2,3,4-Trisubstituted Piperidines
A Stereocontrolled Approach

By

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ABSTRACT

This thesis details a methodology utilising various synthetic pathways towards cyclisation precursors suitable for use in Prins and carbonyl-ene cyclisations to effect 2,3,4-trisubstituted piperidines. Once the precursors were synthesised, we were interested in the stereochemical outcomes of the cyclisations, in particular identity and rational of the kinetic and thermodynamic products and their variation due to differing substituents on C2. Previous work in the Snaith group has addressed various other substitution patterns and 2,3,4-trisubstituted piperidines are central components of a vast array of drug targets and natural products, so it follows that these should also be sought via similar processes. Synthesis of the precursors proved to be much more challenging than anticipated, hence many different routes were investigated with fluctuating successes.

ACKNOWLEDGEMENTS

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Finally thank you to my supervisor, Dr. John Snaith and my wonderful husband Andreas, for continual support and hopefulness!

ABBREVIATIONS

ala	alanine
Alk	alkyl chain
BDPP	(2S,4S)-2,4-Bis(diphenylphosphino)pentane
COD	cyclooctadiene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
e.e.	enantiomeric excess
EIMS	electron impact mass spectrometry
ESMS	electrospray mass spectrometry
EWG	electron withdrawing group
ile	isoleucine
Im-H	imidazole
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
leu	leucine
M	molar
NMDA	N-methyl-D-aspartate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
phe	phenylalanine

phg	phenylglycine
RT	room temperature
SFC	supercritical fluid chromatography
t, tert	tertiary
TBAF	tetra-n-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
triflate	trifluoromethanesulfonate
Trt	trityl, triphenylmethyl
Ts	tosyl, *para*-toluenesulfonyl
val	valine

CONTENTS

1 Introduction

The piperidine ring is a fragment found extensively in natural products and biologically active pharmaceuticals,[1,2,3,4,5] making research into the stereocontrolled synthesis of diverse polysubstituted derivatives, an area of great activity. There is constantly demand for greater selectivity for the target and reduction of side effects from potential new drugs which leads to a higher molecular complexity requirement in order to achieve this.[6] Substituted piperidines have a good record of being useful targets for drug discovery.[7]

Natural products containing the piperidine ring structure include quinine (**1**) and quinidine (**2**), which have been used as antimalarials for several hundred years;[8] dienomycins (**3**), which have antibacterial activity and (-)-incarvillateine (**4**), which has potent analgesic properties.[9] (Figure 1)

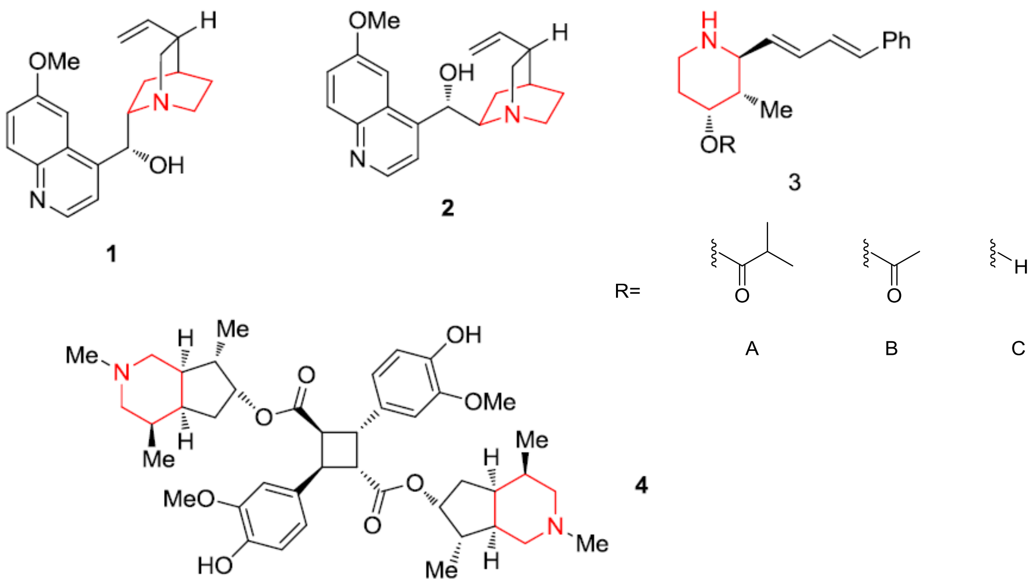


Figure 1: Natural products containing piperidine rings

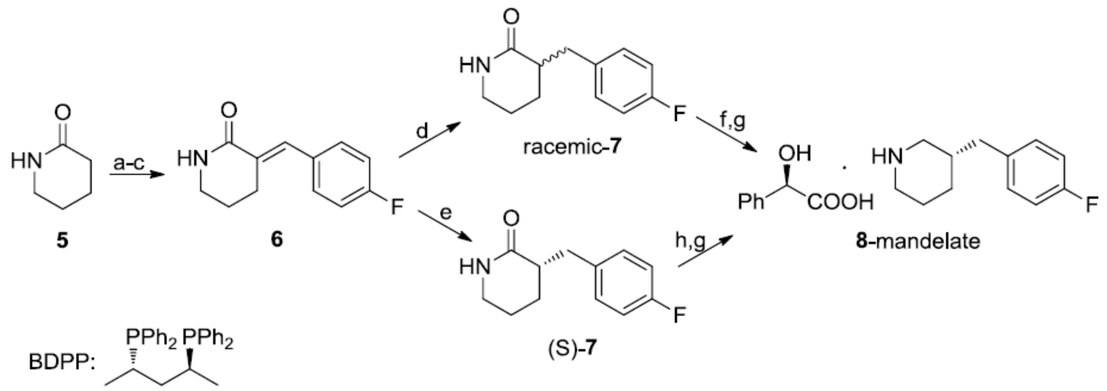
Drug molecules that include the piperidine ring structure have a wide variety of targets. Compounds found in the patent literature[1] could potentially be used to treat, amongst others; Parkinson's, Alzheimer's, psychosis, cognitive and neurological disorders, migraine, inflammation, arthritis, asthma, diabetes, obesity, hypertension, cancer, depression, anxiety and epilepsy.[1,10,11,12] Drug molecules containing the piperidine moiety are also active against bacterial infection, autoimmune conditions, prostate disorders, emesis and growth disorders.[13] The number of potential targets makes simple, versatile routes to substituted piperidines highly sought after.

1.1 Piperidine synthesis in the literature

There are four main synthetic routes to poly-substituted piperidines found in the literature.[14,15,16,17] These are reduction of piperidinones;[18] reduction of pyridines either partially to di- or tetrahydropyridines[19,20] or fully to yield piperidines;[21] cycloadditions, for example imino- or aza-diene [4+2] Diels-Alder type reactions;[22] heterocycle closure from linear precursors.[23] Here follows brief examples of when this type of chemistry has been used to synthesise piperidines in the recent literature.

1.1.1 Piperidinone reduction

A good use of reduction from a piperidinone is seen in Yue and co-workers' stereoselective synthesis of a CCR3 antagonist, which works against inflammation particularly in asthma and allergic rhinitis.[18] A key fragment is (*S*)-3-(4-fluorobenzyl)piperidine (**8**) which can be made in three steps from the simple piperidinone **5**. (Scheme 1)



Scheme 1: a) TFAA, toluene; b) 4-fluorobenzaldehyde; c) KO^{t}Bu, THF; d) Pd/C, H_2, 55 psi, MeOH; e) Ir(COD)(BDPP)BF_4, MeOH, DCM, H_2, 55 psi; f) LAH, THF, 15-30 °C; g) (R)-mandelic acid, MeCN; h) LAH, THF/ toluene, 15-40 °C.

The first step was already well studied[24] to give **6** which then needed to be stereoselectively reduced to give the desired (*S*)-product. The double bond could be removed by simple hydrogenation to give compound **7** as a racemic mixture, which was further reduced with lithium aluminium hydride to give racemic product **8**. This method gave an overall yield of the desired product of just 25 %. To improve on this, as the authors were looking to scale up to 20 kg, an asymmetric hydrogenation process was desired. A screen for a suitable catalyst was run to select one that would give good selectivity and adequate loading and an iridium complex was chosen. After reaction, the catalyst was removed by filtration to give the benzyllactam **7** with 88 % e.e. After reduction to the piperidine, the overall yield of enantiomerically pure product was 79 %, a great improvement over the racemic methods.

1.1.2 Pyridine reduction

A piperidine was made by reduction of the corresponding pyridine when Kohn and co-workers were looking at synthesising novel muscarinic receptor antagonists.[19] Muscarinic receptors are G-protein coupled receptors (GPCRs) located in the cell membrane, predominately in cells of the central nervous system. Malfunctions in these receptor systems have been linked to a number of conditions including Alzheimer's and Parkinson's along with irritable bowel syndrome, urinary incontinence, schizophrenia and chronic obstructive pulmonary disease[25] so research into antagonists holds high importance.

The targets sought were derivatives of the bicyclic amine **9**. (Figure 2)

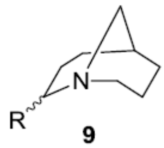


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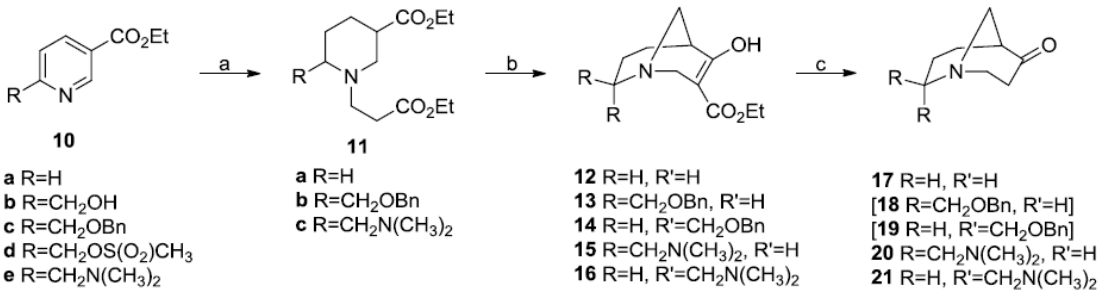
Figure 2

After the reportedly straightforward synthesis of 2,5-disubstituted pyridines (**10**), these were reduced to piperidines by various methods dependent upon the R group in the 2-position. (Scheme 2)



Scheme 2: a)i) PtO_2, H_2, HCl; ii) ethyl acrylate, 80 °C; b) KO^tBu, 110 °C, 1 h;
c) conc. Aq. HCl, 100 °C, 14 h

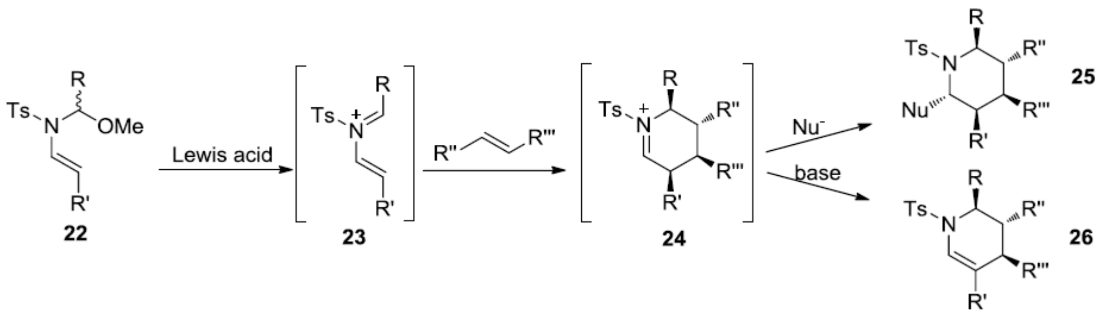
For pyridines **10c** and **10e** a mixture of PtO_2, H_2 and acid gave the best results.[26] These were then converted into the Dieckmann cyclisation precursors (**11**) by heating with ethyl acrylate.

In the case of **10c** the R group was prone to reduction, leaving a product mixture of approximately 1:1 **11c**:$\mathbf{11_{R=Me}}$. With both substrates **c** and **e**, the catalytic reduction was stereoselective to give single diastereomers which were deduced as the cis-isomers. The reduced side product was seen as both cis- and trans- isomers in approximately equal amounts. This suggests the C_2 substituents, when not short aliphatic chains, form a complex with the PtO_2 surface to give the cis addition of hydrogen during the reductions.

The fused ring was made by Dieckmann condensation of the two esters to give products **12** - **16**. Acid decarboxylation of **12**, **15** and **16** gave the desired amines **17**, **20** and **21** respectively. Use of these same conditions to convert **13** and **14** into products **18** and **19** gave complex mixtures.

1.1.3 Cycloadditions

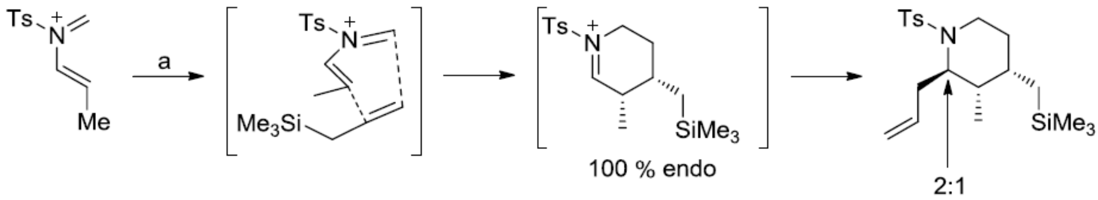
The use of an *N*-alkyl iminium ion and an alkene in an extension to Diels-Alder type cyclisations has been used to make highly substituted piperidines.[27] (Scheme 3)



Scheme 3

The stereochemical outcome of these reactions employing 2-azadienes as in Scheme 3 was investigated by Nelson et al.[22] The *N*-alkenyl iminium ion dienes (**23**) were made from the corresponding *N*-alkoxymethyl enamines (**22**) by treatment with Lewis acid. The enamines were in turn derived from allylic amines. The end product can be designed from this point, either by adding base to give product **26** or alternatively a nucleophile, or excess dienophile, will add to give product **25**.

Using allyltrimethylsilane as an electron-rich dienophile afforded 100 % endo-product. (Scheme 4)



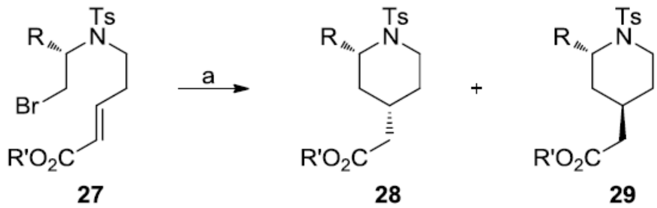
Scheme 4: a) trimethylallylsilane, $TiCl_4$, CH_2Cl_2, -78 °C

The authors of this work speculate that the endo transition state, as seen in Scheme 4, allows stabilisation of the iminium ion. If a nucleophile is present it could attack from either face but due to steric clashing it will preferentially add opposite to the existing substituents. In the above example, excess silane can act as a nucleophile to directly alkylate the tetrahydropyridinium adduct. A 2:1 preference in the stereochemistry at C_2 is seen but with substituents larger than methyl this is further exaggerated.

If the dienophile moiety is particularly bulky, for example cyclooctene, steric effects take control of the transition state and the exo-product is seen exclusively.

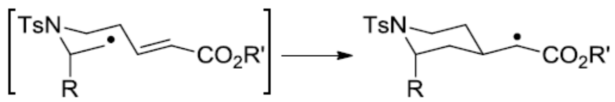
1.1.4 Cyclisation from a linear precursor

There are many methods of ring closure. An interesting example comes from the Snaith group, forming the piperidine ring with a radical cyclisation.[28] Cyclisation precursors were synthesised in four steps from amino acids, introducing one chiral centre from the start of the synthesis.



Scheme 5: a) Bu_3SnH, AIBN, benzene, 80 °C

The radical cyclisation was first carried out with tributyltin hydride which gave high yields (up to 99 %) and a mixture of the two possible diastereomeric products. The major product was identified as the trans-piperidine (**29**) by a series of NMR experiments. It is thought this is due to the R group sitting in an axial position in the chair-like transition state. (Scheme 6)



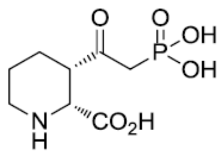
Scheme 6

The R group is preferentially axial to avoid pseudo $A^{1,3}$ strain with the sulfonamide. The minor cis-product (**28**) arises from this group lying in an equatorial position. This theory is substantiated by varying the size of the R group. As the size is increased, the relative amount of minor product is decreased. In contrast, the size of the ester group has little effect on the ratio of products.

When the hydride source was substituted for the bulkier tris(trimethylsilyl)silane, the yield was slightly reduced but the selectivity was increased to over 90 % in favour of the trans-piperidine (**29**) with R groups larger than methyl.

1.1.5 Potential difficulties with asymmetric synthesis

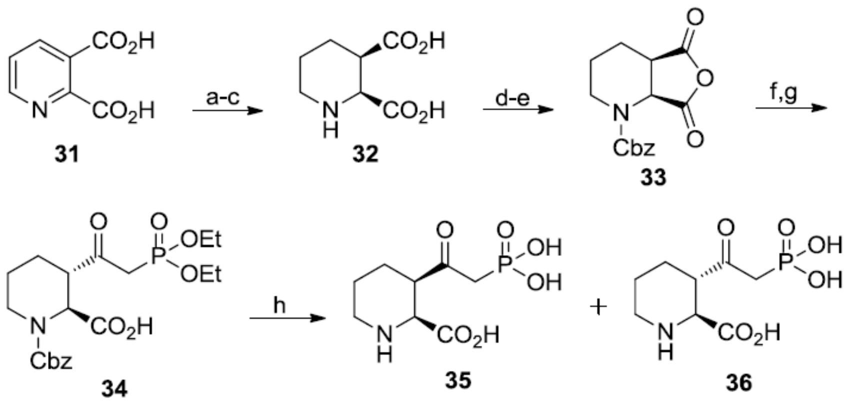
Each of these methods carries problems dependent upon the target molecule. For example in 1991 Whitten and co-workers noted the problem of epimerisation with their attempts to make 3-(*S*)-phosphonoacetyl-2-(*R*)-piperidinecarboxylic acid (**30**).[23] (Figure 3)



30

Figure 3

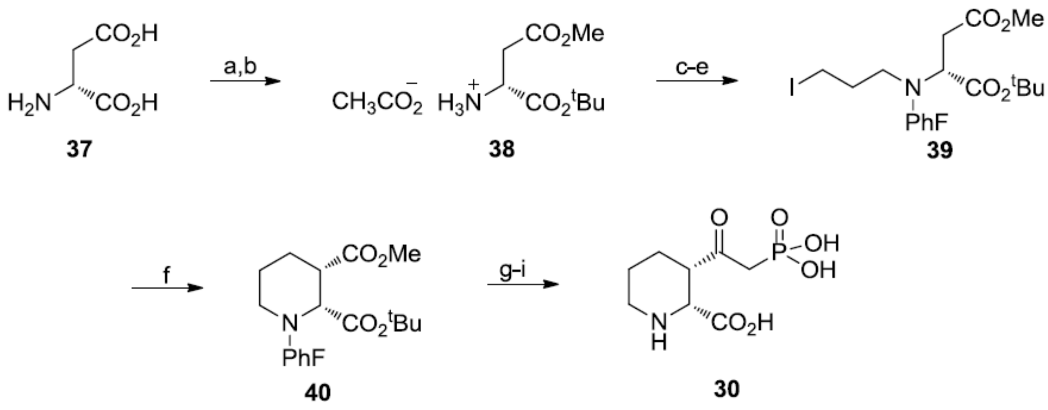
This compound is a competitive antagonist of the NMDA receptor complex. Inhibition of the receptor, which normally binds glutamic acid, showed therapeutic promise for central nervous system disorders such as epilepsy, migraine, anxiety and neurodegenaration linked with several other conditions.[29] Whitten's first synthesis of **30** (Scheme 7) employed complete reduction of pyridine **31**, via the methyl esters, to give mostly the cis-diacid in high yield. This stereochemistry was locked by using a cyclic anhydride intermediate (**33**). Despite this effort, epimerisation of C_3 in compound **34** was visible by TLC. Deprotection gave a 1:1 ratio of cis-(**35**) and trans-product **36**.



Scheme 7: a) MeOH, HCl; b) $Pd(OH)_2$, H_2; c) 1M HCl; d) CbzCl; e) $(CH_3CO)_2O$; f) $LiCH_2PO(OEt)_2$; g) $C_6H_5CH_2Br$, $HN(C_6H_{11})_2$; h) 6M HCl

When the racemic products were analysed for affinity to the NMDA receptor it was found that the cis-isomer (**35**) was much more potent that the trans- (**36**). These results fit with the computer model prediction as although both compounds fit into the binding site, the cis-isomer can align the phosphate to mimic the natural substrate much better.

To remedy the problems that occurred in this synthesis, a new approach to forming the piperidine was undertaken. Instead of starting from a pre-formed heterocycle, a linear, chiral precursor was made from D-aspartic acid (**37**).

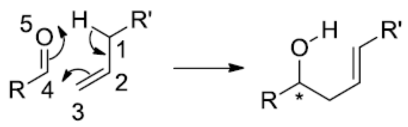


Scheme 8: a) MeOH, $SOCl_2$; b) $CH_3CO_2C(CH_3)_3$, $HClO_4$; c) $Br(CH_2)_3Cl$; d) PhFBr, $Pb(NO_3)_2$, $NEt(^iPr)_2$; e) NaI; f) LDA, 2,6-diisopropylphenol; g) $LiCH_2PO(OCH_2CH_3)_2$; h) TFA, TMSI; i) Propylene oxide, MeOH.

The use of the phenylfluorenyl protecting group helped minimize racemisation at C2. The cyclisation of **39** proceeded by forming the enolate with LDA at -78 °C then allowing the reaction to continue at -35 °C for several hours. Cautious quenching of the resultant piperidinyl enolate, by keeping the temperature low, and careful choice of proton source ensured that significant amounts of the more stable trans-isomer were not formed. When bulky 2,6-diisopropylphenol was used as the proton source at low temperature the cis-isomer (**40**) was produced exclusively. Use of acetic acid produced large amounts of the trans-isomer. Phosphonation and deprotection followed with no apparent epimerisation giving amino acid **30** which was shown to be a potent NMDA glutamate antagonist.

1.2 The carbonyl-ene reaction

A carbonyl-ene reaction is a specialised case of the ene reaction between an alkene with an allylic hydrogen and an enophile, in this case a carbonyl. This is an attractive method of forming a carbon-carbon bond and introducing a chiral centre into a molecule with a high degree of regio- and stereoselectivity. There is a migration of the double bond and a 1,5-hydrogen shift onto the carbonyl oxygen. (Scheme 9)



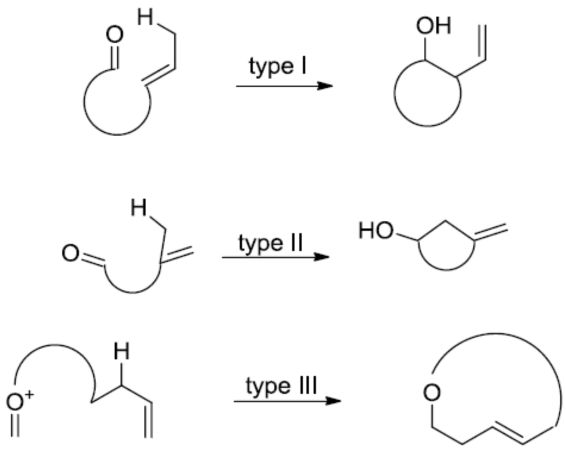
Scheme 9

The mechanism of ene reactions may be considered to be concerted or step-wise and will vary depending on the specific reaction and conditions. The ene component could either be considered as a nucleophile or as a 4-electron coupling partner, similar to a Diels-Alder type reaction. It follows that electron-rich alkenes react faster than electron-poor alternative and that the eneophile should be electron deficient to allow a good rate of reaction.

The carbonyl-ene reaction is also appealing due to the potential for 100 % atom economy and therefore there is no need to remove the metallic waste generated from metal-based nucleophiles used in other C-C bond forming reactions.

1.2.1 Intramolecular carbonyl-ene cyclisations

If the carbonyl and the alkene are part of the same molecule and at a suitable separation an intramolecular carbonyl-ene reaction may proceed to give a cyclised product. This is more entropically favourable than the equivalent intermolecular reaction so can be done under milder conditions with little or no acid promoter. There are three classes of this reaction, dependent upon how the two functionalities are connected in the linear molecule.[30] (Scheme 10)

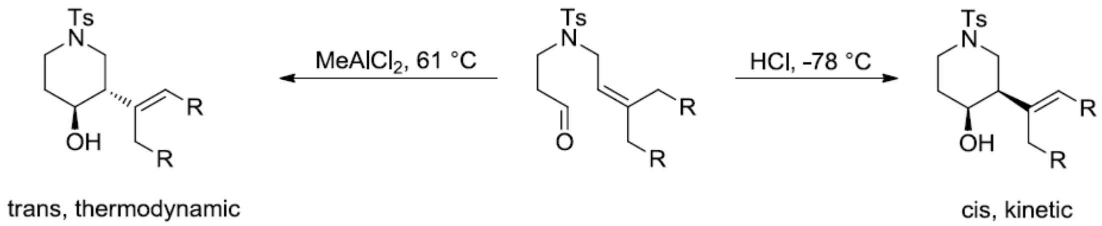


Scheme 10

A type I reaction involves attack of the carbonyl onto the internal carbon of the alkene and type II attacks at the terminal end of a double bond. Type III reactions are rare but a few examples have been observed.[31,32]

1.2.2 Piperidines from carbonyl-ene cyclisations

If a nitrogen atom lies between the carbonyl and the alkene in the precursor then a piperidine ring will be formed in the reaction, creating two new stereogenic centres. The relative stereochemistry of these in type I cyclisations has been shown previously in the Snaith group to depend on whether the conditions used favour the kinetic product (cis) or allow equilibration to the thermodynamic alternative (trans).[33,34] (Scheme 11)



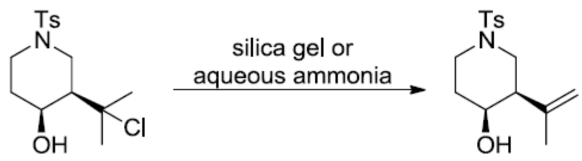
Scheme 11

The reactions shown in Scheme 11 proceeded, with chain length R of up to four additional carbon atoms, with reasonable yields. For the Lewis acid catalysed reactions the diastereomeric ratio was up to 93:7 in favour of the trans-product and the Brønsted acid catalyst gave d.r. of > 98:2 in favour of the cis-product. The stereochemistry has been confirmed with X-ray analysis of the crystalline products.

It was found that if the Lewis acid $MeAlCl_2$ was used to aid the cyclisation at -78 °C, the major product was cis, but raising the temperature to 25 °C gave mostly trans stereochemistry. These observations are strong evidence for the designation of kinetic and thermodynamic products as they show that with greater energy input the system is able to equilibrate and form the more stable product. By increasing the temperature further to 61 °C the preference is much more pronounced. The reversibility of the reaction was further confirmed by heating cis piperidines in the presence of $MeAlCl_2$ to yield the trans-isomer.

Other Lewis acids were tested to see their effects on the stereochemical outcome. Aluminium chloride was found to favour cis-product. Scandium triflate and tin tetrachloride proved good catalysts for the reaction but gave little or no control over the stereochemistry. Alternative Lewis acids that showed little or no catalytic effect were ferric chloride, zinc bromide, ytterbium triflate and copper (II) triflate.

