 2.17 (3H, s, C(O)C*H*$_3$), 2.76 (1H, q, *J* 3.7, NCH$_2$C*H*), 3.08 (1H, dd, *J* 14.2 and 3.7, NC*H*H), 3.65 (1H, dd, *J* 10.1 and 5.4, C*H*HO), 3.73 (1H, dd, *J* 10.1 and 6.8, C*H*HO), 4.20 (1H, dd, *J* 14.2 and 3.7, NC*H*H), 4.26-4.42 (2H, stack, NC*H* and C*H*O), 7.32-7.55 (6H, m, ArC*H*), 7.65 (4H, dd, *J* 7.5 and 1.6, ArC*H*)

δ_C**:** (101 MHz, $CDCl_3$) 0.29 (Si(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 27.0 (SiC(*C*H$_3$)$_3$), 28.5 (OC(*C*H$_3$)$_3$), 31.3 (C(O)*C*H$_3$), 32.0 (NCH*C*H$_2$), 40.4 (N*C*H$_2$), 52.0 (*C*H), 52.1 (*C*H), 64.5

(CH$_2$O), 67.1 (CHO), 79.8 (OC(CH$_3$)$_3$), 127.9 (ArCH), 129.9 (ArCH), 133.3 (ArC_q), 133.4 (ArC_q), 135.6 (ArCH), 135.7 (ArCH), 155.0 OC=O), 208.1 (CH$_3C$=O)

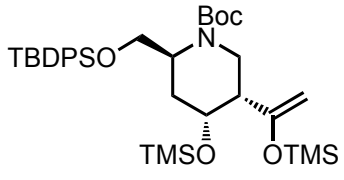
m/z: (ES)$^+$ 606.3 (100%, [M+Na]$^+$)

HRMS: [Found: (M+Na)$^+$ 606.3054. $C_{32}H_{49}NNaO_5Si_2$ requires *M* 606.3047]

General Procedure 5: Silyl Enol Ether Formation

A solution containing the ketone (1 eq) in CH_2Cl_2 (0.1 M) was transferred *via* cannula to a r.b. flask containing 4 Å MS. The solution was stirred for 5 min at room temperature before Et_3N (5 eq) was added and the resulting mixture was cooled to -40 °C. TMSOTf (2 eq) was added dropwise and the resulting solution was stirred at -40 °C for a further 3 h. The solution was diluted with CH_2Cl_2 and then poured into a saturated aqueous solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was further extracted with 3 x CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4 before the solvent was removed *in vacuo* to afford the crude silyl enol ether product. The crude product was diluted with Et_2O and the colourless Et_2O layer was removed while the denser light brown layer, containing triethylammonium triflate, was further extracted with 3 x Et_2O. The Et_2O layers were combined and the solvent removed *in vacuo* to give the silyl enol ether product.

(2*S, 4*R**, 5*S**)-*tert*-butyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((trimethylsilyl) oxy)-5-(1-((trimethylsilyl)oxy)vinyl)piperidine-1-carboxylate (164)**



Silyl enol ether **164** was prepared from: ketone **163** (1.43 g, 2.80 mmol), Et_3N (1.95 mL, 14.0 mmol) and TMSOTf (1.01 mL, 5.60 mmol); in CH_2Cl_2 (30 mL) according to general procedure 5 gave the product **164** as a colourless oil (1.60 g, 97%).

R_f : 0.34 (hexane:EtOAc, 10:1 + 1% Et_3N)

ν_{max}: (film)/cm^{-1} 3076 (ArCH), 3052 (ArCH), 2959 (CH), 2933 (CH), 2858 (CH), 1693 (C=O), 1249, 1104, 838, 701

δ_H: (300 MHz, C_6D_6) 0.17 (9H, s, Si(CH_3)$_3$), 0.26 (9H, s, Si(CH_3)$_3$), 1.18 (9H, s, SiC(CH_3)$_3$), 1.42 (9H, s, OC(CH_3)$_3$), 1.93 (1H, dt, *J* 13.1 and 4.0, NCHC*H*H), 2.29 (1H, dd, *J* 8.7 and 4.0, NCH$_2$C*H*), 2.34-2.46 (1H, m, NCHC*H*H), 3.21 (1H, dd, *J* 14.2 and 4.0, NC*H*H), 3.82-3.97 (2H, m, CH_2O), 4.22-4.32 (4H, stack NC*H*H, C*H*O and =CH_2), 4.44-4.72 (1H, m, NC*H*), 7.21-7.27 (6H, m, ArC*H*), 7.76-7.83 (4H, m, ArC*H*)

δ_C: (101 MHz, C_6D_6) 0.34 (Si(*C*H$_3$)$_3$), 0.44 (Si(*C*H$_3$)$_3$), 19.5 (Si*C*(CH$_3$)$_3$), 27.2 (SiC(*C*H$_3$)$_3$), 28.6 (OC(*C*H$_3$)$_3$), 32.0 (NCH*C*H$_2$), 44.0 (N*C*H$_2$), 46.9 (NCH$_2$*C*H), 53.1 (N*C*H), 65.0 (*C*H$_2$O), 67.3 (*C*HO), 79.0 (O*C*(CH$_3$)$_3$), 91.8 (C=*C*H$_2$), 128.2 (Ar*C*H), 130.1 (Ar*C*H), 133.9 (ArC_q), 134.0 (ArC_q), 136.0 (Ar*C*H), 155.0 (O*C*=O), 158.9 (*C*=CH$_2$)

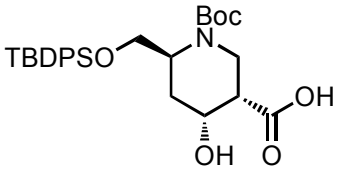
m/z: $(ES)^+$ 678.4 (97%, $[M+Na]^+$), 466.3 (100)

HRMS: [Found: $(M+Na)^+$ 678.3445. $C_{35}H_{57}NNaO_5Si_3$ requires *M* 678.3442]

General procedure 6: Ozonolysis of Silyl Enol Ether

$NaHCO_3$ (10 eq) was added to a stirred solution of silyl enol ether X (1 eq) in CH_2Cl_2 (0.2 M). The resulting solution was cooled to -78 °C before MeOH (0.2 M) was added dropwise over 5 min. A stream of gas containing O_3/O_2 was passed through a glass pipette and bubbled into the solution before passing out through a gas scrubber containing an aqueous solution of 10% KI to remove any excess O_3. The stream of O_3/O_2 was continued until the solution turned in colour from colourless to blue, usually 5 min. O_2 Was then bubbled through the solution for 2 min before Ar was bubbled through the solution for a further 2 min resulting in a colour change of blue to colourless. DMS (10 eq) was added to the solution and stirred at -78 °C for 5 min before being allowed to warm to room temperature and stirred at room temperature until a negative test for peroxides was detected using starch/I_2 paper (positive test equates to a dark purple spot after exposure to water whereas as negative test equates to a colourless spot under the same conditions), usually 2 h. The reaction mixture was cooled to 0 °C and acidified to pH 4 with 1 M HCl before the solvent was removed *in vacuo* and the residue taken up in acetone, filtered and the residue washed with 3 x further portions of acetone. The solvent was removed *in vacuo* to give the carboxylic acid.

(3*S, 4*R**, 6*S**)-1-(*tert*-butoxycarbonyl)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxy piperidine-3-carboxylic acid (166)**



TBDPS Ozonolysis

Carboxylic acid **166** was prepared from: Silyl enol ether **164** (0.53 g, 0.81 mmol), $NaHCO_3$ (0.68g, 8.10 mmol), DMS (0.59

mL, 8.10 mmol): in CH_2Cl_2:MeOH (1:1, 8 mL) according to general procedure 6 to give the product **166** as a white foam (430 mg, quant.).

R_f : 0.54 (hexane:EtOAc, 1:3 + 1% AcOH)

ν_{max}: (film)/cm^{-1} 3396 (OH) 3072 (ArCH), 3051 (ArCH), 2959 (CH), 2929 (CH), 2856 (CH), 1693 (C=O), 1669 (C=O), 1427, 1110, 701

δ_H: (400 MHz, CD_3OD) 0.97 (9H, s, SiC(CH_3)$_3$), 1.36 (9H, s, OC(CH_3)$_3$), 1.80 (1H, dd, *J* 12.9 and 4.3, NCHC*H*H), 2.09 (1H, dt, *J* 12.9 and 6.7, NCHC*H*H), 2.59-2.67 (1H, m, NCH_2CH), 2.87 (1H, dd, *J* 14.2 and 3.5, NC*H*H), 3.60-3.71 (2H, m, CH_2O), 3.83-3.98 (1H, m, C*H*OH), 4.27 (1H, d, *J* 14.2, NC*H*H), 4.46 (1H, dd, *J* 12.6 and 6.2, NC*H*), 7.26-7.41 (6H, m, ArC*H*), 7.56-7.66 (4H, m, ArC*H*)

δ_C: (101 MHz, CD_3OD) 20.0 (Si*C*(CH_3)$_3$), 27.4 (SiC(*C*H_3)$_3$), 28.7 (OC(*C*H_3)$_3$), 30.7 (NCH*C*H_2), 41.6 (N*C*H_2), 46.3 (NCH_2*C*H), 53.5 (N*C*H), 64.2 (*C*H_2O), 66.3 (*C*HOH), 81.1 (O*C*(CH_3)$_3$), 128.9 (Ar*C*H), 131.0 (Ar*C*H), 134.3 (ArC_q), 134.4(ArC_q), 136.6 (Ar*C*H), 136.7 (Ar*C*H), 156.7 (N*C*=O), 175.2 (HO*C*=O)

m/z: $(ES)^-$ 512.3 (100%, $[M-H]^-$)

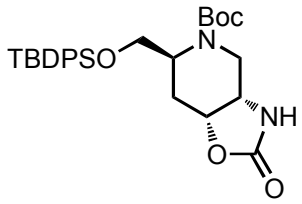
HRMS: [Found: $(M-H)^-$ 512.2474. $C_{28}H_{38}NNaO_6Si$ requires *M* 512.2468]

General Procedure 7: Curtis Rearrangement

Et_3N (2.4 eq) was added to a stirred solution of the carboxylic acid (1 eq) in toluene (0.1 M) at room temperature. The resulting mixture was heated to 80 °C for 2 h before being allowed to cool to room temperature. After cooling the reaction was quenched by the addition of a saturated solution of $NaHCO_3$. The solution was diluted with EtOAc and the organic phase was separated. The aqueous phase was further extracted with 3 x EtOAc and the combined

organic phases were washed water and brine before being dried over $MgSO_4$ and concentrated *in vacuo* to give the crude oxazolidinone product.

(3a*S, 6*S**, 7a*R**)-*tert*-butyl 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxohexahydro oxazolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (167)**



Oxazolidinone **167** was prepared from: carboxylic acid **166** (381 mg, 0.74 mmol), Et_3N (0.25 mL, 1.78 mmol) and DPPA (0.17 mL, 0.74 mmol); in toluene (7 mL) according to general procedure 7 to give the crude product as an orange oil, which was purified by flash column chromatography (R_f = 0.53, hexane:EtOAc, 1:3) to give the product **167** as a white crystalline product (256 mg, 83%).

mp: 174-175 °C (from hexane:EtOAc)

ν_{max}: (film)/cm^{-1} 3293 (NH) 3081 (ArCH), 3063 (ArCH), 2966 (CH), 2931 (CH), 2858 (CH), 1749 (C=O), 1683 (C=O), 1410, 1108, 700

δ_H: (400 MHz, $CDCl_3$) 1.05 (9H, s, SiC(CH_3)$_3$), 1.35 (9H, s, OC(CH_3)$_3$), 2.10-2.28 (2H, m, CH_2CHO), 3.14 (1H, br d, *J* 14.2, NC*H*H), 3.60 (1H, dd, *J* 10.2 and 1.7 , C*H*NH), 3.87 (1H, dd, *J* 10.2 and 4.3, C*H*HO), 4.00 (1H, br d, *J* 9.2, C*H*NH), 4.03-4.25 (2H, stack, NC*H*H and C*H*NCH$_2$), 5.02 (1H, br d, *J* 9.1, C*H*O), 5.36 (1H, br s, N*H*), 7.32-7.50 (6H, m, ArC*H*), 7.62 (4H, t, *J* 7.7, ArC*H*)

δ_C: (101 MHz, $CDCl_3$) 19.3 (Si*C*(CH_3)$_3$), 26.5 (*C*H_2CHNCH$_2$), 27.0 (SiC(*C*H_3)$_3$), 28.7 (OC(*C*H_3)$_3$), 41.9 (N*C*H_2), 49.6 (*C*HNCH$_2$), 51.4 (NCH$_2$*C*H), 65.5 (*C*H_2O), 73.2 (*C*HO), 80.8

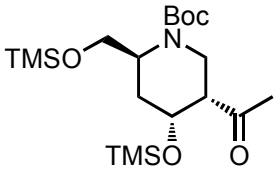
(O*C*(CH_3)$_3$), 128.0 (Ar*C*H), 129.9(Ar*C*H), 130.0 (Ar*C*H), 133.1 (ArC_q), 133.2 ArC_q), 135.5 (Ar*C*H) 135.6 (Ar*C*H), 156.0 (*C*=O), 158.6 (*C*=O)

m/z: $(ES)^+$ 533.2 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 533.2450. $C_{28}H_{38}N_2NaO_5Si$ requires *M* 533.2448]

X-ray: *See Appendix*

(2*S*, 4*R*, 5*S*)-5-Acetyl-4-(trimethylsilyloxy)-2-((trimethylsilyloxy)methyl) piperidine-1-tertbutyl carboxylic acid (168)



Silyl ether **168** was prepared from: alcohol **149** (45 mg, 0.17 mmol), Et_3N (80 μL, 0.59 mmol) and TMSOTf (108 μL, 0.51 mmol); in CH_2Cl_2 (2 mL) according to general procedure 4. The crude product was purified by flash column chromatography (R_f = 0.45, hexane:EtOAc, 6:1 + 1% Et_3N) to give the product **168** as a colourless oil (52 mg, 75%).

ν_{max}**:** (film)/cm^{-1} 2958 (CH), 2936 (CH), 1693 (C=O), 1662 (C=O), 1250, (C-O), 1095 (C-O)

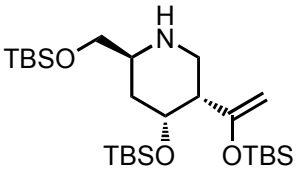
δ_H**:** (300 MHz, $CDCl_3$) 0.05 (9H, s, Si(C*H*$_3$)$_3$), 0.08 (9H, s, Si(C*H*$_3$)$_3$), 1.50 (9H, s, C(C*H*$_3$)$_3$), 1.76-1.84 (1H, m, NCHC*H*HCH), 1.93 (3H, s, CHC(O)C*H*$_3$), 2.13-2.27 (1H, m, NCHC*H*HCH) 2.41 (1H, q, *J* 3.4, NCH_2CH), 3.09 (1H, dd, *J* 14.2 and 3.4, NC*H*H), 3.58 (1H, dd, *J* 10.1 and 4.9, C*H*HOH), 3.68 (1H, dd, *J* 10.1 and 4.9, C*H*HOH), 4.21 (1H, q, *J*, 4.9, C*H*N), 4.32 (1H, dd, *J* 14.2 and 3.4, NC*H*H) 4.39-4.59 (1H, m, C*H*OH)

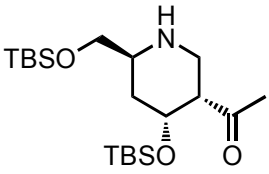
δ_C**:** (75 MHz, $CDCl_3$) -0.6 (Si(*C*H$_3$)$_3$), 0.2 (Si(*C*H$_3$)$_3$), 28.5 (C(*C*H$_3$)$_3$), 31.4 (NCH*C*H$_2$CH), 31.6 (C(O)*C*H$_3$), 41.2 (N*C*H$_2$), 52.1 (NCH_2*C*H), 52.3 (N*C*H), 63.7 (*C*H$_2$O), 67.6 (*C*HOH), 79.4 (*C*(CH$_3$)$_3$), 155.0 (OC=O), 206.2 (CH_3C=O)

m/z: $(ES)^+$ 440.2 (95%, $[M+Na]^+$), 368.2 (100, $[M+Na+H-Si(CH_3)_3]^+$)

HRMS: [Found: $(M+Na)^+$ 440.2267. $C_{19}H_{39}NNaO_5Si_2$ requires *M* 440.2265]

(2*S*, 4*R*, 5*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(((*tert*-butyldimethylsilyl)oxy) methyl)-5-(1-((*tert*-butyldimethylsilyl)oxy)vinyl)piperidine (170) and **1-((3*S*, 4*R*, 6*S*)-4-((*tert*-butyldi methylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)piperidin-3-yl)ethanone (171)**





A solution containing ketone **149** (117 mg, 0.43 mmol) in CH_2Cl_2 (4 mL) was transferred via cannula to a r.b. flask containing 4 Å MS and stirred for 5 min at room temperature. 2,6-Lutidine (187 μL, 1.71 mmol) was added to the mixture and the resulting solution was stirred for a further 5 min before being cooled to 0 °C. TBSOTf (344 μL, 1.50 mmol) was added dropwise over 3 min and the resulting solution was stirred at 0 °C for a further 2 h. The solution was diluted with CH_2Cl_2 (4 mL) and then poured into a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with brine (15 mL) and dried over Na_2SO_4 before the solvent was removed *in vacuo* to give the crude product as a colourless oil. The crude product was purified by flash column chromatography (R_f = 0.46, hexane:EtOAc, 6:1 + 1% Et_3N) to give **170** as a colourless oil (115 mg, 61%).

ν_{max}: (film)/cm^{-1} 3125 (NH), 2985 (CH), 2857 (CH), 1253, 1086, 832, 778

δ_H: (300 MHz, $CDCl_3$) 0.04 (12H, s, SiCH_3), 0.17 (6H, s, SiCH_3), 0.87 (18H, s, C(CH_3)$_3$), 0.93 (9H, s, C(CH_3)$_3$), 1.31-1.44 (1H, m, NCHC*H*HCH), 1.54-1.77 (1H, m, NCHC*H*HCH), 1.83 (1H br s, N*H*), 2.06 (1H, q, *J* 3.8, NCH_2CH), 2.91-3.23 (3H, stack, NCH_2 and C*H*NH), 2.66-3.33 (2H, m, CH_2O), 3.99-4.29 (3H, stack, =CH_2 and C*H*O)

m/z: $(ES)^+$ 538.4 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 538.3640. $C_{26}H_{57}NNaO_3Si_3$ requires *M* 538.3646]

Further elution gave **171** (R_f = 0.11) as a colourless oil (33 mg, 23%).