Similar investigations into Brønsted acids showed *p*-toluenesulfonic acid did not catalyse the reaction at low temperature and trifluoromethane sulfonic acid was effective but gave only limited selectivity. Three equivalents of concentrated hydrochloric acid however gave quantitative cyclisation and a ratio of 95:5 in favour of the kinetic product at -78 °C. A small amount of chloride **41** was also produced in this reaction but could be simply converted back to product (**42**) by stirring the mixture with silica gel or aqueous ammonia to induce elimination of HCl. (Scheme 12)



41 **42**

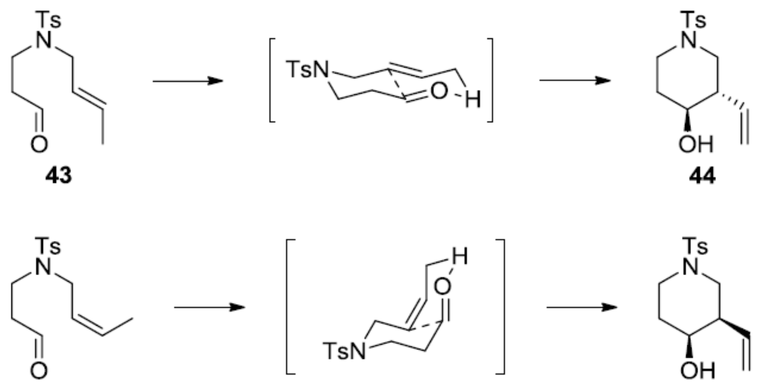
Scheme 12

1.2.3 Rationale of stereochemistry

Carbonyl-ene ring closure was thought to be a completely concerted process due to the precedent set by studies on the closure of citronellal. This process had been proven to give the thermodynamic product directly, with no kinetic intermediate.[35]

The results from earlier Snaith group work, using Lewis acid under equilibrating conditions, agreed with this concerted mechanism but the formation of the kinetic product when using Brønsted acids or Lewis acids at low temperature could not be explained by the classical concerted mechanism.[33]

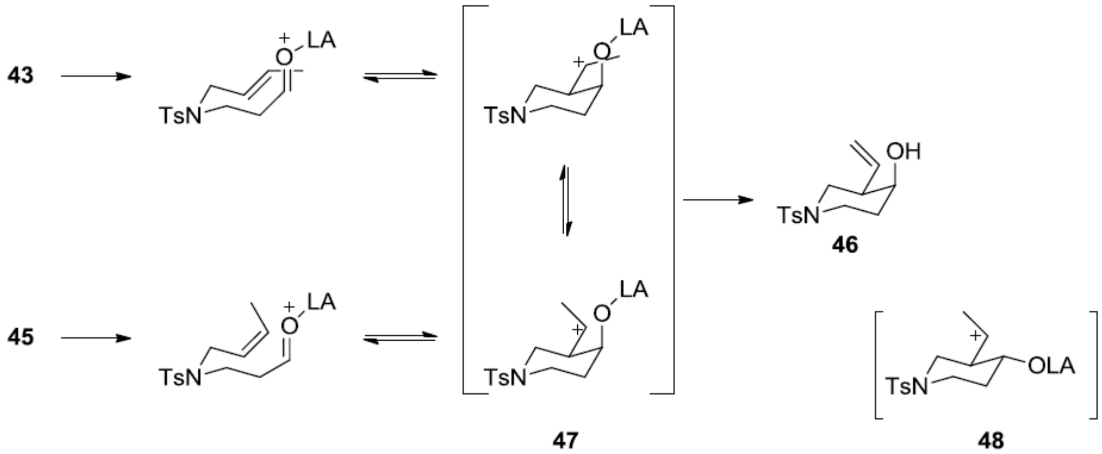
Using crotyl aldehydes **43** and **45** a study was devised to test the nature of the mechanism. (Scheme 13)



Scheme 13: Concerted mechanism probe

It was proposed that if the mechanism were concerted then the *E*-alkene (**43**) would result in the trans-product (**44**) and the *Z*-alkene (**45**) would yield cis-piperidine (**46**) due to the transition states shown.

In fact, when aldehydes **43** and **45** were subjected to cyclisation conditions, using Lewis acid, only cis-piperidine (**46**) was produced. This means the mechanism must be a step-wise non-concerted pathway as laid out in Scheme 14.



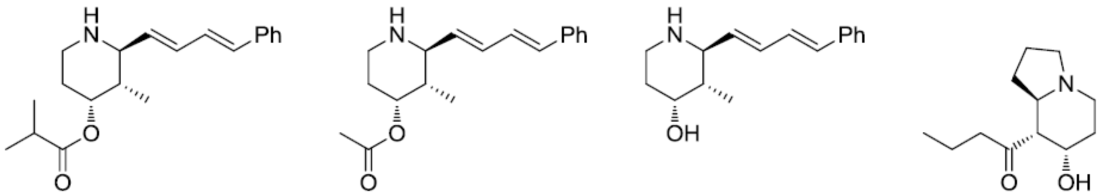
Scheme 14

As only the cis-piperidine is formed, cation **47** must have a lower energy than the trans-cation **48**. This can be rationalised by the intramolecular stabilisation given when the oxygen lone pair overlaps with the empty *p*-orbital at the cationic centre. This only occurs in the cis-cation as it is geometrically unfavourable for the trans-cation. (Figure 4)

Figure 4: Stabilisation of cis-cation by oxygen lone pair

1.3 Natural product applications

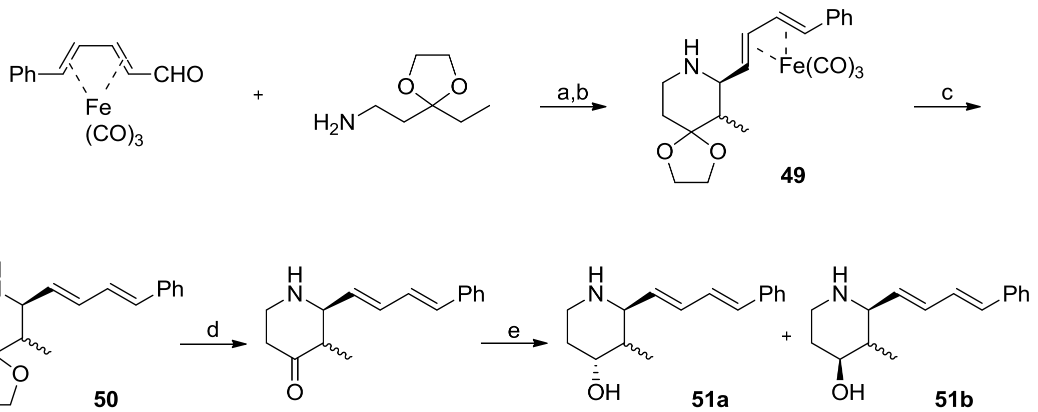
Synthesis of 2,3,4-trisubstituted piperidines will lead to new synthetic routes to natural products such as the Dienomycins and Elaeokanine C. (Figure 5)



Dienomycin A Dienomycin B Dienomycin C Elaeokanine C

Figure 5

The dienomycins were first isolated by Umezawa et al. in the late 1960's from Streptomyces strain MC67-C1.[36] They were the first microbial products isolated with piperidine and phenylbutadiene structures and they were found to show antibiotic activity against mycobacteria. There have been various syntheses of these molecules previously; racemic dienomycin C was made in 1996 by Troin[37] using iron tricarbonyl complexes to catalyse a Mannich-type cyclisation to form the piperidine structure. (Scheme 15).



Scheme 15: a) CH_2Cl_2; b) p-toluenesulfonic acid, 50 °C, toluene; c) trimethylamine N-oxide (TMANO); d) H^+; e) L-selectride, -50 °C, THF

Compound **49** was formed as both cis- and trans- diastereomers, as a mixture of enantiomers. The C_2 isomers were easily separated by flash chromatography, giving mixtures at C_3 to carry forwards to further reactions. The C_2 (*R*)-isomer depicted in Scheme 15 was carried forwards to make dienomycin C (**51a**). The stereoselectivity of the C_4 hydroxyl is determined by the base used in the final step. When sodium borohydride at 20 °C was used, the trans product **51b** was favoured 85:15 but using L-selectride at -50 °C, as shown in Scheme 15, greatly favoured the natural product with a d.r. of 98:2 (**51a**:**51b**).

A few years later a fully asymmetric synthesis was laid out by Comins and Green[38] using enantiomerically pure reagents and a stereoselective reduction of the resulting piperidone using lithium tri-*sec*-butylborohydride (L-selectride). Very shortly after this publication Troin released a refinement of the tricarbonyliron method to give both (+)- and (-)- dienomycin C as the absolute configuration of the streptomyces-isolated compound was still unknown.[39]

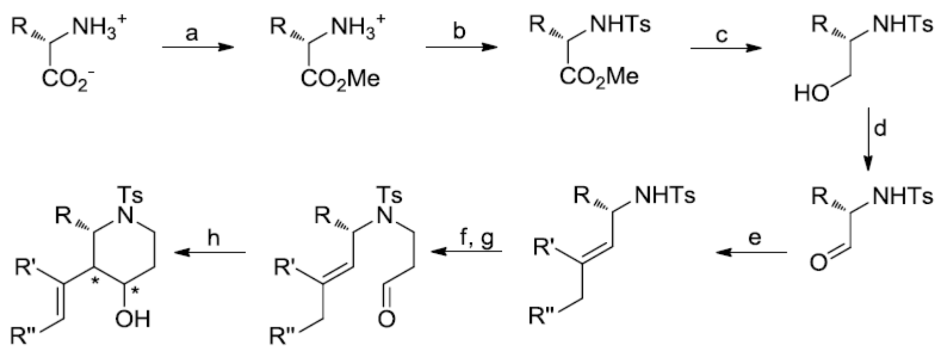
Syntheses of the more potent dienomycins A and B are as yet unpublished but they should be feasible using the chemistry outlined above.

1.4 Project aims

This project aims to find a flexible stereocontrolled synthesis to 2,3,4-trisubstituted piperidines, opening routes to the dienomycins and elaeokanine C.

1.4.1 Methodology

α-Amino acids can be derivatized to exploit their natural chirality. This gives the stereochemistry of C_2 from the beginning of the synthesis. For example, Scheme 16 shows that protection of the amine allows for manipulation of the acid group.

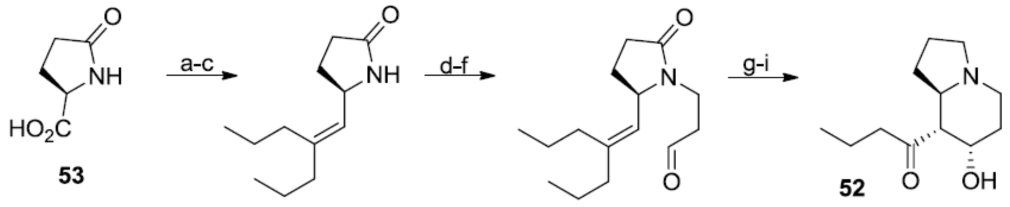


Scheme 16: a) $SOCl_2$, MeOH; b) TsCl, Et_3N; c) $LiBH_4$; d) DMSO, $(COCl)_2$, Et_3N, DCM; e) $R''CH_2R'P{+}Ph_3I^-$, n-BuLi, THF; f) K_2CO_3, CH_3CN, $CH_2{=}CHCO_2Me$; g) DIBAL-H; h) HCl or $MeAlCl_2$

Conversion to the aldehyde will allow Wittig olefination to introduce the alkyl chain at C_3 of the piperidine as well as providing the double bond required in the carbonyl-ene cyclisation. *N*-Alkylation can then be used to introduce the carbonyl moiety followed by acid catalysed cyclisation to close the piperidine ring structure. The stereochemical outcomes of these reactions would be expected to follow those seen in previous work in the Snaith group on 3,4-disubstitued systems as detailed above.

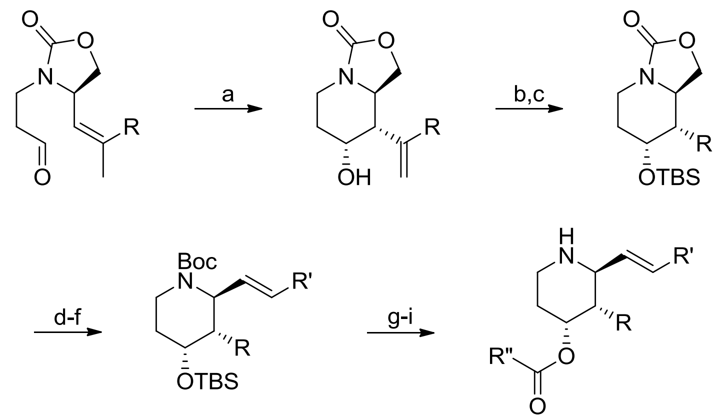
1.4.2 Natural product syntheses

Elaeokanine C (**52**) can be conceivably reached using very similar chemistry starting from readily available pyroglutamic acid (**53**) (Scheme 17).



Scheme 17: a) $SOCl_2$, MeOH; b) DIBAL-H; c) $C(CH_2CH_2CH_3)_2P^+Ph_3I^-$, n-BuLi, THF; d) $Br(CH_2)_3OTBS$; e) TBAF; f) DMSO, $(COCl)_2$, Et3N, DCM; g) HCl, -78 °C; h) $LiAlH_4$; i) O_3

Based on previous results from the Snaith group, Brønsted acid mediated cyclisation is expected to give the desired cis-substitution pattern at C_3 and C_4 and the synthesis will be completed by reduction of the amide and oxidative cleavage of the alkene.



Scheme 18: a) HCl; b) TBSCl, DMF, im-H; c) functionalization of C_3; d) KOH then Boc_2O; e) DMSO, $(COCl)_2$, Et_3N, DCM; f) olefination of C_2; g) TBAF; h) R''COCl, DMAP; i) TFA

Scheme 18 outlines a general route to the dienomycins and their derivatives from an oxazolidinone (**54**). Once again, Brønsted acid mediated cyclisation will be employed to generate the cis-cyclisation product (**55**), with the pre-existing C_2 stereochemistry being provided by the locked cyclic starting material.

2 Synthesis of Linear Precursors

In order to investigate the outcomes of the ring closing reactions, linear precursors needed to be synthesised.

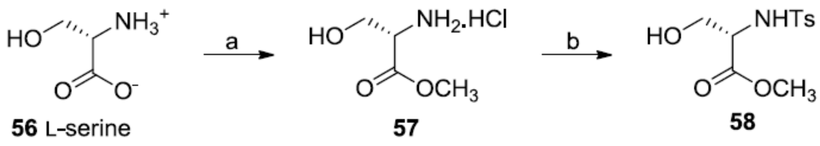
2.1 Amino Acid Derived Precursors

2,3,4-trisubstituted piperidines have three stereocentres leading to eight possible stereoisomers. In order to reduce the number of stereochemical outcomes, α–amino acids were chosen as suitable starting materials. They are a naturally occurring source of enantiopure chirality therefore eliminating synthetic steps and reducing the complications of interpreting the results of cyclisation.

The first amino acid used was serine (**56**), as the side chain terminates with a hydroxyl group, which could be a useful functional handle in the completed piperidine.

2.1.1 Methylation and N-Protection

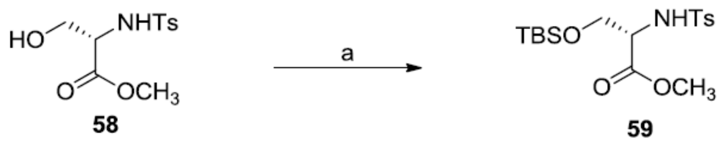
Producing the methyl ester[40] (**57**) proceeded smoothly in near quantitative yield and was followed by tosylation of nitrogen[41] to mask it from subsequent reactions, affording **58** in good yield (Scheme 19).



Scheme 19: a) $SOCl_2$, MeOH >99 %; b) TsCl, Et_3N, DCM 86 %

2.1.2 O-protection

In the next step (Scheme 20), the alcohol was protected with a *tert*-butyldimethylsilyl protecting group (**59**).



Scheme 20: a) TBSCl, Im-H, DMF. 90 %

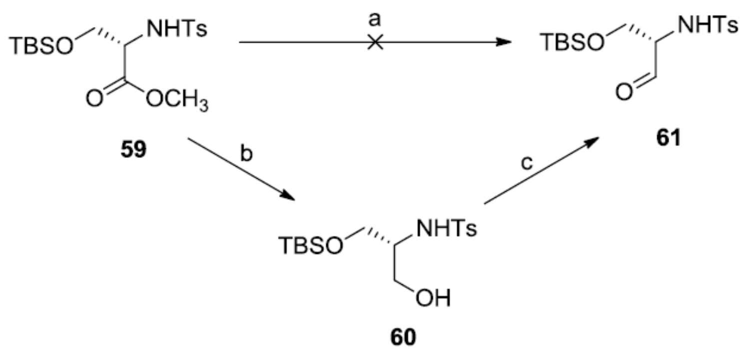
Initially this reaction gave low yields (<10 %). Various different sets of reaction conditions were attempted with somewhat increased yields. After returning to the primary literature[43] the initial reaction was repeated at 1 M – 1.5 M concentration, increased from 0.2 M – 0.3 M, giving 90 % yield at room temperature. The remaining unreacted alcohol was easily removed by recrystallization and the excess silyl chloride eluted much more slowly than product from a silica column.

The tosylation and silylation reactions were combined into a one-pot procedure as detailed in the literature[44] but this only produced a 28 % yield over the two steps so the separate steps were favoured.

2.1.3 Reduction of the ester

The original research plan involved reducing ester **59** directly to the corresponding aldehyde using diisobutylaluminium hydride (DIBAL-H) in DCM at -78 °C.[45] Unfortunately the reaction did not run smoothly, leaving what appeared by ^{1}H-NMR to be ester with the silyl group cleaved. The spectrum was fairly clean and showed no signals at ~0.8 and 0.0 ppm for the silyl *t*-butyl and methyl groups respectively. All other signals expected for the ester (**59**) were present with their appropriate integrals and there was no aldehyde signal around 10 ppm.

ESMS gave a single peak at 296.2 which relates to ester **58** $[M+Na]^+$. This route was abandoned for the simpler full reduction to the alcohol (**60**), followed by a controlled oxidation to the aldehyde (**61**). (Scheme 21)



Scheme 21: (a) DIBAL-H, DCM (b) $LiBH_4$, THF 97 % (c) PCC, DCM 85 %

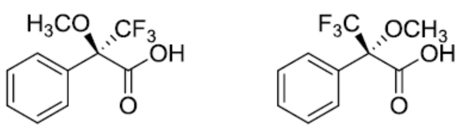
Reduction of ester **59** to alcohol **60** was initially attempted using sodium borohydride as the hydride source[46] but this required 2.5 equivalents to see disappearance of starting material by TLC. Unfortunately ^{1}H-NMR analysis suggested removal of both the tosyl and the silyl protecting groups after work-up. The material recovered contained a tosyl group but the integrals were disproportionately large compared to any of the other signals (~6 - 7 times greater than expected). The rest of the spectrum could not be clearly interpreted as starting material or product. There were also extra signals seen at 0.95 ppm and 0.10 ppm (both singlets, integral approximately 3:2) for the silyl group, suggesting that it had, at least in part, been removed during the reaction.

A white solid was recovered that was insoluble in chloroform but an NMR spectrum was run in D_2O showing this was tosic acid.

Repeating the experiment with lithium borohydride[41,47] required only a small excess of the hydride source with gentle heating to give alcohol **60** in excellent yield.

2.1.3.1 Racemic equivalents

The first four steps of this synthesis were also repeated with racemic starting materials in order to prove the e.e. of these products. This could be achieved by comparison of chiral HPLC data or NMR comparison of amides made from reaction of the compounds with Mosher's Acids (**62**). (Figure 6)



62a **62b**

Figure 6: Mosher's acids

Yields for the racemic series were good to excellent for methylation (>99 %), tosylation (93 %), silylation (86 %) and reduction (75 %).

2.1.4 Oxidation

Oxidation of the primary alcohol **60** proved more difficult than anticipated. Oxidants tested were PCC (**63**), TEMPO (**64**), PDC (**65**), Dess-Martin periodinane (**66**) and activated DMSO (Swern conditions).

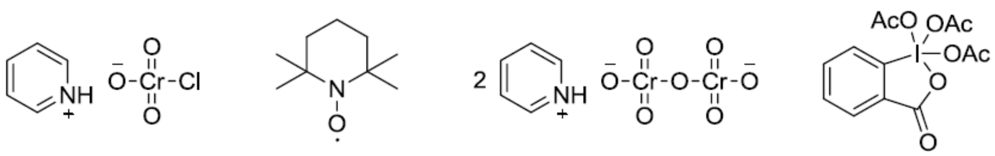
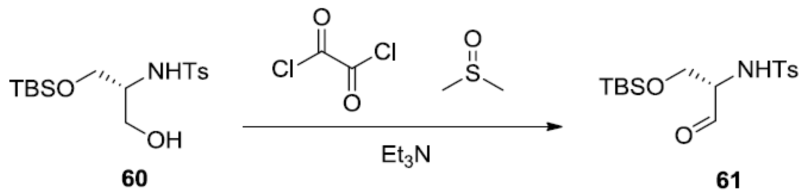


Figure 7: Oxidising agents

The initial procedure involving PCC[48] (**63**) (1.5 eq) also used Celite® to help remove the chromium waste after the reaction. This caused problems as the reaction mixture was filtered through silica but recovery of material was poor. The recovered organic material proved to be mostly unreacted starting material with ~10 % aldehyde present. The PCC was tested for quality with a substrate known to give good results and gave 75 % aldehyde in unoptimised conditions. As PCC was the first reagent tested, it was side lined due to the vast number of other oxidants available.

A series of Swern oxidations (Scheme 22, Table 1) were performed under various conditions[49,50] but none of these showed any promise.

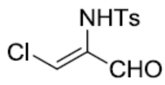


Scheme 22: General Swern oxidation

Reaction	Temp. after base addition	Time after base addition	Quench temperature	Results
A	-78 °C	4 h	RT	Aldehyde, no Si, unsaturated?
B	RT	-	-	2 aldehydes, many products.
C	-78 °C	15 min	-78 °C	Slow/no reaction.
D	-78 °C	1 h	-78 °C	Slow/no reaction.
E	-25 °C	30 min	-25 °C	2 aldehydes, many products.

Table 1: Swern oxidations

Reaction **A** was left at -78 °C for four hours after addition of base before allowing to warm to room temperature for quenching. A significant aldehyde signal was seen in the ^{1}H-NMR spectrum but the signals for the TBS group were absent. The aliphatic region of the spectrum was also very confused, with many extra signals indicating the intended product was not obtained and a variety of related compound were probably present. ESMS possibly indicates some form of chloro-adduct. There are several peaks that have a counterpart 2 mass units apart, with approximate 3:1 intensities, as expected for a chlorine containing compound. A peak at m/z 281.9 could possibly relate to $[M+Na]^+$ for compound **67** (Figure 8) and IR spectroscopy indicates there may be unsaturated compounds present.



67

Figure 8

Reaction **B** was allowed to warm to room temperature immediately after addition of base. Two signals were seen in the aldehyde region of the spectrum but all other signals were highly degraded indicating multiple similar compounds present.

Reaction **C** was left 15 minutes after base addition before quenching at -78 °C. This allowed only minimal reaction. The signals were more intact than had been previously seen but only a trace of aldehyde was visible.

Reaction **D** was the same as **C** except the time was increased to one hour before quenching at -78 °C and again only limited reaction occurred.

As temperature was governing the extent of reaction, an intermediate temperature was tested. Reaction **E** involved addition of base at -78 °C, then immediate warming to -25 °C and stirring for 30 minutes before quenching at this temperature. Two aldehyde signals were observed of equal intensity with degradation of the rest of the signals.

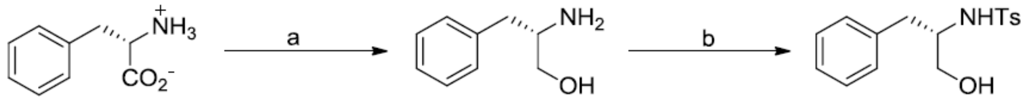
Swern oxidations were not producing the anticipated product and giving no recoverable starting material so alternative oxidants were sought.

Jurczak had demonstrated the desired oxidation in high yield using the TEMPO radical (**64**) and sodium hypochlorite as co-oxidant.[50] Following his procedure gave only 1 - 2 % aldehyde after several attempts. The Dess-Martin Periodinane (**66**) was also tested,[51,52] again resulting in similar levels of aldehyde in the reaction mixture after a prolonged reaction time of several days.

2.1.5 Phenylalanine Route

As the synthesis involving serine derivatives had stalled at the oxidation step, a search of the literature for Wittig olefinations on aminoaldehydes suggested L-phenylalanine (**68**) as a successful starting point.[53,54,55] Although the phenyl function would be less useful than an alcohol in the finished piperidine we were interested in seeing the effect of steric bulk at C_2 on the outcome of the ring closing step. The work on serine could be revisited at a later date.

An advantage of phenylalanine over serine in the synthesis is the absence of the alcohol as there would be no silylation required to mask it. The large silyl group may have also been a contributing factor to the failure of some of the oxidations due to its bulk.



68 **69a** **70**

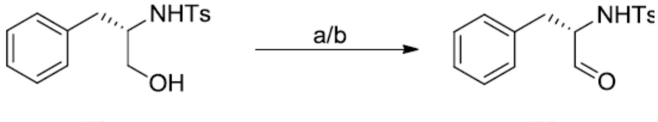
Scheme 23: a) $NaBH_4$, I_2, THF 78 %; b) TsCl, Et_3N, DMAP, DCM 99 %

As in Scheme 23 the α-amino alcohol **70**, the analogue of serine derivative **60**, has been made in just two steps instead of four. Reduction of the amino acid using sodium borohydride and iodine[56] had not been used as the first step with serine as this would have given two indistinguishable primary alcohols that would have in effect racemised the products. The reaction proceeded smoothly on a 25 g scale to give 78 % yield after recrystallisation. The tosylation step to follow was as before but used 10 mol% DMAP to catalyse a faster reaction.[56]

2.1.6 Oxidation of Protected Alcohol

Oxidations of this alcohol were attempted as with the protected serinol, starting with PCC/Celite®. These conditions produced several different aldehyde products but none in significant quantities. The next test was TEMPO with sodium hypochlorite but this resulted in hardly any reaction at all. Starting material was recovered with a trace of aldehyde present. A DMP oxidation was next attempted which gave four aldehyde signals by ^{1}H-NMR, the largest accounting for ~6 % of the sample. PDC[57] (**65**) was also tested but again produced very little aldehyde.

A different approach to PCC oxidations was then found which used 3 equivalents of oxidant, instead of 1.5 equivalents as previously used, and did not involve Celite® in the reaction mixture.[58] This gave much better recovery of organic material and the products were separated by column chromatography to give clean aldehyde (**71**) in good yield (Scheme 24).



70 **71**

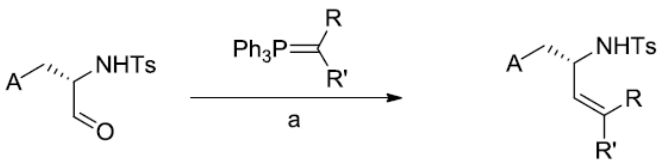
Scheme 24: a) 3 eq. PCC, Celite®, DCM 79 %; b) 3 eq. PCC, DCM 75 %

When this reaction, with an increased amount of PCC, was tested with the Celite® present, aldehyde was produced but the recovery of material was lower, decreasing the yield. This evidence suggests that the product became stuck to the Celite® leading to difficulties in removal by filtration.

The improved PCC method was used with protected serinol **60** and also showed good conversion to aldehyde. Increasing the reaction time from 4 hours to 20 hours proved more convenient and increased yields without degradation of the aldehydes produced, especially for reactions on a larger scale. The best yields obtained were 75 % and 85 % for phenylalaninol and serinol respectively. These would most likely be improved with further optimisation.

2.1.7 Wittig olefinations

In order to incorporate the alkene required to close the piperidine ring via a carbonyl-ene reaction, and at the same time add functionality to C_3, Wittig olefinations were employed.

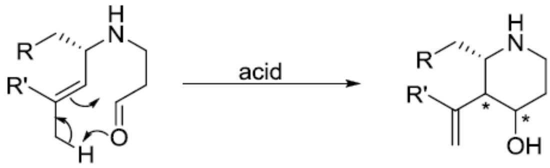


61 A=OTBS
71 A=Ph

72 A=OTBS, R=H, R'=H
73 A=Ph, R=H, R'=H
74 A=OTBS, R=Me, R'=Me
75 A=Ph, R=Me, R'=Me
76 A=Ph, R=H, R'=CO_2Me

Scheme 25: a) $Ph_3P^+CHRR'X^-$, KO^tBu, THF (* not required to produce **76**)*

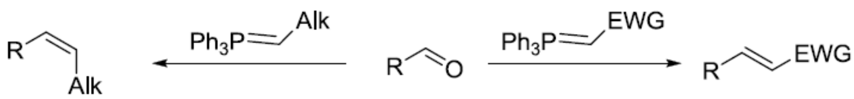
Scheme 25 shows various reactions that were attempted. Compounds **72** and **73** are not suitable for cyclisation as they lack the necessary allylic hydrogen as shown in the mechanism below (Scheme 26). These reactions were used to test the chemistry, to see if the substrates would withstand the Wittig conditions without degradation.



Scheme 26

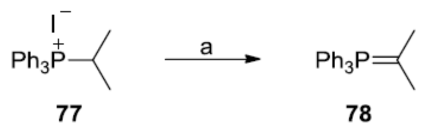
Other Wittig olefinations using non-stabilised ylides to give alternative aliphatic chains in position C_3 may be desired. If these prove difficult or low yielding, compounds **72** and **73** leave the possibility of introducing the aliphatic chains by metathesis.

A stabilised ylide was also tested,[59] producing compound **76**. This particular example can also not be used directly for cyclisation as it has no available protons. The ester could however be reduced to give a product with opposite stereochemistry to the one attainable from using a non-stabilised ylide. This is due to the outcome of the Wittig olefination when using non-symmetrical ylides. With a stabilised ylide the major product is the *E*-alkene, but if the ylide is non-stabilised the major product is the *Z*-alkene (Scheme 27).



Scheme 27

Compounds **74** and **75** were synthesised from the isopropyl ylide **78**, which was made *in situ* from the iodo-precursor **77** (Scheme 28).

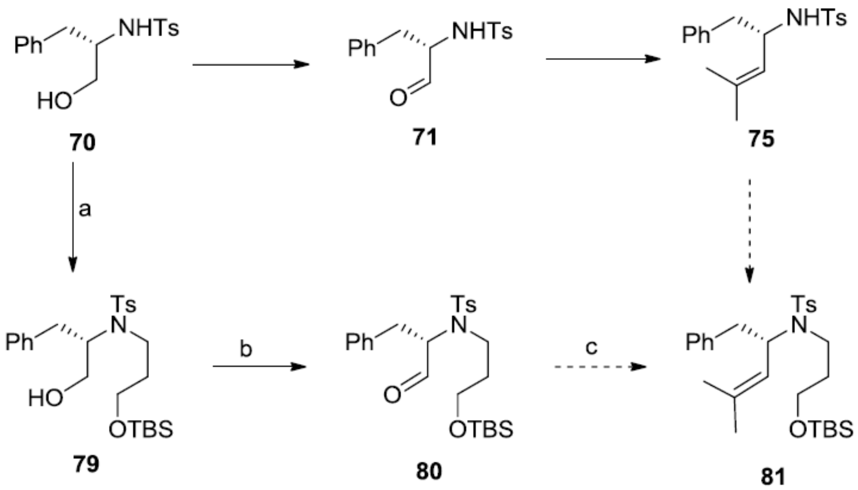


Scheme 28: a) KO^{t}Bu, THF

Alkene **75** was synthesised by this method only in modest yield (~35 %). Alkene **74** was still not possible to produce under the same conditions (RT, 16 h) suggesting that the bulk of the TBS group may have been preventing the reaction.

2.1.8 Alternative forward synthesis

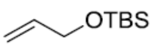
Due to the low yield and non-reproducibility of the reaction, the next step of functionalising the nitrogen (**75** → **81**) was not attempted but instead an alternative synthetic route was pursued (Scheme 29).



70, 71, 75, 79, 80, 81

*Scheme 29: a) $X(CH_2)_3OTBS$, Cs_2CO_3; b) PCC; c) ylide **78***

The functionalization of the nitrogen was attempted with both chloro- and iodo-substituted alkyl chains, both with equally disappointing results.[60] Compound **79** was isolated but only with 9 % maximum yield.



82

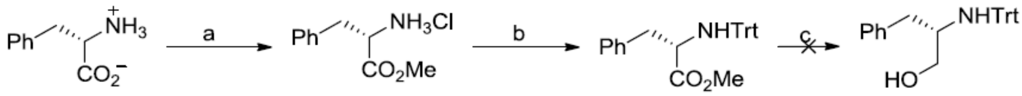
Figure 9

Compound **82** (Figure 9) was isolated from these reactions indicating that the halogen was being eliminated faster than the alkylation could occur.

The small amount of compound **79** that was produced was subjected to the now usual PCC oxidation conditions (3 eq. PCC, DCM, RT, 16 h) and aldehyde **80** was isolated by chromatography. Not enough of this material was brought through to test the Wittig olefination.

2.1.9 Tritylation

The acidity of the amine proton was suspected to be the source of the difficulties in the above reactions. Trityl protection had been reported to reduce this acidity so the project moved in this direction.

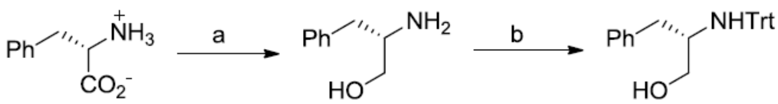


68 **83** **84** **85a**

Scheme 30: a) $SOCl_2$, MeOH; b) TrtCl, Et_3N; c) $LiBH_4$

The earlier protection strategy of producing the methyl ester from the amino acid then reducing this, once protected, to the alcohol was undertaken (Scheme 30). Unfortunately the lithium borohydride reduction did not work as well as expected; it gave a 50/50 mixture of ester and alcohol, even after addition of extra equivalents of $LiBH_4$ and increasing the time to ten days.

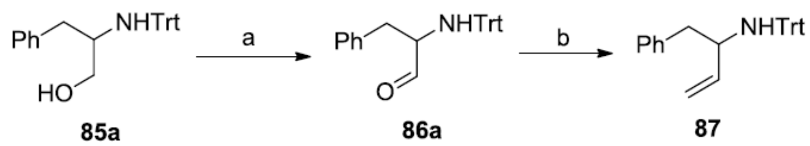
An alternative route was then found in which the reduction of the amino acid precedes the trityl protection (Scheme 31).[61]



68 **69a** **85a**

Scheme 31: a) I_2, $NaBH_4$; b) TrtCl, Et_3N

The alternative route is shown in Scheme 31, which also removes one synthetic step. This synthetic route was not initially chosen due to the possibility of double tritylation onto the oxygen as well as the nitrogen. This was fortunately found not to be an issue in this example. Reduction of phenylalanine had successfully been used previously in the project (Scheme 23). The tritylation product **85a** was isolated in 96 % yield after chromatography.



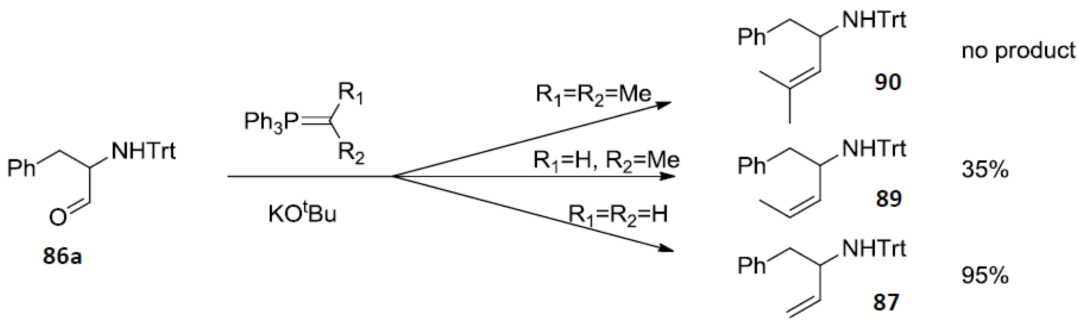
Scheme 32: a) DMSO, $(COCl)_2$, Et_3N, DCM 98 %; b) $Ph_3P^+CH_2I^-$, KO^tBu, THF 98 %

The next steps shown in Scheme 32 proceeded in high yield and were easily purified with column chromatography.[62] The problems returned when trying to install an alkyl chain during the Wittig olefination.

Figure 10

Each time the reaction was attempted with ylide **78**, the only recoverable product was triphenylmethane. Various sets of conditions were trialled including changing the amount of ylide used, the temperature and the reaction time; but all gave triphenylmethane as the major product (80 - 90 %).

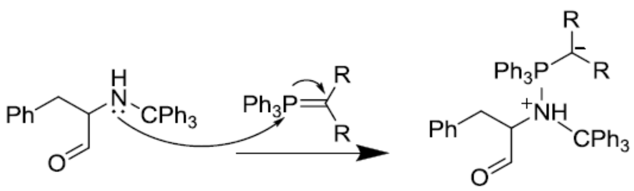
When ylide **88** was examined, the same happened but to a lesser extent. Around 37 % product was achieved with 53 % triphenylmethane also recovered.



Scheme 33: Experimental outcomes of various Wittig olefinations

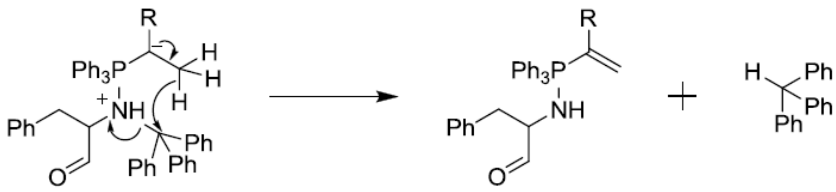
The only literature reference found for removal of a trityl group to give triphenyl methyl, instead of trityl alcohol, involved a single electron transfer. This is not possible under the reaction conditions used.

Scheme 34 shows a possible mechanism to explain these results.



Scheme 34: Interaction between amine and ylide ***47***

Firstly, the ylide is rapidly bound to the nitrogen as seen in Scheme 34. At this point, if R = H, the Wittig olefination occurs as expected. It is unclear if the N-P bond is broken before this or as part of the work-up. The expected product is found in quantitative yield.



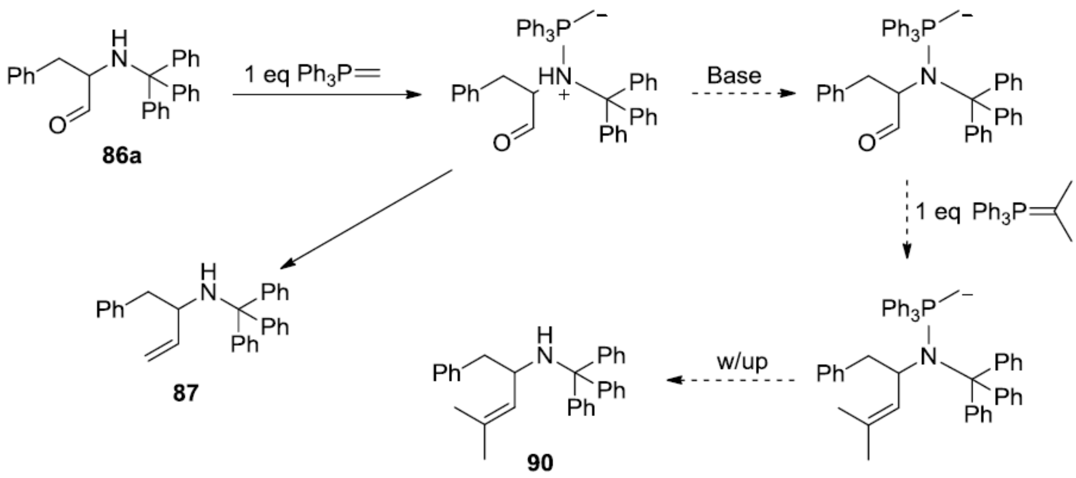
Scheme 35: Possible detritylation mechanism

If there is a proton γ to the phosphorus in the ylide as in the case of **89** and **90**, it can be delivered to the trityl group via a six-membered cyclic transition state as seen in Scheme 35.

The triphenylmethane was collected as a white solid but the larger fragment was never recovered so it was not possible to tell at what point the N-P bond is broken.

2.1.10 Temporary Protection Strategy

A temporary protection strategy was tested to see if the nitrogen could be blocked to allow formation of the substituted alkenes. (Scheme 36)



Scheme 36: Proposed temporary protection

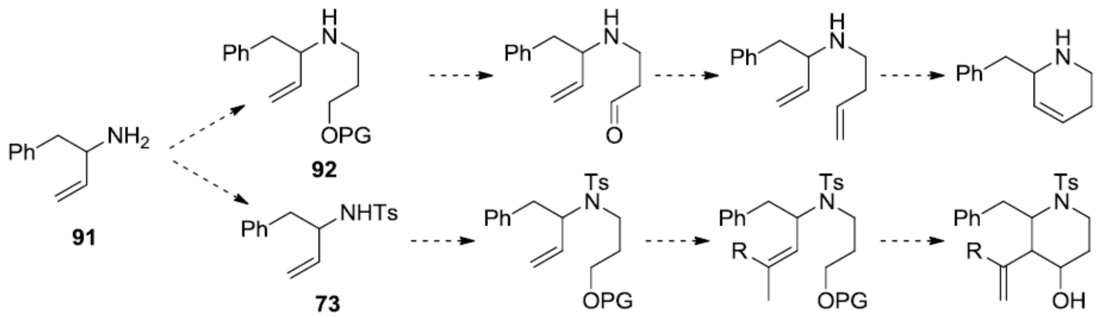
It was hoped that the extra base (in practice added as a solution with the first ylide) would deprotonate the nitrogen and remove the possibility of a reversible first step. This would leave all of the ylide bound to nitrogen so that the second, substituted ylide could then go on to react as desired.

A TLC analysis immediately after the aldehyde and ylide were combined showed no aldehyde remaining, presumably all in the protected form, so the second ylide was added. After an overnight stir the intense red colour associated with the second ylide was still present and indeed after work up compound **87** was isolated. This suggests that the formation of the N-P bond is in fact reversible, and rapidly so. The result also suggests that the aminium ion could be shielded from deprotonation by the base (in this case bulky potassium *tert*-butoxide), probably due to steric hindrance from the six phenyl groups surrounding it.

2.1.11 Detritylation

The small amount of compound **90** that was produced from previous reactions was taken forward to test the detritylation step which was deemed a partial success. The much more available compound **87** was then used to optimise this reaction which became problematic, not in the detritylation itself, but in the work up stages.[63] Initially, the hydrochloride salt of amine **91** was sought, as it was thought the free amine would be too volatile. This was done by basifying the reaction mixture prior to organic extraction and then re-acidifying with HCl. This gave dissapointing yields and after further experimentation it was found that the initial extraction was removing trityl alcohol only. A second extraction was required in order to extract the product from the aqueous layer. The free amine was found to be much simpler to produce. It was found to be extremely water soluble so difficult to extract during work up. The final procedure involved extraction of the trityl alcohol followed by evaporation of the water to dryness to leave the product as a residue in reasonable yield and purity.

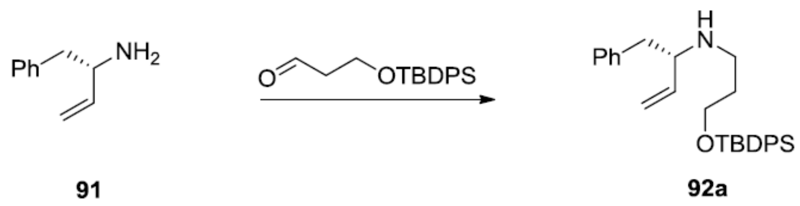
It was decided to continue with the unsubstituted alkene (**91**) as there was the possibility of installing functionality by metathesis. This was probably best left until one of the last stages in the synthesis due to the high cost of the catalysts.



Scheme 37: Possibilities using metathesis

Scheme 37 outlines the next synthetic route towards the piperidine. Starting with a monosilylation of 1,3-propanediol,[64,65] followed by a Swern oxidation produces a protected aldehyde which can then be used in a reductive amination with amine **91**.[66] From this compound there were various options available. We could have continued as laid out in Scheme 37 to furnish a piperidine by ring closing metathesis, with the option to functionalise at the double bond, e.g. dihydroxylation, epoxide formation, etc. Alternatively the double bond of compound **92** could be functionalised by metathesis then the initial plan to close the ring by the well precedented carbonyl-ene cyclisation could be followed. In addition to this amine **91** could be protected with a tosyl group to fit in with previous cyclisations performed in the Snaith group. This compound would then be alkylated as in Scheme 29**a** followed by metathesis to introduce the functionality required for cyclisation.

Amine **91** was alkylated by means of a reductive amination to produce **92a** (Scheme 38)

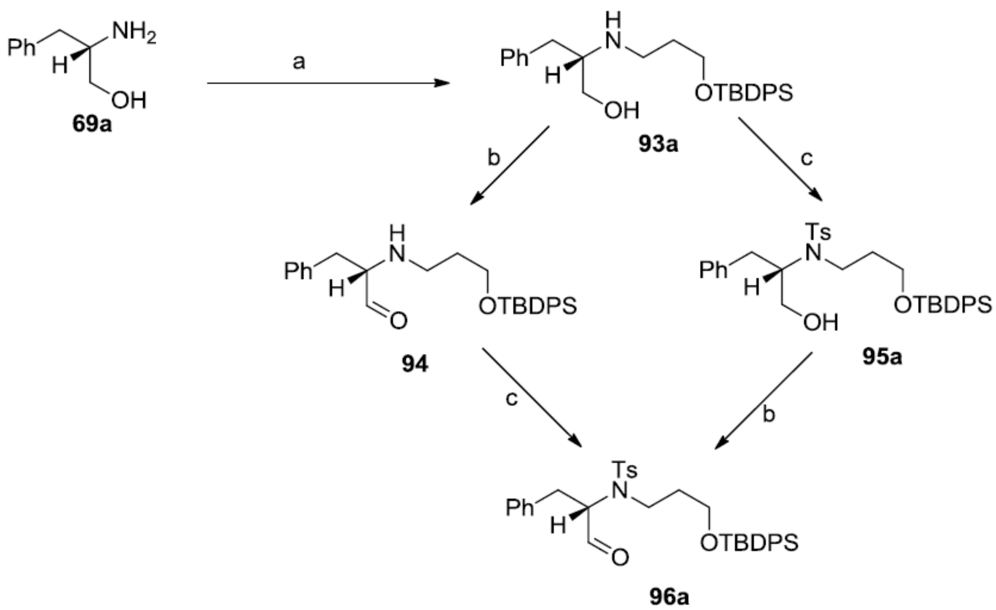


Scheme 38: i) Na_2SO_4, DCM; ii) $NaBH_4$, MeOH

The maximum yield obtained after multiple attempts of this reaction was only 18 % so the route was not pursued any further.

2.1.12 Avoiding metathesis

Tritylation had not furnished a particularly elegant route to the linear piperidine precursors. It was decided to introduce the alkyl chain that would form C_4 - C_6 of the finished piperidine before working on the double bond constituent as had been done up to this point. Scheme 39 below shows the forward synthesis towards the cyclisation precursor.

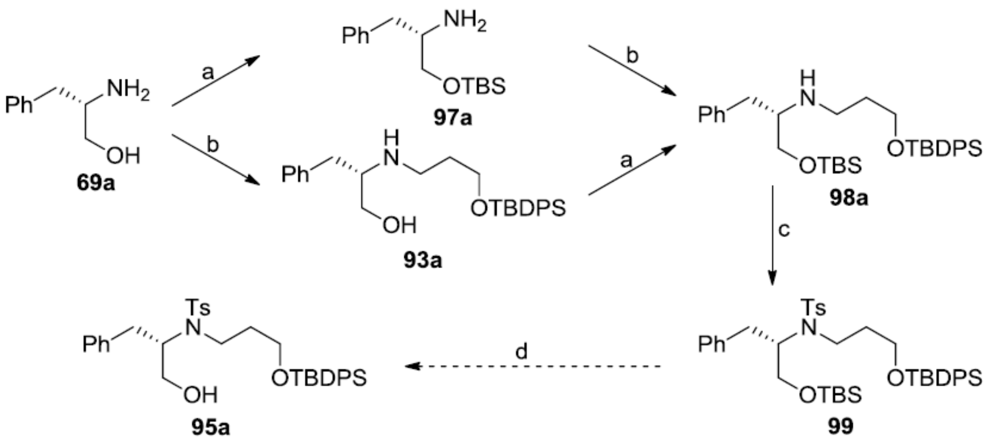


Scheme 39: a)i) O=CH(CH$_2$)$_2$OTBPDS, Na$_2$SO$_4$, DCM; ii) NaBH$_4$, MeOH, 70 %;
b) DMSO, (COCl)$_2$, Et$_3$N, DCM; c) TsCl, DMAP, Et$_3$N, DCM

Beginning with phenylalaninol (**69a**) a reductive amination was performed in reasonable yield. The left hand route (Scheme 39) shows a Swern oxidation followed by tosylation of the nitrogen. This resulted in a complex mixture of products so the steps were reversed. Tosylation of **93a** gave a less than satisfactory yield due to competition from the free hydroxyl group.

2.1.12.1 Parallel protection strategy

Due to the low-yielding tosylation reaction, the synthesis was revised to include a protection of the hydroxyl group and allow tosylation to proceed freely.



Scheme 40: a) TBSCl, Et_3N, DCM; b)i) $O{=}CH(CH_2)_2OTBDPS$, Na_2SO_4, DCM; ii) $NaBH_4$, MeOH; c) TsCl, Et_3N, DCM; d) AcOH/THF/H_2O

Scheme 40 shows the parallel protection strategy employed. Initially, the hydroxyl group of phenylalaninol (**69a**) was protected[67] followed by a reductive amination onto the amine. The silylation proceeded in excellent yield (98 %) but the reductive amination produced only traces of product after multiple alterations to the reaction mixture such as changes to the temperature, time and concentration. The steps were reversed to produce the doubly silylated product (**98a**) yielding 99 % and 91 % respectively over the two steps. The subsequent tosylation proceeded in a much more respectable yield than with the free hydroxyl group (70 %) but unfortunately the selective deprotection that followed could not be achieved.[68,69,70]

When the deprotection was attempted using aqueous acetic acid in THF at 20 °C for 16 hours, no reaction occurred. When the time was extended up to 72 hours a double desilylation resulted in the diol. Heating at 50 °C for 16 hours again resulted in recovery of unreacted compound **99**, but extending this time again resulted in the diol as the only product of the reaction.

This was unexpected as the *tert*-butyldiphenylsilyl protecting group was thought to be much more stable than the *tert*-butyldimethylsilyl group, making it non-labile under the reaction conditions used.[71]

Another approach involved using a THP protected alcohol in place of the second silicon-based protecting group used to alkylate the nitrogen but problems producing a mono protected propanediol lead to this method being abandoned.

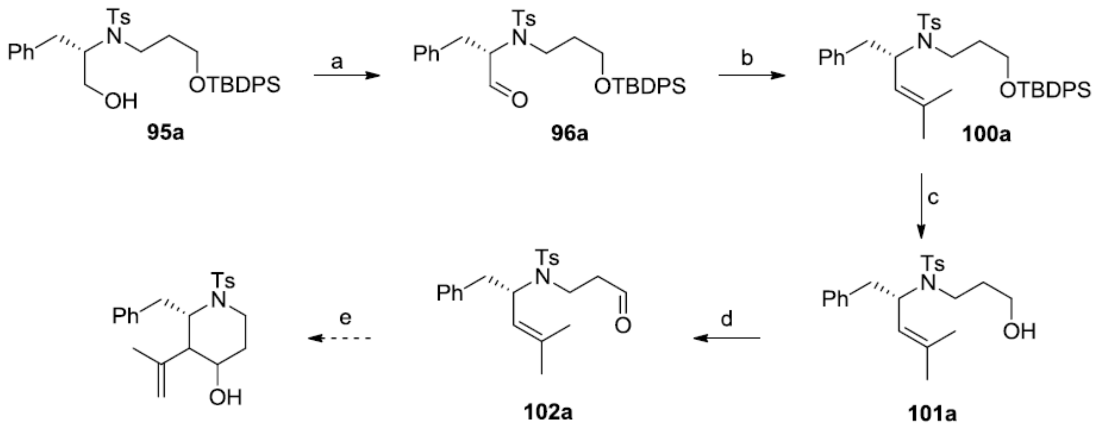
As the monosilylated compound **95a** was not accessible via this route and it would have added an extra two synthetic steps, the previous synthesis with tosylation in the presence of the free hydroxyl was resumed despite the disappointing yields (max. 50 %).

2.1.13 Completion of linear precursor synthesis

The remainder of the synthesis as shown in Scheme 41 proceeded smoothly.

The Swern oxidation of alcohol **95a** to aldehyde **96a** was clean and high yielding. Initially the Wittig olefination was attempted using potassium *tert*-butoxide as the base as had by now become a standard procedure, but this furnished no reaction. This was probably due to steric hindrance.

The *tert*-butoxide anion is fairly large and when combined with the triphenylphosphonium cation, it was little surprise that the reaction was unsuccessful. This reagent was used first as it is a standard agent used in the literature for ylide production and is easily handled in its granular form in the laboratory. When the reaction failed the base was changed to *n*-butyllithium, which turned out to be a very effective base in this reaction and compound **100a** was synthesised in good yield.[72]

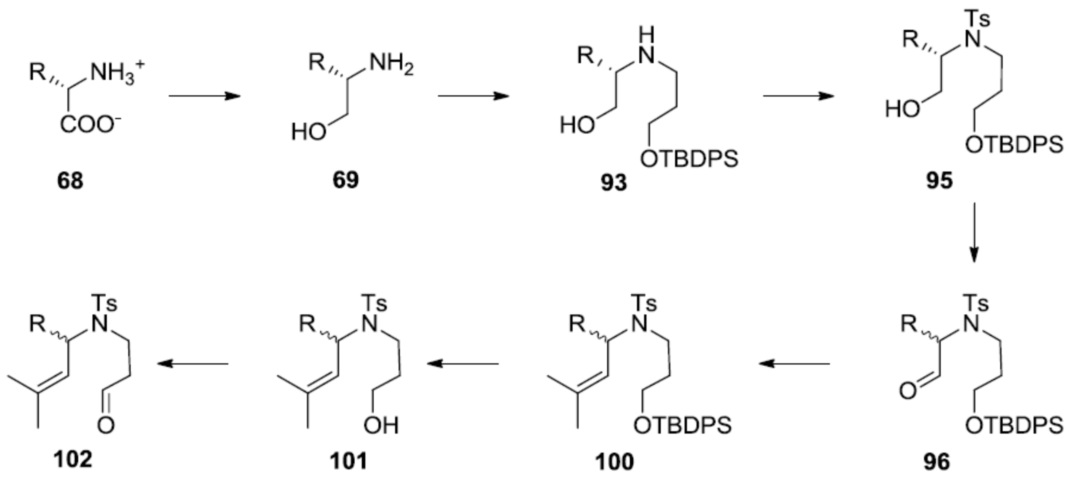


Scheme 41: a) DMSO, $(COCl)_2$, Et_3N, DCM, 95 %; b) $^{i}PrP^{+}Ph_3I^{-}$, n-BuLi, THF, 84 %; c) TBAF, THF, 65 %; d) DMSO, $(COCl)_2$, Et_3N, DCM, 87 % e) acid

Once the double bond had been installed, the deprotection with TBAF[73] and oxidation followed in good yield to produce a linear cyclisation precursor (**102a**).