ν_{max}**:** (film)/cm^{-1} 3124 (NH), 2952 (CH), 2929 (CH) 2857 (CH), 1712 (C=O), 1252, 1085, 830, 774

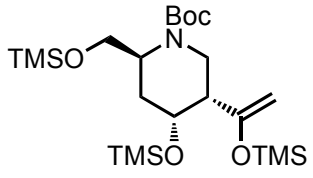
δ_H**:** (300 MHz, $CDCl_3$) 0.01-0.09 (12H, s, SiCH_3), 0.88 (18H, s, C(CH_3)$_3$), 1.27 (1H, br s, N*H*), 1.42 (1H, dt, *J* 13.4 and 4.1, NCHC*H*H), 1.59-1.47 (1H, m, NCHC*H*H), 2.21 (3H, s, C(O)CH_3), 2.35-2.48 (1H, m, NCH_2CH), 3.03 (1H, m, C*H*NH), 3.21 (2H, d, *J* 3.5, CH_2O), 3.40 (1H, dd, *J* 9.8 and 7.0, NC*H*H), 3.50 (1H, dd, *J* 9.8 and 4.1, NC*H*H), 4.37 (1H, dd, *J* 7.0 and 4.1, C*H*O),

δ_C**:** (101 MHz, $CDCl_3$) -5.2 (SiCH_3), 18.4 ($C(CH_3)_3$), 25.8 (C(CH_3)$_3$), 26.0 (C(CH_3)$_3$), 28.3 (C(O)CH_3), 36.4 ($NCHCH_2$), 42.5 (CH_2N), 51.6 (NCH_2CH), 55.3(*C*HN), 66.3 (CH_2O), 67.5 (*C*HO), 208.3 (*C*=O),

m/z: $(ES)^+$ 402.2 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 402.2852. $C_{20}H_{44}NNaO_3Si_2$ requires *M* 402.2860

(2*S*, 4*R*, 5*S*)-4-(Trimethylsilyloxy)-2-((trimethylsilyloxy)methyl)-5-(1-(trimethyl silyloxy)vinyl) piperidine-1-carboxylic acid *tert*butyl ester (172)



A solution containing ketone **149** (8.98 g, 32.9 mmol) in CH_2Cl_2 (150 mL) was transferred *via* cannula to a r.b. flask containing 4 Å MS with further portions of CH_2Cl_2 (3 x 5 mL) to complete the transfer. The solution was stirred for 5 min at room temperature before Et_3N (36.5 mL, 263 mmol) was added and the resulting mixture was cooled to -40 °C. TMSOTf (19.0 mL, 105

mmol) was added dropwise over 20 min to the stirred solution at -40 °C and the resulting solution was stirred for a further 3 h. The solution was diluted with CH_2Cl_2 (100 mL) and then poured into a saturated aqueous solution of $NaHCO_3$ (200 mL). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4 before the solvent was removed *in vacuo* to afford the crude product as a light brown oil. The crude product was diluted with Et_2O (100 mL) and the colourless Et_2O layer was removed while the denser light brown layer containing triethylammonium triflate was further extracted with Et_2O (4 x 20 mL). The Et_2O layers were combined and the solvent removed *in vacuo* to give the product **173** as a colourless oil (15.6 g, 92%).

R_f : 0.65 (6:1, hexane:EtOAc + 1% Et_3N)

$[\alpha]_D^{20}$: -13.2 (*c* 1 in CH_2Cl_2)

ν_{max}: (film)/cm^{-1} 2958 (CH), 2932 (CH), 2905 (CH), 1693 (C=O), 1249, 1084, 835, 747

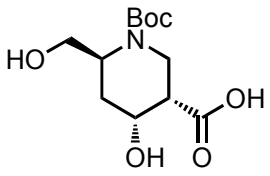
δ_H: (400 MHz, CD_2Cl_2) 0.10 (9H, s, Si(CH_3)$_3$), 0.11 (9H, s, Si(CH_3)$_3$), 0.21 (9H, s, Si(CH_3)$_3$), 1.43 (9H, s, OC(CH_3)$_3$), 1.70 (1H, dt, *J* 13.2 and 3.7, NCHC*H*HC), 2.08 (1H, ddd, *J* 13.2, 10.4 and 6.3, NCHC*H*HC), 2.26 (1H, q, *J* 4.2, NCH_2CH), 3.18 (1H, dd, *J* 13.7 and 4.2, NC*H*H), 3.60-3.71 (2H, m, CH_2O), 4.01 (1H, dd, *J* 13.7 and 4.2, NC*H*H), 4.11 (2H, s, =CH_2), 4.13-4.22 (2H, stack, NC*H* and C*H*O)

δ_C: (101 MHz, CD_2Cl_2) -0.22 (Si(CH_3)$_3$), 0.53 (Si(CH_3)$_3$), 28.9 (OC(CH_3)$_3$), 31.5 (NCHCH_2), 44.1 (NCH_2), 46.9 (NCH_2CH), 53.2 (NCH), 63.4 (CH_2O), 67.3 (CHO), 79.6 (OC(CH_3)$_3$), 92.0 (C=CH_2, 155.5 (OC=O), 158.9 (C=CH_2)

m/z: $(ES)^+$ 512.2 (20%, $[M+Na]^+$), 440.2 (100, $[M+Na-C_3H_9Si]^+$), 368.2 (60 $[M+Na-C_6H_{18}Si_2]^+$)

HRMS: [Found: $(M+Na)^+$ 512.2657. $C_{22}H_{47}NNaO_5Si_3$ requires *M* 512.2660]

(3*S*, 4*R*, 6*S*)-1-(*tert*-Butoxycarbonyl)-4-hydroxy-6-(hydroxymethyl)piperidine-3-carboxylic acid (173)



$NaHCO_3$ (25.2 g, 299 mmol) was added to a stirred solution of silyl enol ether **172** (14.7 g, 30.0 mmol) in CH_2Cl_2 (75 mL). The resulting suspension was cooled to -78 °C before MeOH (75 mL) was added dropwise over 20 min. A stream of gas containing O_3/O_2 was passed through a gas dispersion tube and bubbled into the solution before passing out through a gas scrubber containing an aqueous solution of 10% KI to remove any excess O_3. The stream of O_3/O_2 was continued for 10 min, resulting in the solution turning in colour from colourless to blue. O_2 was then bubbled through the solution for 5 min before Ar was bubbled through the solution for a further 5 min resulting in the solution turning in colour from blue to colourless. DMS (22.0 mL, 300 mmol) was added over 5 min to the stirred solution at -78 °C. The resulting solution was stirred at -78 °C for 15 min before being allowed to warm to room temperature and stirred at room temperature until a negative test for peroxides was detected using starch/I_2 paper, usually 2 h. The reaction mixture was cooled to 0 °C and acidified to pH 4 with concentrated HCl. The solution was concentrated *in vacuo* to give a white solid that was taken up in acetone (50 mL), filtered and washed with further portions of acetone (4 x 20 mL). The solvent was removed *in vacuo* to give the product **173** as white amorphous solid (8.26 g, quant.).

R_f : 0.21 (9:1, $CHCl_3$:MeOH + 1% AcOH)

$[\alpha]_D^{21}$: -80.2 (*c* 1 in MeOH)

mp: 141-143 °C (from $CHCl_3$:MeOH)

ν_{max}: (film)/cm^{-1} 3384 (OH), 2920 (CH), 2851 (CH), 1695 (C=O), 1664 (C=O), 1417, 1161, 1049

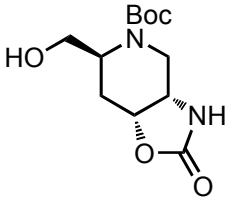
δ_H: (400 MHz, CD_3OD) 1.29 (9H, s, OC(CH_3)$_3$), 1.71 (1H, ddd, *J* 13.2, 4.6 and 1.4, NCHC*H*H), 1.88-2.03 (1H, m, NCHC*H*H), 2.58-2.62 (1H, m, NCH_2CH), 3.01 (1H, dd, *J* 14.4 and 3.7, NC*H*H), 3.44 (1H, dd, *J* 11.3 and 7.0, CH_2O), 3.49 (1H, dd, *J* 11.3 and 7.4, CH_2O), 3.93 (1H, dt, *J* 10.5 and 4.6, C*H*OH), 4.15-4.26 (2H, stack, NC*H* and NC*H*H)

δ_C: (101 MHz, CD_3OD) 28.8 (OC(CH_3)$_3$), 30.8 (NCHCH_2), 41.8 (NCH_2), 46.6 (NCH_2CH), 54.0 (NCH), 62.0 (CH_2O), 66.3 (CHOH), 81.4 (OC(CH_3)$_3$), 157.2 (NC=O), 175.7 (HOC=O)

m/z: $(ES)^-$ 274.1 (100%, $[M-H]^-$)

HRMS: [Found: $(M-H)^-$ 274.1294. $C_{12}H_{20}NNaO_6$ requires *M* 274.1291]

(3a*S*, 6*S*, 7a*R*)-*tert*-Butyl 6-(hydroxymethyl)-2-oxohexahydrooxazolo[4,5-c]pyridine-5(6*H*)-carboxylate (27)



TBAF Deprotection

TBAF (1 M soln. in THF, 0.59 mL, 0.59 mmol) was added dropwise over 30 s to a solution of silyl ether **167** (209 mg, 0.39 mmol) in THF (2 mL). The solution was stirred at room temperature for 5 h before the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (R_f = 0.20, EtOAc) to give the product **27** as a white crystalline (111 mg, quant.).

Curtius Rearrangement

Et_3N (11.5 mL, 83.1 mmol) was added to a solution of acid **173** (9.15 g, 33.2 mmol) in toluene (330 mL) and the resulting mixture was heated to 80 °C. DPPA (7.46 mL, 33.2 mmol) was added dropwise over 5 min to the solution and heating was continued for a further 2 h, with gas evolution noticed for 30 min. The solution was allowed to cool to room temperature and the reaction quenched by the addition of saturated aqueous solution of $NaHCO_3$ (150 mL). The solution was diluted with EtOAc (300 mL) and the organic phase was separated. The aqueous phase was further extracted with EtOAc (3 x 300 mL) and the combined organic layers were washed with brine (300 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to afford the crude product as a light brown solid. The crude product was purified by flash column chromatography (R_f = 0.20, EtOAc) to give the product **27** as a white crystalline solid (6.79 g, 75%).

[α]$_D^{19}$: -107 (*c* 1.0 in MeOH) (Lit.[24] [α]$^{21}_D$: -111.4 (*c* 0.92 in MeOH))

mp: 147-148 °C (from hexane:EtOAc)

μ: (Found: C, 52.99; H, 7.47; N, 7.47 $C_{12}H_{20}N_2O_5$ requires C, 52.93; H, 7.40; N, 7.40%)

ν$_{max}$: (neat)/cm^{-1} 3295 (OH, NH), 2978 (CH), 2934 (CH), 2881 (CH), 1733 (C=O), 1666 (C=O), 1412, 1365, 1246, 1135, 1054 (C-O)

δ$_H$: (300 MHz, $CDCl_3$) 1.45 (9H, s, OC(C*H*$_3$)$_3$), 1.69-2.05 (1H, m, C*H*$_2$CHO), 2.06-2.35 (1H, m, C*H*$_2$CHO), 2.42 (1H, br s, O*H*), 2.95-3.08 (1H, m, NC*H*H), 3.43-3.67 (1H, m, C*H*HO), 3.68-3.90 (1H, m, C*H*HO), 3.96 (1H, br d, *J* 8.6, C*H*NH), 4.01-4.29 (2H, stack, NC*H*H and C*H*NCH$_2$), 4.97 (1H, br d, *J* 8.5, C*H*O), 5.73-5.98 (1H, m, N*H*)

δ$_H$: (400 MHz, CD_3OD) 1.51 (9H, s, OC(C*H*$_3$)$_3$), 1.98-2.14 (1H, m, C*H*$_2$CHO), 2.16-2.33 (1H, m, C*H*$_2$CHO), 3.05-3.30 (1H, m, NC*H*H), 3.50-3.67 (1H, m, C*H*HO), 3.71-3.86 (1H, dd, *J*

10.2 and 4.3, C*H*HO), 3.92 (1H, br d, *J* 14.9, C*H*NH), 3.97-4.11 (2H, stack, NC*H*H and C*H*NCH$_2$), 5.06 (1H, br dd, *J* 2.4 and 6.3, C*H*O)

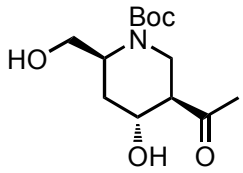
δ_C: (101 MHz, CD_3OD) 26.9 (*C*H$_2$CHNCH$_2$), 28.7 (C(*C*H$_3$)$_3$), 42.6 (N*C*H$_2$), 51.0 (*C*HNCH$_2$), 52.7 (NCH$_2$*C*H), 64.5 (*C*H$_2$O), 75.1 (*C*HO), 81.6 (*C*(CH$_3$)$_3$), 157.5 (*C*=O), 161.4 (*C*=O)

m/z: (ES)$^+$ 295.1 (100%, [M+Na])

HRMS: [Found: (M+Na)$^+$ 295.1277. $C_{12}H_{20}N_2NaO_5$ requires *M* 295.1270]

X-ray: See *Appendix*

(2*S*, 4*R*, 5*R*)-*tert*-Butyl 5-acetyl-4-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (175)



NaIO$_4$/Na$_2$SO$_3$ Epimerisation

NaIO$_4$ (4.27 g, 20.0 mmol) was added in one portion to a stirred solution of ketone **149** (2.18 g, 7.99 mmol) in dioxane (40 mL). A saturated aqueous solution of Na_2SO_3 (40 mL) was added and the resulting mixture was heated to 40 °C for 1 h. The solvent was removed *in vacuo* and the reaction mixture was diluted with water (100 mL) and EtOAc (100 mL). The organic phase was separated and the aqueous phase was further extracted with EtOAc (4 x 100 mL). The combined organic fractions were washed with brine and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the product **175** as a colourless oil (2.16 g, 99%).

DBU Epimerisation

DBU (54 μL, 0.36 mmol) was added to solution of ketone **149 (**49 mg, 0.18 mmol) in CH_2Cl_2 (1.8 mL). The resulting solution was stirred at room temperature for 4 h before being

quenched by the addition of water (5 mL). The solution was diluted with CH_2Cl_2 (5 mL) and the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$ before the solvent was removed *in vacuo* to give the product **175** as a colourless oil (48 mg, 98%).

R_f: 0.34 (EtOAc)

$[\alpha]_D^{20}$: +10.4 (*c* 1.0 in $CHCl_3$)

ν_{max}: (film)/cm^{-1} 3394 (OH), 2975 (CH), 2932 (CH), 1692 (C=O), 1662 (C=O), 1159, (C-O), 1052 (C-O)

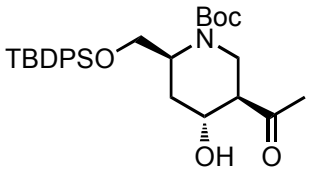
δ_H: (400 MHz, $CDCl_3$) 1.44 (9 H, s, $C(CH_3)_3$), 1.49-1.63 (1H, m, C*H*HCHOH) 2.01 (1H, dd, *J* 13.1 and 4.1, C*H*HCHOH), 2.24 (3H, s, $CHC(O)CH_3$), 2.54 (1H, ddd, *J* 12.2, 10.1 and 4.1, NCH_2CH), 2.65-2.93 (2H, stack, O*H* and NC*H*H), 3.16 (1H, br s, O*H*), 3.51-3.74 (2H, m, CH_2OH), 3.95-4.16 (1H, m, C*H*OH), 4.20-4.52 (2H, stack, C*H*N and NC*H*H)

δ_C: (101 MHz, $CDCl_3$) 28.5 ($C(CH_3)_3$), 31.0 ($C(O)CH_3$), 33.1 ($NCHCH_2CH$), 39.6 (NCH_2), 53.0 (NCH), 57.0 (NCH_2CH), 61.7 (CH_2O), 66.4 (CHOH), 80.9 ($C(CH_3)_3$), 155.4 (OC=O), 210.6 ($CH_3C=O$)

m/z: $(ES)^+$ 296.2 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 296.1470. $C_{13}H_{23}NNaO_5$ requires *M* 296.1474]

(2*S*, 4*R*, 5*R*)-*tert*-Butyl 5-acetyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxypiperidine-1-carboxylate (176)



Silyl ether **176** was prepared from: Alcohol **175** (1.38 g, 5.05 mmol), Et_3N (0.85 mL, 6.06 mmol), DMAP (124 mg, 1.02 mmol) and TBDPSCl (1.3 mL, 5.05 mmol) in CH_2Cl_2 (17 mL) according to general procedure 1. The crude product was purified by flash column chromatography (R_f = 0.30, hexane:EtOAc, 2:1) to give the product **176** as a colourless oil (2.47 g, 96%).

[α]$_D^{21}$: +4.8 (*c* 1.0 in MeOH)

ν_{max}: (film)/cm^{-1} 3428 (OH), 3079 (ArCH), 3056 (ArCH), 2970 (CH), 2932 (CH), 2859 (CH), 1690 (C=O), 1671 (C=O), 1425, 1105, 1077, 700

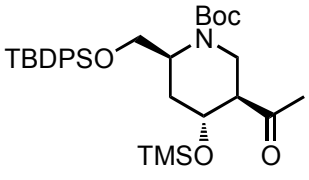
δ_H: (300 MHz, $CDCl_3$) 1.07 (9H, s, SiC(C*H*$_3$)$_3$), 1.42 (9H, s, OC(C*H*$_3$)$_3$), 1.51-1.70 (1H, m, NCHC*H*H), 1.86-2.08 (1H, m, NCHC*H*H), 2.24 (3H, s, C(O)C*H*$_3$), 2.40-2.61 (1H, m, NCH$_2$C*H*), 2.65-2.79 (1H, m, NC*H*H), 3.05 (1H, br s, O*H*), 3.65 (2H, m, C*H*$_2$O), 4.02-4.15 (1H, m, C*H*OH), 4.35-4.60 (2H, stack, NC*H* and NC*H*H), 7.35-7.49 (6H, m, ArC*H*), 7.64 (4H, dd, *J* 1.7 and 7.5, ArC*H*)

δ_C: (101 MHz, $CDCl_3$) 19.1 (Si*C*(CH$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 28.3 (OC(*C*H$_3$)$_3$), 30.3 (C(O)*C*H$_3$), 29.9 (NCH*C*H$_2$), 39.7 (N*C*H$_2$), 52.6 (N*C*H), 56.9 (NCH$_2$*C*H), 62.9 (*C*H$_2$O), 66.1 (*C*HOH), 80.2 (O*C*(CH$_3$)$_3$), 127.7 (Ar*C*H), 129.7 (Ar*C*H), 133.0 (Ar*C*$_q$), 135.4 (Ar*C*H), 154.5 (O*C*=O), 209.1 (CH$_3$*C*=O)

m/z: (ES)$^+$ 534.3 (100%, [M+Na]$^+$)

HRMS: [Found: (M+Na)$^+$ 534.2660. $C_{29}H_{41}NNaO_5Si$ requires *M* 534.2652]

(2*S*, 4*R*, 5*R*)-*tert*-Butyl 5-acetyl-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((trimethylsilyl)oxy)piperidine-1-carboxylate (177)



Silyl ether **177** was prepared from: alcohol **176** (221 mg, 0.43 mmol), TMSOTf (0.19 mL, 0.86 mmol), Et_3N (0.12 mL, 0.86 mmol); in CH_2Cl_2 (4 mL) according to general procedure 4. Purification by flash column chromatography (R_f = 0.20, hexane:EtOAc, 6:1) gave the product **177** as a colourless oil (276 mg, 78%).

ν_{max}: (film)/cm^{-1} 3077 (ArCH), 3056 (ArCH), 2958 (CH), 2935 (CH), 2859 (CH), 1714 (C=O), 1693 (C=O), 1411, 1161, 1097, 840, 701

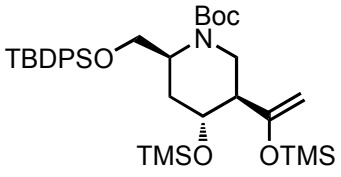
δ_H: (400 MHz, $CDCl_3$) 0.08 (9H, s, Si(CH_3)$_3$), 1.05 (9H, s, SiC(CH_3)$_3$), 1.35 (9H, s, OC(CH_3)$_3$), 1.45-1.58 (1H, m, NCHC*H*H), 1.97-2.09 (1H, m, NCHC*H*H), 2.16 (3H, s, C(O)CH_3), 2.51-2.62 (1H, m, NCH_2C*H*) 2.63-2.74 (1H, m, NC*H*H), 3.48-3.69 (2H, m, CH_2O), 3.95-4.06 (2H, stack, NC*H*H and C*H*O), 4.20-4.34 (1H, m, NC*H*), 7.29-7.50 (6H, m, ArC*H*), 7.66 (4H, dd, *J* 7.4 and 1.6 , ArC*H*)

δ_C: (101 MHz, $CDCl_3$) 0.04 (Si(*C*H_3)$_3$), 19.0 (Si*C*(CH$_3$)$_3$), 26.6 (SiC(*C*H_3)$_3$), 28.1 (OC(*C*H_3)$_3$), 32.6 (C(O)*C*H_3), 34.1 (NCH*C*H_2), 40.1 (N*C*H_2), 52.4 (N*C*H), 56.6 (NCH_2*C*H), 62.3.5 (*C*H_2O), 68.5 (*C*HO), 79.8 (O*C*(CH$_3$)$_3$), 127.6 (Ar*C*H), 129.6 (Ar*C*H), 133.9 (ArC_q), 135.3 (Ar*C*H), 154.5 (O*C*=O), 209.8 (CH_3*C*=O)

m/z: $(ES)^+$ 606.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 606.3050. $C_{32}H_{49}NNaO_5Si_2$ requires *M* 606.3047]

(2*S*, 4*R*, 5*R*)-*tert*-Butyl 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((trimethylsilyl) oxy)-5-(1-((trimethylsilyl)oxy)vinyl)piperidine-1-carboxylate (178)



Silyl enol ether **178** was prepared from: ketone **176** (2.09 g, 4.08 mmol), Et_3N (2.74 mL, 16.3 mmol) and TMSOTf (1.84 mL, 10.2 mmol); in CH_2Cl_2 (40 mL) according to general procedure **5** to give the product **178**as a colourless oil (2.14 g, 80%).

R_f: 0.20 (hexane:EtOAc, 10:1 + 1% Et_3N)

$[\alpha]_D^{20}$: +7.6 (*c* 1.0 in CH_2Cl_2)

ν_{max}: (film)/cm^{-1} 2958 (CH), 2934 (CH), 2859 (CH), 2903 (CH), 1695 (C=O), 1250, 1099, 839, 740, 701

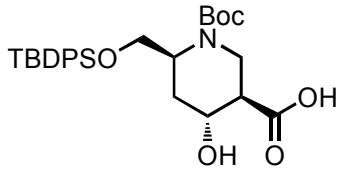
δ_H: (300 MHz, C_6D_6) 0.11 (9H, s, Si(CH_3)$_3$), 0.22 (9H, s, Si(CH_3)$_3$), 1.21 (9H, s, SiC(CH_3)$_3$), 1.45 (9H, s, OC(CH_3)$_3$), 1.63-1.74 (1H, m, NCHC*H*H), 2.25-2.41 (1H, m, NCHC*H*H), 2.43-2.59 (1H, m, NCH_2CH)), 3.01-3.19 (1H, m, NC*H*H), 3.82-3.96 (2H, m, CH_2O), 4.10-4.48 (4H, stack NC*H*H, C*H*O and =CH_2), 4.47-4.59 (1H, m, NC*H*), 7.21-7.27 (6H, m, ArC*H*), 7.80 (4H, d, *J* 7.1, ArC*H*)

δ_C: (101 MHz, C_6D_6) 0.1 (Si(*C*H_3)$_3$), 0.6 (Si(*C*H_3)$_3$), 19.4 (Si*C*$(CH_3)_3$), 27.1 (SiC(*C*H_3)$_3$), 28.4 (OC(*C*H_3)$_3$), 34.6878 (N*C*H_2), 51.1 (NCH*C*H_2), 46.9 (NCH_2*C*H), 53.0 (N*C*H), 62.7 (*C*H_2O), 66.6 (*C*HO), 79.1 (O*C*$(CH_3)_3$), 91.6 (C=*C*H_2), 128.1 (Ar*C*H), 130.0 (Ar*C*H), 133.6 (ArC_q), 135.8 (Ar*C*H), 154.5 (O*C*=O), 157.4 (*C*=CH_2)

m/z: $(ES)^+$ 678.4 (100%, $[M+Na]^+$), 556.4 (22)

HRMS: [Found: $(M+Na)^+$ 678.3452. $C_{35}H_{57}NNaO_5Si_3$ requires *M* 678.3442]

(3*R*, 4*R*, 6*S*)-1-(*tert*-Butoxycarbonyl)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-hydroxy piperidine-3-carboxylic acid (179)



Carboxylic acid **179** was prepared from: Silyl enol ether **178** (0.69 g, 1.05 mmol), $NaHCO_3$ (0.89 g, 10.5 mmol) and DMS (0.77 mL, 10.5 mmol); in CH_2Cl_2:MeOH (1:1, 10 mL) according to general procedure 6 to give the product **179** as a white foam (533 mg, 92%).

R_f: 0.45 (hexane:EtOAc, 1:3 + 1% AcOH)

$[\alpha]_D^{20}$: +5.6 (*c* 1.0 in MeOH)

ν_{max}: (film)/cm^{-1} 3426 (OH), 3074 (ArCH), 3051 (ArCH), 2960 (CH), 2932 (CH), 2859 (CH), 1694 (C=O), 1667 (C=O), 1427, 1164, 1106, 823, 700

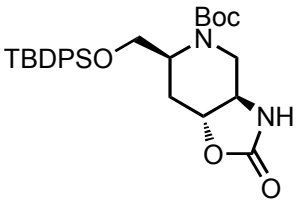
δ_H: (400 MHz, CD_3OD) 0.97 (9H, s, SiC(CH_3)$_3$), 1.27-1.55 (10H, stack, OC(CH_3)$_3$ and NCHC*H*H), 1.88-2.08 (1H, m, NCHC*H*H), 2.12-2.33 (1H, m, NCH_2CH), 2.80 (1H, t, *J* 12.4, NC*H*H), 3.65 (2H, d, *J* 6.2, CH_2O), 3.77-4.23 (2H, stack, C*H*OH and NC*H*H), 4.30-4.57 (1H, m, NC*H*), 7.24-7.47 (6H, m, ArC*H*), 7.53-7.66 (4H, m, ArC*H*)

δ_C: (101 MHz, CD_3OD) 19.7 (Si*C*(CH_3)$_3$), 27.4 (SiC(*C*H_3)$_3$), 28.7 (OC(*C*H_3)$_3$), 34.7 (NCH*C*H_2), 40.4 (N*C*H_2), 52.0 (NCH_2CH), 54.2 (N*C*H), 64.4 (*C*H_2O), 67.3 (*C*HOH), 81.6 (O*C*(CH_3)$_3$), 128.9 (Ar*C*H), 131.0 (Ar*C*H), 134.0 (ArC_q), 136.6 (Ar*C*H), 156.2 (N*C*=O), 175.6 (HO*C*=O)

m/z: $(ES)^-$ 512.3 (100%, $[M-H]^-$)

HRMS: [Found: $(M-H)^-$ 512.2471. $C_{28}H_{38}NNaO_6Si$ requires *M* 512.2468]

(3a*R*, 6*S*, 7a*R*)-*tert*-Butyl 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxohexa hydrooxazolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (180)



Oxazolidinone **180** was prepared from: carboxylic acid **179** (313 mg, 0.61 mmol), Et_3N (187 μL, 1.34 mmol) and DPPA (137 μL, 0.61 mmol); in toluene (6 mL) according to general procedure 7. Purification by flash column chromatography (R_f = 0.31, hexane:EtOAc, 2:1) gave the product **180** as a white foam (230 mg, 74%).

[]$_D^{20}$: +3.5 (*c* 1.0 in $CHCl_3$)

$_{max}$: (film)/cm^{-1} 3305 (NH) 3077 (ArCH), 3062 (ArCH), 2934 (CH), 2931 (CH), 2890 (CH), 1762 (C=O), 1691 (C=O), 1390, 1231, 1106, 701

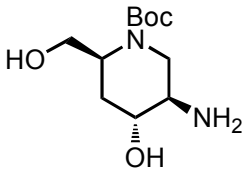
$_H$: (400 MHz, $CDCl_3$) 1.06 (9H, s, SiC(C*H*$_3$)$_3$), 1.39 (9H, s, OC(C*H*$_3$)$_3$), 1.85-2.07 (1H, m, C*H*HCHO), 2.52 (1H, dd, *J* 3.2 and 11.9, C*H*HCHO), 2.80 (1H, t, *J* 12.1, NC*H*H), 3.20-3.38 (1H, m, C*H*NH), 3.54-3.79 (2H, m, C*H*HO), 4.19-4.33 (1H, m, C*H*O), 4.55 (1H, dd, *J* 4.3 and 12.1, NC*H*H), 4.70-4.78 (1H, m, C*H*NCH$_2$), 5.89 (1H, br s, N*H*), 7.32-7.52 (6H, m, ArC*H*), 7.56-7.75 (4H, m, ArC*H*)

$_C$: (101 MHz, $CDCl_3$) 19.1 (Si*C*(CH$_3$)$_3$), 26.9 (SiC(*C*H$_3$)$_3$, 28.4 (OC(*C*H$_3$)$_3$), 28.5 (*C*H$_2$CHNCH$_2$), 43.9 (NCH$_2$), 52.7 (*C*HNCH$_2$), 58.4 (*C*HNH), 63.5 (*C*H$_2$O), 79.0 (*C*HO), 80.9 (O*C*(CH$_3$)$_3$), 127.9 (Ar*C*H), 129.9(Ar*C*H), 130.0 (Ar*C*H), 132.6 (ArC_q), 132.7 (ArC_q), 135.5 (Ar*C*H), 154.7 (*C*=O), 160.7 (*C*=O)

m/z: $(ES)^+$ 533.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 533.2456. $C_{28}H_{38}N_2NaO_5Si$ requires *M* 533.2448]

(2*S*, 4*R*, 5*R*)-*tert*-Butyl 5-amino-4-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (181)



TBAF (1 M soln. in THF, 0.10 mL, 0.10 mmol) was added to a solution of silyl ether **180** (53 mg, 0.10 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature overnight before the solvent was removed *in vacuo* and the residue purified by flash column chromatography (R_f = 0.17, $CHCl_3$:MeOH, 8:2 + 1% $NH_{3(aq)}$) to give the product **181** as a colourless oil (21 mg, 74%).

[α]$_D^{21}$: +15.3 (*c* 1.5 in MeOH)

ν$_{max}$: (film)/cm^{-1} 3353 (NH, OH), 2966 (CH), 2924 (CH), 2931 (CH), 2855 (CH), 1668 (C=O), 1416, 1365, 1248, 1164, 1053

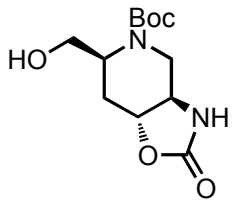
δ$_H$: (400 MHz, CD_3OD) 1.35 (9H, s, OC(C*H*$_3$)$_3$), 1.36-1.45 (1H, m, C*H*HCHO), 2.91-2.10 (1H, m, C*H*HCHO), 2.34-2.42 (1H, m, C*H*NH$_2$), 2.47-2.65 (1H, m, NC*H*H), 3.34-3.41 (1H, m, C*H*OH), 3.43-3.58 (2H, m, C*H*HO), 3.96-4.07 (1H, m, NC*H*H), 4.15-4.26 (1H, m, C*H*NCH$_2$)

δ$_C$: (101 MHz, CD_3OD) 28.7 (OC(*C*H$_3$)$_3$), 33.9 (*C*H$_2$CHNCH$_2$), 43.8 (N*C*H$_2$), 52.9 (*C*HNCH$_2$), 55.9 (*C*HNH$_2$), 61.5 (*C*H$_2$O), 71.2 (*C*HOH), 81.4 (O*C*(CH$_3$)$_3$), 156.7 (*C*=O)

m/z: (ES)$^+$ 269.2 (100%, [M+Na]$^+$)

HRMS: [Found: (M+Na)$^+$ 269.1479. $C_{11}H_{22}N_2NaO_4$ requires *M* 269.1477]

(3a*R*, 6*S*, 7a*R*)-*tert*-Butyl 6-(hydroxymethyl)-2-oxohexahydrooxazolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (182)



A solution of HF.pyridine (70% HF in pyridine, 62 μL, 2.78 mmol) was added to a solution of silyl ether **180** (71 mg, 0.14 mmol) in THF:pyridine (1:1, 1 mL). The resulting mixture was stirred at rt for 3 h before being cooled to 0 °C and quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL). The mixture was extracted with EtOAc (4 x 5 mL) and the combined organic fractions washed with brine and dried over $MgSO_4$ before the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (R_f = 0.22, hexane:EtOAc, 1:3) to give the product **182** as a white amorphous solid (31 mg, 81%).

[α]$_D^{20}$: +19.2 (*c* 1.0 in MeOH)

mp: 135-136 °C (from hexane:EtOAc)

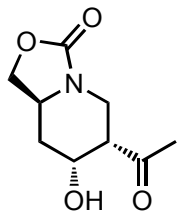
ν$_{max}$: (film)/cm^{-1} 3328 (NH, OH), 2934 (CH), 2922 (CH), 2853 (CH), 1746 (C=O), 1670 (C=O), 1237, 1161, 1085, 1030

δ$_H$: (400 MHz, $CDCl_3$) 1.39 (9H, s, OC(C*H*$_3$)$_3$), 1.49-1.60 (1H, br s, O*H*), 1.77-2.01 (1H, m, C*H*HCHO), 2.22-2.31 (1H, m, C*H*HCHO), 2.78-3.01 (1H, m, NC*H*H), 3.21-3.34 (1H, m, C*H*NH), 3.62-3.74 (2H, m, C*H*HO), 4.15-4.27 (1H, m, C*H*O), 4.42-4.73 (2H, stack, NC*H*H and C*H*NCH$_2$), 4.46 (1H, br s, N*H*)

m/z: (ES)$^+$ 295.2 (100%, [M+Na]$^+$), 327.2 (29, [M+MeOH+Na]$^+$)

HRMS: [Found: (M+Na)$^+$ 295.1274. $C_{12}H_{20}N_2NaO_5$ requires *M* 295.1270]

(6*S*, 7*R*, 8*aS*)-6-Acetyl-7-hydroxytetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (185)



Dihydroxylation/oxidative cleavage

2,6-Lutidine (700 μL, 0.60 mmol) was added to a solution of piperidine **96** (60 mg, 0.30 mmol) in dioxane:water (3:1, 4 mL). OsO_4 (one small crystal) followed by $NaIO_4$ (0.26 g, 1.20 mmol) was added to the solution. After 15 min a white precipitate began to fall out of solution. The reaction was stirred for a further 2 h before being quenched with saturated aqueous solution of Na_2SO_3 (5 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product as a yellow solid, which was purified by flash column chromatography (R_f = 0.21, EtOAc) to give the product **185** as a white crystalline solid (54 mg, 90%).

Ozonolysis

Ozone was bubbled through a solution of piperidine **96** (105 mg, 0.53 mmol) in CH_2Cl_2:MeOH (3:1, 4 mL) at -78 °C and out into an aqueous KI scrubber. After 15 min the solution turned in colour from colourless to clear blue. O_2 was bubbled through the solution followed by Ar, each for 10 min, resulting in a colour change from blue to colourless. DMS (470 μL, 0.64 mmol) was added and after warming to room temperature the solvent was removed *in vacuo* obtain the crude product as an off white crystalline solid, which was purified by flash column chromatography (R_f = 0.21, EtOAc) to give the product **185** as a white crystalline solid (106 mg, quant.).

$[\alpha]_D^{20}$: -173 (*c* 1.0 in $CHCl_3$)

mp: 160-162 °C (from hexane:EtOAc)

ν_{max}: (film)/cm^{-1} 3514 (OH), 2925 (CH), 1747 (C=O), 1704 (C=O)

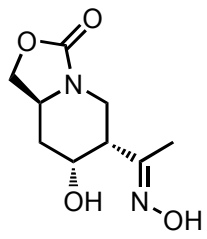
δ_H: (300 MHz, $CDCl_3$): 1.41-1.50 (1H, m, C*H*HCHOH), 1.99 (1H, dt, *J* 13.3 and 3.7, CH*H*CHOH), 2.20 (3H, s, CH_3), 2.65-2.69 (1H, m, C*H*COCH$_3$), 3.29 (1H, t, *J* 12.5, NC*H*H), 3.85-3.96 (2H, stack, NCH*H* and C*H*HO), 4.04-4.13 (1H, m, NC*H*), 4.38 (1H, t, *J* 8.2 CH*H*O), 4.44 (1H, br s, C*H*OH)

δ_C: (75 MHz, $CDCl_3$) 29.2 (*C*H$_3$), 35.7 (C*H*$_2$CHO), 37.4 (N*C*H$_2$), 48.7 (NCH$_2$C*H*), 51.5 (N*C*H), 64.0 (C*H*OH), 67.5 (*C*H$_2$OCO), 157.1 (O*C*O), 209.8 (*C*OCH$_3$)

m/z: $(ES)^+$ 222.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 222.0748. $C_9H_{13}NNaO_4$ requires *M* 222.0742]

(6*R*, 7*R*, 8a*S*)-7-Hydroxy-6-((*E*)-1-(hydroxyimino)ethyl)tetrahydro-1*H*-oxazolo [3,4-*a*]pyridin-3(5*H*)-one (186)



Et_3N (0.23 mL, 1.67 mmol) was added to a stirred solution of ketone **185** (111 mg, 0.56 mmol) dissolved in EtOH (6 mL) followed by the addition of hydroxylamine hydrochloride (58 mg, 0.84 mmol). The reaction was heated to reflux for 5 h before being allowed to cool to room temperature and quenched by the addition of water (10 mL). The solvent was removed *in vacuo* and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic fractions were washed with brine (10 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give the oxime product **186** as a white crystalline solid (92 mg, 78%).

R_f : 0.24 (EtOAc)

mp: 153-155 °C (from EtOAc)

ν_{max}: (neat)/cm^{-1} 3404 (OH), 3243 (OH), 2923 (CH), 2877 (CH), 1710 (C=O), 1433, 1244, 1006, 960

δ_H: (300 MHz, CD_3OD): 1.61-1.74 (1H, m, C*H*HCHOH), 1.94 (3H, s, CH_3), 2.05 (1H, dt, *J* 12.5 and 3.5, C*H*HCHOH), 2.40-2.49 (1H, m, C*H*$COCH_3$), 3.41 (1H, t, *J* 12.5, NC*H*H), 3.66 (1H, dd, *J* 12.5 and 4.5, NCH*H*) 3.95-4.04 (1H, m, C*H*HO), 4.12-4.20 (1H, m, NC*H*), 4.38 (1H, br s, C*H*OH) 4.49 (1H, t, *J* 8.2 C*H*HO),

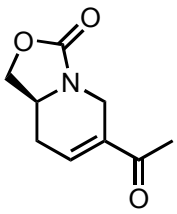
δ_C: (75 MHz, CD_3OD) 11.6 (*C*H_3), 36.5 (CH_2CHO), 38.2 (N*C*H_2), 55.7 (NCH_2C*H*), 49.4 (N*C*H), 64.6 (C*H*OH), 68.1 (*C*H_2OCO), 155.4 (*C*=O), 158.1 (*C*=N-OH)

m/z: $(ES)^+$ 237.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 237.0839. $C_9H_{14}N_2NaO_4$ requires *M* 237.0851]

X-ray: See *Appendix*

(*S*)-6-Acetyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (188)



O-(mesitylsulfonyl)hydroxylamine **162** (37 mg, 0.17 mmol) was added to a stirred solution of ketone **185** (32mg, 0.16 mmol) dissolved in EtOH (1.5 mL). The resulting mixture was heated to 120 °C in a sealed tube for 3 h before being allowed to cool to room temperature and concentrated *in vacuo* to give the crude product that was purified by flash column chromatography (R_f = 0.22, hexane:EtOAc, 1:3) to give the enone **188** as a white crystalline solid (27 mg, 93%).

mp: 112-114 °C (from hexane:EtOAc)

ν_{max}: (neat)/cm^{-1} 2964 (CH), 2908 (CH), 1749 (C=O), 1658 (C=O), 1641, 1417, 1248, 1069, 750

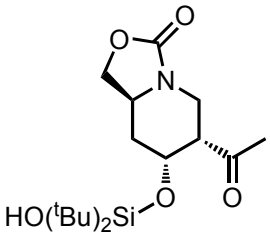
δ_H: (300 MHz, $CDCl_3$) 2.24 (3H, s, C*H*$_3$), 2.30-2.39 (1H, m, C*H*HCH=), 2.42-2.55 (1H, m, C*H*HCH=), 3.67-3.81 (2H, stack, and NC*H*H and NC*H*), 4.01 (1H, dd, *J* 8.2 and 4.0, C*H*HO,) 4.35 (1H, d, *J* 14.0 NCH*H*), 4.46 (1H, t, *J* 8.2 C*H*HO), 6.82-6.91 (1H, m, C*H*=)

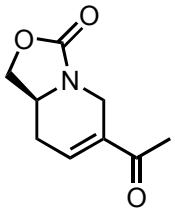
δ_C: (75 MHz, $CDCl_3$) 25.2 (*C*H$_3$), 29.9 (C*H*$_2$CH=), 39.9 (N*C*H$_2$), 49.4 (N*C*H), 68.2 (*C*H$_2$O), 135.6 (*C*H=), 137.7 (*C*$_q$=) 155.6 (N*C*=O), 196.2 (*C*=O)

m/z: $(ES)^+$ 204.0 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 204.0629. $C_9H_{11}NNaO_3$ requires *M* 204.0637]

(6*S*, 7*R*, 8a*S*)-6-Acetyl-7-((di-*tert*-butyl(hydroxy)silyl)oxy)tetrahydro-1*H*-oxazolo [3,4-*a*]pyridin-3(5*H*)-one (190) and **(*S*)-6-Acetyl-8,8a-dihydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (188)**





Et_3N (105 μL, 0.75 mmol) was added to a solution of ketone **185** (50 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) cooled to -78 °C. di(*tert*-butyl)silylbis(trifluoromethanesulfonate) (92 μL, 0.25 mmol) was added dropwise over 1 min and the resulting solution stirred at -78 °C for 1 h before being allowed to warm to 0 °C and stirred for a further 3 h. The reaction was concentrated *in vacuo* and the crude product was purified by flash column chromatography (R_f = 0.50, hexane:EtOAc, 1:3) to give the silyl ether **190** as a colourless oil (34 mg, 38%).