2.1.14 Stereochemistry

Now that a complete synthetic route had been worked out (Scheme 42) racemic equivalents of each of the compounds were made to allow for measurement of the e.e. in each case.



Scheme 42: Completed synthetic route

The compounds synthesised from enantiomerically pure L-phenylalanine were compared with those made from a racemic mixture of DL-phenylalanine by supercritical fluid chromatography. This is a technique similar to HPLC but CO_2 cooled and pressurised to keep it in a supercritical fluid state is used as the mobile phase. Methanol was used as the co-solvent to initially solubilise the compound mixtures. The first three compounds (**69**, **93** & **95**) showed they had retained the stereochemistry from the chiral starting material (eg **95**; 98.6 % ee). Unfortunately from the first Swern oxidation (**96**) all samples showed racemisation (0.4 % ee). This is due to the ease of racemisation of α-amino aldehydes owing to the planar intermediate which can be formed when base is present. (Figure 11)

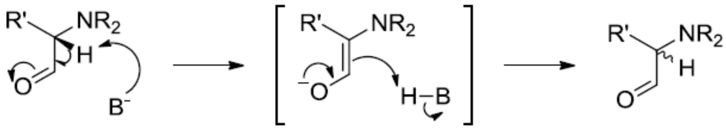


Figure 11: Epimerisation of aldehyde

The Swern procedure used to this point had used triethylamine as the base. There is literature precedent that using a bulkier base such as Hünig’s base (Figure 12) and lower temperature quenching can prevent α-racemisation.[49] A longer reaction time may be required due to the increased steric bulk.

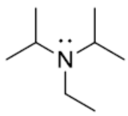


Figure 12: Hünig's base - N,N-diisopropylethylamine

Three variables in the standard Swern oxidation were altered in an attempt to eliminate the racemisation that was occurring during the reaction. The standard Swern oxidation procedure being followed involved addition of base at -78 °C then, after stirring for 15 minutes, the mixture was allowed to warm to room temperature prior to quenching with water. Firstly the triethylamine was substituted for Hünig’s base but all other aspects remained the same. In the second reaction, the quench was performed at -20 °C and in the third, the reaction stirred for two hours at -78 °C after addition of the base before quenching with water and then allowing to slowly warm to room temperature.

All three of these samples were sent for SFC analysis but each one was deemed to be a racemic mixture.

2.1.15 Other R-groups installed at position 2

Although it was not possible to synthesise enantiomerically pure linear precursors by the above methods, this is not in fact important when looking at the stereochemical outcomes of the ring closing reactions as we were interested, at this stage, in the diastereocontrol in these cyclisations. For this reason, due to the availability, variety and the time spent in arriving at a synthetic pathway, further amino acids were chosen as starting materials (Figure 13).

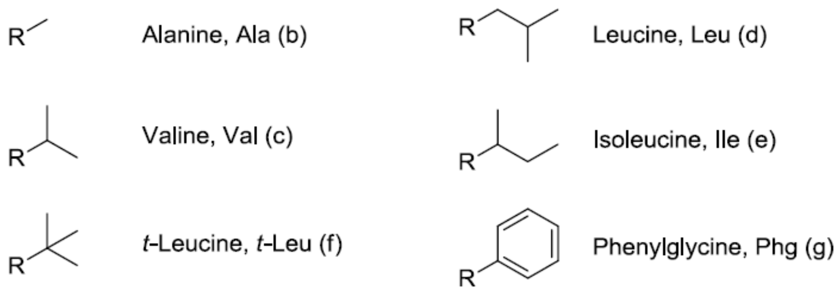


Figure 13: Other amino acid side chains used

For each of these amino acids, the route shown in Scheme 42 was followed with varying successes dependant largely on steric effects.

	reduction (69)	alkylation (93)	tosylation (95)	Swern (96)	Wittig (100)	deprotection (101)	Swern (102)
phe (a)	78	70	42	95	84	65	87
ala (b)	-	66	69	-	-	-	-
val (c)	64	92	60	99	75	90	58
leu (d)	96*	81	80				
ile (e)	99*	81	80				
***t*-leu (f)**	-	59	22	-	-	-	-
phg (g)	-	65	16**	-	-	-	-

*Table 2: Yields obtained following Scheme 42. * Reductions of leu and ile were taken through without distillation due to difficulty in collecting product and cleanliness of ^{1}H-NMR spectra.*
*** Tosylation occurred on oxygen.*

Table 2 shows the yields obtained from the reactions shown in Scheme 42. Some of the routes began with the commercially available amino alcohol as the reduction from the amino acid was difficult and collection of the products was complicated by the product volatility.[74] The routes for leucine and isoleucine are incomplete due to insufficient time and the exploration of more profitable avenues instead, but it is expected there would be little problem based on the reactivity of the valine example as they are structurally similar.

tert-Leucine was abandoned after the tosylation as the yield was very low. This was presumably due to the steric crowding around the reaction centre. This was even more apparent for phenylglycine as the yield was even lower and after more detailed analysis it was found that the tosyl group had been added to the free hydroxyl terminus, being more accessible than the amine nitrogen.

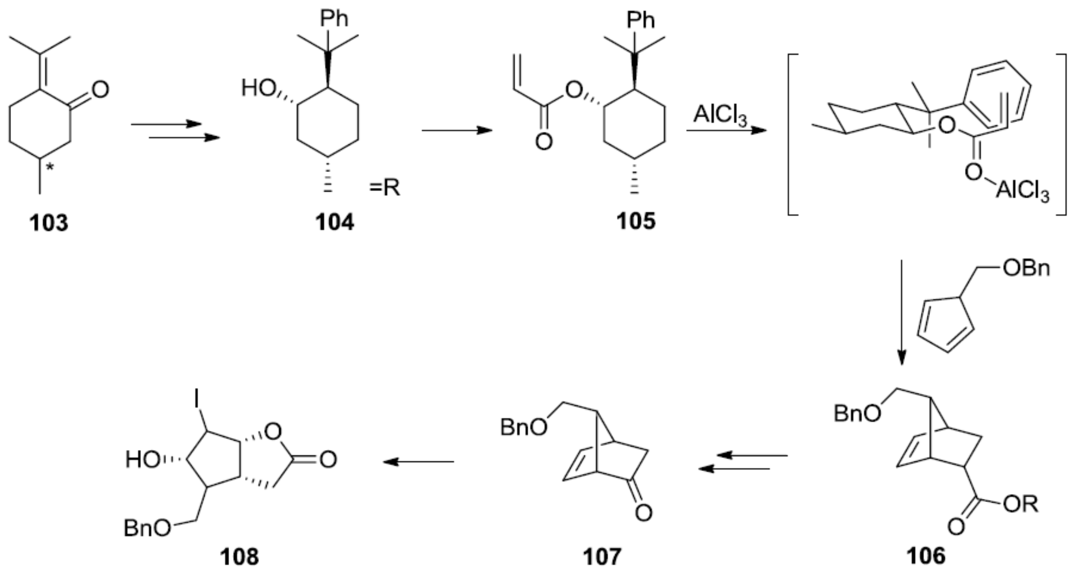
The alanine reactions were not optimised and not continued along this path as a more efficient route was being pursued that would retain the integrity of the stereogenic centre.

2.2 Introduction of the stereogenic centre by use of a chiral auxiliary

A chiral auxiliary is a unit employed to control the stereochemical outcome of an otherwise non-stereoselective reaction. The inherent chirality of the auxiliary can be transferred to the molecule of interest usually by controlling the position of various reactants in a transition state during the reaction in question.

2.2.1 Early literature occurrences

One of the first uses of a chiral auxiliary was by Corey in 1975 in his synthesis of prostaglandin intermediates.[75] Starting from either isomer of pulegone (**103**) he synthesised (+)-8-phenylmenthol (**104**) which is then used as the chiral auxiliary.[76]



Scheme 43: Use of a chiral auxiliary in the synthesis of prostaglandin intermediates

Scheme 43 shows how addition of a Lewis acid to the acrylate ester of (+)-8-phenylmenthol (**105**) causes a conformational change which is postulated to block the rear face of the acrylate. This means that during the Diels-Alder addition only the front face is available so only the *endo* adduct (**106**) is produced. After several more synthetic steps the target molecule (**108**), a key intermediate in the synthesis of prostaglandins, was successfully produced in an optically pure state.

As this type of procedure became more popular, the need for a more accessible auxiliary was necessary so alternatives such as trans-2-phenylcyclohexanol (**109**)[77] and trans-2-(1-phenyl-1-methylethyl) cyclohexanol (**110**)[78] were developed.

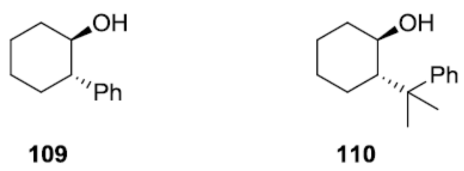


Figure 14

2.2.2 *tert*-Butanesulfinamide

Since their introduction, many small chiral molecules have been used as auxiliaries. One which has been extensively studied by Ellman and co-workers is *t*-butanesulfinamide (**111**).[79]

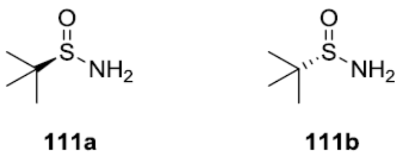
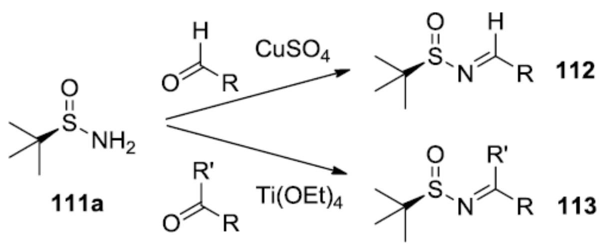


Figure 15: (R)-(+)- and (S)-(-)-t-butanesulfinamide

The imines formed on reaction with these compounds are stable and easily isolated. Additionally, the sulfinyl group activates the imine and it is easily removed by brief treatment with mild acid.



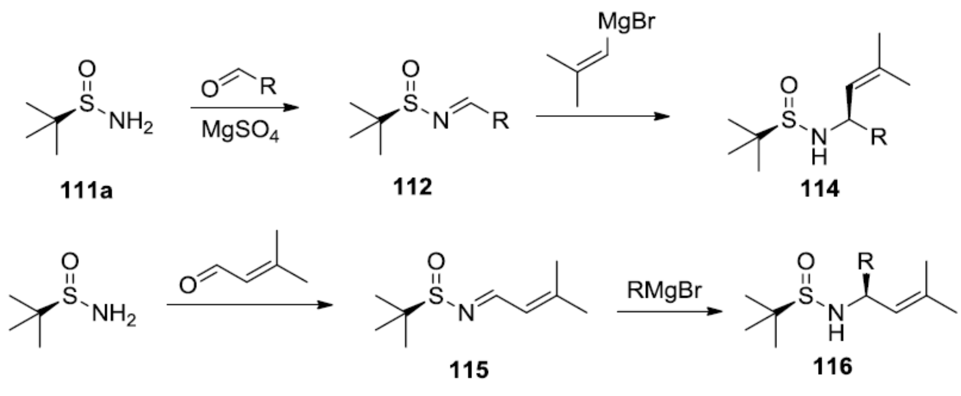
Scheme 44: use of t-butanesulfinamide as a chiral auxiliary

Ellman *et al.* produced a whole range of aldimines (**112**) and ketimines (**113**) in excellent yields. They even showed imines synthesised from unreactive, sterically hindered and electronically deactivated starting materials.

Addition of Grignard reagents to sulfinyl aldimines **112** again give very good yields and diastereoselectivities. Aliphatic and aromatic aldimines were successfully used with alkyl, aryl and vinyl Grignard reagents, followed by decoupling with hydrochloric acid, to give an array of α-branched amines.

2.2.3 Stereocontrolled installation of R-group at position 2

In just two synthetic steps a whole range of R-groups could be installed at what would become position 2 in the finished piperidine. This method meant that a wider scope of functionalities could be used than was possible from amino acids.



Scheme 45

The two routes shown in Scheme 45 reach the same product but with opposite stereochemistry.[80] The lower route turned out to be slightly higher yielding and also has the benefit of differentiation of R-groups one synthetic step later.[81,82,83]

There was the possibility that the Grignard reagent would add to **115** in the 4 position instead of the desired 2 position. All of the ^{1}H-NMR data show no evidence of this as the imine proton is no longer seen.

The stereochemical outcome of the Grignard addition is governed by the stereochemistry of the six membered ring transition state formed between the sulfinimine and the magnesium bromide as seen in Figure 16.[79]

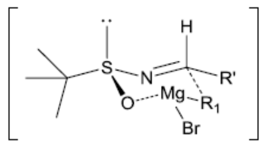
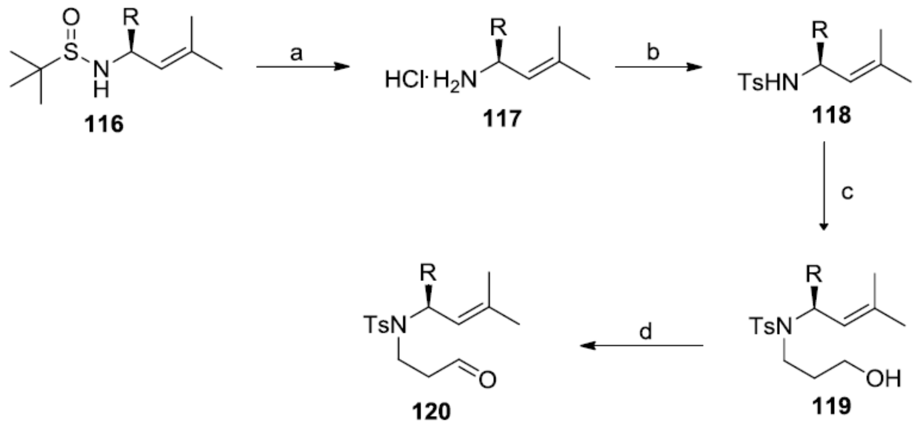


Figure 16: six-membered ring formed during the Grignard addition.

A regular six-membered ring in a chair conformation is able to form as the lone pair on the sulfur causes it to adopt a tetrahedral shape. From this transition state it is easy to see that R_1 is delivered to the same face as the sulfur-oxygen double bond. This is how the chiral auxiliary works to install a stereogenic centre with reliable specific stereochemistry that will remain after the auxiliary has been removed. In most examples there was only a single diastereomer seen by ^{1}H-NMR spectroscopy. When the R-group is very small (methyl) a minor isomer is also recovered as up to 33 % of the overall product yield.

2.2.4 Completion of linear cyclisation precursor synthesis

This route removes the need to oxidise an α-amino alcohol so there is no possibility of racemisation of the newly installed stereocentre. (Scheme 46)



Scheme 46: a) HCl, MeOH; b)TsCl, Et_3N, DMAP, DCM; c)i) $I(CH_2)_3OTBS$, Cs_2CO_3, DMF; ii) HCl or TBAF/THF; d) DMSO, $(COCl)_2$, Et_3N, DCM

Removal of the chiral auxiliary was straightforward by stirring with hydrochloric acid in anhydrous ether for 30 minutes.[84] Extraction of the amine (**117**) was difficult due to water solubility and in some cases volatility. Various methods were investigated, including trituration with ether, steam distillation from aqueous sodium hydroxide and organic extraction from an aqueous work-up, but all failed. For these reasons the amine was left as the hydrochloride salt and the excess acid and solvent evaporated off leaving a product that was clean enough to be used without further purification.

2.2.4.1 Alkylation of the amine

Initially the plan had been to resume the synthesis as set out in Scheme 42 with a reductive amination onto the amine with the same aldehyde as previously used. Unfortunately, even with addition of extra base equivalents to neutralise the hydrochloride salt, or addition of butyllithium to precipitate out LiCl and release the free amine, multiple attempts at reductive amination failed.

Instead the salt was tosylated, again with additional equivalents of base present. This product was then easily separated by chromatography to remove any impurities (**118**).

A simple S_N2 substitution reaction followed. Firstly a silylated chloropropanol was used but the yield and efficiency were disappointingly low. A Finkelstein substitution was employed to produce the corresponding iodide which was a much more potent alkylating agent.[85] The Finkelstein product had to be used crude as column chromatography promoted elimination of HI and subsequent desilylation to leave 2-propenol as the only recoverable product. The iodide was also susceptible to decomposition under UV light so the Finkelstein substitution and following alkylation reactions (**119**) were conducted in complete darkness.

2.2.4.2 Desilylation and oxidation

Once these complications were understood they were simple to accommodate. The TBS group used as protection for the alcohol during the alkylation was found to be particularly labile in the reaction mixture used. This allowed it to be cleanly and effectively removed with dilute hydrochloric acid during the workup of the alkylation in most cases. This was a very useful consequence as it removed a synthetic step from the overall synthesis. In the rare examples where the protecting group was not removed 1M TBAF in THF followed by chromatography yielded the alcohol.

A standard Swern oxidation followed by chromatography gave the aldehydes ready for cyclisation in high yield (**120**).

2.2.5 Variety of side-chains

Introducing the side-chain by way of a Grignard addition allows for almost any R-group to be inserted. There is much greater scope than the limitations of using amino acids as the starting material. For comparison to the amino acid derived syntheses above, work was undertaken on methyl, isopropyl and benzyl side-chains, relating to alanine, valine and phenylalanine respectively. Other R-groups investigated were allyl, prenyl and nitrile. If time and resources had permitted, a vinyl side chain would also have been studied. These unsaturated alkyl chains will allow for different functionality to be added to the finished piperidine to allow for further manipulation.

	Grignard (116)	**deprotection (117)**	**tosylation (118)**	**alkylation (119)**	**oxidation (120)**
methyl (a)	75	-	98*	83	84
isopropyl (b)	83	-	99*	38	
benzyl (c)	59	-	94*	63	71
allyl (d)	94	-	91	93**	79
prenyl (e)	<2				
nitrile	no reaction				

Table 3: percentage yields of reactions.

** yield over two steps. **desilylation by TBAF required*

Table 3 shows the outcomes of the reactions shown in Scheme 45 and Scheme 46.

Although the reaction with allyl Grignard occurred in good yield (**116d**), when the reaction was repeated with prenyl Grignard there was almost no reaction (**116e**). A very small amount of product was recovered but the main isolated compound was unreacted imine. This was quite unexpected as the structural difference is at the opposite end of the molecule to that involved on the reaction. This reaction may require additional investigation.

There were several attempts made to introduce the nitrile from trimethylsilyl cyanide with scandium (III) triflate[86] and cesium fluoride[87] but all of these were unfruitful. The referenced articles show additions of a nitrile group to similar *tert*-butanesulfinimines but none of the referenced compounds were α,β-unsaturated imines so this may have added extra complication.

Due to the difficulty in isolating the free amine (**117**) after removal of the chiral auxiliary yields were not recorded but instead the residues were used crude for the following tosylation (**118**). The combined yields shown over the two steps are excellent, showing the deprotection was very efficient.

The alkylation (**119**) and subsequent Swern oxidation (**120**) of three of the four remaining substrates progressed well to give the linear cyclisation precursors. The fourth, isopropyl, did not alkylate well under the same conditions. Optimisation of this reaction would begin with extending the time and/or increasing the temperature to encourage more favourable collisions.

Alkylation of the allyl variant gave excellent yield but this was the only example not to spontaneously desilylate upon mild acid work up. A separate step using TBAF was required.

3 Cyclisations

Previous work in the Snaith group has shown a marked difference in the relative stereochemistry of the two stereocentres produced during the carbonyl-ene ring closure dependent upon the type of acid catalyst used. Brønsted acids at low temperature favour formation of the kinetic product, whereas Lewis acids at elevated temperature allow for equilibration to the thermodynamic product.[23,24]

3.1 Isomers from cyclisation

Assuming fixed stereochemistry at position 2 there are four possible outcomes of the ring closing reactions as shown in Figure 17. The enantiomer to each of these would also be formed, although undetectable by ^{1}H-NMR, if the linear precursor was not enantiomerically pure. Not all of these isomers were expected to be formed or be detectable in each instance but their ratios are variable dependent upon the reaction conditions. In most cases only two isomers were detected and occasionally a third.

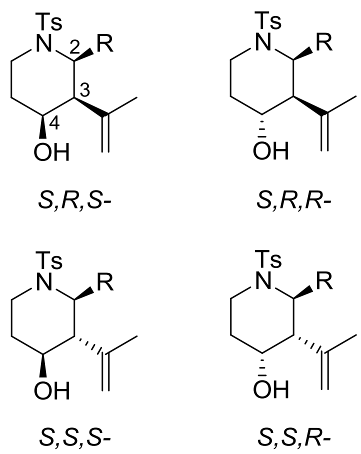


Figure 17: Possible isomers from ring closure

During the cyclisation, the six-membered ring is formed preferentially into a chair conformation. The tosyl group protecting the nitrogen is very large and has been seen in previous work in the Snaith group to force the substituent on C_2 into the usually unfavourable axial position as shown in figure 18.[88,89,90]

Figure 18

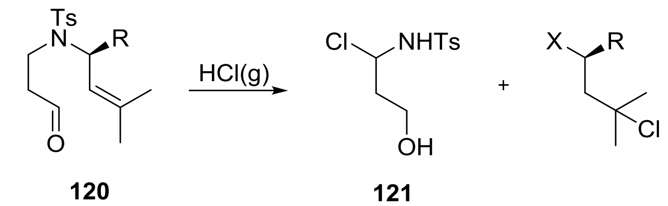
3.2 Brønsted acid catalysis

Brønsted acids used at low temperature favour the formation of the kinetic product. In this research hydrochloric acid was used as it had previously given the best results for the Prins cyclisation to give 3,4-disubstituted piperidines.[15] There are a few methods of introducing the catalyst into the reaction mixture, either as a concentrated aqueous solution or bubbling HCl gas through the reaction mixture to give a saturated solution. Both methods have their flaws and virtues. As the reactions are taking place at -78 °C, concentrated aqueous acid (~36 %) is prone to freezing into an ice droplet on contact with the solvent. This calls for additional equivalents to be used to compensate for acid that is trapped and therefore not part of the reaction mixture. It means essentially that an unknown number of equivalents are in the reaction mixture. In addition, due to the low temperature, reaction times are extended and this poses operational difficulties in maintaining a constant temperature.

Conversely using compressed HCl gas allows much faster reactions, typically less than one hour rather than up to 48 hours, so temperature control is not an issue. It does however require a much more complex apparatus setup and there is no control to the amount of HCl used.

3.2.1 HCl gas cyclisations

In previous work in the Snaith group, bubbling HCl gas through a solution of the cyclisation precursor had proved an effective way of introducing the catalyst. Unfortunately, when this method was used with the compounds synthesised in this thesis, cyclisation did not occur, but instead the linear molecule (**120**) was cleaved, possibly into the compounds shown in scheme 47.



Scheme 47: Cleavage of cyclisation precursor by HCl gas.

Compound **121** was isolated in up to 85 % yield indicating this is the major reaction that occurs faster than cyclisation can occur. Reaction times were typically 5 – 10 minutes only. The structure above is tentatively suggested although has not yet been fully confirmed.

Mass spectrometry could identify the cation of the other fragment but X could not be identified by any of the spectroscopic techniques used. It is most likely another chloride.

3.2.2 Concentrated aqueous HCl cyclisations

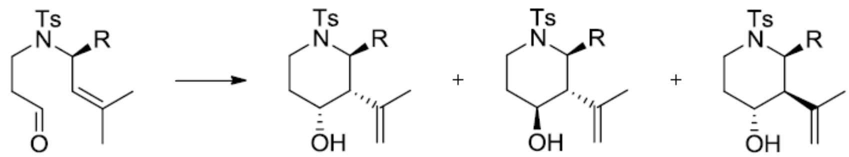
As using HCl gas was unsuccessful, concentrated aqueous HCl was used instead. This time cyclisation did occur and the results are shown in table 4.

R-group	temperature	time	product ratio*
methyl (a)	-78	18h	72:28
	-78	40h	70:30
benzyl (c)	-78	48h	60:40
	20	24h	74:26
allyl (d)	-78	48h	spectra unclear: vast majority **122**
	20	24h	

Table 4: Results of conc. HCl cyclisations

** from ^{1}H-NMR of crude sample*

There were two and in some cases three products isolated from this set of reactions as shown in Scheme 48.