ν_{max}: (film)/cm^{-1} 3514 (OH), 2925 (CH), 2809 (CH), 1747 (C=O), 1704 (C=O), 1050

δ_H: (300 MHz, $CDCl_3$): 0.97 (9H, s, C(C*H*$_3$)$_3$), 1.03 (9H, s, C(C*H*$_3$)$_3$), 1.57 (1H, ddd, *J* 13.4, 11.7 and 1.9, C*H*HCHO), 2.18 (1H, dt, *J* 13.4 and 3.7, CH*H*CHO), 2.23 (3H, s, C*H*$_3$), 2.50 (1H, ddd, *J* 11.9, 4.7 and 1.7, NCH$_2$C*H*), 2.65 (1H, br s, O*H*), 3.52 (1H, dd, *J* 13.2 and 11.9,

NC*H*H), 3.89-4.04 (2H, stack, NCH*H* and C*H*HO), 4.08-4.20 (1H, m, NC*H*), 4.46 (1H, t, *J* 8.2 CH*H*O), 4.89-5.02 (1H, br s, C*H*O)

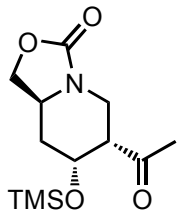
C: (75 MHz, $CDCl_3$) 20.9 (*C*$(CH_3)_3$), 27.2 (C(*C*$H_3)_3$), 28.7 (C(O)*C*H_3), 37.3 (*C*H_2), 37.4 (C*H*$_2$), 49.0 (NCH_2C*H*), 53.7(N*C*H), 65.8 (C*H*O), 67.4 (*C*H_2O), 15731 (O*C*O), 206.2 (*C*OCH_3)

m/z: $(ES)^+$ 380.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 380.1872. $C_{17}H_{31}NNaO_5Si$ requires *M* 380.1869]

Further elution (R_f = 0.22) gave the enone **188** as a white crystalline solid (19 mg, 41%). Data *vide supra.*

(6*S*, 7*R*, 8a*S*)-6-acetyl-7-(trimethylsilyloxy)tetrahydro-1*H*-oxazolo[3,4-a]pyridin-3(5*H*)-one (191)



A solution of ketone **185** (100 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was transferred via cannula to a r.b. flask containing 4 Å MS and stirred for 5 min at room temperature. Et_3N (140 µL, 1.00 mmol) was added to the solution and the resulting mixture was stirred for a further 5 min before being cooled to -78 °C. TMSOTf (182 µL, 0.50 mmol) was added dropwise over 5 min and the resulting solution was stirred at -78 °C for a further 5h. The solution was diluted with CH_2Cl_2 (5 mL) and then poured into a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to afford the crude product as a light brown oil. The crude product was purified by flash column chromatography (R_f = 0.57,

hexane:EtOAc, 3:1 + 1% Et_3N) to give the product **191** as a white crystalline solid (102 mg, 75%).

mp: 64-65 °C (from hexane:EtOAc)

ν_{max}: (neat)/cm^{-1} 2957 (CH), 1736 (C=O), 1709 (C=O), 1433, 1250, 1026, 849, 756

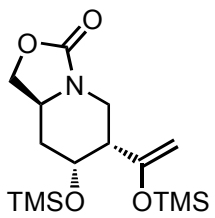
δ_H: (300 MHz, $CDCl_3$): 0.04 (9H, s, $Si(CH_3)_3$), 1.56 (1H, ddd, *J* 13.4, 11.6 and 1.9, C*H*HCHO), 1.85 (1H, dt, *J* 13.4 and 3.8, CH*H*CHO), 2.10 (3H, s, CH_3), 2.43 (1H, ddd, *J* 11.9, 4.9 and 2.1, NCH_2CH), 3.45 (1H, dd, *J* 13.4 and 11.9, NC*H*H), 3.79 (1H, dd, *J* 13.4 and 4.9, NCH*H*), 3.86 (1H, dd, *J* 8.2 and 5.1, C*H*HO), 3.91-4.04 (1H, m, NC*H*), 4.37 (1H, t, *J* 8.2 CH*H*O), 4.53-4.68 (1H, m, C*H*O)

δ_C: (75 MHz, $CDCl_3$) 0.02 ($Si(CH_3)_3$), 28.1 ($C(O)CH_3$), 36.9 (CH_2CHO), 37.5 (NCH_2), 48.7 (NCH_2CH), 52.8 (NCH), 66.3 (CHO), 67.2 (CH_2O), 157.2 (OC=O), 205.9 ($C=OCH_3$)

m/z: $(ES)^+$ 294.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 294.1134. $C_{12}H_{21}NNaO_4Si$ requires *M* 294.1138]

(6*S*, 7*R*, 8a*S*)-7-(Trimethylsilyloxy)-6-(1-(trimethylsilyloxy)vinyl)tetrahydro-1*H*-oxazolo [3,4-a]pyridin-3(5*H*)-one (192)



A solution containing ketone **185** (516 mg, 2.59 mmol) in CH_2Cl_2 (26 mL) was transferred *via* cannula to a r.b. flask containing 4 Å MS and stirred for 5 min at room temperature. Et_3N (1.44 mL, 10.36 mmol) was added to the mixture and the resulting solution was stirred for a further 5 min before being cooled to 0 °C. TMSOTf (1.17 mL, 6.48 mmol) was added dropwise over 5 min and the resulting solution was stirred at 0 °C for a further 1 h. The solution was diluted with CH_2Cl_2 (20 mL) and then poured into a saturated aqueous solution of $NaHCO_3$ (25 mL).

The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (50 x 3 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to afford the crude product as a light brown oil, which was purified by flash column chromatography (R_f = 0.84, hexane:EtOAc, 1:3 + 1% Et_3N) to give the product **192** as a white crystalline (757 mg, 84%).

mp: 77-79 °C (from benzene)

$[\alpha]_D^{20}$: -32.1 (*c* 1 in CH_2Cl_2)

ν_{max}: (neat)/cm^{-1} 2959 (CH), 2909 (CH), 1760 (C=O), 1633, 1427, 1250, 1230, 1042, 829, 756

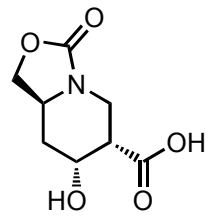
δ_H: (400 MHz, C_6D_6): 0.07 (9H, s, Si(C*H*$_3$)$_3$), 0.14 (9H, s, Si(C*H*$_3$)$_3$), 0.83 (1H, ddd, *J* 13.2, 11.7 and 1.9, C*H*HCHO), 1.18 (1H, dt, *J* 13.2 and 3.8, CH*H*CHO), 1.94 (1H, dd, *J* 12.2 and 4.5, NCH$_2$C*H*), 3.12 (1H, t, *J* 12.2, NC*H*H), 3.18 (1H, dd, *J* 8.1 and 5.0, C*H*HO), 3.39-3.52 (1H, m, NC*H*), 3.65 (1H, t, *J* 8.1, CH*H*O), 3.86 (1H, s, =C*H*H), 3.91 (1H, dd, *J* 12.2 and 4.5, NC*H*H), 4.10 (1H, s, =C*H*H), 4.13-4.17 (1H, m, C*H*O)

δ_C: (101 MHz, $CDCl_3$) 0.14 (Si(*C*H$_3$)$_3$), 0.22 (Si(*C*H$_3$)$_3$), 37.7 (C*H*$_2$CHO), 38.7 (N*C*H$_2$), 46.3 (NCH$_2$C*H*), 48.9 (N*C*H), 66.2 (C*H*O), 66.9 (*C*H$_2$O), 90.7 (=*C*H$_2$), 156.8 (*C*$_q$=CH$_2$) 156.9 (*C*=O)

m/z: $(ES)^+$ 366.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 366.1519. $C_{15}H_{29}NNaO_4Si_2$ requires *M* 366.1533]

(6*S*, 7*R*, 8a*S*)-7-Hydroxy-3-oxohexahydro-1*H*-oxazolo[3,4-a]pyridine-6-carboxylic acid (193)



Carboxylic acid **193** prepared from: silyl enol ether **192** (543 mg, 1.58 mmol), $NaHCO_3$ (1.34 g, 15.8 mmol) and DMS (1.18 mL, 15.8 mmol); in CH_2Cl_2:MeOH (1:1, 16 mL) according to general procedure 6. The crude product was purified by flash column chromatography (R_f = 0.21, $CHCl_3$:MeOH, 8:2 + 1% AcOH) to give the product **193** as a white amorphous solid (299 mg, 95%).

mp: decomposition at 130 °C (from MeOH)

$[\alpha]_D^{20}$: -62.5 (*c* 1 in MeOH)

ν_{max}: (neat)/cm^{-1} 3476 (OH), 2919 (CH), 1718 (C=O), 1682 (C=O), 1464, 1276, 1190, 1030, 1042, 754

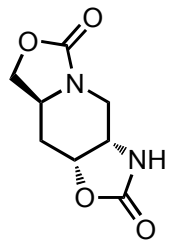
δ_H: (400 MHz, d^6-DMSO): 1.39-1.55 (1H, m, C*H*HCHO), 1.79 (1H, dt, *J* 13.2 and 3.7, CH*H*CHO), 2.36-2.48 (1H, m, NCH_2CH), 3.13-3.20 (1H, m, NC*H*H), 3.52 (1H, dd, *J* 13.1 and 5.2, NC*H*H), 3.81 (1H, dd, *J* 8.4 and 5.7, C*H*HO), 3.86-3.98 (1H, m, NC*H*), 4.27-4.39 (2H, stack, CH*H*O and C*H*O)

δ_C: (101 MHz, d^6-DMSO) 36.3 (CH_2CHO), 36.5 (NCH_2), 44.2 (NCH_2CH), 48.0 (NCH), 63.8 (C*H*O), 67.0 (CH_2O), 156.2 (N*C*=O), 172.4 (*C*=OOH)

m/z: $(ES)^-$ 200.0 (100%, $[M+Na]^-$)

HRMS: [Found: $(M+Na)^-$ 200.0562. $C_8H_{10}NO_5$ requires *M* 200.0559]

(3a*S*, 8a*S*, 9a*R*)-Hexahydro-2*H*-dioxazolo[3,4-*a*:5',4'-*d*]pyridine-2,6(3*H*)-dione (184)



Et_3N (333 μL, 2.39 mmol) was added to a solution of acid **193** (192 mg, 0.96 mmol) in toluene (10 mL) at room temperature. The resulting mixture was heated to 80 °C and DPPA (236 μL, 1.05 mmol) was added dropwise over 1 min to the solution and heating was continued for a further 4 h. The solution was allowed to cool to room temperature and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The solution was diluted with EtOAc (10 mL) and the organic phase was separated. The aqueous phase was further extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the crude product as a light brown solid. The crude product was purified by flash column chromatography (R_f = 0.24, $CHCl_3$:MeOH, 9:1) to give the product **184** as a white amorphous solid (142 mg, 75%).

mp: 134-135 °C (from MeOH)

$[\alpha]_D^{20}$: -80.4 (*c* 1 in $CHCl_3$)

ν_{max}: (neat)/cm^{-1} 3245 (NH), 2994 (CH), 2992 (CH), 1780 (C=O), 1719 (C=O), 1430, 1220, 759

δ_H: (300 MHz, d^6-DMSO): 1.73-1.90 (1H, m, C*H*HCHO), 2.10-2.26 (1H, m, CH*H*CHO), 2.93 (1H, dd, *J* 13.3 and 7.1, NC*H*H), 3.62 (1H, dd, *J* 13.3 and 6.0, NC*H*H), 3.82-3.96 (3H, stack, NC*H*, NCH_2CH and C*H*HO), 4.31-4.51 (1H, m, C*H*HO), 4.66-4.78 (1H, m, C*H*O), 7.81 (1H, br s, N*H*)

δ_C: (101 MHz, d^6-DMSO) 30.5 (CH_2CHO), 42.1 (NCH_2), 47.4 (NCH_2CH), 47.6 (NCH), 67.8 (CH_2O), 791 (CHO), 156.7 (C=O) 158.3 (C=O)

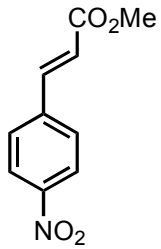
m/z: $(ES)^+$ 221.1 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 221.0529. $C_8H_{10}N_2NaO_4$ requires *M* 221.0538]

General Procedure 8: Wittig Reaction

Methyl(triphenylphosphoranylidene)acetate (1.5 eq) was added in one portion to a stirred solution of aldehyde (1 eq) dissolved in toluene (0.2 M) at room temperature. The resulting solution has heated to reflux until the reaction was judged to be complete by TLC analysis. After cooling to room temperature the solvent was removed *in vacuo* and the resulting residue was taken up in Et_2O (0.2 M) and cooled to 0 °C for 30 min. The precipitates were filtered off and filter cake washed with further portions of ice cold 3 x Et_2O. The combined filtrates were concentrated *in vacuo* to afford the crude allylic ester.

Methyl 4-nitrocinnamate (202a)



Ester **202a** was prepared from aldehyde **200a** (1.28 g, 8.50 mmol) and methyl(triphenylphosphoranylidene)acetate (4.26 g, 12.75 mmol) according to General Procedure 8. After 2 h and purification by flash column chromatography (R_f = 0.35, hexane:EtOAc, 3:1) afforded the product **202a** as a yellow solid (1.41 g, 80%). Ester **202a** was obtained as a 7:1 mixture of *E*:Z stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 136-137 °C (from toluene) (lit. *E*-isomer[115] 159-160 °C, *Z*-isomer[116] 86-88 °C)

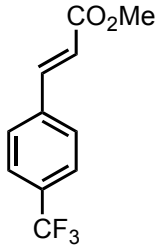
ν_{max}**:** (film)/cm^{-1} 3030 (ArCH), 1718 (C=O), 1642 (C=C), 1598 (ArC=C), 1523 (ν_{as} NO_2), 1348 (ν_s NO_2), 1216, 759

δ_H: (300 MHz, $CDCl_3$) 3.84 (3H, s, C*H*$_3$), 6.56 (1H, d, *J* 16.0, =C*H*), 7.64-7.75 (3H, stack, =C*H* and ArC*H*), 8.25 (2H, d, *J* 8.8, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 52.5 (*C*H$_3$), 122.2 (=*C*H), 124.3 (Ar*C*H), 128.8 (Ar*C*H), 140.6 (C_q), 142.0 (=*C*H), 148.6 (C_q), 166.6 (*C*=O)

m/z: (EI)$^+$ 207 (42%, [M]$^+$), 176 (100, [M-OMe]$^+$)

Methyl 4-trifluoromethylcinnamate (202b)



Ester **202b** was prepared from aldehyde **200b** (1.37 mL, 10.0 mmol) and methyl(triphenylphosphoranylidene)acetate (5.02 g, 15.0 mmol) according to General Procedure 8. After 5 h and purification by flash column chromatography (R_f = 0.68, hexane:EtOAc, 3:1) afforded the **202b** product as a white powder (2.08 g, 90%). Ester **202b** was obtained as a 42:1 mixture of *E*:Z stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 75-76 °C (from hexane:EtOAc) (lit.[117] *E*-isomer 77-79 °C)

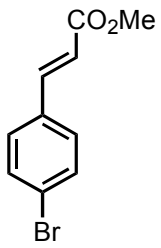
ν_{max}: (film)/cm^{-1} 3021 (ArCH), 1718 (C=O), 1642 (C=C), 1512 (ArC=C), 1324 (CF_3), 1215, 1068, 755

δ_H: (300 MHz, $CDCl_3$) 3.67 (3H, s, C*H*$_3$), 6.35 (1H, d, *J* 16.2, =C*H*), 7.35-7.47 (4H, stack, ArC*H*), 7.52 (1H, d, *J* 16.2, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 51.5 (*C*H$_3$), 120.2 (=*C*H), 123.8 (q, *J* 272, *C*F$_3$), 125.6 (Ar*C*H), 128.0 (Ar*C*H), 131.5 (q, *J* 32, C_qCF_3), 137.7 (C_q), 142.7 (=*C*H), 166.5 (*C*=O)

m/z: (EI)$^+$ 230 (48%, [M]$^+$), 199 (100, [M-OMe]$^+$)

Methyl 4-bromocinnamate (202c)



Ester **202c** was prepared from aldehyde **200c** (1.83 mL, 10.0 mmol) and methyl(triphenylphosphoranylidene)acetate (5.02 g, 15.0 mmol) according to General Procedure 8. After 3 h and purification by flash column chromatography (R_f = 0.66, hexane:EtOAc, 3:1) afforded the product **202c** as a white powder (2.19 g, 90%). Ester **202c** was obtained as a 37:1 mixture of *E*:Z stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 81-83 °C (from toluene) (lit.[118] *E*-isomer 82-84 °C (from ethanol))

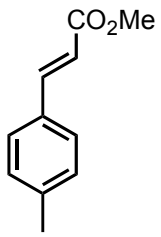
ν_{max}: (film)/cm^{-1} 3032 (ArCH), 1712 (C=O), 1636 (C=C), 1586 (ArC=C), 1486 (ArC=C), 1170 (C-O)

δ_H: (300 MHz, $CDCl_3$) 3.72 (3H, s, C*H*$_3$), 6.33 (1H, d, *J* 16.1, =C*H*), 7.26 (2H, d, *J* 8.5, ArC*H*), 7.46 (2H, d, *J* 8.5, Ar*C*H), *7.52* (1H, d, *J* 16.1, =C*H*)

δ_C: (75 MHz, $CDCl_3$) 51.7 (*C*H$_3$), 118.4 (=*C*H), 124.4 (C_q), 129.4 (Ar*C*H), 132.0 (Ar*C*H), 133.2 (C_q), 143.3 (=*C*H), 166.9 (*C*=O)

m/z: (EI)$^+$ 238 (62%, [M(^{81}Br)]$^+$), 240 (64, [M(^{79}Br)]$^+$), 207 (97, [M(^{81}Br)-OMe]$^+$), 209 (100, [M(^{79}Br)]-OMe$^+$)

Methyl 4-methylcinnamate (202d)



Ester **202d** was prepared from aldehyde **200d** (0.98 mL, 8.17 mmol) and methyl(triphenylphosphoranylidene)acetate (4.09 g, 12.24 mmol) according to General Procedure 8. After 2 h and purification by flash column chromatography (R_f = 0.82, hexane:EtOAc, 3:1) afforded the product **202d** as a

white powder (1.30 g, 90%). Ester **202d** was obtained as a 12:1 mixture of *E*:*Z* stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 51-54 °C (from Et_2O) (lit.[119] *E*-isomer 52-54 °C)

ν_{max}: (film)/cm^{-1} 3021 (ArCH), 2951 (CH), 1715 (C=O), 1636 (C=C), 1436, 1315, 1214, 1172, 755

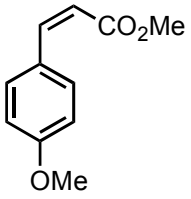
δ_H: (300 MHz, $CDCl_3$) 2.35 (3H, s, C*C*H_3), 3.81 (3H, s, OC*H*$_3$), 6.48 (1H, d, *J* 16.0, =C*H*), 7.16 (2H, d, *J* 8.7, ArC*H*), 7.40 (2H, d, *J* 8.7, ArC*H*), 7.66 (1H, d, *J* 16.0, =C*H*)

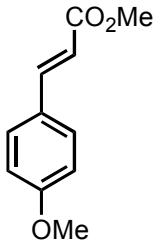
δ_C: (75 MHz, $CDCl_3$) 19.6 (C*C*H_3), 49.7 (O*C*H_3), 114.9 (=*C*H), 126.3 (Ar*C*H), 127.8 (Ar*C*H), 129.4 (C_q), 138.8 (C_q), 143.0 (=*C*H), 165.6 (*C*=O)

m/z: $(EI)^+$ 176 (25%, $[M]^+$), 145 (100, $[M\text{-}OMe]^+$)

HRMS: [Found: $(M)^+$ 176.0845. $C_{11}H_{12}O_2$ requires *M* 176.0837]

(*Z*)-Methyl 4-methoxycinnamate (202ei) and **(*E*)-Methyl 4-methoxycinnamate (202eii)**





Esters **(202ei)** and **(202eii)** were prepared from aldehyde **(200e)** (1.22 g, 10.0 mmol) and methyl(triphenylphosphoranylidene)acetate (5.02 g, 15.0 mmol) according to General Procedure 8. After 2 h and purification by flash column chromatography (R_f = 0.43, hexane:EtOAc, 3:1) afforded the *Z*-isomer **202ei** as a colourless oil (60 mg, 3%).