SSR SSS SRR

120 **122** **123** **124**

Scheme 48: outcomes of cyclisation reactions

In all cases the major product was piperidine **122** with the stereochemistry 2S*,3S*,4R*. This has been confirmed with an X-ray structure of crystals of the major product when R was benzyl. (Figure 19)

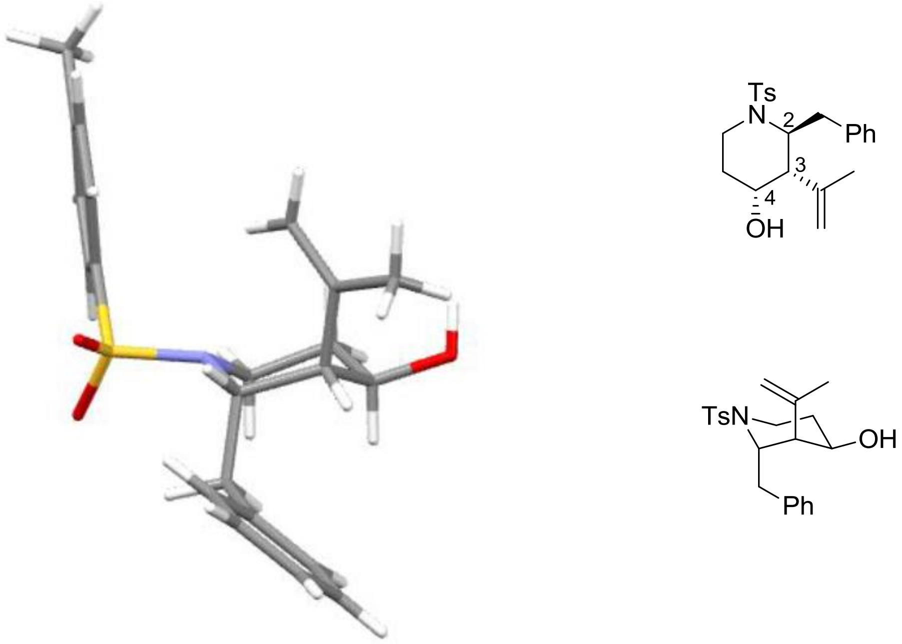


Figure 19: ***122c*** *SSR*

The minor product was piperidine **123** (2S*,3S*,4S*), again confirmed using X-ray diffraction. In order to crystallise the piperidine it was necessary to derivatise the free hydroxyl with a bulky group, in this case as a bromobenzoate. The data show that all of the substituent groups are in the axial positions. (Figure 20)

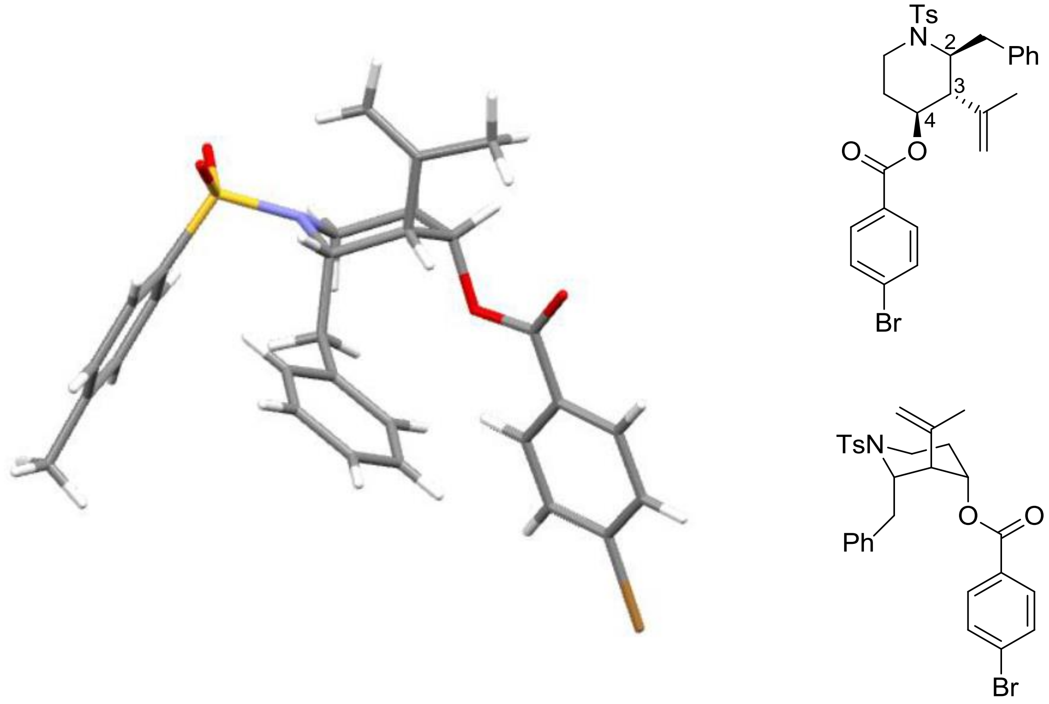


*Figure 20: der-**123c** SSS*

When R = Me the stereochemistry of the minor product is not entirely clear from the NMR data and crystals were not grown. By comparison to other NMR data it is clear that it is not piperidine **124a** (Figure 21). This can also be deduced by looking at the coupling constants at H_3 and H_4. In the 2S*,3R*,4R* isomer both of these hydrogen atoms lie in axial positions and so would have a large coupling constant (<9.5 Hz) between the two protons with a dihedral angle of 180 °.

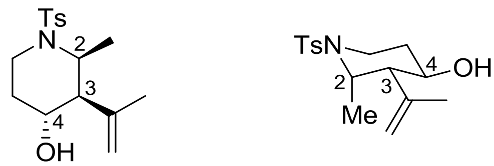


*Figure 21: piperidine **124a***

One proton signal visible in the spectrum of the crude mixture is a ddd and has coupling constants of 5.3 Hz, 7.2 Hz and 13.4 Hz. This is from H_4. The proton must be axial with the large coupling to H_5, leaving only smaller *J* values for the interaction to H_3, indicating that it cannot also be axial. Assuming H_2 lies equatorially would give piperidine **122a** which is the major product. This leads to one of two conclusions: the methyl group is small enough to allow it to lie equatorial without a steric clash with the *N*-tosyl giving the 2R*,3S*,4R* isomer; the conformation is not chair-shaped so the coupling constants are less useful in determining the stereochemistry. No C_2 substituent has been seen in the equatorial position in previous work, but due to the different substitution pattern in this substrate this could now be the case. This could be resolved by growing crystals to obtain X-ray analysis.

3.3 Lewis acid catalysis

Previous work in the Snaith group had determined that the most efficient Lewis acid catalyst for carbonyl-ene cyclisation is methylaluminium dichloride[15,91]. Coordination of the oxygen to the Lewis acid during the reaction stabilises the intermediate and should allow formation of the thermodynamic product. Increasing the temperature to introduce more energy into the system should also facilitate this.

Results from the cyclisations are shown in table 5.

	Temperature (°C)	Time	Isomer ratio	Products
Methyl (a)	-78	45m	91:9	major **122** (SSR) minor RSR?*
		3h	87:13	
	20	3h	77:15:8	**124**(SRR):**122**(SSR):RSR?*
	60($CHCl_3$)	3h	decomposition	
isopropyl (b)	-78	75m	83:17	Stereochemical assignment not clear by ^{1}H-NMR
	20	75m	65:35	
Benzyl (c)	-78	2.5-3.5h	78:22	major **122** (SSR) minor **123** (SSS) tricycle SSR
	20	2-5h	75:25	
		3d	tricycle	
	40	4h	64:36	
		18h	decomposition	
	60 ($CHCl_3$)	2h	decomposition	
allyl (d)	-78	30m	72:28	major **122** (SSR) minor **124** (SRR) trace **123** (SSS)
	0	30m	82:18	
	20	20m	73:27	

Table 5: Lewis acid catalysed cyclisation results.

**see HCl data, RSR speculative only*

As with the Brønsted acid catalysed cyclisations, the major products at low temperature were piperidines **122**. The major allyl piperidine was derivatised with 4-bromobenzyl chloride to allow crystallisation in order to prove the stereochemistry by X-ray diffraction. (Figure 22)

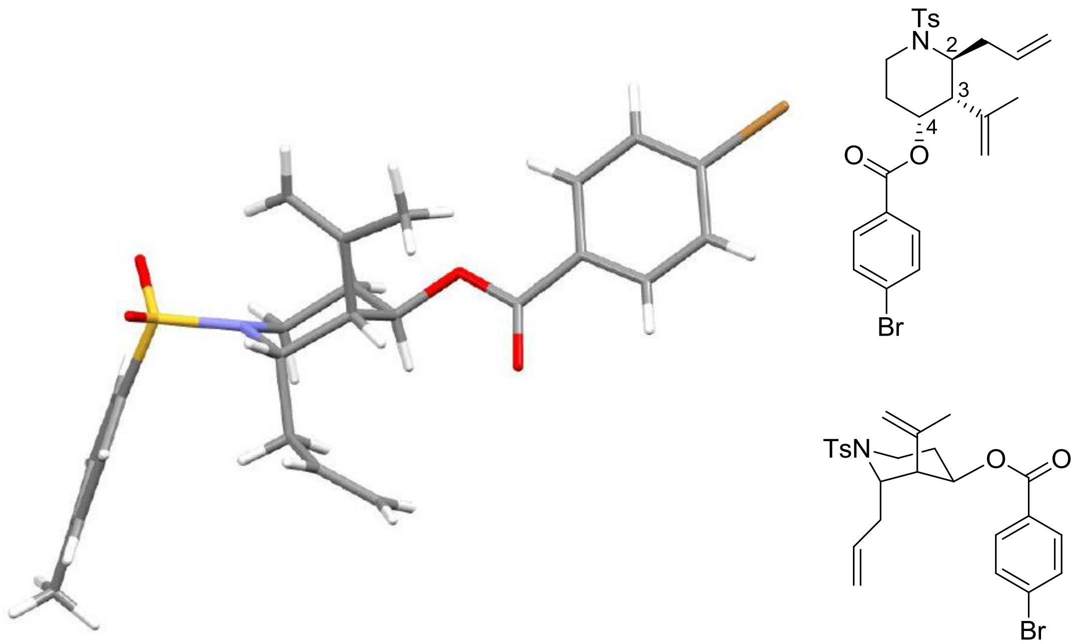


*Figure 22: der-**122d***

The same piperidine as seen with the Brønsted acid catalyst when there is a methyl group at position 2 is seen again here as a minor product. As discussed earlier this could potentially be the 2R*,3S*,4R* isomer (**125**) (Figure 23) but confirmation by X-ray analysis is required.

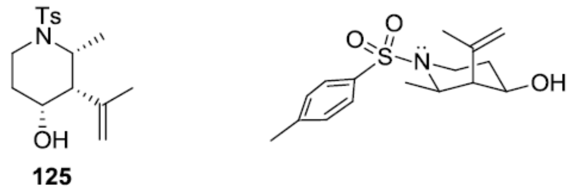
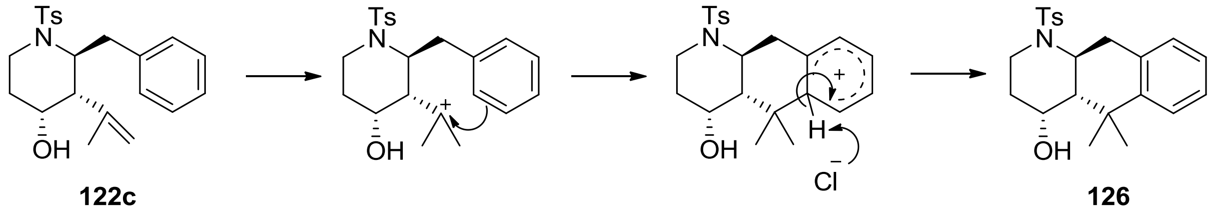


Figure 23: 2R,3S,4R piperidine

The minor products when the R-group is benzyl or allyl are again those seen previously.

An interesting side product of the benzyl cyclisations is a tricycle formed through an intra-molecular Friedel-Crafts type alkylation (**126**). The Lewis acid in the reaction mixture facilitates this. The reaction is quite slow as this product was only isolated from reactions left for a prolonged time. Additionally **126** was formed as a by-product (~25 %) from the hydroxyl derivatisation used to enable crystallisation of the piperidines. (Scheme 49)



*Scheme 49: Rearrangement of piperidine **122c** to tricycle **126***

The tricycle is made from the major product of the cyclisation reactions, which was initially a little surprising as the benzyl and alkene groups are anti-periplanar to one another. This can be seen in the image below showing the X-ray diffraction data of the crystallised compound. (Figure 24)

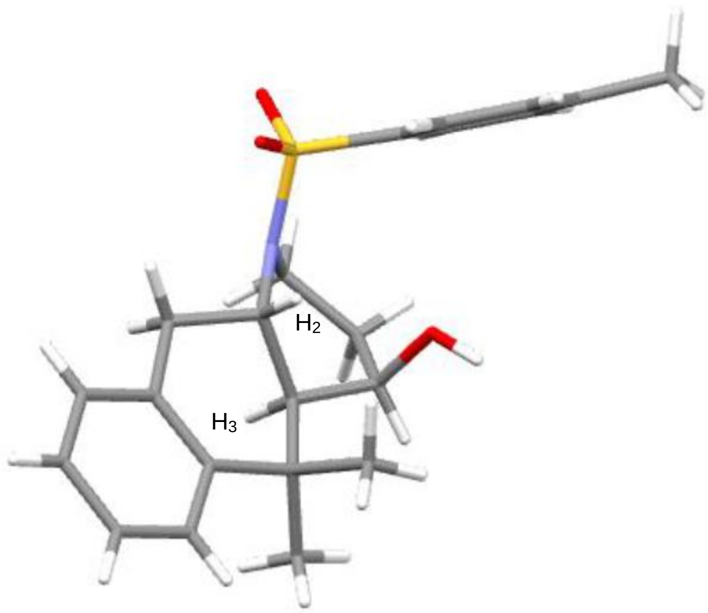


*Figure 24: Tricycle **126***

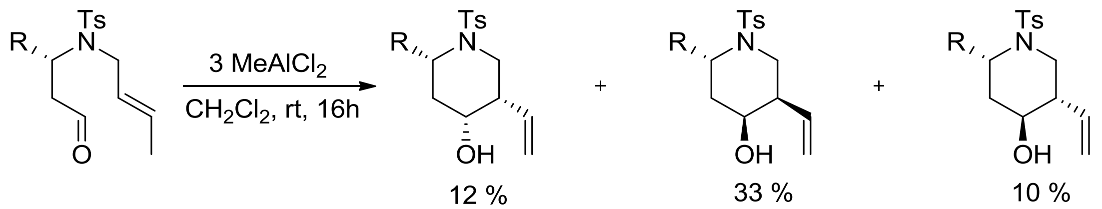
The centre of the image shows H_2 and H_3 on opposite faces of the piperidine ring

It is possible that a tricycle was also produced from the minor isomer **123c** but was in too small a quantity to extract from the product mixture.

3.4 Discussion of results

Initially, the axial conformation of the substituent on C_3 was unexpected, especially as the major product of all of the cyclisation reactions. This should be disfavoured due to 1,3-diaxial interactions across the ring. Evidence was found in the ^{1}H-NMR data. The coupling constants for H_3 showed no large (>9 Hz) *J* values which would indicate a dihedral angle approaching 180 ° between H_3 and either H_2 or H_4. We knew H_2 was lying in the equatorial position due to steric hindrance from the tosyl group as mentioned above. Using coupling constants in this way assumes the six-membered ring is in a chair conformation. These assumptions were confirmed, at least in the solid state, by the crystal X-ray diffraction data (Figures 19, 20 & 22).

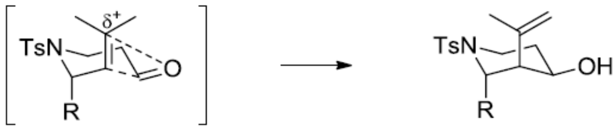
In previous work from the Snaith group,[48] this type of compound had been seen as a component of the reaction mixture. (Scheme 50)



Scheme 50: cyclisation data from related work in the Snaith group

The component in 33 % yield has the alkene substituent, in addition to the R group, in the axial position.

The formation of the major isomer in these reactions can be rationalised by looking at the transition state of the ring closing reaction. (Scheme 51)



Scheme 51: formation of the kinetic product

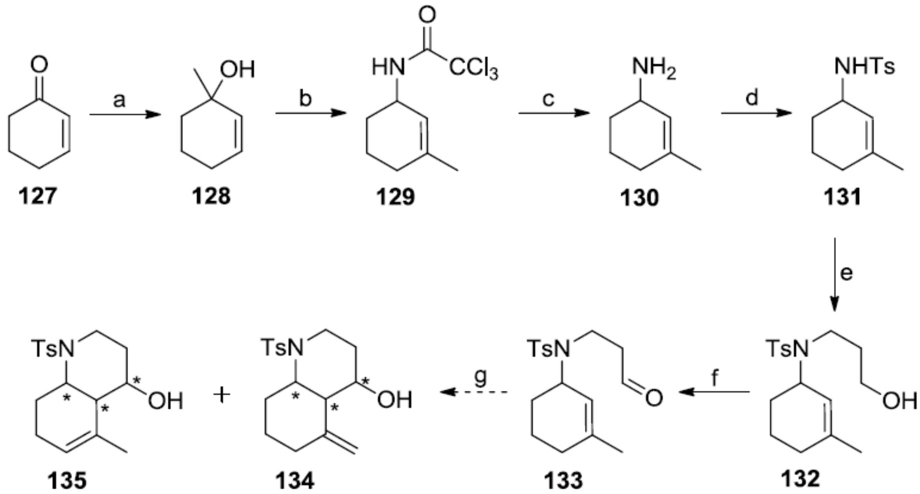
With the alkene substituent in the axial position, the partial cationic character is stabilised by the lone pair on the oxygen. This is not possible when the oxygen is axial so piperidine **122** is likely to be the kinetic product.

This same stabilisation could occur with the oxygen axial and the alkene equatorial, as has been seen in previous Snaith group work. Presumably the gauche interaction between the bulky alkene and the axial R group (and the OH), plus the 1,3-diaxial interaction between the OH and the R group, combine to disfavour this stereoisomer.

It is unclear from the cyclisation data whether piperidine **123** or **124** is the thermodynamic product. What the data do show is that, when more energy is put into the system or the reaction time is increased, **122** can transform into the other stereoisomers. This is because the reactions are in equilibrium until they are quenched, so the kinetic product can ring-open and reform in an energetically more favourable conformation.

3.5 Bicyclic piperidines

Detailed below (Scheme 52) is the synthesis towards a cyclisation precursor (**133**) that would ring-close to form two possible bicyclic piperidine regioisomers, each with stereocentres at positions 2, 3 and 4 (**134**, **135**).



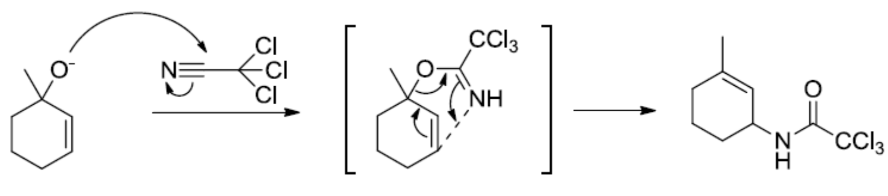
*Scheme 52: a) $CeCl_3.7H_2O$, THF, MeLi, 81 % **or** MeMgBr, THF, 76 %; b) KH, Et_2O, CCl_3CN, 45 %; c) EtOH, NaOH, H_2O, 33 %; d) TsCl, Et_3N, DMAP, DCM, 45 %; e)(i) Cs_2CO_3, $I(CH_2)_3OTBS$, DMF; (ii) HCl, 60 %; f) DMSO, $(COCl)_2$, Et_3N, DCM.*

3.5.1 Methylation of cyclohexenone

Cerium (III) was used to direct the 1,2- rather that 1,4-addition of methyl into cyclohexenone (**127**). The literature procedure for the dehydration of cerium chloride[92] was very time consuming and not all that effective. It involved heating the heptahydrate at > 150 °C for 24 hours under vacuum to draw off the water. Problems included a remainder of hydrated compound in the centre of the flask and also blockage of the vacuum tube due to sublimation of the dehydrated product. After multiple attempts, the procedure was much improved by flame drying of the compound under high vacuum for periods of a few minutes, followed by grinding by pestle and mortar and repeating 2-3 times. This method also controlled sublimation and gave a much more consistent, granular dehydrated cerium chloride.

Once this problem had been overcome, the methylation was fairly straightforward and the product (**128**) easily purified by column chromatography. An alternative methylation utilising Grignard chemistry was also investigated[93]. This was much simpler to prepare than the cerium chloride method and gave a crude product that was exceptionally clean by NMR analysis and that had been methylated at the correct position. Unexpectedly, when using compound **128** made by Grignard addition, no reaction occurred in the subsequent nucleophilic addition and rearrangement reactions. The reason for this is unclear and with limited time to investigate, the cerium chloride method was returned to, to bring material through.

3.5.2 Forward synthesis to cyclisation precursor



128 **129**

Scheme 53

Scheme 53 shows the mechanisms involved in the conversion of alcohol **128** into amide **129**. This reaction leaves a six-membered ring with the double bond the correct distance from the nitrogen to be used in carbonyl-ene cyclisations, just as with the linear cyclisation precursors.

After hydrolysis of amide **129** to amine **130**, tosylation (**131**) and alkylation (**132**) followed as had been used previously. Once again, alkylation with *tert*-butyl(3-iodopropoxy) dimethylsilane followed by a mild acidic work up, lead to the desilylated product being recovered, therefore eliminating the need for a separate desilylation step.

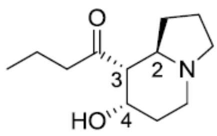
3.5.3 Oxidation

A Swern oxidation of alcohol **132** gave aldehyde **133** as seen by ^{1}H-NMR analysis of the crude product. Upon purification by column chromatography, the aldehyde underwent spontaneous cyclisation on the silica surface to give piperidine **134**.

Further investigation of this reaction is required along with controlled cyclisations to determine the stereochemical and regiochemical outcomes of the ring closure.

4 NATURAL PRODUCT SYNTHESIS

The natural product elaeokanine C (**136**, Figure 25) is one of a family of alkaloids isolated from sub-tropical trees and shrubs of the genus *Elaeocarpus*. It comprises an indolizidine with substitution at positions 2, 3 and 4 of the piperidine moiety, which is in keeping with the other work in this thesis.



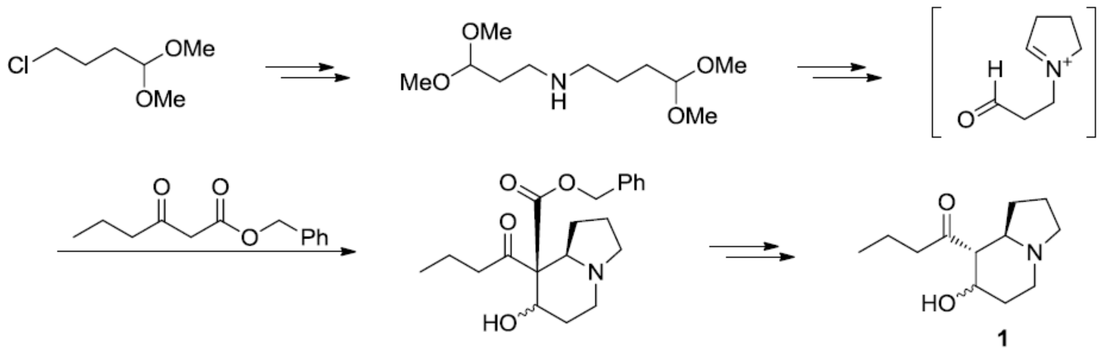
136

Figure 25: (-)-elaeokanine C

4.1 Previous syntheses of Elaeokanine C

Several of the *Elaeocarpus* alkaloids were isolated by Johns and co-workers in the early seventies.[94,95] At this time there was insufficient spectroscopic evidence to assign absolute stereochemistry so only relative stereochemistries were reported.

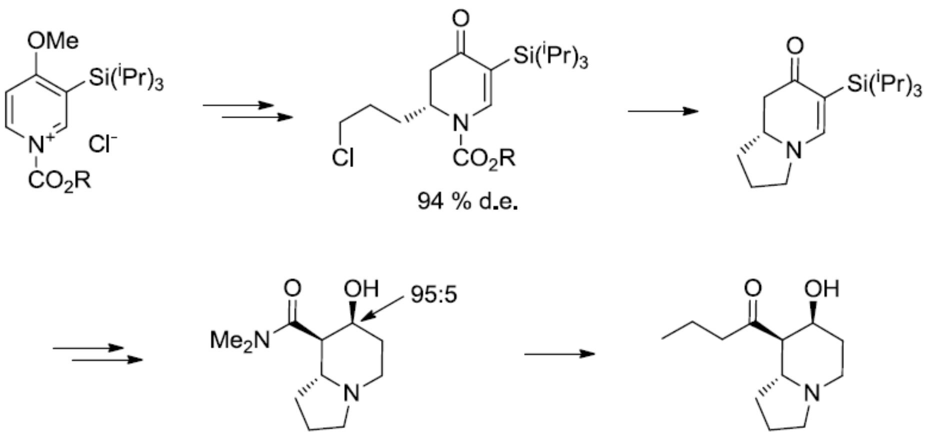
Scheme 54 shows the major intermediates in a synthesis of Elaeokanine C by Gribble et al.[96]



Scheme 54: Synthesis of (±) Elaeokanine C by Gribble et al. 1988

A key step in this synthesis was the tandem Mannich-aldol condensation between the shown pyrollium and benzyl 3-oxohexanoate. This successfully achieved the correct relative stereochemistry at positions 2 and 3 but there was poor selection at position 4. Only 25 % of the recovered product was the naturally occurring isomer shown in Figure 25.

A fully stereocontrolled synthesis was published in 1991 by Comins and Hong.[97] They used a chiral auxiliary to direct cyclisation and maintain stereocontrol. (Scheme 55)



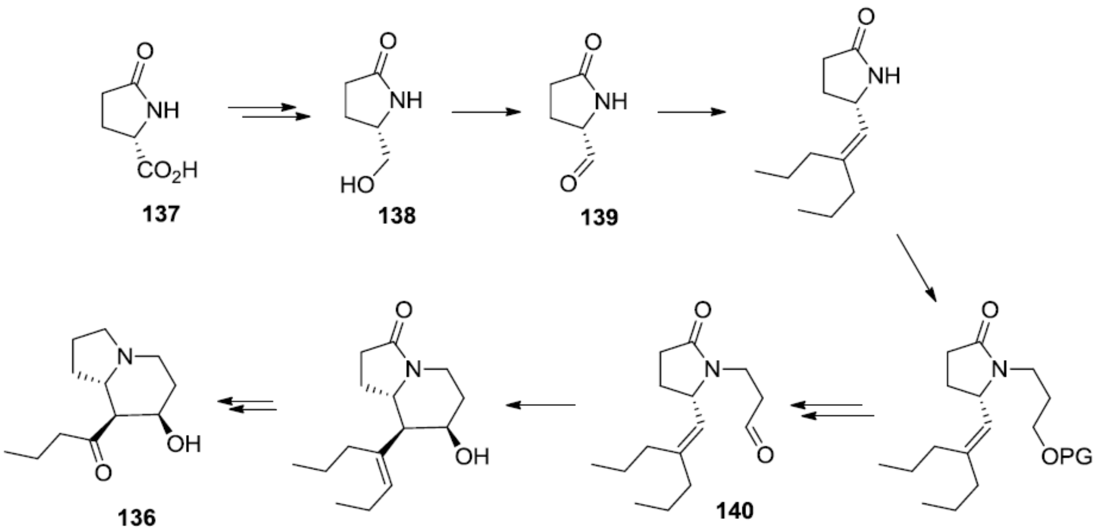
Scheme 55: synthesis of elaeokanine C by Comins and Hong, 1991.

R = (-)-8-(4-phenoxyphenyl)methyl

The end product was the unnatural enantiomer (+)-elaeokanine C which was isolated with over 95 % optical purity.

4.2 Synthesis using carbonyl-ene cyclisation

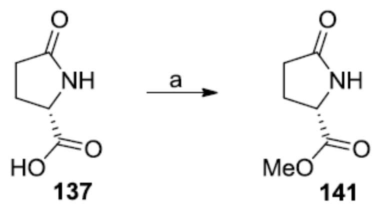
A proposed synthesis of elaeokanine C (**136**) from readily available pyroglutamate (**137**) is laid out in Scheme 56. This shows the synthesis of the unnatural enantiomer as the starting material, (*S*)-pyroglutamate, is much cheaper than the alternative enantiomer.



Scheme 56: Initial synthesis plan of elaeokanine C from pyroglutamate

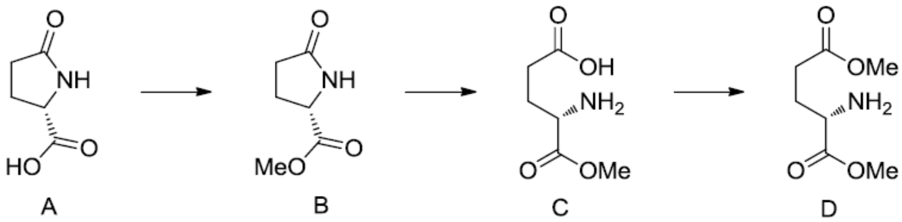
4.2.1 Methylation of pyroglutamate

The first step of the synthesis was methylation of pyroglutamate following the method used by Aggarwal et al.[98] (Scheme 57)



Scheme 57: a) $SOCl_2$, MeOH, 0 °C, 2 hr

Following the literature procedure led to an incomplete reaction, so the reaction time was extended. This produced the unexpected result of ring-opening, firstly to methyl glutamate and eventually to dimethyl glutamate (scheme 58). This was verified by making an authentic sample from glutamic acid.



Scheme 58: Products from extended methylation reaction time

A time-trial study was conducted to find the optimum reaction time. The results are shown in Table 6.