ν_{max}: (film)/cm^{-1} 2951 (CH), 2838 (CH), 1721 (C=O), 1624, 1604, 1512, 1444, 1260, 1165, 1031

δ_H: (300 MHz, $CDCl_3$) 3.71 (3H, s, *C*H_3), 3.82 (3H, s, C*H*$_3$), 5.72 (1H, d, *J* 16.0, =C*H*), 6.85 (3H, stack, ArC*H* and =C*H*), 7.60 (2H, d, *J* 8.7, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 54.2 (*C*H_3), 57.7 (*C*H_3), 115.9 (Ar*C*H), 119.1 (=*C*H), 127.1 (C_q), 134.6 (Ar*C*H), 145.9 (=*C*H), 162.0 (C_q), 167.8 (*C*=O)

Further elution (R_f = 0.41) gave the *E*-isomer **202eii** as a white powder (1.59 g, 81%)

mp: 82-83 °C (from EtOAc) (Lit.[120] 84-86 °C)

ν_{max}: (film)/cm^{-1} 2964 (CH), 2844 (CH), 1719 (C=O), 1639, 1604, 1515, 1289, 1177, 1026

δ_H: (300 MHz, $CDCl_3$) 3.72 (3H, s, *C*H_3), 3.75 (3H, s, C*H*$_3$), 6.25 (1H, d, *J* 16.7, =C*H*), 6.85 (2H, d, *J* 8.5 ArC*H*), 7.39 (2H, d, *J* 8.5, ArC*H*), 7.12 (1H, d, *J* 16.7, =C*H*)

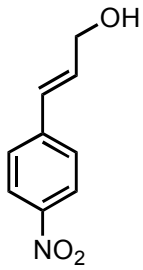
δ_C: (75 MHz, $CDCl_3$) 52.3 (*C*H_3), 55.9 (*C*H_3), 57.7 (*C*H_3), 115.0 (Ar*C*H), 115.9 (=*C*H), 127.7 (C_q), 130.3 (Ar*C*H), 145.1 (=*C*H), 162.0 (C_q), 167.5 (*C*=O)

m/z: $(EI)^+$ 192 (77%, $[M]^+$), 161 (100, $[M\text{-}OMe]^+$)

General Procedure 9: DIBAL Reduction

A solution of DIBAL-H 1.0 M in toluene (2.2 eq) was added dropwise over 5 min to a stirred solution of cinnamate ester (1 eq) dissolved in THF (0.2 M) cooled to 0 °C. The reaction was stirred at 0 °C until the reaction was judged to be complete by TLC analysis. The reaction was quenched by the addition of a saturated aqueous solution of Rochelle's salt. The aqueous phase was extracted with Et_2O x 4. The combined organic phases were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo* to afford the crude allylic alcohol.

Hydroxymethyl 4-nitrocinnamol (203a)



Alcohol **203a** was prepared from ester **202a** (309 mg, 1.49 mmol) and DIBAL-H (1 M soln. in hexanes, 3.7 mL, 3.73 mmol) according to General Procedure 9. After 4 h and purification by flash column chromatography (R_f = 0.27, hexane:EtOAc, 1:1) afforded the product **203a** as a yellow powder (168 mg, 63%). Alcohol **203a** was obtained as a 7:1 mixture of *E*:*Z* stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 111-114 °C (from hexane:EtOAc) (Lit. *E*-isomer[121] 107 °C, *Z*-isomer[122] 127-129 °C (benzene)

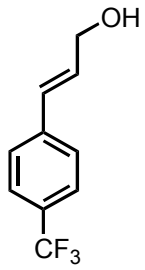
ν_{max}: (film)/cm^{-1} 3445 (OH), 3020 (ArCH), 1598 (ArC=C), 1519 (ν_{as} NO_2), 1345 (ν_s NO_2), 1216, 756

δ_H: (300 MHz, $CDCl_3$) 1.94 (1H, br s, O*H*), 4.39 (2H, d, *J* 5.2, *C*H_2), 6.53 (1H, dt, *J* 16.2 and 5.2, =C*H*CH_2), 6.70 (1H, d, *J* 16.2, C_qC*H*=), 7.49 (2H, d, *J* 8.6 ArC*H*), 8.15 (2H, d, *J* 8.6, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 63.2 (*C*H_2), 124.1 (Ar*C*H), 127.0 (Ar*C*H), 128.3 (=C*H*), 133.8 (=*C*H), 143.4 (C_q), 147.0 (C_q)

m/z: (EI)$^+$ 179 (81%, $[M]^+$), 137 (100)

Hydroxymethyl 4-trifluoromethylcinnamol (203b)



Alcohol **203b** was prepared from ester **202b** (2.06 g, 9.94 mmol) and DIBAL-H (1 M soln. in hexanes, 19.7 mL, 19.7 mmol) according to General Procedure 9. After 4 h and purification by flash column chromatography (R_f = 0.27, hexane:EtOAc, 3:1) afforded the product **203b** as a white powder (1.73 g, 96%).

mp: 61-60 °C (from hexane:EtOAc) (lit.[123] 62-64 °C)

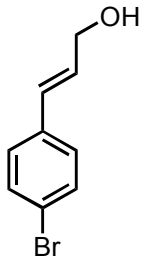
ν_{max}: (film)/cm^{-1} 3333 (OH), 3052 (=CH), 2926 (CH), 2870 (CH), 1614 (C-O), 1414, (CF_3), 1125

δ_H: (300 MHz, $CDCl_3$) 1.73 (1H, t, *J* 5.3, O*H*), 4.37 (2H, t, *J* 5.3, CH_2), 6.45 (1H, dt, *J* 16.0 and 5.3, =C*H*CH_2), 6.66 (1H, dd, *J* 16.0, C_qC*H*=), 7.46 (2H, d, *J* 8.3, ArC*H*), 7.56 (2H, d, *J* 8.3, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 62.8 (*C*H_2), 124.2 (q, *J* 272, *C*F_3), 125.4 (Ar*C*H), 126.2 (Ar*C*H), 128.9 (=*C*H), 129.2 (q, *J* 32, $C_q$$CF_3$), 131.4 (=*C*H), 140.3 (C_q)

m/z: (EI)$^+$ 202 (71%, [M]$^+$), 160 (100, [M]$^+$)

Hydroxymethyl 4-bromocinnamol (203c)



Alcohol **203c** was prepared from ester **202c** (2.19 g, 9.08 mmol) and DIBAL-H (1 M soln. in hexanes, 22.7 mL, 22.7 mmol) according to General Procedure 9. After 1 h and purification by flash column chromatography (R_f = 0.33, hexane:EtOAc, 2:1) afforded the product **203c** as a white powder (1.88 g, 97%).

Alcohol **203c** was obtained as a 47:1 mixture of *E*:*Z* stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 66-68 °C (from hexane:EtOAc) (Lit.[124] *E*-isomer 68-69 °C)

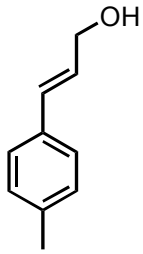
ν_{max}: (film)/cm^{-1} 3400 (OH), 3052 (=CH), 2923 (CH), 2871 (CH), 1651 (C-O), 1487, 1400, 1215

δ_H: (300 MHz, $CDCl_3$) 3.34 (1H, s, O*H*), 4.31 (2H, d, *J* 5.5, CH_2), 6.34 (1H, dt, *J* 15.8 and 5.5, =C*H*CH_2), 6.55 (1H, d, *J* 15.8, C_qC*H*=), 7.23 (2H, d, *J* 8.5, ArC*H*), 7.43 (2H, d, *J* 8.5, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 63.4 (*C*H_2), 121.5 (C_q), 128.0 (Ar*C*H), 129.4 (=*C*H), 129.7 (=*C*H), 131.7 (Ar*C*H), 135.7 (C_q)

m/z: (EI)$^+$ 214 (35%, [M(^{81}Br)]$^+$), 212 (37, [M(^{79}Br)]$^+$), 171 (46), 160 (48), 133 (100), 115 (65), 91 (85), 77 (78)

Hydroxymethyl 4-methylcinnamol (203d)



Alcohol **203d** was prepared from ester **202d** (1.28 g, 7.24 mmol) and DIBAL-H (1 M soln. in hexanes, 15.9 mL, 15.9 mmol) according to General Procedure 9. After 1 h and purification by flash column chromatography (R_f = 0.31, hexane:EtOAc, 3:1) afforded the product **203d** as a white powder (1.01 g, 94%).

Alcohol **203d** was obtained as a 16:1 mixture of *E*:*Z* stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 43-45 °C (from hexane:EtOAc) (Lit.[125] *E*-isomer 52-3 °C)

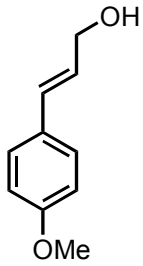
ν_{max}: (film)/cm^{-1} 3279 (OH), 3034 (ArCH), 2948 (CH), 2918 (CH), 2853 (CH), 1512, 1010, 972, 759

δ_H: (300 MHz, $CDCl_3$) 1.93 (1H, br s, O*H*), 2.34 (3H, s, *C*H_3), 4.35 (2H, d, *J* 5.0, *C*H_2), 6.31 (1H, dt, *J* 16.0 and 5.0, =C*H*CH_2), 6.55 (1H, d, *J* 16.0, C_qC*H*=), 7.19 (2H, d, *J* 8.5, ArC*H*), 7.26 (2H, d, *J* 8.5, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 20.5 (*C*H_3), 63.0 (*C*H_2), 125.7 (Ar*C*H), 126.7 (=C*H*), 128.6 (Ar*C*H), 130.4 (=*C*H), 133.4 (C_q), 136.5 (C_q)

m/z: (EI)$^+$ 148 (66%, $[M]^+$), 105 (100), 92 (65)

Hydroxymethyl 4-methoxycinnamol (203e)



Alcohol **203e** was prepared from ester **202e** (1.06 g, 5.53 mmol) and DIBAL-H (1 M soln. in hexanes, 13.8 mL, 13.8 mmol) according to General Procedure 9. After 1 h and purification by flash column chromatography (R_f = 0.14, hexane:EtOAc, 3:1) afforded the product **203e** as a white powder (870 mg, 94%).

mp: 72-73 °C (from EtOAc) (Lit. [1264] 72-74 °C (from hexane:Et_2O)

ν_{max}: (film)/cm^{-1} 3410 (OH), 3028 (ArCH), 2933 (CH), 2839 (CH), 1606, 1511, 1335, 1157

δ_H: (300 MHz, $CDCl_3$) 1.86 (1H, br s, O*H*), 3.78 (3H, s, *C*H_3), 4.25 (2H, d, *J* 5.0, *C*H_2), 6.21 (1H, dt, *J* 16.3 and 5.0, =C*H*CH_2), 6.51 (1H, d, *J* 16.3, C_qC*H*=), 6.82 (2H, d, *J* 8.7, ArC*H*), 7.29 (2H, d, *J* 8.7, ArC*H*)

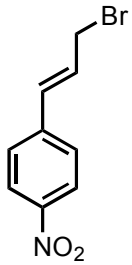
δ_C: (75 MHz, $CDCl_3$) 55.5 (*C*H_3), 63.8 (*C*H_2), 113.1 (Ar*C*H), 126.5 (=C*H*), 128.4 (Ar*C*H), 129.5 (C_q), 131.5 (=*C*H), 158.2 (C_q)

m/z: (EI)$^+$ 164 (44%, $[M]^+$), 121 (100), 108 (35)

General Procedure 10: PBr_3 Bromination

A solution of PBr_3 (1 M soln. in CH_2Cl_2, 1.2 eq) was added dropwise over 1 min to a stirred solution of allylic alcohol (1eq) dissolved in CH_2Cl_2 (0.1 M) cooled to 0 °C. The reaction was stirred at 0 °C until the reaction was judged to be complete by TLC analysis. The reaction was quenched by the addition of water. The organic phase was separated and the aqueous phase further extracted with CH_2Cl_2 x 3. The combined organic phases were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo* to afford the crude allylic bromide.

Bromomethyl 4-nitrocinnamol (204a)



Bromide **204a** was prepared from alcohol **203a** (1.88 g, 8.81 mmol) and PBr_3 (1 M soln. in CH_2Cl_2, 4.40 mL, 4.40 mmol) according to General Procedure 11. After 2 h and purification by flash column chromatography (R_f = 0.32, hexane:EtOAc, 5:1) afforded the product **204a** as a yellow powder (191 mg, 84%). Bromide **204a** was obtained as a 7:1 mixture of *E*:*Z* stereoisomers. In the case of the NMR spectra, only data for the major *E* stereoisomer is reported.

mp: 66-68 °C (from hexane:EtOAc) (Lit.[126] *E*-isomer 76 °C)

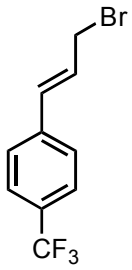
ν_{max}: (film)/cm^{-1} 3057 (ArCH), 1598 (ArC=C), 1519 (ν_{as} NO_2), 1436, 1345 (ν_s NO_2,),

δ_H: (300 MHz, $CDCl_3$) 4.15 (2H, d, *J* 7.4, *C*H_2), 6.55 (1H, dt, *J* 15.8 and 7.4, =C*H*CH_2), 6.70 (1H, d, *J* 15.8, C_qC*H*=), 7.50 (2H, d, *J* 8.8, ArC*H*), 8.16 (2H, d, *J* 8.8, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 32.0 (*C*H_2), 124.1 (Ar*C*H), 127.4 (Ar*C*H), 130.0 (=C*H*), 132.2 (=*C*H), 142.3 (C_q), 147.4 (C_q)

m/z: (EI)$^+$ 243 (7%, [M(^{81}Br)]$^+$), 241 (7, [M(^{79}Br)]$^+$), 162 (70), 115 (100

Bromomethyl 4-trifluoromethylcinnamol (204b)



Bromide **204b** was prepared from alcohol **203b** (1.48 g, 7.31 mmol) and PBr_3 (1 M soln. in CH_2Cl_2, 8.8 mL, 8.8 mmol) according to General Procedure 10. After 1 h and purification by flash column chromatography (R_f = 0.75, hexane:EtOAc, 6:1) afforded the product **204b** as a white crystalline solid (1.91 g, 99%)

mp: 35-36 °C (from hexane:EtOAc) (Lit.[127] 35.9-36.8 °C)

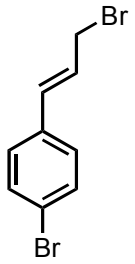
ν_{max}: (film)/cm^{-1} 3042 (=CH), 2968 (CH), 2929 (CH), 1614 (C-O), 1413, 1325 (CF_3), 1123

δ_H: (300 MHz, $CDCl_3$) 4.15 (2H, d, *J* 7.5, C*H*$_2$), 6.48 (1H, dt, *J* 15.6 and 7.5, =C*H*CH_2), 6.65 (1H, d, *J* 15.6, C_qC*H*=), 7.45 (2H, d, *J* 8.1, ArC*H*), 7.57 (2H, d, *J* 8.1, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 32.4 (*C*H_2), 124.2 (q, *J* 272, *C*F_3), 125.6 (Ar*C*H), 126.9 (Ar*C*H), 127.9 (=*C*H), 129.9 (q, *J* 32, $C_q$$CF_3$), 132.8 (=*C*H), 139.3 (C_q)

m/z: $(EI)^+$ 266 (55%, $[M(^{81}Br)]^+$), 264 (55, $[M(^{79}Br)]^+$), 185 (100)

Bromomethyl 4-bromocinnamol (204c)



Bromide **204c** was prepared from alcohol **203c** (1.88 g, 8.81 mmol) and PBr_3 (1 M soln. in CH_2Cl_2, 4.4 mL, 4.4 mmol) according to General Procedure 10. After 2 h and purification by flash column chromatography (R_f = 0.75, hexane:EtOAc, 1:1) afforded the product **204c** as a white powder (2.38 g, 99%).

mp: 72-74 °C (from hexane:EtOAc) (Lit.[128] 72-76 °C)

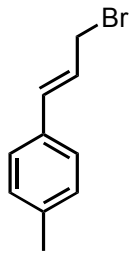
ν_{max}: (film)/cm^{-1} 3014 (CH), 1643 (C=C), 1584 (ArC=C), 1487 (ArC=C), 1214, 1202, 973, 756

δ_H: (300 MHz, $CDCl_3$) 4.13 (2H, d, *J* 7.7, C*H*$_2$), 6.37 (1H, dt, *J* 15.5 and 7.7, =C*H*CH$_2$), 6.55 (1H, d, *J* 15.5, C_qC*H*=), 7.23 (2H, d, *J* 8.5, ArC*H*), 7.44 (2H, d, *J* 8.5, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 33.1 (*C*H$_2$), 122.1 (C_q), 125.9 (=*C*H), 128.2 (Ar*C*H), 131.7 (Ar*C*H), 133.3 (=*C*H), 134.7 (C_q)

m/z: (EI)$^+$ 278 (5%, [M(^{81}Br, ^{81}Br]$^+$), 276 (5%, [M(^{81}Br, ^{79}Br]$^+$), 274 (2%, [M(^{79}Br, ^{79}Br]$^+$), 228 (30), 147 (100), 116 (85), 84 (90)

Bromomethyl 4-methylcinnamol (204d)



Bromide **204d** was prepared from alcohol **203d** (0.97 g, 6.57 mmol) and PBr_3 (1 M soln. in CH_2Cl_2, 7.9 mL, 7.9 mmol) according to General Procedure 10. After 1 h and purification by flash column chromatography (R_f = 0.75, hexane:EtOAc, 6:1) afforded the product **204d** as a white powder (1.15 g, 83%).

mp: 64-66 °C (from hexane:EtOAc) (Lit.[129] 64-65 °C)

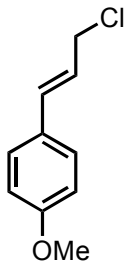
ν_{max}: (film)/cm^{-1} 3023 (ArCH), 2962 (CH), 2921 (CH), 1641, 1511, 1199, 971, 801

δ_H: (300 MHz, $CDCl_3$) 2.31 (C*H*$_3$), 4.15 (2H, d, *J* 7.4, *C*H$_2$), 6.33 (1H, dt, *J* 7.4 and 15.8, =C*H*CH$_2$), 6.61 (1H, d, *J* 15.8, C_qC*H*=), 7.12 (2H, d, *J* 8.8, ArC*H*), 7.26 (2H, d, *J* 8.8, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 20.0 (*C*H$_3$), 32.6 (*C*H$_2$), 123.0 (=C*H*), 125.5 (Ar*C*H), 128.1 (Ar*C*H), 131.0 (C_q), 133.3 (=*C*H), 136.8 (C_q)

m/z: (EI)$^+$ 212 (5%, [M(^{81}Br)]$^+$), 210 (5, [M(^{79}Br)]$^+$), 131 (100, [M-Br]$^+$)

Chloromethyl 4-methoxycinnamol (205)



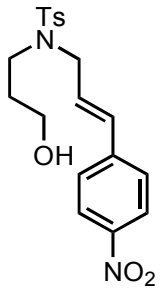
Thionyl chloride (0.27 mL, 3.71 mmol) was added to a stirred solution of alcohol **203e** (580 mg, 3.53 mmol) in Et_2O (7 mL) cooled to 0 °C. The reaction was stirred for 1 min at 0 °C before the solvent was removed *in vacuo* to give the crude product **203e** as a pale yellow oil (603 mg) that was used straight away in the next reaction without further purification.

δ_H**:** (300 MHz, $CDCl_3$) 3.79 (3H, s, *C*H_3), 4.23 (2H, d, *J* 5.0, *C*H_2), 6.27 (1H, dt, *J* 16.3 and 5.0, =C*H*CH_2), 6.55 (1H, d, *J* 16.3, C_qCH=), 6.83 (2H, d, *J* 8.7, ArC*H*), 7.31 (2H, d, *J* 8.7, ArC*H*)

General Procedure 11: Alkylation of 3-(*p*-Toluenesulfonyl)aminopropanol)

Cesium carbonate (1.3 eq) was added to a stirred solution of sulfonamide (1 eq) dissolved in MeCN (0.1 M). The resulting mixture was cooled to 0 °C and the alkylating agent (1 eq) was added in one portion. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of water and the solvent removed *in vacuo*. The aqueous phase was extracted with CH_2Cl_2 x 4 and the combined organic phases were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo* to afford the crude alkylated product.

(*E*)-*N*-(3-Hydroxypropyl)-4-methyl-*N*-(3-(4-nitrophenyl)allyl)benzenesulfonamide (207a)



Alcohol **207a** was prepared from sulfonamide **206** (0.58 g, 2.53 mmol), Cs_2CO_3 (0.91 g, 2.79 mmol) and bromide **204a** (0.61 g, 2.53 mmol) according to General Procedure 11. Purification by flash column chromatography (R_f = 0.30, hexane:EtOAc, 1:2) afforded the product **207a** as a yellow oil (0.62 g, 63%).

ν_{max}: (film)/cm^{-1} 3533 (OH), 2926 (CH), 2876 (CH), 2855(CH), 1597 (ArC=C), 1517 (ν_{as} NO_2), 1343 (ν_{as} SO_2, ν_s NO_2), 1157 (ν_s SO_2)

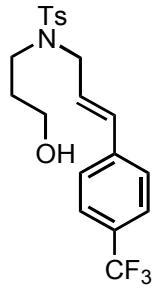
δ_H: (300 MHz, $CDCl_3$) 1.15 (1H, br s, O*H*), 1.69-1.78 (2H, m, $CH_2CH_2CH_2$), 2.40 (3H, s, CH_3), 3.20 (2H, t, *J* 6.6, NCH_2CH_2), 3.70 (2H, t, *J* 5.7, CH_2OH), 3.97 (2H, d, *J* 6.3, CH_2CH=), 6.16 (1H, dt, *J* 16.3 and 6.3, CH_2CH=), 6.51 (1H, d, *J* 16.3, C_qCH=), 7.29 (2H, d, *J* 8.1, ArC*H*), 7.35 (2H, d, *J* 8.8, ArC*H*), 7.70 (2H, d, *J* 8.1, ArC*H*), 8.10 (2H, d, *J* 8.8, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 21.5 (CH_3), 31.0 ($CH_2CH_2CH_2$), 44.8 (NCH_2), 50.3 (NCH_2), 58.9 (OCH_2), 123.9 (Ar*C*H), 127.0 (Ar*C*H), 127.1 (Ar*C*H), 129.5 (=*C*H), 129.8 (Ar*C*H), 131.4 (=*C*H), 136.4 (C_q), 142.5 (C_q), 143.7 (C_q), 147.0 (C_q)

m/z: $(ES)^+$ 413.1 (100%, $[M+Na]^+$)

HRMS: Found: $(M+Na)^+$ 413.1153. $C_{19}H_{22}N_2NaO_5S$ requires *M*, 413.1147

(*E*)-*N*-(3-Hydroxypropyl)-4-methyl-*N*-(3-(4-(trifluoromethyl)phenyl)allyl)benzene sulfonamide (207b)



Alcohol **207b** was prepared from sulfonamide **206** (1.01 g, 4.41 mmol), Cs_2CO_3 (1.87 g, 5.73 mmol) and bromide **204b** (1.17 g, 4.41 mmol) according to General Procedure 11. Purification by flash column chromatography (R_f = 0.33, hexane:EtOAc, 1:1) afforded the product **207b** as a white crystalline powder (1.63 g, 90%).

mp: 58-60 °C (from hexane:EtOAc)

µ: Found: C, 58.45; H, 5.47; N, 3.87. $C_{20}H_{22}F_3NO_3S$ requires C, 58.10; H, 5.36; N, 3.39%

ν_{max}: (film)/cm^{-1} 3520 (OH), 2930 (CH), 1615 (C=C), 1598 (ArC=C), 1494 Ar(C=C), 1326 (CF_3), 1158 (SO_2), 1067 (C-O)

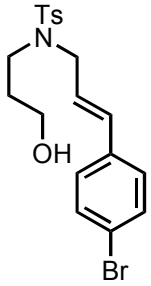
δ_H: (300 MHz, $CDCl_3$) 1.67-1.78 (2H, m, $CH_2CH_2CH_2$), 2.37 (3H, s, CH_3), 2.72 (1H, br s, O*H*), 3.28 (2H, t, *J* 6.6, NCH_2CH_2), 3.68 (2H, t, *J* 5.7, CH_2OH), 3.95 (2H, d, *J* 6.6, CH_2CH=), 6.03 (1H, dt, *J* 15.8 and 6.6, CH_2CH=), 6.45 (1H, d, *J* 15.8, C_qCH=), 7.23-7.32 (4H, stack, ArC*H*), 7.48 (2H, d, *J* 8.1, ArC*H*), 7.69 (2H, d, *J* 8.1, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 21.1 (CH_3), 30.8 ($CH_2CH_2CH_2$), 44.4 (NCH_2), 50.2 (NCH_2), 58.8 (OCH_2), 124.4 (q, *J* 272, CF_3), 125.8 (Ar*C*H), 126.9 (Ar*C*H), 127.4 (=*C*H), 127.5 (Ar*C*H), 129.9 (q, *J* 32, C_qCF_3), 130.2 (Ar*C*H), 132. (=*C*H), 137.0 (C_q), 140.0 (C_q), 144.1 (C_q)

m/z: $(ES)^+$ 436.2 (100%, $[M+Na]^+$)

HRMS: Found: $(M+Na)^+$ 436.1173. $C_{20}H_{22}F_3NNaO_3S$ requires *M*, 436.1170

(*E*)-*N*-(3(4-Bromophenyl)allyl)*N*(3-hydroxypropyl)-4-methylbenzenesulfonamide (207c)



Alcohol **207c** was prepared from sulfonamide **204** (1.92 g, 8.36 mmol), Cs_2CO_3 (3.54 g, 11.8 mmol) and bromide **204d** (2.30 g, 8.36 mmol) according to General Procedure 11. Purification by flash column chromatography (R_f = 0.36, hexane:EtOAc, 1:1) afforded the product **207c** as a colourless oil (3.11 g, 88%).

ν_{max}: (film)/cm^{-1} 3526 (OH), 3030 (ArCH), 2928 (CH), 2877 (CH), 1652 (C=C), 1598 (ArC=C), 1487 (ArC=C), 1334 (ν_{as} SO_2), 1157 (ν_s SO_2), 1071 (C-O)

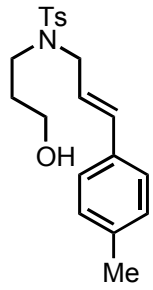
δ_H: (300 MHz, $CDCl_3$) 1.66-1.67 (2H, m, $CH_2CH_2CH_2$), 2.39 (3H, s, CH_3), 2.60 (1H, br s, O*H*), 3.26 (2H, t, *J* 6.4, NCH_2CH_2), 3.68 (2H, t, *J* 5.9, CH_2OH), 3.91 (2H, d, *J* 6.6, CH_2CH=), 5.91 (1H, dt, *J* 6.6 and 15.8, CH_2CH=), 6.35 (1H, d, *J* 15.8, C_qCH=), 7.06 (2H, d, *J* 8.5, ArC*H*), 7.27 (2H, d, *J* 8.1, ArC*H*), 7.36 (2H, d, *J* 8.5, ArC*H*), 7.68 (2H, d, *J* 8.1, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 21.4 (CH_3), 31.0 ($CH_2CH_2CH_2$), 44.4 (NCH_2), 50.3 (NCH_2), 58.8 (OCH_2), 121.7 (C_q), 124.9 (=CH), 127.1 (ArCH), 127.9 (ArCH), 129.7 (ArCH), 131.8 (ArCH), 132.4 (=CH), 135.0 (C_q), 136.6 (C_q), 143.4 (C_q)

m/z: $(ES)^+$ 448.0 (89%, $[M(^{81}Br)+Na]^+$), 446.0 (100, $[M(^{79}Br)+Na]^+$)

HRMS: [Found: $(M(^{79}Br)+Na)^+$ 446.0421. $C_{19}H_{22}BrNNaO_3S$ requires *M*, 446.0401]

(*E*)-*N*-(3-Hydroxypropyl)-4-methyl-*N*-(3-(*p*-tolyl)allyl)benzenesulfonamide (207d)



Alcohol **207d** was prepared from sulfonamide **206** (1.05 g, 4.56 mmol), Cs_2CO_3 (1.93 g, 5.93 mmol) and bromide **204d** (0.97 g, 4.56 mmol) according to General Procedure 11. Purification by flash column chromatography (R_f = 0.33, hexane:EtOAc, 1:1) afforded the product **207d** as a colourless oil (1.46 g, 89%).

ν_{max}: (film)/cm^{-1} 3533 (OH), 3027 (=CH), 2924 (CH), 2876 (CH), 1653, 1598 (ArC=C), 1513 (C=C), 1494 (ArC=C), 1453, 1335 (ν_{as} SO_2), 1157 (ν_s SO_2), 1089 (C-O)

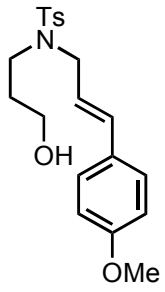
δ_H: (300 MHz, $CDCl_3$) 1.65-1.76 (2H, m, $CH_2CH_2CH_2$), 2.30 (3H, s, CH_3), 2.35-2.43 (4H, stack, CH_3 and OH), 3.25 (2H, t, *J* 6.6, NCH_2CH_2), 3.71 (2H, q, *J* 5.7, CH_2OH), 3.93 (2H, d, *J* 7.0, CH_2CH=), 5.84 (1H, dt, *J* 15.5 and 7.0, CH_2CH=), 6.35 (1H, d, *J* 15.5, C_qCH=), 7.05-7.16 (5H, stack, ArCH), 7.25 (2H, d, *J* 8.0, ArCH), 7.73 (2H, d, *J* 8.0, ArCH)

δ_C: (75 MHz, $CDCl_3$) 20.9 (CH_3), 30.6 ($CH_2CH_2CH_2$), 43.6 (NCH_2), 50.3 (NCH_2), 58.4 (CH_2OH), 122.4 (=CH), 126.0 (ArCH), 127.0 (ArCH), 128.9 (ArCH), 130.5 (ArCH), 132.9 (C_q), 133.5 (=CH), 136.0 (C_q), 137.6 (C_q), 143.1 (C_q)

m/z: $(ES)^+$ 382.2 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 382.1455. $C_{20}H_{25}NNaO_3S$ requires *M*, 382.1453]

(*E*)-*N*-(3-Hydroxypropyl)-*N*-(3-(4-methoxyphenyl)allyl)-4-methylbenzene sulfonamide (207e)



Alcohol **207e** was prepared from sulfonamide **204** (0.58 g, 3.53 mmol), Cs_2CO_3 (1.50 g, 4.59 mmol) and chloride **205** (603 mg) according to General Procedure 11. Purification by flash column chromatography (R_f = 0.38, hexane:EtOAc, 1:1) afforded the product **207e** as a colourless oil (101 mg, 44% over 2 synthetic steps).

ν_{max}: (film)/cm^{-1} 3525 (OH), 3032 (=CH), 2934 (CH), 2838 (CH), 1651, 1607, 1511 (C=C), 1455, 1332 (ν_{as} SO_2), 1250, 1156 (ν_s SO_2), 1089 (C-O), 1032

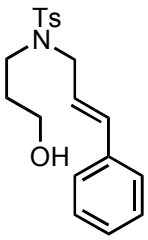
δ_H: (300 MHz, $CDCl_3$) 1.65-1.79 (2H, m, $CH_2CH_2CH_2$), 2.39 (3H, s, CH_3), 2.49 (1H, br s, O*H*), 3.25 (2H, t, *J* 6.4, NCH_2CH_2), 3.72 (2H, br s, CH_2OH), 3.76 (3H, s, CH_3), 3.91 (2H, d, *J* 7.2, CH_2CH=), 5.85 (1H, dt, *J* 15.8 and 7.2, CH_2CH=), 6.35 (1H, d, *J* 15.8, C_qCH=), 6.78 (2H, d, *J* 8.0, ArC*H*), 7.13 (2H, d, *J* 8.0, ArC*H*), 7.28 (2H, d, *J* 8.8, ArC*H*), 7.71 (2H, d, *J* 8.8, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 21.4 (C_qCH_3), 30.7 ($CH_2CH_2CH_2$), 43.6 (NCH_2), 50.6 (NCH_2), 55.2 (OCH_3), 58.6 (CH_2OH), 113.9 (Ar*C*H), 121.4 (=*C*H), 127.1 (Ar*C*H), 127.6 (Ar*C*H), 128.7 (C_q), 129.7 (Ar*C*H), 133.4 (=*C*H), 136.6 (C_q), 143.4 (C_q), 159.4 (C_q)

m/z: $(ES)^+$ 398.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 398.1392. $C_{20}H_{25}NNaO_4S$ requires *M*, 398.1402]

***N*-Cinnamyl-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (207f)**



Alcohol **207f** was prepared from sulfonamide **206** (1.02 g, 4.44 mmol), Cs_2CO_3 (1.59 g, 4.88 mmol) and cinnamyl bromide (0.87 g, 4.43 mmol) according to General Procedure 11. Purification by flash column chromatography (R_f = 0.30, hexane:EtOAc, 1:1) afforded the product **207f** as a white amorphous powder (1.24 g, 81%).

mp: 69-70 °C (from hexane:EtOAc)

μ: Found: C, 66.10; H, 6.87; N, 4.18. $C_{19}H_{23}NO_3S$ requires C, 66.06; H, 6.71; N, 4.05%

ν_{max}: (film)/cm^{-1} 3535 (OH), 3027 (=CH), 2927 (CH), 1598 (ArC=C), 1495 (ArC=C), 1335 (ν_{as} SO_2), 1157 (ν_s SO_2), 1089 (C-O)

δ_H: (300 MHz, $CDCl_3$) 1.66-1.77 (2H, m, $CH_2CH_2CH_2$), 2.36 (3H, s, CH_3), 2.51 (1H, t *J* 5.7, O*H*), 3.27 (2H, t, *J* 6.6, NCH_2CH_2), 3.67 (2H, t, *J* 5.7, CH_2OH), 3.93 (2H, d, *J* 7.0, CH_2CH=), 5.91 (1H, dt, *J* 15.8 and 7.0, CH_2CH=), 6.42 (1H, d, *J* 15.8, C_qCH=), 7.19-7.27 (7H, stack, ArC*H*), 7.70 (2H, d, *J* 8.1, ArC*H*)

δ_C: (75 MHz, $CDCl_3$) 21.3 (CH_3), 30.9 ($CH_2CH_2CH_2$), 44.1 (NCH_2), 50.3 (NCH_2), 58.8 (CH_2OH), 123.9 (=*C*H), 126.3 (Ar*C*H), 127.0 (Ar*C*H), 128.4 (Ar*C*H), 129.7 (Ar*C*H), 133.7 (=*C*H), 136.0 (C_q), 136.6 (C_q), 143.3 (C_q)

m/z: $(ES)^+$ 368.0 (100%, $[M+Na]^+$)

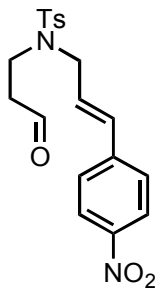
HRMS: [Found: $(M+Na)^+$ 368.1301. $C_{19}H_{23}NNaO_3S$ requires *M*, 368.1296]

General Procedure 12: Swern oxidation

Anhydrous DMSO (3 eq) was added at a rapid rate to a solution of oxalyl chloride (1.5 eq) dissovled in CH_2Cl_2 (0.2 M) at -78 °C. The resulting mixture was stirred for 5 min before a

solution of the alcohol (1 eq) dissolved in CH_2Cl_2 (0.2 M) was added dropwise over 10 min. After 30 min Et_3N (5 eq) was added dropwise over 1 min and the resulting solution was stirred for a further 3 h at -78 °C before being allowed to warm to room temperature. Water was added and the organic phase was separated before the aqueous phase was further extracted with 3 x CH_2Cl_2. The combined organic phases were washed with water and brine before being dried over $MgSO_4$ and evaporated *in vacuo* to give the crude aldehyde.

(*E*)-4-Methyl-*N*-(3-(4-nitrophenyl)allyl)-*N*-(3-oxopropyl)benzenesulfonamide (194a)



Aldehyde **194a** was prepared from alcohol **207a** (0.60 g, 1.55 mmol), oxalyl chloride (170 μL, 1.90 mmol), DMSO (260 μL, 3.66 mmol) and Et_3N (1.10 mL, 7.86 mmol) according to general procedure 12. Work-up afforded **194a** as a yellow oil (0.60 g, quant.).

R_f : 0.43 (hexane:EtOAc, 1:1)

ν_{max}: (film)/cm^{-1} 2924 (CH), 2857 (CH), 1721 (C=O), 1597, 1607, 1516 (ν_{as} NO_2), 1338 (ν_s NO_2, ν_{as} SO_2), 1155 (ν_s SO_2)

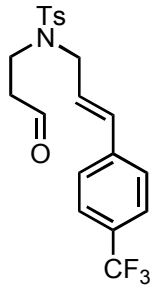
δ_H: (300 MHz, $CDCl_3$) 2.42 (3H, s, *C*H_3), 2.83 (2H, t, *J* 6.8, C*H*$_2$CHO), 3.46 (2H, t, *J* 6.8, N*C*H_2CH_2), 3.98 (2H, d, *J* 6.3, C*H*$_2$CH=), 6.18 (1H, dt, *J* 15.8 and 6.3, CH_2C*H*=), 6.53 (1H, d, *J* 15.8, C_qC*H*=), 7.32 (2H, d, *J* 8.1, ArC*H*), 7.39 (2H, d, *J* 8.6, ArC*H*), 7.70 (2H, d, *J* 8.1, ArC*H*), 8.13 (2H, d, *J* 8.6, ArC*H*), 9.73 (1H, s, *C*HO)

δ_C: (75 MHz, $CDCl_3$) 21.5 (*C*H_3), 41.6 (*C*H_2), 43.7 (*C*H_2), 50.9 (*C*H_2CH=), 123.9 (Ar*C*H), 127.0 (Ar*C*H), 127.2 (Ar*C*H), 129.3 (=*C*H), 129.9 (Ar*C*H) 131.5 (=*C*H), 136.1 (C_q), 142.5 (C_q), 143.9 (C_q), 147.1 (C_q), 200.2 (*C*=O),

m/z: $(ES)^+$ 411.3 (100%, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 411.0982. $C_{19}H_{20}N_2NaO_5S$ requires *M*, 411.0991]

(*E*)-4-Methyl-*N*-(3-oxopropyl)-*N*-(3-(4-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (194b)



Aldehyde **194b** was prepared from alcohol **207b** (1.07 g, 2.59 mmol), oxalyl chloride (280 μL, 3.14 mmol), DMSO (440 μL, 6.20 mmol) and Et_3N (1.82 mL, 13.00 mmol) according to general procedure 12. Work-up afforded **194b** as a white crystalline powder (1.02 g, 96%).