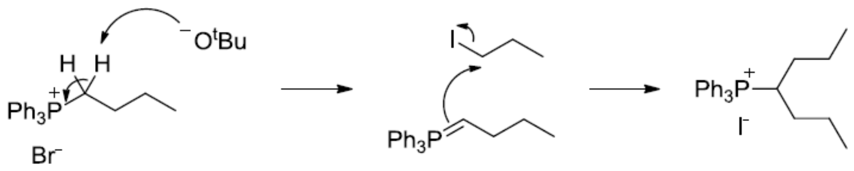
Time	relative product ratio	^{1}H-NMR evidence
30 min	A>B	comparison of acid signals
60 min	A=B	acid peak smaller
90 min	A<B	-"-
2 hr	A<<B>>C	trace acid A, 2nd acid signal (trace)
3 ½ hr	B>C	disappearance of acid A, comparison of methyl signals
5 ¼ hr	C>D	2nd Me signal
24 hr	D only	no remaining acid peaks

Table 6: methylation time-trial results

The optimum time was found to be two hours. Some of the material is still non-methylated and a small portion has also ring-opened but the overwhelming majority is the desired methylpyroglutamate (**141**).

4.2.2 Continuation of synthesis

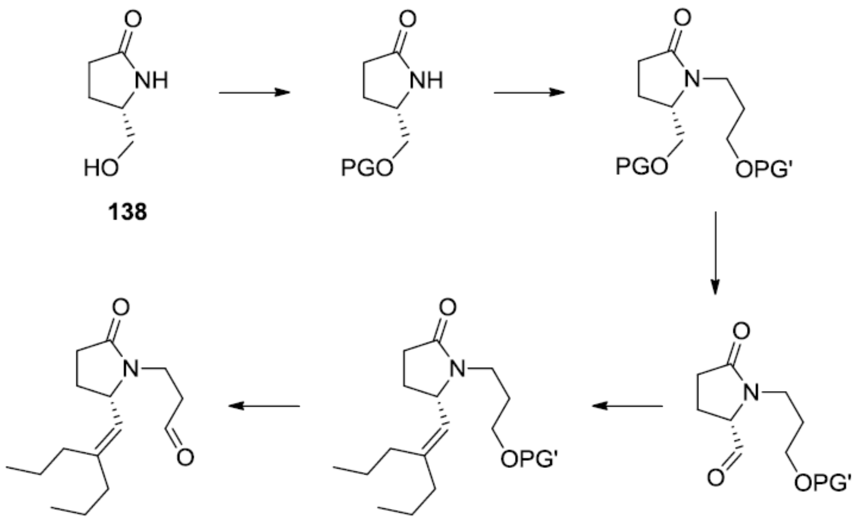
After optimisation of the methylation of pyroglutamate, the product was reduced to alcohol **138** in good yield (83 %).[99,100] It was not possible from this point to oxidise this alcohol to the corresponding aldehyde (**139**) in preparation for a Wittig olefination to install what would become the side chain at position 3 of the closed piperidine. Synthesis of the aldehyde was also attempted as a partial reduction from **141** using DIBAL[101,44] but this was similarly unsuccessful. In preparation for the Wittig olefination reaction the appropriate ylide was constructed as shown in Scheme 59.



Scheme 59: Preparation of ylide

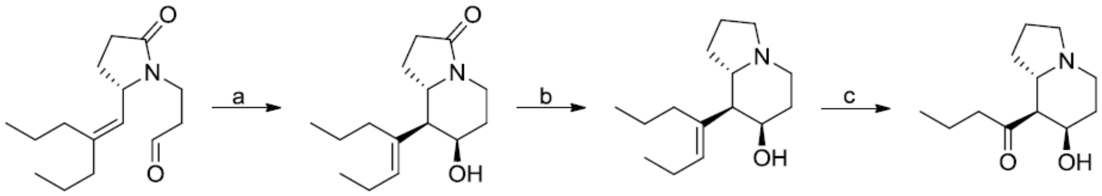
As installation of this ylide was not possible via the proposed route, due to the required aldehyde being unobtainable at this point, a second synthetic route was devised (Scheme 60) which involved a change in order of work on the alcohol and amide.

4.2.3 Alternative route



Scheme 60

Starting from alcohol **138**, a protecting group would be added to enable installation of the *N*-alkyl group, before returning to the original plan of alcohol oxidation followed by Wittig olefination. This would use the same ylide as previously constructed and result in the same cyclisation precursor (**140**). From this point the original route is resumed and completed to give the natural product (**136**) (scheme 61).



140 **136**

Scheme 61: a) HCl; b) $LiAlH_4$; c) O_3

From the previous work done by the Snaith group,[33,34] it is thought that the correct stereochemical outcome of the cyclisation reaction could be achieved under kinetic conditions i.e. Brønsted acid at low temperature.

4.2.4 Synthetic problems encountered

Various silicon based groups (TMS, TBS, TBDPS) were used to protect the alcohol[102] whilst work was focussed on alkylation of the amide. Multiple alkylation methods based on literature precedent[103,104,105,106,107,108] were followed with very little success. These all involve use of a halogenated alkylating agent with various bases and solvents used. Alkylation was also attempted, unsuccessfully, with the free alcohol (**138**) and the methyl ester (**137**).

The targets of these alkylations are shown in figure 25.

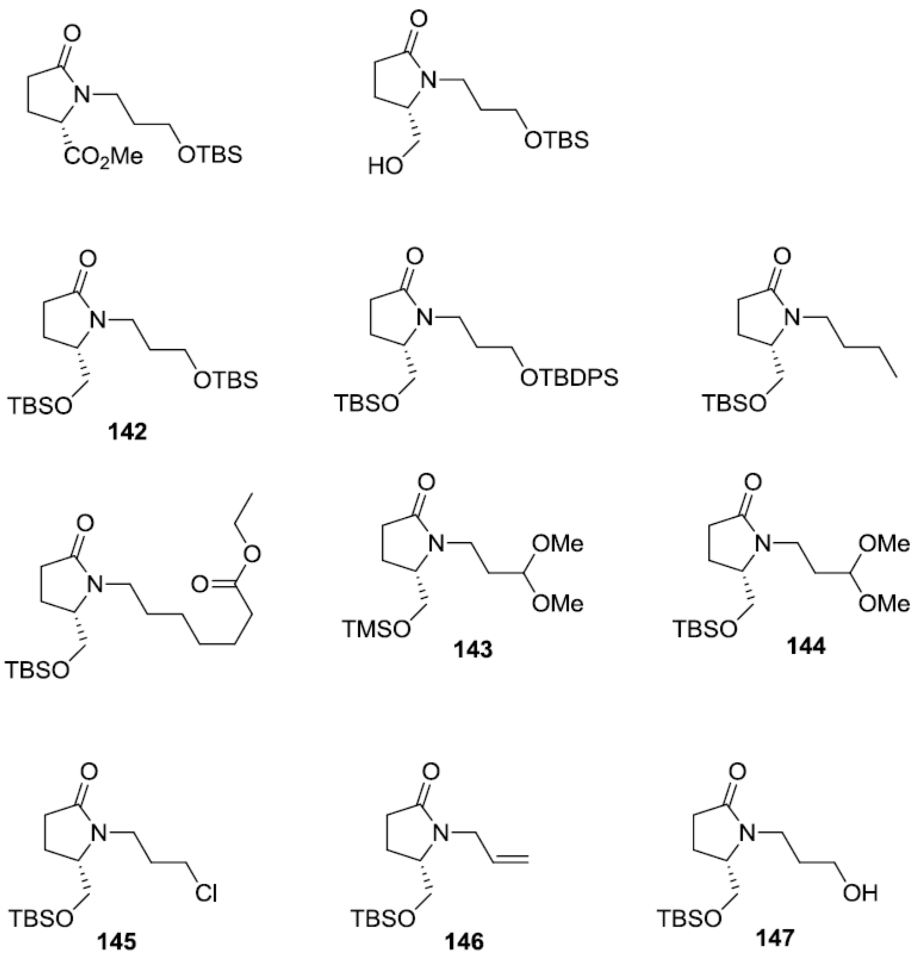


Figure 26: Alkylation targets sought

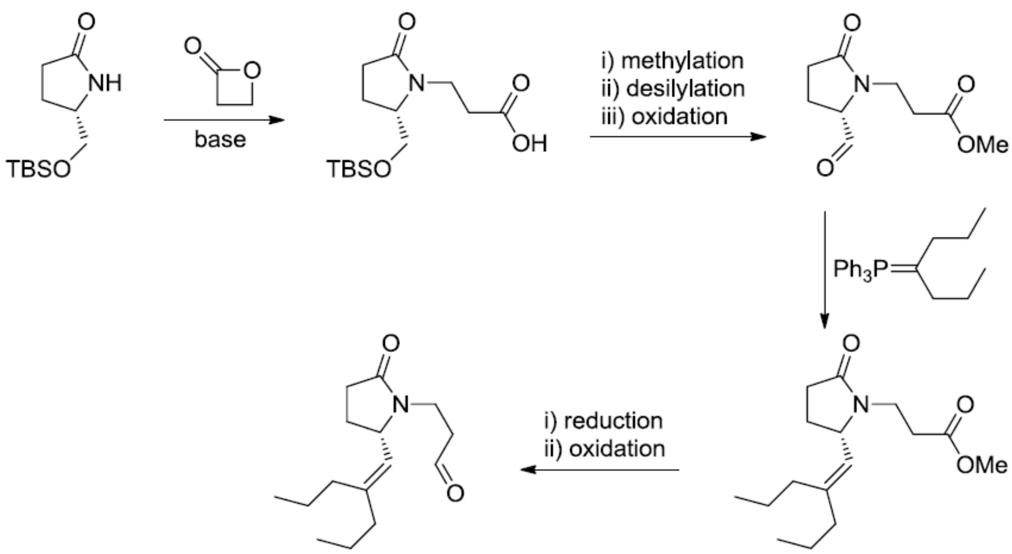
Of those shown in Figure 26, some targets were achieved. Compound **142** was made as a proof of technique with an alkyl halide that was available at the time. Unfortunately this compound could not be used further as both protecting groups were the same and therefore indistinguishable in future reactions. When the same method was employed with a different protecting group (TBDPS) there was again no reaction. The following two compounds (n-butyl and ethyl heptanoate) were again method tests taken from the literature, but were not made in good enough yield to continue.

Acetals **143** and **144** were isolated in 71 % and 69 % yield respectively but the alcohol deprotections lead to decomposition.

Compound **145** was made using 1-bromo-3-chloropropane with microwave radiation. Terminal alkene **146** was the major product of this reaction and was in fact a more useful compound for further reaction. The alkene was subsequently synthesised using allyl bromide under the microwave conditions in 91 % yield. A hydroboration of alkene **146** to alcohol **147** led to many compounds that were inseparable by TLC so once again this branch of the synthesis was dropped.

4.2.5 Future work

As the microwave reactions had shown good successes this seems like a good alkylation method to pursue. A possible forward synthesis is shown in Scheme 62 using β-propiolactone as the alkylating agent.



Scheme 62: Proposed synthesis of cyclisation precursor

5 EXPERIMENTAL

Instruments

Analytical thin layer chromatography (TLC) was performed on Merck 60G UV254 pre coated glass-backed plates and visualised by UV (254 nm) or a variety of commonly used TLC dips. Infra red spectra were recorded as thin films (neat) on a Perkin Elmer 100 FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded in the solvent stated at 300 and 400 MHz (^{1}H-NMR) and 75 and 100 MHz (^{13}C-NMR), respectively, using Bruker AV 300, Bruker AVIII 300 and Bruker AVIII 400 spectrometers. Chemical shifts are reported as δ values (ppm) referenced to tetramethylsilane. 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 resonances arising from a single nucleus (or equivalent nuclei) are coincident, but coupling constants cannot be readily assigned. ^{1}H-NMR multiplets are assigned as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, etc. Coupling constants are quoted to the nearest 0.5 Hz. Apparent doublets seen in aromatic protons are noted app d. In the case of unseparated isomers the ppm quoted is the major component with the minor component given in square brackets. ^{13}C-NMR notations used are Ar = aromatic, Q = quaternary. Mass spectra were recorded on a Micromass ZABspec spectrometer utilizing electrospray ionisation in most cases and reported as *m/z*. HRMS were recorded on a Micromass LCT spectrometer using a lock incorporated in the mobile phase.

Chemicals and Reagents

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. Toluene was distilled from sodium and used immediately. Alternatively, dry solvents were drawn from a PureSolv EN solvent purification system. Other chemicals were used as purchased, unless otherwise stated. Aqueous solutions are saturated unless otherwise stated. Flash column chromatography was carried out using Merck 60 (40 - 60 µm mesh) silica gel.

Evaporation and concentration under reduced pressure was carried out at (50 - 500 mBar). Residual solvent was removed under high vacuum (1 mBar).

Reactions

All reactions were carried out under an Argon atmosphere in flame-dried or oven-dried glassware where necessary. Molecular sieves (3 and 4 Å) were activated by flame-heating under high vacuum for 15 min and used immediately.

Unless otherwise stated all reactions were followed by aqueous workup, extracted into an organic solvent (stated), dried with magnesium sulfate and concentrated under reduced pressure.

General procedures

Solvent molarities are given with respect to the reactant used in 1 eq unless otherwise stated.

Procedure A – methylation of amino acids

Amino acid (1 eq) was dissolved in methanol (1 M) at 0 °C then thionyl chloride (1 eq) was added dropwise. The solution was stirred at 0 °C for 60 minutes then continued at room temperature for 72 hours. The reaction mixture was concentrated under reduced pressure to yield the target compound.

Procedure B – Tosylation

Amine (1 eq) was suspended in CH_2Cl_2 (0.6 M) at 0 °C and triethylamine (2 eq) was added dropwise. After stirring at 0 °C for 15 minutes *p*-toluene sulfonyl chloride (1 eq) [and DMAP (10 mol%) in some cases] in minimal CH_2Cl_2 was slowly added. The reaction mixture was stirred for the prescribed time, warming to room temperature. The mixture was concentrated under reduced pressure and the resulting residue taken up into ethyl acetate, precipitating a white solid which was removed by filtration under suction. The filtrate was washed with $NaHCO_3$ and water. The aqueous layers were further extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$, filtered and concentrated.

Procedure C – PCC oxidation

To a stirred suspension of PCC (3 eq) in DCM (0.04 M) at room temperature was added alcohol (1 eq) in DCM (0.2 M) over 10 minutes. After stirring for the specified time, ether was added and stirring continued for a further 15 minutes. The solvents were carefully decanted then additional ether added to the residue to repeat the process twice more. The combined ether extracts were washed with brine then dried and filtered through a plug of silica before removing solvents.

Procedure D – Wittig olefination 1

To a solution of ylide precursor (2 eq) in THF (0.25 M) at 0 °C, was added potassium *tert*-butoxide (2 eq). The mixture stirred for 30 minutes then aldehyde (1 eq) in chilled (0 °C) THF (0.65 M) was added to the ylide over 15 minutes inducing loss of the bright colour. After 15 minutes at 0 °C the temperature was slowly raised to 50 °C for a further 20 hours. The mixture was cooled to ambient temperature before water and 1 M aq. HCl were added to dissolve the precipitate. The product was extracted twice with ethyl acetate, washed with brine then purified by column chromatography.

Procedure E – *N*-alkylation

Amine (1 eq) was dissolved in DMF (0.1 M) before cesium carbonate (1.5 eq) and halogenated alkyl group (1.5 eq) were added. The mixture was stirred at room temperature overnight before diluting with water and 1 M HCl. After 1 hour the products were extracted into ether and purified by column chromatography.

Procedure F – Swern oxidation

Oxalyl chloride (1.1 eq) in DCM (0.4 M) was cooled to -78 °C. DMSO (2.4 eq) in DCM (2 M) was added dropwise and stirred for 10 minutes. A solution of alcohol (1 eq) in DCM (1 M) was added dropwise and the reaction stirred for a further 15 minutes. Triethylamine (5 eq) was added dropwise and after 15 minutes the mixture was allowed to warm to room temperature before quenching with water and extracting into DCM.

Procedure G – Reductive amination

Amine (1 eq) was dissolved in DCM (1.0 M) and sodium sulfate (1.02 eq) was added. Aldehyde (1 eq) in DCM (1.75 M) was added slowly and the mixture stirred at room temperature overnight. Sodium borohydride (1.5 eq) was added, immediately followed by anhydrous methanol (1.0 M). After 60 minutes the reaction was quenched with saturated $NaHCO_3$ and the products extracted into DCM and washed with brine.

Procedure H – Wittig Olefination 2

To a solution of ylide precursor (3 eq) in THF (0.05 M) at 0 °C, was added a solution of n-butyllithium [1.6 M/hex] (3 eq) dropwise. The mixture stirred for 15 minutes before cooling to -78 °C then aldehyde (1 eq) in chilled (0 °C) THF (0.1 M) was added to the ylide dropwise inducing loss of the bright colour. After 15 minutes at -78 °C the temperature was slowly raised to room temperature and the mixture stirred until no more aldehyde was visible by TLC. Water was added and the product was extracted with ethyl acetate, washed with brine then purified by column chromatography.

Procedure I – Addition of Grignard reagent

A solution of imine (1 eq) in DCM (0.25 M) was cooled to -50 °C. A solution of Grignard reagent (3 eq) was added dropwise. The mixture was allowed to warm to room temperature overnight (The cooling Dewar was left in position but no further dry ice was added). The reaction was quenched with saturated aq. ammonium chloride and products extracted into ethyl acetate.

Procedure J – Brønsted acid mediated cyclisation.

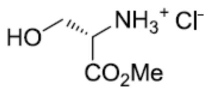
To a solution of linear precursor (1 eq) in DCM (0.033 M) at -78 °C was added concentrated HCl [~37 %] (3 eq). After 24 - 48 hours the reaction was quenched with water and the products extracted into DCM.

Procedure K – Lewis acid mediated cyclisation

Linear precursor (1 eq) was dissolved in DCM (0.05M) and cooled to the appropriate temperature before a solution of $MeAlCl_2$ [1M] (2 eq) was added dropwise. After the prescribed time the reaction was quenched with water and the products extracted into DCM.

57

(*S*)-3-Hydroxy-1-methoxy-1-oxopropan-2-ammonium chloride[40]



Chemical Formula: $C_4H_{10}ClNO_3$
Exact Mass: 155.03
Molecular Weight: 155.58

General procedure **A** was followed using the following amounts:

Methanol (1 M, 300 mL)

Thionyl chloride (1 eq, 285.71 mmol, 20.75 mL)

L-serine (1 eq, 285.71 mmol, 30.00 g)

Yield: 4.28 g (>99 %) white solid

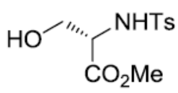
mp 164-165 °C [lit. 161-162 °C]; R_f 0.36 (50 % MeOH in EtOAc); IR υ (cm^{-1}) 3344 (OH), 2918 (NH_3^+), 1745 (CO_2Me); ^{1}H-NMR (300 MHz, D_2O) δ 4.25 (dd, 1H, *J* = 3.5, 4.0 Hz (C*H*)), 4.07 (dd, 1H, *J* = 4.0, 12.5 Hz (CH*H*)), 3.96 (dd, 1H, *J* = 3.5, 12.5 Hz (CH*H*)), 3.82 (s, 3H (OC*H₃*)); ^{13}C-NMR (75 MHz, D_20) δ 167.5 (*C*=O), 57.91 (*C*H_2), 53.38 (N*C*H), 52.39 (O*C*H_3); m/z (ES) $[M+H]^+$ 120.1; $C_4H_{10}NO_3$ requires 120.0661, found 120.0660

Racemate:

mp 135-138 °C; IR υ (cm^{-1}) 3394 (OH), 2907 (NH_3^+), 1739 (CO_2Me); ^{1}H-NMR (300 MHz, D_2O) δ 4.26 (dd, 1H, *J* = 3.5, 4.0 Hz (C*H*)), 4.09 (dd, 1H, *J* = 4.0, 12.5 Hz (CH*H*)), 4.00 (dd, 1H, *J* = 3.5, 12.5 Hz (CH*H*)), 3.84 (s, 3H (OCH_3)); ^{13}C-NMR (75 MHz, D_2O) δ 168.9 (*C*=O), 59.2 (*C*H_2), 54.7 (N*C*H), 53.7 (O*C*H_3); m/z (EI) $[M+H]^+$ 120

58

(*S*)-Methyl-3-hydroxy-2-(4-methylphenylsulfonamido)propanoate[41]



Chemical Formula: $C_{11}H_{15}NO_5S$
Exact Mass: 273.07
Molecular Weight: 273.31

General procedure **B** was followed with the following amounts used:

Methyl serinate hydrochloride (**51**) (1 eq, 121.74 mmol, 18.94 g)

DCM (0.6 M, 400 mL)

Triethylamine (2 eq, 243.48 mmol, 33.94 mL)

p-Toluene sulfonyl chloride (1 eq, 121.74 mmol, 23.21 g)

Time: 48 hours

Crude product was recrystallized from EtOAc/hexanes yielding a white solid (28.63 g, 86 %)

mp 87-88 °C [lit. 92-93 °C]; R_f 0.68 (25 % Hexane in EtOAc); IR υ(cm^{-1}) 3480 (OH), 3269 (NH), 1743 (CO_2Me), 1434 (Ar), 1327/1161 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (app d, 2H (Ar*H*)), 7.32 (app d, 2H (Ar*H*)), 5.49 (d, 1H, *J* = 7.5 Hz (N*H*)), 3.99-3.94 (m, 1H (C*H*)), 3.89 (dd, 2H, *J* = 3.5, 6.5 Hz (CH_2)), 3.63 (s, 3H (OCH_3)), 2.43 (s, 3H, (ArCH_3)), 1.56 (t, 1H, *J* = 6.5 Hz (O*H*)); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.2 (*C*=O), 143.9 (*Ar*SO_2), 136.1 (*Ar*CH_3), 129.8 (ArH*C*SO_2), 127.2 (ArH*C*CH_3), 63.7 (*C*H_2), 57.6 (N*C*H), 52.9 (O*C*H_3), 21.5 (Ar*C*H_3); m/z (ES) $[M+Na]^+$ 296.1; $C_{11}H_{15}NO_5SNa$ requires 296.0569, found 296.0568

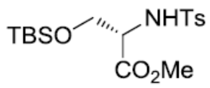
Racemate:

mp 81-83 °C; IR υ(cm^{-1}) 3487 (OH), 3272 (NH), 1745 (CO_2Me), 1427 (Ar), 1326/1159 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (app d, 2H (Ar*H*SO_2)), 7.31 (app d, 2H (Ar*H*CH_3)) 5.54 (d, 1H,

J = 7.5 Hz (N*H*)), 3.97 (dt, 1H, J = 6.5, 7.5 Hz (C*H*)), 3.89 (dd, 2H, J = 3.5, 6.5 Hz (CH_2)), 3.63 (s, 3H (OCH_3)), 2.43 (s, 3H (ArCH_3)), 2.16 (t, 1H, J = 6.5 Hz (O*H*)); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.2 (*C*=O), 143.9 (*Ar*SO_2), 136.4 (*Ar*CH_3), 129.8 (ArH*C*SO_2), 127.2 (ArH*C*CH_3), 63.7 (*C*H_2), 57.6 (N*C*H), 53.0 (O*C*H_3), 21.6 (Ar*C*H_3); m/z (ES) $[M+Na]^+$ 296.0; $C_{11}H_{15}NO_5SNa$ requires 296.0569, found 296.0561

59

(*S*)-Methyl-3-(*tert*-butyldimethylsilyloxy)-2-(4-methylphenylsulfonamido)propanoate[44]



Chemical Formula: $C_{17}H_{29}NO_5SSi$
Exact Mass: 387.15
Molecular Weight: 387.57

(*N*-Tosyl)-methyl serinate (**58**) (1 eq, 3.66 mmol, 1.00 g) was dissolved in DCM (10 mL) at 0 °C. Imidazole (2 eq, 7.32 mmol, 498 mg), TBSCl (1.25 eq, 4.57 mmol, 697 mg) and DMF (2 mL) were added successively. The reaction mixture was stirred continuously, whilst warming to room temperature, for 72 hours. The reaction was quenched with saturated NH_4Cl (aq.) (15 mL) at 0 °C, diluted with water (100 mL) and the product extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give a colourless oil, which solidified on standing. This was recrystallised from EtOAc/Hex, concentrated to a yellow oil, then separated by flash chromatography eluting with 25 % EtOAc in hexane. The product was concentrated to give a white solid (0.71 g, 51 %).

One-pot synthesis from methyl serinate hydrochloride:

To a stirred suspension of methyl serinate hydrochloride (**57**) (1 eq, 6.43 mmol, 1 g) and *p*-toluene sulfonyl chloride (1 eq, 6.43 mmol, 1.23 g) in a mixed solvent of chloroform and dichloromethane (1:1, 6 mL total) at 0 °C, was added triethylamine (2 eq, 12.86 mmol, 1.79 mL). The mixture was stirred at room temperature for 60 hours. Imidazole (2 eq, 12.86 mmol, 0.88 g), TBDMSCl (1 eq, 6.43 mmol, 0.97 g) and DMF (0.6 mL) were added successively at 0 °C and the reaction mixture stirred at room temperature for 48 hours.

Saturated ammonium chloride solution (3 mL) was added dropwise with vigorous stirring at -5 °C. The product was extracted with hexane and washed with 5 % citric acid (2 x 15 mL), water (2 x 15 mL), saturated $NaHCO_3$ (10 mL) and water (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a pale yellow oil. Flash chromatography over silica with hexane and ethyl acetate (4:1) gave a translucent white solid (0.64 g, 26 %).

mp 45 - 47 °C [lit. 56-57 °C]; R_f 0.71 (40 % EtOAc in hexane); IR υ (cm^{-1}) 3270 (NH), 1743 (CO_2Me), 1434 (Ar), 1327/1162 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (app d, 2H (Ar*H*)), 7.29 (app d, 2H (Ar*H*)), 5.36 (d, 1H, *J* = 9.0 Hz (N*H*)), 4.52-4.00 (m, 1H (C*H*)), 3.95 (dd, 1H, *J* = 3.0, 10.0 Hz (CH*H*)), 3.76 (dd, 1H, *J* = 3.5, 10.0 Hz (CH*H*)), 3.54 (s, 3H (OCH_3)), 2.42 (s, 3H (ArCH_3)), 0.82 (s, 9H (Si^t*Bu*)), 0.00 (s, 3H (Si*Me*)), -0.02 (s, 3H (Si*Me*)); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.5 (*C*=O), 144.7 (*Ar*SO_2), 139.0 (*Ar*CH_3), 130.7 (ArHCSO_2), 128.2 (ArHCCH_3), 65.6 (*C*H_2), 58.6 (N*C*H), 53.5 (O*C*H_3), 26.7 (SiCCH_3), 22.6 (Ar*C*H_3), 19.7 (Si*C*CH_3), -3.7 (Si*C*H_3); m/z (ES) $[M+Na]^+$ 410.1; $C_{17}H_{29}NO_5SSiNa$ requires 410.1433, found 410.1431

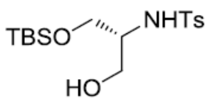
Racemate:

mp 80-82 °C; R_f 0.68 (33 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62 (app d, 2H (Ar*H*SO_2)), 7.18 (app d, 2H (Ar*H*CH_3)), 5.24 (d, 1H, *J* = 9.0 Hz (N*H*)), 3.92 (ddd, 1H, *J* = 3.0, 3.5, 9.0 Hz (C*H*)), 3.84 (dd, 1H, *J* = 3.0, 10.0 Hz (CH*H*)), 3.65 (dd, 1H, *J* = 3.5, 10.0 Hz (CH*H*)), 3.44 (s, 3H (OCH_3)), 2.31 (s, 3H (ArCH_3)), 0.71 (s, 9H (Si^t*Bu*)), -0.11 (s, 3H (Si*Me*)), -0.13 (s, 3H (Si*Me*));

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.0 (*C*=O), 143.5 (*Ar*SO_2), 137.2 (*Ar*CH_3), 129.6 (ArH*C*SO_2), 127.1 (ArH*C*CH_3), 64.5 (*C*H_2), 57.6 (N*C*H), 52.4 (O*C*H_3), 25.6 (Si*C*CH_3), 21.5 (Ar*C*H_3), 18.1 (Si*C*CH_3), -5.6 (Si*C*H_3); m/z (ES) $[M+Na]^+$ 410.1; $C_{17}H_{29}NO_5SSiNa$ requires 410.1433, found 410.1440

60

N-Tosyl-(*R*)-2-amino-3-(*tert*-butyldimethylsilyloxy)propan-1-ol[44]



Chemical Formula: $C_{16}H_{29}NO_4SSi$
Exact Mass: 359.16
Molecular Weight: 359.56

To [*N,O*]-protected methyl serinate (**59**) (1 eq, 100.96 mmol, 39.13 g) in THF (300 mL) at 0 °C, was added portionwise lithium borohydride (1.25 eq, 126.20 mmol, 2.75 g). The solution was allowed to warm to room temperature then stirred for an additional 48 hours at a slightly elevated temperature (40 - 50 °C) until no more starting material was seen by TLC.