R_f : 0.54 (hexane:EtOAc, 1:1)

mp: 60-62 °C (from CH_2Cl_2:EtOAc)

ν_{max}: (film)/cm^{-1} 2956 (CH), 2934 (CH), 1722 (C=O), 1613 (C=C), 1324 (CF_3), 1154 (SO_2), 1107

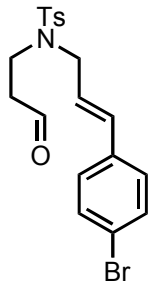
δ_H: (300 MHz, $CDCl_3$) 2.41 (3H, s, *C*H_3), 2.81 (2H, t, *J* 7.0, CH_2CHO), 3.45 (2H, t, *J* 7.0, NCH_2CH_2), 3.95 (2H, d, *J* 6.3, CH_2CH=), 6.06 (1H, dt, *J* 6.3 and 15.8, CH_2C*H*=), 6.47 (1H, d, *J* 15.8, C_qC*H*=), 7.29 (2H, d, *J* 8.1, ArC*H*), 7.33 (2H, d, *J* 8.5, ArC*H*), 7.51 (2H, d, *J* 8.1, ArC*H*), 7.69 (2H, d, *J* 8.15 ArC*H*), 9.71 (1H, s, *C*HO)

δ_C: (75 MHz, $CDCl_3$) 21.5 (*C*H_3), 41.5 (*C*H_2), 43.9 (*C*H_2), 51.1 (*C*H_2), 124.1 (q, *J* 272, *C*F_3), 125.7 (Ar*C*H), 126.7 (Ar*C*H), 126.9 (=*C*H), 127.3 (Ar*C*H), 129.8 (q, *J* 32, $C_q$$CF_3$), 129.9 (Ar*C*H), 132.5 (=*C*H), 136.3 (C_q), 139.5 (C_q), 143.9 (C_q), 200.2 (*C*=O)

m/z: $(ES)^+$ 466.1 (100%, $[M+Na+MeOH]^+$), 434.1 (50, $[M+Na]^+$

HRMS: Found: $(M+Na)^+$ 434.1029. $C_{20}H_{20}F_3NNaO_3S$ requires *M*, 436.1170

(*E*)-*N*-(3-(4-Bromophenyl)allyl)-4-methyl-*N*-(3-oxopropyl)benzenesulfonamide (194c)



Aldehyde **194c** was prepared from alcohol **207c** (1.14 g, 2.69 mmol), oxalyl chloride (290 μL, 3.25 mmol), DMSO (460 μL, 6.48 mmol) and Et_3N (1.90 mL, 13.58 mmol) according to general procedure 12. Work-up afforded **207c** as a white crystalline powder (1.02 g, 96%).

R_f : 0.29 (hexane:EtOAc, 2:1)

mp: 61-63 °C (from hexane:EtOAc)

ν_{max}: (film)/cm^{-1} 2956 (CH), 2917 (CH), 1720 (C=O), 1333 (ν_{as} SO_2), 1154 (ν_s SO_2)

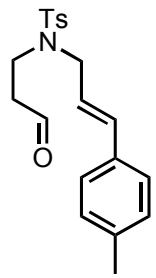
δ_H: (300 MHz, $CDCl_3$) 2.43 (3H, s, *C*H_3), 2.82 (2H, t, *J* 7.0, C*H*$_2$CHO), 3.44 (2H, t, *J* 7.0, NC*H*$_2$CH$_2$), 3.92 (2H, d, *J* 6.6, C*H*$_2$CH=), 5.96 (1H, dt, *J* 15.8 and 6.6, CH$_2$C*H*=), 6.39 (1H, d, *J* 15.8, C_qC*H*=), 7.12 (2H, d, *J* 8.5, ArC*H*), 7.31 (2H, d, *J* 8.1, ArC*H*), 7.41 (2H, d, *J* 8.5, ArC*H*), 7.70 (2H, d, *J* 8.1, ArC*H*), 9.72 (1H, s, C*H*O)

δ_C: (75 MHz, $CDCl_3$) 21.5 (*C*H_3), 41.3 (N*C*H$_2$CH$_2$), 43.8 (*C*H_2CHO), 51.1 (N*C*H$_2$CH=), 121.9 (*C*$_q$Br), 124.8 (CH$_2$*C*H=), 127.1 (Ar*C*H), 127.3 (Ar*C*H), 128.0 (Ar*C*H), 129.9 (Ar*C*H), 131.7 (Ar*C*H) 132.8 (=*C*HC$_q$), 135.0 (=CH*C*$_q$), 136.2 (*C*$_q$CH$_3$), 143.7 (*C*$_q$SO$_2$), 200.1 (*C*=O)

m/z: (ES)$^+$ 477.9 (98%, [M(^{81}Br)+MeOH+Na]$^+$), 477.9 (100, [M(^{79}Br)+MeOH+Na]$^+$), 445.9 (95, [M(^{81}Br)+ Na]$^+$), 443.8 (100, [M(^{79}Br+Na]$^+$),

HRMS: [Found: (M(^{79}Br)+Na)$^+$ 444.0244. $C_{19}H_{20}BrNNaO_3S$ requires *M*, 444.0245]

(*E*)-4-Methyl-*N*-(3-oxopropyl)-*N*-(3-(*p*-tolyl)allyl)benzenesulfonamide (194d)



Aldehyde **194d** was prepared from alcohol **207d** (690 mg, 1.92 mmol), oxalyl chloride (252 μL 2.88 mmol), DMSO (409 μL, 5.76 mmol) and Et_3N (1.39 mL, 9.60 mmol) according to general procedure 12. Work-up afforded **194d** as a colourless oil (685 mg, 94%).

R_f : 0.60 (hexane:EtOAc, 1:1)

ν_{max}: (film)/cm^{-1} 2922 (CH), 1722 (C=O), 1598 (ArC=C), 1494 (ArC=C), 1335 (ν_{as} SO_2), 1155 (ν_s SO_2)

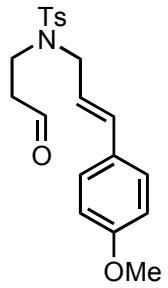
δ_H: (400 MHz, $CDCl_3$) 2.31 (3H, s, *C*H_3), 2.44 (3H, s, *C*H_3), 2.82 (2H, t, *J* 7.0, C*H*$_2$CHO), 3.47 (2H, t, *J* 7.0, NC*H*$_2$CH$_2$), 3.93 (2H, d, *J* 8.7, C*H*$_2$CH=), 5.85 (1H, dt, *J* 16.0 and 8.7, CH$_2$C*H*=), 6.40 (1H, d, *J* 16.0, C_qC*H*=), 7.09 (2H, d, *J* 8.0, ArC*H*), 7.17 (2H, d, *J* 8.0, ArC*H*), 7.31 (2H, d, *J* 9.0, ArC*H*), 7.73 (2H, d, *J* 9.0, ArC*H*), 9.72 (1H, s, C*H*O)

δ_C: (101 MHz, $CDCl_3$) 21.8 (*C*H_3), 22.1 (*C*H_3), 41.8 (*C*H_2CHO), 44.5 (N*C*H_2CH$_2$), 51.9 (N*C*H$_2$CH=), 123.4 (=*C*H), 127.0 (Ar*C*H), 128.0 (Ar*C*H), 128.0 (Ar*C*H), 130.0 (Ar*C*H), 130.5 (Ar*C*H), 133.9 (C_q), 134.8 (=*C*H), 137.2 (C_q), 138.7 (C_q), 144.2 (C_q), 200.8 (*C*HO)

m/z: $(ES)^+$ 412 (45%, $[M+MeOH+Na]^+$), 380.0 (100, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 380.1292. $C_{20}H_{23}NNaO_3S$ requires *M*, 380.1296]

(*E*)-*N*-(3-(4-Methoxyphenyl)allyl)-4-methyl-*N*-(3-oxopropyl)benzenesulfonamide (194e)



Aldehyde **194e** was prepared from alcohol **207e** (350 mg, 0.93 mmol), oxalyl chloride (122 μL, 1.40 mmol), DMSO (199 μL, 2.80 mmol) and Et_3N (0.65 mL, 4.67 mmol) according to general procedure 12. Work-up afforded the product **194e** as a colourless oil (319 mg, 92%).

R_f : 0.48 (hexane:EtOAc, 1:1)

ν_{max}: (film)/cm^{-1} 2960 (CH), 2933 (CH), 1720 (C=O), 1606 (ArC=C), 1510 (ArC=C), 1334 (ν_{as} SO_2), 1155 (ν_s SO_2)

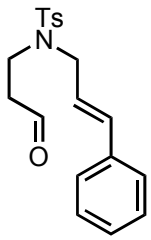
δ_H: (300 MHz, C_6D_6) 2.04 (3H, s, C_qCH_3), 2.48 (2H, t, *J* 7.0, CH_2CHO), 3.34-3.49 (4H, stack, OCH_3 and NCH_2CH_2), 3.75 (2H, d, *J* 7.7, CH_2CH=), 5.84 (1H, dt, *J* 16.0 and 7.7, CH_2CH=), 6.30 (1H, d, *J* 16.0, C_qCH=), 6.78 (2H, d, *J* 7.8, ArC*H*), 6.93 (2H, d, *J* 7.0, ArC*H*), 7.34 (2H, d, *J* 7.0, ArC*H*), 7.65 (2H, d, *J* 7.8, ArC*H*), 9.45 (1H, s, C*H*O)

δ_C: (101 MHz, C_6D_6) 21.0 (C_qCH_3), 41.3 (CH_2CHO), 43.9 (NCH_2CH_2), 51.4 (NCH_2CH=), 54.8 (OCH_3), 114.3 (Ar*C*H), 122.0 (=*C*H), 127.5 (Ar*C*H), 128.0 (Ar*C*H), 129.2 (C_q), 129.7 (Ar*C*H), 133.7 (=*C*H), 137.4 (C_q), 143.1 (C_q), 160.0 (C_q), 199.5 (*C*HO)

m/z: $(ES)^+$ 428.2 (30%, $[M+MeOH+Na]^+$), 396.2 (100, $[M+Na]^+$)

HRMS: [Found: $(M+Na)^+$ 396.1240. $C_{20}H_{23}NNaO_4S$ requires *M*, 396.1245]

***N*-Cinnamyl-4-methyl-*N*-(3-oxopropyl)benzenesulfonamide (194f)**



NMO (611 mg, 5.22 mmol) was added to a stirred solution of alcohol **207f** (1.00 g, 2.90 mmol) in CH_2Cl_2 (15 mL) containing 4 Å MS cooled to 0 °C. The reaction was stirred for 15 min before TPAP (91 mg, 0.29 mmol) was added in one portion and the reaction stirred for a further 10 min before being allowed to warm to room temperature. After 0.5 h the reaction was filtered through a plug of silica and washed with further portions of CH_2Cl_2 (3 x 10 mL). The combined filtrates were concentrated *in vacuo* and the crude product purified by flash column chromatography (R_f = 0.55, hexane:EtOAc, 1:1) to give the product **194f** as a colourless oil (848 mg, 85 % yield).

ν_{max}: (film)/cm^{-1} 3027 (=CH), 2924 (CH), 1721 (C=O), 1597 (ArC=C), 1494 (ArC=C), 1449, 1334 (ν_{as} SO_2), 1153 (ν_s SO_2)

δ_H: (300 MHz, $CDCl_3$) 2.43 (3H, s, *C*H_3), 2.83 (2H, t, *J* 7.0, C*H*$_2$CHO), 3.45 (2H, t, *J* 7.0, NC*H*$_2$CH$_2$), 3.94 (2H, d, *J* 6.6, C*H*$_2$CH=), 5.95 (1H, dt, *J* 15.8 and 6.6, CH$_2$C*H*=), 6.45 (1H, d, *J* 15.8, C_qC*H*=), 7.20-7.33 (7H, stack, ArC*H*), 7.72 (2H, d, *J* 8.5, ArC*H*), 9.73 (1H, s, C*H*O)

δ_C: (75 MHz, $CDCl_3$) 21.5 (*C*H_3), 41.2 (*C*H_2CHO), 43.8 (N*C*H_2CH$_2$), 51.1 (N*C*H_2CH=), 123.8 (=*C*H), 126.4 (Ar*C*H), 127.2 (Ar*C*H), 128.0 (Ar*C*H), 128.6 (Ar*C*H), 129.8 (Ar*C*H), 134.1 (=*C*H), 135.9 (C_q), 136.3 (C_q), 142.5 (C_q), 143.6 (C_q), 200.3 (*C*HO)

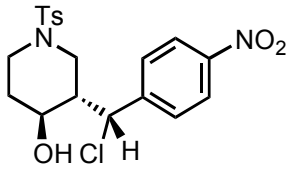
m/z: (ES)$^+$ 398.2 (20%, [M+MeOH+Na]$^+$), 366.1 (100%, [M+Na]$^+$)

HRMS: [Found: (M+Na)$^+$ 366.1146. $C_{19}H_{21}NNaO_3S$ requires *M*, 366.1140]

General Procedure 13: Prins Cyclisation

$MeAlCl_2$ (2 eq) was added dropwise over 1 min to a solution of the aldehyde (1 eq) dissolved in CH_2Cl_2 (0.1 M) at -78 °C. The resulting solution was stirred at -78 °C for 8 h before being allowed to warm to room temperature overnight. The solution was quenched by the addition of water. The organic phase was separated and the aqueous phase was further extracted with 3 x CH_2Cl_2. The combined organic phases were washed with water and brine before being dried over $MgSO_4$ and evaporated *in vacuo* to give the crude cyclisation product.

(3*S,4*S**)-3-((*R**)-chloro(4-nitrophenyl)methyl)-1-tosylpiperidin-4-ol (197a)**



Piperidine **207a** was prepared from aldehyde **194a** (99 mg, 0.26 mmol) and $MeAlCl_2$ (1 M soln. in hexanes, 0.52 mL, 0.52 mmol) in CH_2Cl_2 (2.6 mL) according to General Procedure 13. Purification by flash column chromatography (R_f = 0.30, hexane:EtOAc, 1:1) afforded the products **197(*R*)a** and **198(*S*)a** in a 5:1 mixture as a colourless oil (49 mg, 77%). In he case of the NMR spectra, only data for the major piperidine **197(*R*)a** are reported.

ν_{max}: (film)/cm^{-1} 3539 (OH), 2925 (CH), 2857 (CH), 1518 (ν_{as} NO_2), 1341 (ν_{as} SO_2, ν_s NO_2), 1156 (ν_s SO_2)

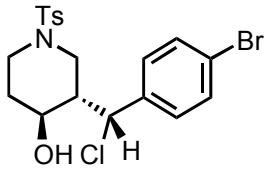
δ_H: (300 MHz, $CDCl_3$) 1.48-1.55 (1H, m, C*H*HCHOH), 1.74-1.86 (2H, stack, CH*H*CHOH and O*H*), 1.94-1.98 (1H, m, C*H*CHOH), 2.34 (3H, s, CH_3), 2.56-2.63 (1H, m, NC*H*HCH_2), 2.83 (1H, dd, *J* 11.9 and 8.9, NC*H*HCH), 3.31-3.45 (2H, stack, NCH*H*CH_2 and NCH*H*CH), 3.98-3.63 (1H, m, C*H*OH), 5.35 (1H, d, *J* 5.27, C*H*Cl), 7.17-7.33 (6H, stack, ArC*H*), 7.48 (2H, d, *J* 8.2, ArC*H*)

δ_C: (101 MHz, $CDCl_3$) 21.6 (*C*H_3), 31.2 (NCH_2*C*H_2), 43.9 (*C*H_2), 44.0 (*C*H_2), 49.8 (*C*HCHOH), 62.1 (*C*HCl), 67.7 (*C*HOH), 123.9 (Ar*C*H), 127.1 (Ar*C*H), 129.1 (Ar*C*H), 129.8 (Ar*C*H), 133.4 (C_q), 139.0 (C_q), 143.7 (C_q), 147.0 (C_q)

m/z: $(ES)^+$ 447.0 (100%, $[M+Na]^+$)

HRMS: Found: $(M+Na)^+$ 447.0798. $C_{19}H_{22}ClN_2NaO_5S$ requires *M*, 447.0757

(3*S,4*S**)-3-((*R**)-(4-bromophenyl)chloromethyl)-1-tosylpiperidin-4-ol (197c)**



Piperidine **207c** was prepared from aldehyde **194c** (105 mg, 0.25 mmol) and $MeAlCl_2$ (1 M soln. in hexanes, 0.50 mL, 0.50 mmol) in CH_2Cl_2 (2.5 mL) according to General Procedure 13. Purification by flash column chromatography (R_f = 0.38, hexane:EtOAc, 1:1) afforded the products **197(*R*)c** and **198(*S*)c** in a 6:1 mixture as a white foam (88 mg, 77%). In the case of the NMR spectra, only data for the major piperidine **197(*R*)c** are reported.

ν_{max}: (film)/cm^{-1} 3535 (OH), 2924 (CH), 2857 (CH), 1333 (ν_{as} SO_2), 1154 (ν_s SO_2)

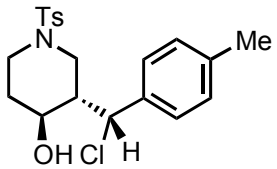
δ_H: (400 MHz, $CDCl_3$) 1.53 (1H, dt, *J* 9.1 and 3.6, C*H*HCHOH), 1.73-1.83 (1H, m, CH*H*CHOH), 1.93-1.98 (2H, stack, C*H*CHOH and O*H*), 2.36 (3H, s, CH_3), 2.59-2.65 (1H, m, NC*H*HCH_2), 2.79 (1H, dd, *J* 11.4 and 8.9, NC*H*HCH), 3.28 (1H, dd, *J* 11.4 and 2.3, NCH*H*CH). 3.39-3.42 (1H, m, NCH*H*CH), 3.50-3.55 (1H, m, C*H*OH), 5.34 (1H, d, *J* 5.0, C*H*Cl), 7.16 (2H, d, *J* 8.4, Ar*H*), 7.24 (2H, d, *J* 8.2, Ar*H*), 7.42 (2H, d, *J* 8.2, Ar*H*), 7.50 (2H, d, *J* 8.4, Ar*H*)

δ_C: (101 MHz, $CDCl_3$) 21.6 (*C*H_3), 32.2 (NCH_2*C*H_2), 43.8 (*C*H_2), 43.9 (*C*H_2), 49.7 (*C*HCHOH), 60.5 (*C*HCl), 67.5 (*C*HOH), 123.3 (Ar*C*H), 127.6 (Ar*C*H), 129.1 (Ar*C*H), 131.9 (Ar*C*H), 133.4 (C_q), 133.2 (C_q), 138.1 (C_q), 143.9 (C_q)

m/z: (ES)$^+$ 481.9 (100%, [M(^{81}Br)+Na]$^+$), 479.9 (72, [M(^{79}Br)+Na]$^+$), 445.9 (90, [M(^{81}Br)+Na-Cl]$^+$), 443.8 (86, [M(^{79}Br+Na-Cl]$^+$)

HRMS: Found: (M+Na)$^+$ 480.0010. $C_{19}H_{21}BrClNNaO_3S$ requires *M*, 447.0012

(3*S,4*S**)-3-((*R**)-chloro(*p*-tolyl)methyl)-1-tosylpiperidin-4-ol (197d)**



Piperidine **197d** was prepared from aldehyde **194d** (74 mg, 0.21 mmol) and $MeAlCl_2$ (1 M soln. in hexanes, 0.42 mL, 0.42 mmol) in CH_2Cl_2 (2.0 mL) according to General Procedure 13. Purification by flash column chromatography (R_f = 0.47, hexane:EtOAc, 1:1) afforded the products **197(*R*)d** and **198(*S*)d** in a 3:1 mixture as a colourless oil (26 mg, 32%). In the case of the NMR spectra, only data for the major piperidine **197(*R*)d** are reported.

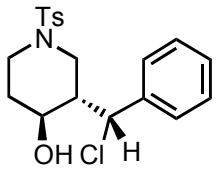
ν_{max}: (film)/cm^{-1} 3537 (OH), 2924 (CH), 2855 (CH), 1333 (ν_{as} SO_2), 1153 (ν_s SO_2)

δ_H: (400 MHz, $CDCl_3$) 1.53-1.56 (2H, stack C*H*HCHOH and O*H*), 1.75-1.84 (1H, m, CH*H*CHOH), 1.98-1.09 (1H, m, C*H*CHOH), 2.25 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.60-2.68 (1H, m, NC*H*HCH$_2$), 2.83 (1H, dd, *J* 11.6 and 9.2, NC*H*HCH), 3.33-3.40 (2H, stack, NCH*H*CH$_2$ and NCH*H*CH), 3.50-3.56 (1H, m, C*H*OH), 5.32 (1H, d, *J* 5.1, C*H*Cl), 7.16-7.22 (4H, stack, Ar*H*), 7.42 (2H, d, *J* 8.3, Ar*H*), 7.50 (2H, d, *J* 8.3 Ar*H*)

m/z: (ES)$^+$ 416.1 (100%, [M+Na]

HRMS: Found: (M+Na)$^+$ 416.1032. $C_{20}H_{24}ClNNaO_3S$ requires *M*, 416.1063

(3*S,4*S**)-3-((*R**)-chloro(phenyl)methyl)-1-tosylpiperidin-4-ol (197f)**



Piperidine **197f** was prepared from aldehyde **194f** (100 mg, 0.29 mmol) and $MeAlCl_2$ (1 M soln. in hexanes, 0.58 mL, 0.58 mmol) in CH_2Cl_2 (3.0 mL) according to General Procedure 13. Purification by flash column chromatography (R_f = 0.47, hexane:EtOAc, 1:1) afforded the products **197(*R*)f** and **198(*S*)f** in a 5:1 mixture as a colourless oil (78 mg, 71%). In the case of the NMR spectra, only data for the major piperidine **197(*R*)f** are reported.

ν_{max}: (film)/cm^{-1} 3535 (OH), 2925 (CH), 2856 (CH), 1334 (ν_{as} SO_2), 1154 (ν_s SO_2)

δ_H: (400 MHz, $CDCl_3$) 1.48-1.504 (1H, stack C*H*HCHO), 1.74-1.90 (2H, stack, CH*H*CHOH and O*H*), 1.99-1.08 (1H, m, C*H*CHOH), 2.37 (3H, s, CH_3), 2.58-2.67 (1H, m, NC*H*HCH$_2$), 2.87 (1H, dd, *J* 11.4 and 8.9, NC*H*HCH), 3.36-3.41 (2H, stack, NCH*H*CH$_2$ and NCH*H*CH), 3.46-3.55 (1H, m, C*H*OH), 5.35 (1H, d, *J* 5.0, C*H*Cl), 7.12-7.22 (6H, stack, Ar*H*), 7.48 (2H, d, *J* 8.3, Ar*H*)

δ_C: (101 MHz, $CDCl_3$) 21.6 (*C*H$_3$), 29.7 (NCH$_2$*C*H$_2$), 43.8 (*C*H$_2$), 43.9 (*C*H$_2$), 49.8 (*C*HCHOH), 61.4 (*C*HCl), 67.5 (*C*HOH), 127.1 (Ar*C*H), 127.6 (Ar*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 129.8 (Ar*C*H), 133.4 (C_q), 133.3 (C_q), 139.0 (C_q), 143.7 (C_q)

m/z: (ES)$^+$ 404.1 [22%, M^{37}Cl], 402.1 (100, [M^{35}Cl+Na]

HRMS: Found: (M+Na)$^+$ 402.08084. $C_{19}H_{22}ClNNaO_3S$ requires *M*, 402.0907

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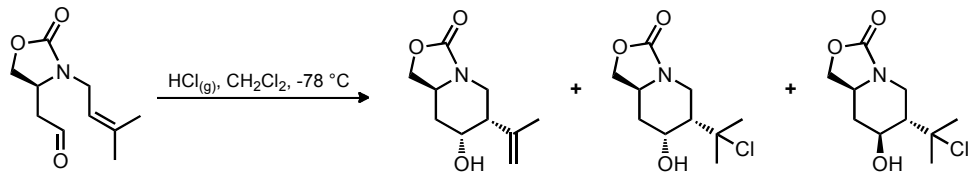
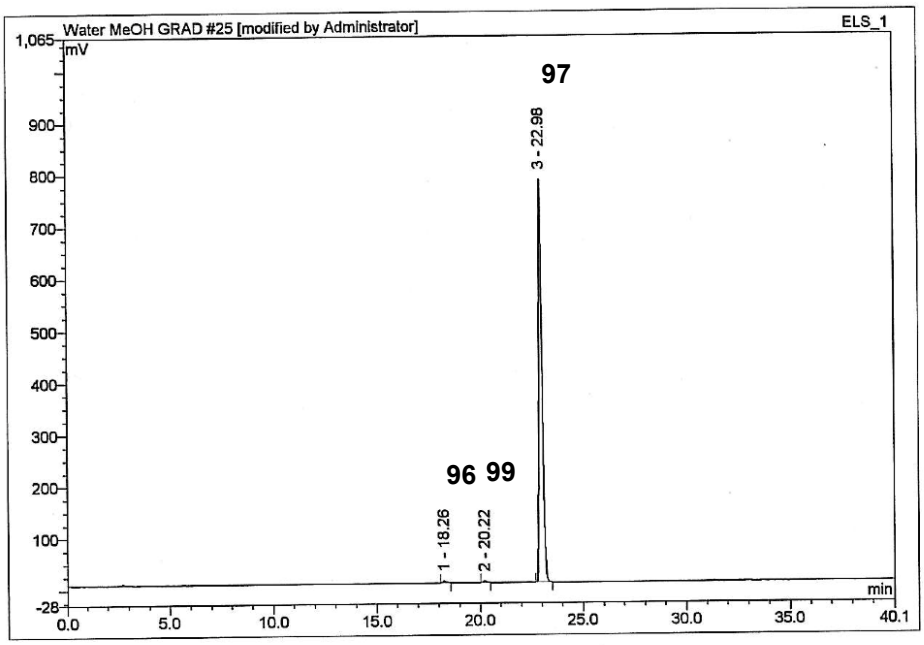
6. Appendix

HPLC trace of the crude reaction mixture from the Prins cyclisation

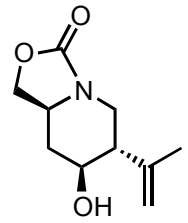


95 **96** **97** 98% **99**

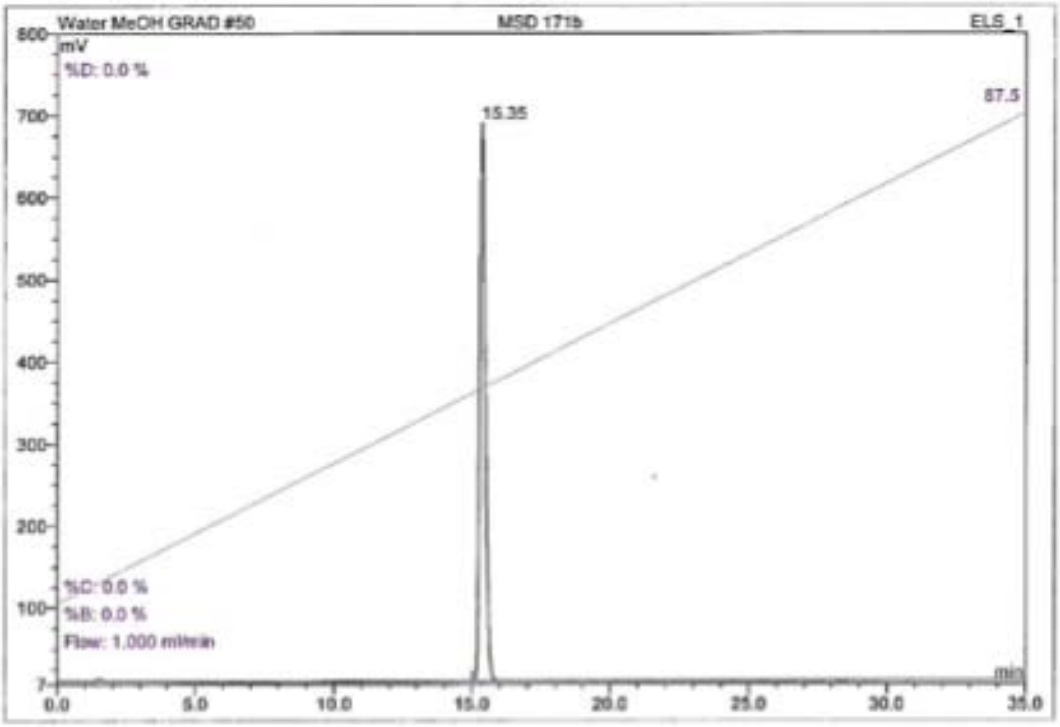


No.	Ret.Time min	Peak Name	Height mV	Area mV*min	Rel.Area %	Amount	Type
1	18.26	n.a.	4.400	0.778	0.53	n.a.	BMB*
2	20.22	n.a.	3.538	0.619	0.42	n.a.	BMB*
3	22.98	n.a.	776.677	145.952	99.05	n.a.	BMB
Total:			784.615	147.349	100.00	0.000	

HPLC trace of *trans* piperidine 98

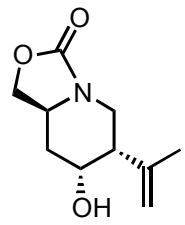


98

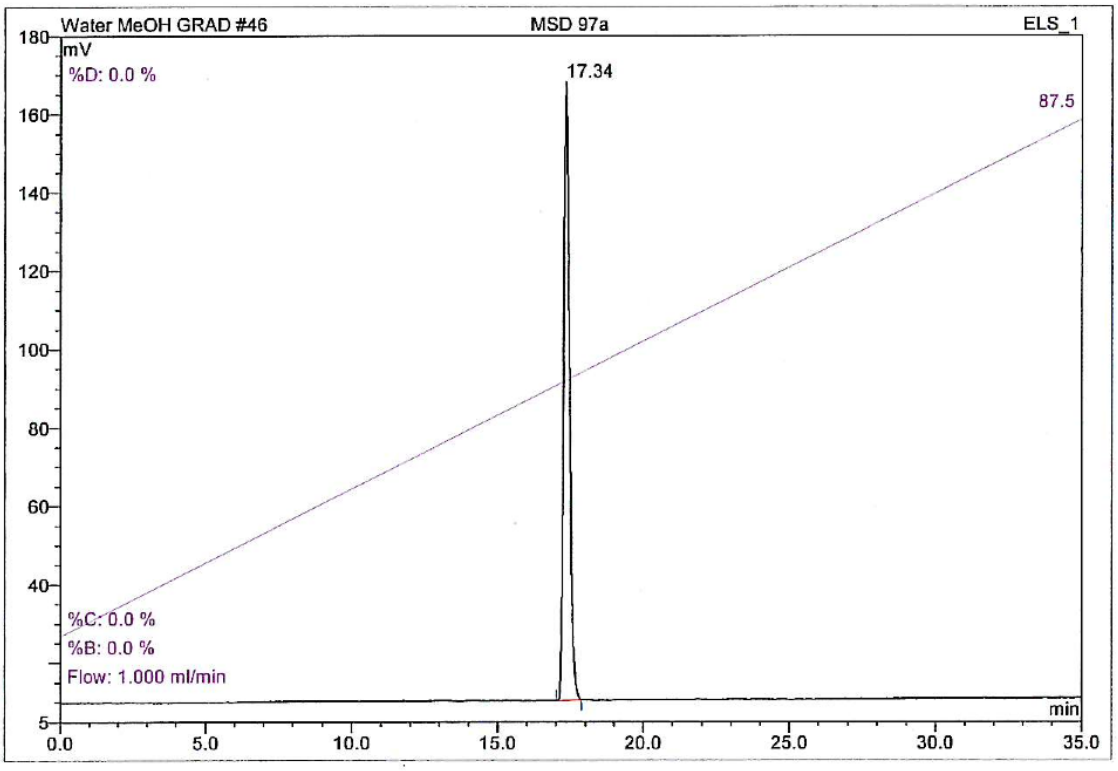


No.	Ret.Time min	Peak Name	Height mV	Area mV*min	Rel.Area %	Amount	Type
1	15.35	n.a.	680.060	160.425	99.31	n.a.	BMB
2	54.05	n.a.	6.174	1.119	0.69	n.a.	BMB
Total:			686.234	161.544	100.00	0.000	

HPLC trace of *cis* piperidine 96

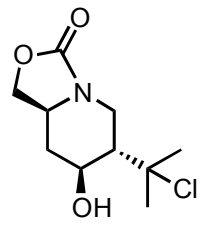


96

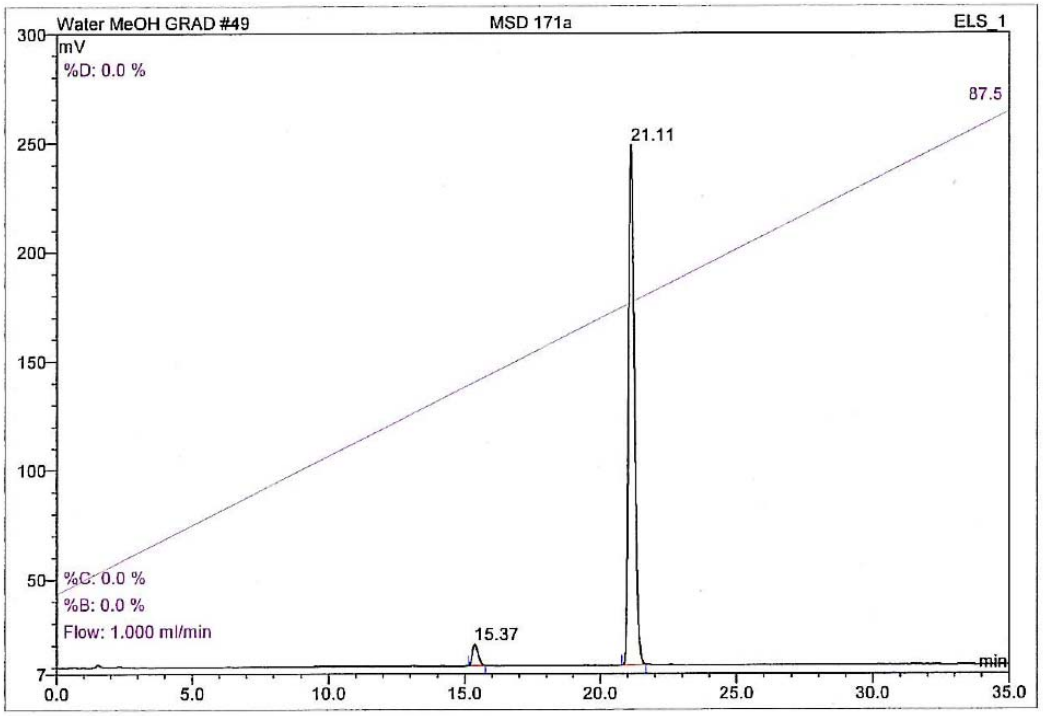


No.	Ret.Time min	Peak Name	Height mV	Area mV*min	Rel.Area %	Amount	Type
1	17.34	n.a.	157.757	36.485	93.59	n.a.	BMB
2	53.93	n.a.	6.909	2.497	6.41	n.a.	BMB
Total:			164.665	38.982	100.00	0.000	

HPLC trace of *trans* chloride 99

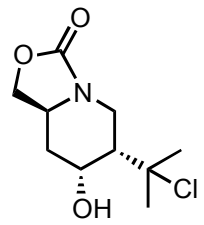


99

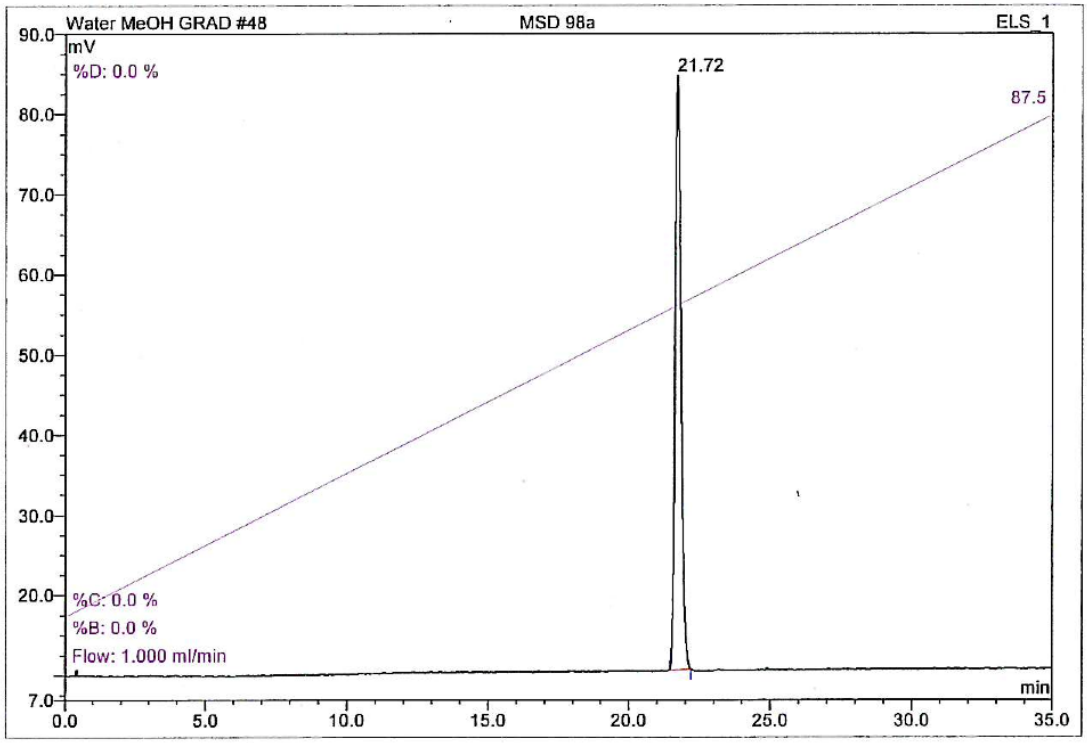


No.	Ret.Time min	Peak Name	Height mV	Area mV*min	Rel.Area %	Amount	Type
1	15.37	n.a.	9.727	2.345	3.78	n.a.	BMB
2	21.11	n.a.	238.241	58.642	94.54	n.a.	BMB
3	54.04	n.a.	5.492	1.043	1.68	n.a.	BMB
Total:			253.459	62.030	100.00	0.000	

HPLC trace of *cis* chloride 97



97



No.	Ret.Time min	Peak Name	Height mV	Area mV*min	Rel.Area %	Amount	Type
1	21.72	n.a.	74.064	18.046	94.21	n.a.	BMB
2	54.05	n.a.	6.075	1.109	5.79	n.a.	BMB
Total:			80.139	19.154	100.00	0.000	