The reaction mixture was cooled to 0 °C then quenched with slow addition of sat. NH_4Cl (aq). The mixture was diluted with water (200 mL) then extracted with ethyl acetate (250 mL) and washed with brine (200 mL). The combined aqueous layers were further extracted with EtOAc (3 x 100 mL) then the organic layers were dried over $MgSO_4$, filtered and concentrated to yield 35.16 g (97 %) as a dark brown oil. An analytical sample was purified by column chromatography, eluting with 25 % EtOAc in hexane to give a colourless oil.

R_f 0.40 (50 % EtOAc in hexane); IR υ(cm^{-1}) 3518 (OH), 3286 (NH), 2929/2857 (CH, CH_2), 1329/1158 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (app d, 2H (Ar*H*SO_2)), 7.30 (app d, 2H (Ar*H*CH_3)), 5.19 (d, 1H, *J* = 7.5 Hz (N*H*)), 3.63 (dd, 2H, *J* = 4.0, 10.5 Hz (C*H₂*OH)), 3.52 (dd, 2H, *J*

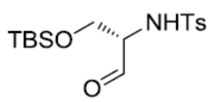
= 5.0, 10.0 Hz (CH_2OSi)), 3.30-3.24 (m, 1H (C*H*)), 2.42 (s, 3H (ArCH_3)), 1.71 (brs, 1H (O*H*)), 0.83 (s, 9H (^{t}*Bu*Si)), -0.00 (s, 3H (*Me*Si)), -0.02 (s, 3H (*Me*Si)) [literature agreement]; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.6 (*Ar*SO_2), 137.5 (*Ar*CH_3), 129.8 (ArH*C*SO_2), 127.1 (ArH*C*CH_3), 63.5 (*C*H_2OSi), 63.0 (*C*H_2OH), 55.5 (N*C*H), 25.8 (Ar*C*H_3), 21.5 (Si*C*CH_3), 18.1 (Si*C*CH_3), -5.6 (Si*C*H_3); m/z (ES) $[M+Na]^+$ 382.2; $C_{16}H_{29}NO_4SSiNa$ requires 382.1484, found 382.1480

Racemate:

mp 58-61 °C; R_f 0.55 (33 % EtOAc in hexane); IR υ(cm^{-1}) 3479 (OH), 3211 (NH), 2930-2850 (CH_2CHCH_2), 1304/1157 (SO_2N), 1244 (OH), 1105 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (app d, 2H (Ar*H*SO_2)), 7.29 (app d, 2H (Ar*H*CH_3)), 5.17 (d, 1H, *J* = 7.5 Hz (N*H*)), 3.63 (dd, 2H, *J* = 4.0, 10.0 Hz (CH_2OH)), 3.52 (dd, 2H, *J* = 5.0, 10.0 Hz (CH_2OSi)), 3.31-3.22 (m, 1H (C*H*)), 2.41 (s, 3H (ArCH_3)), 1.71 (brs, 1H (O*H*)), 0.83 (s, 9H (Si^t*Bu*)), -0.00 (s, 3H (Si*Me*)), -0.01 (s, 3H (Si*Me*)); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.5 (*Ar*SO_2), 137.5 (*Ar*CH_3), 129.7 (ArH*C*SO_2), 127.0 (ArH*C*CH_3), 63.3 (*C*H_2OSi), 62.8 (*C*H_2OH), 55.5 (N*C*H), 25.7 (Si*C*CH_3), 21.5 (Ar*C*H_3), 18.1 (Si*C*CH_3), -5.6 (Si*C*H_3); m/z (ES) $[M+Na]^+$ 382.2; $C_{16}H_{29}NO_4SSiNa$ requires 382.1484, found 382.1487

61

N-Tosyl-(*S*)-2-amino-3-(*tert*-butyldimethylsilyloxy)propanal



Chemical Formula: $C_{16}H_{27}NO_4SSi$
Exact Mass: 357.14
Molecular Weight: 357.54

General procedure **C** was followed using the following quantities:

PCC (3 eq, 16.69 mmol, 3.60 g) in DCM (125 mL)

Protected serinol (1 eq, 5.56 mmol, 2 g) in DCM (25 mL)

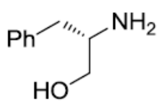
Time: 4 ½ hours

Yield: brown oil (1.68 g, 84.5 %)

R_f 0.65 (40 % EtOAc in hexane); IR υ(cm^{-1}) 3280 (br) (NH), 2929 (C=O), 1333/1159 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H, (C*H*O)), 7.74 (app d, 2H (Ar*H*SO_2)), 7.30 (app d, 2H (Ar*H*CH_3)), 5.47 (d, 1H, *J* = 6.5 Hz (N*H*)), 4.09 (dd, 1H, *J* = 3.5, 10.5 Hz (CH*H*OSi), 3.86-3.80 (m, 1H (C*H*)), 3.71 (dd, 1H, *J* = 5.0, 10.5 Hz (CH*H*OSi)), 2.42 (s, 3H (ArC*H_3*)), 0.82 (s, 9H (^{t}*Bu*Si)), 0.014 (s, 3H (*Me*Si)), 0.007 (s, 3H (*Me*Si)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.3 (*C*HO), 134.5 (*Ar*), 129.8 (*Ar*), 129.7 (*Ar*), 129.3 (*Ar*), 128.9 (*Ar*), 128.7 (*Ar*), 127.4 (*Ar*), 127.1 (*Ar*), 62.3 (*C*HCHO), 36.4 (Ph*C*H_2CH), 21.5 (Ar*CH_3*); m/z (ES) $[M+Na]^+$ 326.1; $C_{16}H_{17}NO_3SNa$ requires 326.0827, found 326.0819

69a

(*S*)-2-Amino-3-phenylpropan-1-ol[109]



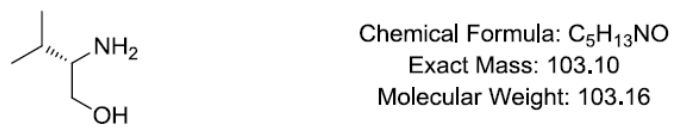
Chemical Formula: $C_{17}H_{29}NO_5SSi$
Exact Mass: 387.15
Molecular Weight: 387.57

To a suspension of sodium borohydride (2.4 eq, 363.22 mmol, 13.74 g) in THF (1 M, 150 mL) at 0 °C was added L-phenylalanine (1 eq, 151.34 mmol, 25.00 g). A solution of iodine (1 eq, 151.34 mmol, 38.41 g) in THF (1.9 M, 80 mL) was added dropwise over 3 hours with immediate loss of the iodine colouration on contact with the stirring mixture. The reaction was heated at reflux for 20 hours then chilled to 0 °C and methanol (1.5 M, 100 mL) was added cautiously. Vigorous gas evolution and dissolution of the precipitate were observed. The solvents were removed *in vacuo* to give a thick white slurry which was dissolved in 20 % KOH solution (300 mL) and stirred at room temperature for 16 hours. The solution was extracted with DCM (4 x 200 mL) and the combined organic layers washed with water (2 x 200 mL) and brine (200 mL). The solution was dried over $MgSO_4$, filtered and concentrated to yield a pale green solid (25.71 g, 112 % crude). The product was recrystallised from toluene to give a white solid (17.74 g, 78 %).

R_f 0.32 (5 % DCM in MeOH); mp 89-91 °C [lit. 91-92 °C]; IR υ (cm^{-1}) 3356/3299 (NH_2), 3022 (br) (OH), 1064 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.21 (stack, 5H (Ar*H*)), 3.67 (dd, 1H, *J* = 4.0, 10.5 Hz (CH*H*OH)), 3.41 (dd, 1H, *J* = 7.0, 10.5 Hz (CH*H*OH)), 3.19-3.11 (m, 1H (NC*H*)), 2.83 (dd, 1H, *J* = 5.0, 13.5 Hz (CH*H*Ph)), 2.56 (dd, 1H, *J* = 8.5, 13.5 Hz (CH*H*Ph)), 1.72 (brs, 3H (O*H,* N*H*$_2$)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.7 (*QAr*), 129.2 (*Ar*), 128.6 (*Ar*), 126.4 (*Ar*), 66.4 (*C*H_2OH), 54.1 (*C*H), 41.0 (Ph*C*H_2); m/z (EI) $[M - CH_3O]^+$ 120.0

69c

(*S*)-2-Amino-3-methylbutan-1-ol[110]

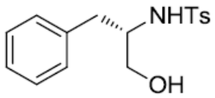


To a suspension of sodium borohydride (2.4 eq, 204.87 mmol, 7.75 g) in THF (0.9 M, 222 mL) at 0 °C was added L-valine (1 eq, 85.36 mmol, 10.0 g). A solution of iodine (1 eq, 85.36 mmol, 21.67 g) in THF (1.5 M, 56 mL) was added dropwise over 30 minutes with immediate loss of the iodine colouration on contact with the stirring mixture. After evolution of gas was complete, the reaction was heated at reflux for 20 hours then chilled to 0 °C and methanol was added cautiously until complete dissolution of the precipitate was observed. After 30 minutes the solvents were removed *in vacuo* to give a thick white slurry which was dissolved in 20 % KOH solution (170 mL) and stirred at room temperature for 16 hours. The solution was extracted with DCM (3 x 170 mL). The product was distilled with the Kugelrohr apparatus (85 °C, ~5 mmHg) to give a white solid (5.66 g, 64 %).

mp 30-32 °C; IR υ (cm^{-1}) 3338/3284 (NH_2), 3081 (br) (OH), 1606 (NH_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.64 (dd, 1H, *J* = 4.0, 10.5 Hz (C*H*HOH)), 3.29 (dd, 1H, *J* = 9.0, 10.5 Hz (CH*H*OH)), 2.56 (ddd, 1H, *J* = 4.0, 6.5, 9.0 Hz (NC*H*)), 1.90 (brs, 3H (O*H*, NH_2)), 1.56 (dsept, 1H, *J* = 4.0, 6.5 Hz (C*H*Me_2)), 0.93 (d, 3H, *J* = 4.0 Hz (*Me*)), 0.91 (d, 3H, *J* = 4.0 Hz (*Me*)) [literature agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 64.7 (*C*H_2OH), 58.5 (*C*HN), 31.4 (*C*HMe_2), 19.3 (*Me*), 18.4 (*Me*); m/z (EI) $[M - H_3O]^+$ 84.0

70

N-Tosyl-(*S*)-2-amino-3-phenylpropan-1-ol [58]



Chemical Formula: $C_{16}H_{19}NO_3S$
Exact Mass: 305.11
Molecular Weight: 305.39

General procedure **B** was followed using the following amounts:

Phenylalaninol (**69a**) (1 eq, 89.23 mmol, 13.50 g)

DMAP (10 mol%, 8.92 mmol, 1.09 g)

Triethylamine (2 eq, 178.56 mmol, 24.89 mL)

DCM (0.45 M, 200 mL)

Tosylchloride (1.05 eq, 93.74 mmol, 17.87 g)

DCM (0.9 M, 100 mL)

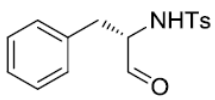
Time: 20 hours

The crude product was purified by column chromatography, eluting with 5 % DCM in methanol to give pure product as a pale yellow oil which solidified on standing (26.92 g, 99 %).

R_f 0.47 (5 % MeOH in DCM); mp 58-60 °C [lit. 63-67 °C]; IR υ (cm^{-1}) 3449 (OH), 3156 (Ar), 1599 (NH), 1381/1158 (SO_2N), 1035 (C-OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.59 (app d, 2H (Ar*H*)), 7.20-7.14 (stack, 5H (Ar*H*)), 7.00-6.96 (stack, 2H (Ar*H*)), 5.26 (d, 1H, *J* = 7.0 Hz (N*H*)), 3.63 (dd, 1H, *J* = 4.0, 11.0 Hz (CH*H*OH)), 3.54-3.44 (stack, 2H (CHHO*H*, NC*H*)), 2.77 (dd, 1H, *J* = 7.0, 13.5 Hz (CH*H*Ph)), 2.66 (dd, 1H, *J* = 7.0, 13.5 Hz (CH*H*Ph)), 2.40 (s, 1H (ArC*H₃*)), 1.49 (brs, 1H (O*H*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3 (*QAr*), 137.0 (*QAr*), 136.8 (*Ar*), 129.6 (*Ar*H), 129.1 (*Ar*H), 128.5 (*Ar*H), 126.9 (*Ar*H), 126.6 (*Ar*H), 63.9 (*C*H_2OH), 56.7 (*C*H), 37.7 (*C*H_2Ph), 21.5 (Ar*C*H_3); m/z (ES) $[M+Na]^+$ 328.1; $C_{16}H_{19}NO_3SNa$ requires 328.0983, found 328.0968

71

N-Tosyl-(*S*)-2-amino-3-phenylpropanal



Chemical Formula: $C_{16}H_{17}NO_3S$
Exact Mass: 303.09
Molecular Weight: 303.38

General procedure **C** was followed using the following quantities:

PCC (3 eq, 2.46 mmol, 529 mg) in DCM (20 mL)

Alcohol **70** (1 eq, 0.82 mmol, 250 mg) in DCM (5 mL)

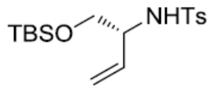
Time: 3½ hours

The crude product was purified by column chromatography, eluting with 40 % EtOAc in hexane, to yield a pale yellow oil. (196 mg, 79 %)

R_f 0.41 (40 % EtOAc in hexane); IR υ (cm^{-1}) 3267 (NH), 1705 (C=O), 1598 (NH), 1331/1221 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H (C*H*O)), 7.61 (app d, 2H (Ar*H*)), 7.27- 7.17 (stack, 5H (Ar*H*)), 7.08-7.02 (stack, 2H (Ar*H*)), 5.15 (d, 1H, *J* = 6.0 Hz (N*H*)), 4.04 (dt, 1H, *J* = 6.0, 6.5 Hz (C*H*N)), 3.05 (d, 2H, *J* = 6.5 Hz (C*H₂*)), 2.42 (s, 1H (ArC*H₃*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.3 (*C*HO), 134.5 (*Ar*), 129.8 (*Ar*), 129.7 (*Ar*), 129.3 (*Ar*), 128.9 (*Ar*), 128.7 (*Ar*), 127.4 (*Ar*), 127.1 (*Ar*), 62.3 (*C*HCHO), 36.4 (Ph*C*H_2), 21.5 (Ar*C*H_3); m/z (ES) $[M+Na]^+$ 326.1; $C_{16}H_{17}NO_3SNa$ requires 326.0827, found 326.0819

72

N-Tosyl-(*R*)-1-(*tert*-butyldimethylsilyloxy)but-3-en-2-amine



Chemical Formula: $C_{17}H_{29}NO_3SSi$
Exact Mass: 355.16
Molecular Weight: 355.57

General procedure **D** was followed using the following amounts:

Methyltriphenylphosphonium iodide (2 eq, 4.20 mmol, 1.70 mg) in THF (2.8 mL)

Potassium *tert*-butoxide (2 eq, 4.20 mmol, 471 mg)

Aldehyde **61** (1 eq, 1.40 mmol, 500 mg) in chilled THF (2.8 mL)

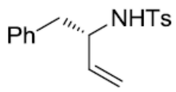
Ylide colour: bright yellow

Purification was by column chromatography, eluting with 20 % ethyl acetate in hexane to yield a yellow oil. (78 mg, 16 %)

R_f 0.50 (20 % EtOAc in hexane); IR υ (cm^{-1}) 1623 (=), 1503(Ar), 1360/1164 (SO_2N), 1057 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (app d, 2H (Ar*H*)), 7.30 (app d, 2H (Ar*H*)), 5.68 (ddd, 1H, *J* = 6.5, 10.5, 17.0 Hz (RC*H*=)), 5.15 (dd, 1H, *J* = 1.5, 10.5 Hz (=C*H*H)), 5.10 (dd, 1H, *J* = 1.5, 17.0 Hz (=CH*H*)), 5.02 (d, 1H, *J* = 6.0 Hz (N*H*)), 3.85-3.64 (m, 1H (C*H*)), 3.52 (d, 1H, *J* = 4.5 Hz (C*H*HO)), 3.51 (d, 1H, J = 5.5 Hz (CH*HO*)), 2.43 (s, 3H (ArCH_3)), 0.85 (s, 9H (^{t}*Bu*)), 0.01 (s, 3H (*Me*)), -0.01 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.5 (*QAr*), 137.6 (*QAr*), 131.4 (*C*H=), 129.3 (*Ar*H), 128.3 (*Ar*H), 117.7 (=*C*H_2), 70.7 (*C*H_2O), 56.7 (*C*HN), 30.6 (*Q*^{t}*Bu*), 25.9 (^{t}*Bu*), 21.3 (Ar*C*H_3), -2.3 (*Me*); m/z (ES) $[M+Na]^+$ 378.2

73

N-Tosyl-(*S*)-1-phenylbut-3-en-2-amine



Chemical Formula: $C_{17}H_{19}NO_2S$
Exact Mass: 301.11
Molecular Weight: 301.40

General procedure **D** was followed using the following amounts:

Methyltriphenylphosphonium iodide (2 eq, 1.32 mmol, 533 mg) in THF (2.5 mL)

Potassium *tert*-butoxide (2 eq, 1.32 mmol, 148 mg)

Aldehyde **71** (1 eq, 0.66 mmol, 200 mg) in chilled THF (1 mL)

Ylide colour: bright yellow

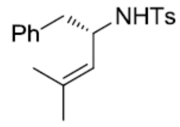
Purification was by column chromatography, eluting with 5 % methanol in DCM to yield a yellow oil. (162 mg, 82 %)

R_f 0.37 (20 % EtOAc in hexane); IR υ (cm^{-1}) 2979 (NH), 1718 (=), 1156 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (app d, 2H (Ar*H*)), 7.22 (stack, 5H (Ar*H*)), 7.03 (app dd, 2H (Ar*H*)), 5.68 (ddd, 1H, J = 6.0, 10.5, 17.0 Hz (RC*H*=)), 5.04 (d, 1H, J = 17.0 Hz (=C*H*H)), 5.02 (d, 1H, J = 10.5 Hz (=CH*H*)), 4.46 (d, 1H, J = 7.5 Hz (N*H*)), 4.01 (dddd, 1H, J = 5.0, 5.5, 6.0, 7.5 Hz (C*H*)), 2.84 (dd, 1H, J = 5.0, 12.5 Hz (C*H*HPh)), 2.78 (dd, 1H, J = 5.5, 12.5 Hz (CH*H*Ph)), 2.41 (s, 3H (ArCH_3)) [lit. agreement][112]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.0 (*QAr*), 138.0 (*QAr*), 137.2 (*C*H=), 136.1

(*QAr*), 129.5 (*Ar*), 129.4 (*Ar*), 128.5 (*Ar*), 127.1 (*Ar*), 126.8 (*Ar*), 116.3 (=CH_2), 56.9 (*C*H), 42.0 (*C*H_2), 21.5 (*C*H_3); m/z (ES) $[M]^+$ 301.0

75

N-Tosyl-(*S*)-4-methyl-1-phenylpent-3-en-2-amine



Chemical Formula: $C_{19}H_{23}NO_2S$
Exact Mass: 329.14
Molecular Weight: 329.46

General procedure **D** was followed using the following quantities:

Isopropyltriphenylphosphonium iodide (2 eq, 1.65 mmol, 712 mg) in THF (1.70 mL)

Potassium *tert*-butoxide (2 eq, 1.65 mmol, 185 mg)

Aldehyde **71** (1 eq, 0.82 mmol, 250 mg) in chilled THF (1 mL)

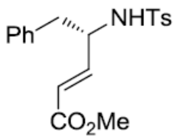
Ylide colour: Deep red

Purification was by column chromatography, eluting with 10 % EtOAc in hexane to give a yellow oil. (162 mg, 82 %)

IR υ (cm^{-1}) 2917/2849 (NH), 1739 (=), 1160 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (app d, 2H (Ar*H*)), 7.50-6.95 (stack, 7H (Ar*H*)), 5.54 (d, 1H, *J* = 9.5 Hz (C*H*=)), 5.26 (d, 1H, *J* = 8.5 Hz (N*H*)), 4.14 (dddd, 1H, *J* = 6.0, 7.5, 8.5, 9.5 Hz (C*H*)), 3.45 (s, 3H (ArC*H₃*)), 2.95 (dd, 1H, *J* = 6.0, 14.0 Hz (C*H*H)), 2.85 (dd, 1H, *J* = 7.5, 14.0 Hz (CH*H*)), 2.42 (s, 3H (CH_3)), 2.39 (s, 3H (CH_3)), 2.33 (s, 3H (ArCH_3)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.5 (*QAr*), 137.6 (*QAr*), 136.7 (=*C*Me_2), 136.6 (*QAr*), 130.2 (*Ar*H), 129.7 (*Ar*H), 129.4 (*Ar*H), 128.7 (*Ar*H), 127.8 (*Ar*H), 126.9 (=*C*H), 57.3 (*C*H), 43.5 (*C*H2), 21.7 (*C*H_3), 21.5 (*C*H_3), 21.5 (Ar*C*H_3); m/z (ES) $[M+Na]^+$ 352.1

76

N-Tosyl-methyl-(*S,E*)-4-amino-5-phenylpent-2-enoate



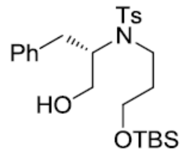
Chemical Formula: $C_{19}H_{21}NO_4S$
Exact Mass: 359.12
Molecular Weight: 359.44

To a solution of aldehyde **71** (1 eq, 1.64 mmol, 500 mg) in DCM (13 mL) was added methyl (triphenylphosphoranylidene)acetate (2 eq, 3.28 mmol, 1.10 g). The reaction was stirred at RT overnight. The solvent was removed to yield a pink solid which was purified by column chromatography, eluting with 40 % EtOAc in hexane to give a white solid. (240 mg, 48 %)

R_f 0.54 (40 % EtOAc in hexane); IR υ (cm^{-1}) 3259 (NH), 1702 (unsaturated ester), 1597 (NH), 1303/1147 (SO_2N), 928 (trans =); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57 (app d, 2H (Ar*H*)), 7.21 (stack, 5H (Ar*H*)), 6.99 (stack, 2H (Ar*H*)), 6.76 (dd, 1H, *J* = 6.0, 15.5 Hz (=C*H*CH)), 5.81 (dd, 1H, *J* = 1.5, 15.5 Hz (=C*H*CO)), 4.47 (d, 1H, *J* = 7.5 Hz (NH)), 4.14 (ddt, 1H, *J* = 6.0, 6.5, 7.5 Hz (C*H*)), 3.70 (s, 3H (OC*H₃*)), 2.81 (dd, 2H, *J* = 6.5, 10.0 Hz (CH*H*)), 2.79 (dd, 2H, *J* = 6.5, 10.0 Hz (CH*H*)), 2.41 (s, 3H (ArCH_3)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.2 (*C*=O), 146.4 (=*C*HCH), 143.5 (*QAr*), 137.1 (*QAr*), 135.2 (*QAr*), 129.5 (*Ar*H), 129.4 (*Ar*H), 128.7 (*Ar*H), 127.1 (*Ar*H), 126.8 (*Ar*H), 122.0 (=*C*HC=O), 55.5 (*C*H), 51.7 (OCH_3), 41.1 (CH_2), 21.5 (ArCH_3); m/z (ES) $[M+Na]^+$ 382.1; $C_{19}H_{21}NO_4SNa$ requires 382.1089, found 382.1093

79

N-Tosyl-(*S*)-2-((3-(*tert*-butyldimethylsilyloxy)propyl)amino)-3-phenylpropan-1-ol



Chemical Formula: $C_{25}H_{39}NO_4SSi$
Exact Mass: 477.24
Molecular Weight: 477.73

Procedure **E** was followed using the following amounts:

Amine **70** (1 eq, 6.55 mmol, 2.00 g) in anhydrous DMF (65 mL)

Cesium carbonate (1.5 eq, 9.82 mmol, 3.20 g)

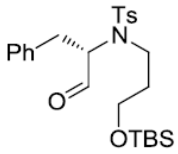
tert-Butyl(3-iodopropoxy)dimethylsilane (1.15 eq, 7.53 mmol, 2.26 g) in minimal DMF

Yield: colourless oil (1.13g, 36 %)

R_f 0.90 (50 % EtOAc in hexane); IR υ (cm^{-1}) 3511 (OH), 2928 (NR_3), 1599 (Ar), 1254/833 ($SiMe_2$), 1152 (SO_2N), 1088 (C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (app d, 2H (Ar*H*)), 7.21 (stack, 5H, Ar*H*)), 7.02 (app dd, 2H (Ar*H*)), 4.00 (ddt, 1H, *J* = 4.0, 5.0, 9.5 Hz (C*H*)), 3.69 (stack, 4H, (C*H₂*OH, C*H₂*N)), 3.40 (t, 2H, *J* = 7.5 Hz (C*H₂*OSi)), 2.73 (dd, 1H, *J* = 9.5, 13.5 Hz (CH*H*Ph)), 2.54 (dd, 1H, *J* = 5.0, 13.5 Hz (C*H*HPh)), 2.41 (s, 3H, (ArC*H₃*)), 1.93 (m, 2H (C*H₂*CH_2N)), 1.65 (brs, 1H, (O*H*)), 0.91 (s, 9H (Si^t*Bu*)), 0.07 (s, 6H (Si*Me*)) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3 (*QAr*), 137.7 (*QAr*) 137.6 (*QAr*), 129.7 (*Ar*H), 129.0 (*Ar*H), 128.6 (*Ar*H), 127.3 (*Ar*H), 126.6 (*Ar*H), 62.4 (*C*H_2OH), 62.1 (*C*H), 60.4 (*C*H_2OSi), 41.8 (*C*H_2N), 35.8 (*C*H_2Ph), 34.0 (*C*$H_2$$CH_2$N), 25.9 (Si^t*Bu*), 21.5 (Ar*C*H_3), 18.3 (*Q*Si^t*Bu*), -5.3 (Si*C*H_3); m/z (ES) $[M+Na]^+$ 500.3; $C_{25}H_{39}NO_4SiSNa$ requires 500.2267, found 500.2261

80

N-Tosyl-(*S*)-2-((3-(*tert*-butyldimethylsilyloxy)propyl)amino)-3-phenylpropanal



Chemical Formula: $C_{25}H_{37}NO_4SSi$
Exact Mass: 475.22
Molecular Weight: 475.72

General procedure **C** was followed using the following quantities:

PCC (3 eq, 0.63 mmol, 135 mg) in DCM (5 mL)

Alcohol **79** (1 eq, 0.21 mmol, 100 mg) in DCM (1 mL)

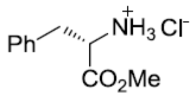
Time: 20 hours

Purified by column chromatography, eluting with 25 % EtOAc in hexane, to yield a yellow residue (37 mg, 37 %)

R_f 0.91 (50 % EtOAc in hexane); IR υ (cm^{-1}) 2931 (NR_3), 16.2 (Ar), 1256/830 (SiMe), 1153 (SO_2N), 1730 (CHO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H (C*H*O)), 7.55 (app d, 2H (Ar*H*)), 7.20 (stack, 5H (Ar*H*)), 7.07 (stack, 2H, (Ar*H*)), 4.54 (m, 1H, (C*H*)), 3.56 (stack, 5H (CH_2OSi, CH_2N, CH*H*Ph)), 2.76 (dd, 1H, *J* = 8.0, 14.5 Hz (C*H*HPh)), 2.41 (s, 3H (ArCH_3)), 1.70 (m, 2H (CH_2CH_2N)), 0.87 (s, 9H (Si^t*Bu*)), 0.02 (s, 3H (Si*Me*)), 0.02 (s, 3H (Si*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.0 (*C*HO), 143.6 (*QAr*), 137.2 (*QAr*), 137.1 (*QAr*), 129.7 (*Ar*H), 129.0 (*Ar*H), 128.6 (*Ar*H), 127.3 (*Ar*H), 126.7 (*Ar*H), 68.2 (*C*H), 60.1 (*C*H_2O), 44.8 (*C*H_2N), 33.2 (*C*H_2CH_2N), 29.7 (*C*H_2Ph), 25.9 (Si^t*Bu*), 21.5 (Ar*C*H_3), 18.2 (*Q*Si^t*Bu*), -5.4 (Si*Me*); m/z (ES) $[M+Na]^+$ 498.3; $C_{25}H_{37}NO_4SiSNa$ requires 498.2210, found 498.2107

83

(*S*)-1-Methoxy-1-oxo-3-phenylpropan-2-aminium chloride[113]



Chemical Formula: $C_{10}H_{14}NO_2^+$
Exact Mass: 180.10
Molecular Weight: 180.22

General procedure **A** was followed using the following amounts:

L-phenylalanine (1 eq, 151.34 mmol, 25.00 g)

Methanol (1 M, 150 mL)

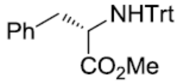
Thionyl chloride (1 eq, 151.34 mmol, 11.00 mL)

Yield: 32.18 g white solid (99 %)

mp 156 – 160 °C [lit. 159 °C]; R_f 0.11 (25% EtOAc in Hexane); IR υ (cm^{-1}) 2839 (NH_3^+), 1743 (C=O), 1583 (Ar); ^{1}H-NMR (300 MHz) ($CDCl_3$/DMSO) δ 8.65 (brs, 3H (NH_3^+)), 7.31-7.18 (stack, 5H (Ar*H*)), 4.15 (dd, 1H, *J* = 6.0, 7.0 Hz (C*H*)), 3.66 (s, 3H (OCH_3)), 3.21 (dd, 1H, *J* = 6.0, 14.0 Hz (CH*H*)), 3.12 (dd, 1H, *J* = 7.0, 14.0 Hz (C*H*H)); ^{13}C-NMR (100 MHz) δ 169.1 (*C*=O), 134.2 (Q*Ar*), 129.2 (*Ar*H), 128.4 (*Ar*H), 127.1 (*Ar*H), 53.3 (O*C*H_3), 52.3 (*C*H), 35.8 (*C*H_2); m/z (ES) $[M+H]^+$ 180.1; $C_{10}H_{15}NO_2$ requires 180.1025, found 180.1017

84

N-Trityl-methyl-(*S*)-3-phenyl-2-aminopropanoate [114]



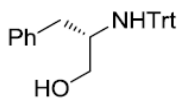
Chemical Formula: $C_{29}H_{27}NO_2$
Exact Mass: 421.20
Molecular Weight: 421.53

A mixture of amine **83** (1 eq, 1.16 mmol, 250 mg), triphenylmethyl chloride (1 eq, 1.16 mmol, 323 mg) and triethylamine (2 eq, 2.32 mmol, 0.32 mL) in DCM (0.2 M, 6 mL) was stirred for 48 hours. The mixture was diluted with water and product extracted with DCM then purified by column chromatography to yield a clear oil (488 mg, >99 %).

R_f 0.78 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3303 (NH), 1600 (C=O), 1021 (C-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45-7.11 (stack, 20H (Ar*H*)), 3.55 (dt, 1H, *J* = 6.0, 11.0 Hz (C*H*)), 3.03 (s, 3H (OC*H₃*)), 2.98 (dd, 1H, *J* = 6.0, 12.5 (CH*H*)), 2.92 (dd, 1H, *J* = 6.0, 12.5 Hz (C*H*H)), 2.62 (d, 1H, *J* = 11.0 Hz (N*H*)) [lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.9 (*C*=O), 145.9 (*QArTrt*), 137.5 (*QArPh*), 129.8 (Ar*H*), 128.8 (Ar*H*), 128.2 (Ar*H*), 127.8 (Ar*H*), 126.7 (Ar*H*), 126.3 (Ar*H*), 71.0 (*QTrt*), 58.4 (*C*H), 51.3 (O*C*H₃), 42.4 (*C*H2); m/z (ES) $[M+Na]^+$ 444.2; $C_{29}H_{27}NO_2Na$ requires 444.1939, found 444.1928

85a

N-Trityl-(*S*)-3-phenyl-2-aminopropan-1-ol [114]



Chemical Formula: $C_{28}H_{27}NO$
Exact Mass: 393.21
Molecular Weight: 393.52

Reduction of **84**:

Ester **84** (1 eq, 1.19 mmol, 500 mg) was dissolved in THF (0.33 M, 3.60 mL) at 0 °C then lithium borohydride (1.25 eq, 1.48 mmol, 32 mg) was added in one portion. The mixture was warmed to 45 °C and stirred for 72 hours. After an aqueous workup a 50/50 mixture of starting material and product was recovered.

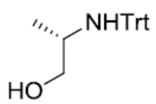
Tritylation of **69a**:

Amine **69a** (1 eq, 1.65 mmol, 250 mg) was dissolved in DCM (0.2 M, 8.25 mL), then triethylamine (1 eq, 1.65 mmol, 230 μl) and trityl chloride (1 eq, 1.65 mmol, 460 mg) were added. The mixture was stirred at room temperature for several days before an aqueous workup. Purification by column chromatography yielded a clear oil (592 mg, 91 %).

R_f 0.60 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3604 (OH), 3452 (NH), 1506 (Ar); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60-7.50 (stack, 6H (Ar*H*)), 7.33-7.079 (stack, 12H (Ar*H*)), 6.94-6.89 (stack, 2H (Ar*H*)), 3.11 (dd, 1H, *J* = 2.5, 11.0 Hz (C*H*HOH)), 2.93 (dd, 1H, *J* = 4.5, 11.0 Hz (CHHOH)), 2.81 (dddd, 1H, *J* = 2.5, 4.5, 5.0, 9.5 Hz (C*H*)), 2.51 (dd, 1H, *J* = 9.5, 13.0 (C*H*HPh)), 2.28 (dd, 1H, *J* = 5.0, 13.0 (CH*H*Ph)), 1.92 (brs, 2H (N*H*, O*H*)) [lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.0 (*QAr*), 138.0 (*QAr*), 129.2 (*Ar*H), 128.8 (*Ar*H), 128.1 (*Ar*H), 126.2 (*Ar*H), 126.0 (*Ar*H), 76.1 (*QTrt*), 66.8 (*C*H_2OH), 56.5 (*C*H), 39.1 (*C*H_2Ph); m/z (ES) $[M+Na]^+$ 416.2; $C_{28}H_{27}NONa$ requires 416.1990, found 416.1973

85b

N-Trityl-(*S*)-2-aminopropan-1-ol



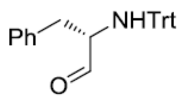
Chemical Formula: $C_{22}H_{23}NO$
Exact Mass: 317.18
Molecular Weight: 317.42

L-alaninol (1 eq, 6.66 mmol, 500 mg) was dissolved in DCM (0.2 M, 35 mL), then triethylamine (1 eq, 6.66 mmol, 928 μl) and trityl chloride (1 eq, 6.66 mmol, 1.86 g) were added. The mixture was stirred at room temperature for 48 hours before an aqueous workup. Purification by column chromatography, eluting with 20 % EtOAc in hexane, yielded a clear oil (1.71 g, 81 %).

R_f 0.38 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3460 (NH), 3254 (br) (OH), 1594 (Ar); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56-7.52 (stack, 6H (Ar*H*)), 7.31-7.17 (stack, 9H (Ar*H*)), 3.16 (dd, 1H, *J* = 4.0, 10.5 Hz (C*H*HOH)), 3.05 (dd, 1H, *J* = 5.0, 10.5 Hz (CH*H*OH)), 2.77 (m, 1H (C*H*)), 1.88 (brs, 2H (N*H*, O*H*)), 0.66 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.8 (*QAr*), 128.8 (*Ar*H), 127.9 (*Ar*H), 126.5 (*Ar*H), 72.0 (*QC*Ph_3), 67.0 (*C*H_2OH), 49.5 (*C*H), 19.8 (*C*H_3); m/z (ES) $[M+Na]^+$ 340.3; $C_{22}H_{23}NONa$ requires 340.1677, found 340.167

86a

N-Trityl-(*S*)-2-amino-3-phenylpropanal [114]



Chemical Formula: $C_{28}H_{25}NO$
Exact Mass: 391.19
Molecular Weight: 391.50

General procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 75.47 mmol, 6.39 mL) in DCM (0.45 M, 150 mL)

DMSO (2.4 eq, 164.66 mmol, 11.70 mL) in DCM (2 M, 35 mL)

Alcohol **85a** (1 eq, 68.61 mmol, 27.00 g) in DCM (1 M, 70 mL)

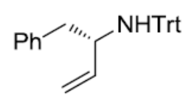
Triethylamine (5 eq, 343.05 mmol, 47.81 mL)

The product was purified by column chromatography to yield a colourless crystalline solid (26.4 g, 98 %).

R_f 0.70 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3031 (NH), 1720 (CHO), 1595/1488 (Ar); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.85 (d, 1H, *J* = 2.2 Hz (C*H*O)), 7.42-7.15 (stack, 20 H (Ar*H*)), 3.57 (ddd, 1H, *J* = 2.0, 6.5, 7.0 Hz (C*H*N)), 2.79 (dd, 1H, *J* = 7.0, 16.5 Hz (C*H*HPh)), 2.78 (brs, 1H (N*H*)), 2.73 (dd, 1H, *J* = 6.5, 16.5 Hz (CH*H*Ph)) [lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.2 (*C*HO), 145.9 (*QAr*), 136.7 (*QAr*), 129.9 (*Ar*H), 128.7 (*Ar*H), 128.6 (*Ar*H), 128.1 (*Ar*H), 126.9 (*Ar*H), 126.7 (*Ar*H), 71.0 (*Q*N*C*Ph$_3$), 63.0 (*C*HN), 38.7 (*C*H$_2$Ph); m/z (EI) [C_6H_5]$^+$ 77.0, [$PhCH_2$]$^+$ 91.1, [Trt]$^+$ 243.1

87

N-Trityl-(*S*)-1-phenylbut-3-en-2-amine [114]



Chemical Formula: $C_{29}H_{27}N$
Exact Mass: 389.21
Molecular Weight: 389.53

Procedure **D** was followed using the following amounts:

Methyltriphenylphosphonium iodide (2 eq, 5.11 mmol, 2.07 g) in THF (0.25 M, 10 mL)

Potassium *t*-butoxide (2 eq, 5.11 mmol, 573 mg)

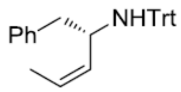
Aldehyde **86a** (1 eq, 2.55 mmol, 1.00 g) in minimal THF

The product was purified by column chromatography, loading by solid adsorption to silica, eluting with 10 % EtOAc in hexane, to yield a clear oil (979 mg, 98 %)

R_f 0.86 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3027 (NH), 1595/1489/1447 (Ar); ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.56-7.52 (stack, 6H (Ar*H*)), 7.31-7.08 (stack, 12H (Ar*H*)), 6.90 (app dd, 2H (Ar*H*)), 5.54 (ddd, 1H, *J* = 7.5, 10.5, 17.0 Hz (=C*H*)), 4.79 (d, 1H, *J* = 17.0 Hz(=CHH_{trans})), 4.75 (d, 1H, *J* = 7.5 Hz (=CHH_{cis})), 3.24 (ddd, 1H, *J* = 5.0, 8.0, 10.5 Hz (C*H*)), 2.30 (dd, 1H, *J* = 5.0, 13.0 Hz (C*H*HPh)), 2.17 (dd, 1H, *J* = 8.0, 13.0 Hz (CH*H*Ph)), 1.68 (s, 1H (N*H*)) [lit. agreement]; ^{13}C-NMR (100 MHz, CDCl$_3$) δ 147.0 (*QArTrt*), 141.6 (=*C*H), 138.7 (*QAr*), 129.8 (*Ar*H), 129.0 (*Ar*H), 127.9 (*Ar*H), 127.7 (*Ar*H), 126.3 (*Ar*H), 126.0 (*Ar*H), 113.4 (=*C*H2), 71.53 (*QTrt*), 57.3 (*C*H), 43.6 (*C*H$_2$); m/z (ES) [M+Na]$^+$ 412.1; $C_{29}H_{27}NNa$ requires 412.2041, found 412.2052

89

N-Trityl-(*S,Z*)-1-phenylpent-3-en-2-amine



Chemical Formula: $C_{30}H_{29}N$
Exact Mass: 403.23
Molecular Weight: 403.56

Procedure **D** was followed using the following amounts:

Ethyltriphenylphosphonium iodide (2 eq, 2.55 mmol, 1.07 g) in THF (0.25 M, 5 mL)

Potassium *t*-butoxide (2 eq, 2.55 mmol, 287 mg)

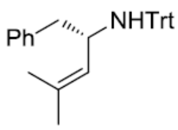
Aldehyde **86a** (1 eq, 1.28 mmol, 500 mg) in minimal THF

The product was purified by column chromatography, loading by solid adsorption to silica, eluting with 10 % EtOAc in hexane, to yield a clear oil (191 mg, 37 %)

R_f 0.90 (10 % EtOAc in hexane); IR υ (cm^{-1}) 3022 (NH), 1597/1481 (Ar) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58-7.50 (stack, 6H (Ar*H*)), 7.35-7.11 (stack, 12H (Ar*H*)), 7.06-7.00 (stack, 2H (Ar*H*)), 5.14-4.98 (stack, 2H (*H*C=C*H*)), 3.56-3.46 (m, 1H (C*H*)), 2.36 (dd, 1H, *J* = 5.0, 12.5 (C*H*HPh)), 2.25 (dd, 1H, *J* = 8.5, 12.5 (CH*H*Ph)), 1.28 (brs, 1H (N*H*)), 0.88 (d, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.0 (QAr), 136.6 (QAr), 135.2 (=CH), 129.2 (ArH), 128.6 (ArH), 127.7 (ArH), 127.0 (ArH), 126.2 (ArH), 125.9 (ArH), 125.7 (=CH), 76.2 (QTrt), 51.6 (CH), 42.8 (CH_2Ph), 11.6 (Me); m/z (ES) $[M+Na]^+$ 426.3; $C_{30}H_{29}NNa$ requires 426.2198, found 426.2183

90

N-Trityl-(*S*)-4-methyl-1-phenylpent-3-en-2-amine



Chemical Formula: $C_{31}H_{31}N$
Exact Mass: 417.25
Molecular Weight: 417.58

Procedure **D** was followed using the following amounts:

Isopropyltriphenylphosphonium iodide (2 eq, 10.22 mmol, 4.42 g) in THF (0.25 M, 20 mL)

Potassium *t*-butoxide (2 eq, 10.22 mmol, 1.15 g)

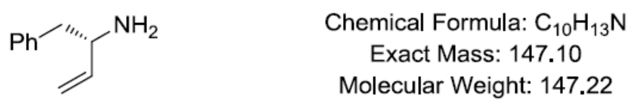
Aldehyde **86a** (1 eq, 5.11 mmol, 2.0 g) in minimal THF

The product was purified by column chromatography, loading by solid adsorption to silica, eluting with 2 % EtOAc in hexane, to yield a yellow oil (918 mg, 43 %)

R_f 0.83 (25% EtOAc in Hexane); IR υ (cm^{-1}) 2923 (NH), 1597/1446 (Ar); ^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.53-7.49 (stack, 6H (Ar*H*)), 7.32-7.11 (stack, 12H (Ar*H*)), 6.95-6.92 (stack, 2H (Ar*H*)), 4.71 (dsept, 1H, *J* = 1.0, 9.0 Hz (=C*H*)), 3.37 (ddd, 1H, *J* = 5.0, 8.0, 9.0 Hz (C*H*)), 2.42 (dd, 1H, *J* = 5.0, 12.5 Hz (CH*H*)), 2.32 (dd, 1H, *J* = 8.0, 12.5 Hz (C*H*H)), 1.71 (brs, 1H (N*H*)), 1.37 (d, 1H, *J* = 1.0 Hz (CH_3)), 0.83 (d, 3H, *J* = 1.0 Hz (CH_3)); ^{13}C-NMR (100 MHz) δ 147.0 (*QArTrt*), 143.9 (=*C*Me_2), 139.2 (*QAr*Ph), 130.0 (*Ar*H), 129.5 (*Ar*H), 129.0 (*Ar*H), 128.3 (*Ar*H), 127.7 (*Ar*H), 126.2 (*Ar*H), 125.7 (=*C*H), 72.3 (*QTrt*), 53.4 (*C*H), 44.2 (*C*H_2), 25.5 (*C*H_{3trans}), 17.6 (*C*H_{3cis}); m/z (ES) $[M+Na]^+$ 440.2; $C_{31}H_{31}NNa$ requires 440.2354, found 440.2357

91

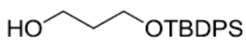
(*S*)-1-Phenylbut-3-en-2-amine[115]



Tritylated amine **87** (1 eq, 4.24 mmol, 1.65 g) was dissolved in anhydrous acetone (0.12 M, 35 mL) and concentrated HCl (6 M, 0.71 mL) was added. The reaction mixture was heated at reflux for 3 hours before dilution with water. The aqueous portion was extracted into DCM to remove trityl alcohol. The aqueous layer was then evaporated to dryness to yield a yellow solid (568 mg, 73 %)

IR υ (cm^{-1}) 2914 (NH), 1585 (Ar); ^{1}H-NMR (300 MHz, D_2O) δ 7.34-7.15 (stack, 5H (Ar*H*)), 5.79 (ddd, 1H, *J* = 7.5, 10.5, 17.0 Hz (=C*H*)), 5.24 (d, 1H, *J* = 10.5 Hz (=CH*H*)), 5.19 (d, 1H, *J* = 17.0 Hz (=C*H*H)), 3.97 (q, 1H, *J* = 7.5 Hz (C*H*N)), 2.94 (dd, 2H, *J* = 1.0, 7.5 Hz (CH_2Ph)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.6 (QAr), 131.4 (=CH), 128.6 (ArH), 127.7 (ArH), 125.9 (ArH), 117.7 (=CH_2), 56.5 (CH), 44.1 (CH_2); m/z (ES) $[M+H]^+$ 148.1; $C_{10}H_{14}N$ requires 148.1126, found 148.1127

3-(*tert*-Butyldiphenylsilyloxy)propan-1-ol[116]



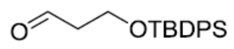
Chemical Formula: $C_{19}H_{26}O_2Si$
Exact Mass: 314.17
Molecular Weight: 314.49

To a solution of propane diol (3 eq, 109.14 mmol, 7.89 mL) in DCM (0.5 M, 73 mL), was added triethylamine (1.5 eq, 54.57 mmol, 7.61 mL) and *t*-butyldiphenylsilyl chloride (1 eq, 36.38 mmol, 10 g). After 18 hours at room temperature the reaction mixture was diluted with DCM and washed with water and then brine. The crude product was purified by column chromatography, eluting with 20 % EtOAc in hexane, to yield a white solid (9.98 g, 87 %).

R_f 0.54 (25 % EtOAc in hexane); IR υ (cm^{-1}) 2926/2859 (CH), 3598 (CO), 1095 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (stack, 4H (Ar*H*)), 7.48-7.37 (stack, 6H (Ar*H*)), 3.85 (t, 2H, *J* = 5.5 Hz (CH_2OSi)), 3.85 (q, 2H, *J* = 5.5 Hz (CH_2OH)), 2.36 (t, 1H, *J* = 5.5 Hz (O*H*)), 1.81 (quin, 2H, *J* = 5.5 Hz (CH_2CH_2O)), 1.05 (s, 9H (^{t}*Bu*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6

(QAr), 133.3 (ArH), 129.8 (ArH), 127.8 (ArH), 63.3 (CH_2OH), 62.0 (CH_2OSi), 34.3 (CH_2CH_2O), 26.8 (^tBu), 19.1 (Q^tBu); m/z (ES) $[M+Na]^+$ 337.3

3-(*tert*-Butyldiphenylsilyloxy)propanal[116]



Chemical Formula: $C_{19}H_{24}O_2Si$
Exact Mass: 312.15
Molecular Weight: 312.48

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 9.09 mmol, 0.77 mL) in DCM (0.4 M, 23 mL)

DMSO (2.4 eq, 19.84 mmol, 1.41 mL)

3-((tert-butyldiphenylsilyl)oxy)propan-1-ol (1 eq, 8.27 mmol, 2.6 g) in DCM (0.8 M, 10 mL)

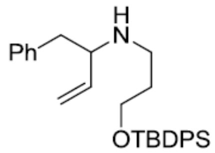
Triethylamine (5 eq, 41.30 mmol, 5.75 mL)

The product was purified by column chromatography to yield a yellow oil (2.54 g, 98 %).

R_f 0.52 (20 % EtOAc in heptane); IR υ (cm^{-1}) 2931/2888 (CH), 1729 (C=O), 1093 (Si-O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.84 (t, 1H, J = 2.0 Hz (CHO)), 7.68 (app dd, 4H (ArH)), 7.48-7.36 (stack, 6H (ArH)), 4.04 (t, 2H, J = 6.0 Hz (CH_2O)), 2.63 (dt, 2H, J = 2.0, 6.0 Hz (CH_2CH_2O)), 1.06 (s, 9H (^tBu)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.9 (CHO), 135.5 (ArH), 133.3 (QAr), 129.8 (ArH), 127.8 (ArH), 58.3 (CH_2O), 46.4 (CH_2CH_2O), 26.7 (^tBu), 19.1 (Q^tBu); m/z (ES) $[M+Na]^+$ 335.3

92a

N-3-(*tert*-Butyldiphenylsilyloxy)propyl-1-phenylbut-3-en-2-amine



Chemical Formula: $C_{29}H_{37}NOSi$
Exact Mass: 443.26
Molecular Weight: 443.70

Procedure **G** was followed using the following amounts:

Amine **91** (1 eq, 13.58 mmol, 2.00 g) in DCM (1 M, 14 mL)

Na_2SO_4 (1.02 eq, 13.86 mmol, 1.97 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 13.58 mmol, 4.24 g) in DCM (1.75 M, 8.0 mL)

$NaBH_4$ (1.5 eq, 20.38 mmol, 771 mg)

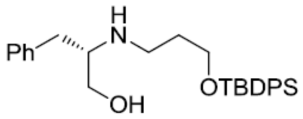
MeOH (1 M, 14 mL)

Yield: 1.11 g, colourless oil (18 %).

R_f 0.23 (15 % EtOAc in hexane); IR υ (cm^{-1}) 1586/1574 (Ar), 1101 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71-7.64 (stack, 4H (Ar*H*)), 7.50-7.35 (stack, 6H (Ar*H*)), 7.33-7.17 (stack, 5H (Ar*H*)), 5.68 (ddd, 1H, *J* = 7.5, 9.0, 15.0 Hz (=C*H*)), 5.09 (d, 1H, *J* = 9.0 Hz (=C*H*H)), 5.06 (dd, 1H, *J* = 1.5, 7.5 Hz (=CH*H*)), 3.68 (t, 2H, *J* = 6.0 Hz (CH_2O)), 3.30 (dt, 1H, *J* = 7.0, 15.0 Hz (C*H*)), 2.86- 2.71 (stack, 3H (CH_2N, C*H*HPh)), 2.61 (dd, 1H, *J* = 7.0, 11.5 Hz (CH*H*Ph)), 1.82-1.58 (m, 2H, C$H_2$$CH_2$O)), 1.29 (brs, 1H (N*H*)), 1.06 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.6 (*QAr*), 134.0 (*QAr*), 131.4 (=*C*H), 130.0 (*Ar*H), 129.9 (*Ar*H), 129.5 (*Ar*H), 128.6 (*Ar*H), 127.7 (*Ar*H), 125.9 (*Ar*H), 117.7 (=CH_2), 63.7 (*C*H), 61.4 (CH_2O), 43.8 (CH_2N), 41.9 (CH_2Ph), 33.9 (CH_2CH_2N), 31.7 (Q^t*Bu*), 26.8 (^{t}*Bu*) ; m/z (ES) $[M+Na]^+$ 466.3

93a

(S)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)-3-phenylpropan-1-ol



Chemical Formula: $C_{28}H_{37}NO_2Si$
Exact Mass: 447.26
Molecular Weight: 447.68

Procedure **G** was followed using the following amounts:

Amine **69a** (1 eq, 6.40 mmol, 967 mg) in DCM (1 M, 6.5 mL)

Na_2SO_4 (1.02 eq, 6.53 mmol, 927 mg)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 6.40 mmol, 2.00 g) in DCM (1.75 M, 4.00 mL)

$NaBH_4$ (1.5 eq, 9.60 mmol, 363 mg)

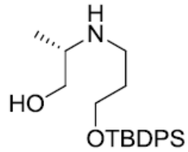
MeOH (1 M, 6.5 mL)

Yield: 2.86 g, >99 %, purple oil.

IR υ (cm^{-1}) 3248 (OH), 2930 (CH), 1589 (Ar), 1105 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (app dd, 4H (Ar*H*)), 7.47-7.36 (stack, 6H (Ar*H*)), 7.31-7.15 (stack, 5H (Ar*H*)), 3.69 (t, 2H, J = 6.0 Hz (CH_2OSi)), 3.58 (dd, 1H, J = 4.0, 10.5 Hz (C*H*HOH)), 3.27 (dd, 1H, J = 5.5, 10.5 Hz (CH*H*OH)), 2.87 (m, 1H, (C*H*)), 2.74 (stack, 4H (CH_2Ph, CH_2N)), 2.03 (brs, 2H (O*H*, N*H*)), 1.67 (p, 2H, J = 6.0 Hz (CH_2CH_2N)), 1.05 (s, 9H, (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.6 (*QAr*), 135.6 (*Ar*H), 133.8 (*QAr*), 129.6 (*Ar*H), 129.2 (*Ar*H), 128.5 (*Ar*H), 127.7 (*Ar*H), 126.4 (*Ar*H), 62.3 (CH_2O), 62.1 (CH_2O), 60.1 (*C*H), 43.8 (CH_2N), 38.1 (CH_2Ph), 33.0 (CH_2CH_2N), 26.9 (^{t}*Bu*), 19.2 (*Q*^{t}*Bu*); m/z (ES) $[M+Na]^+$ 470.5; $C_{28}H_{37}NO_2SiNa$ requires 470.2491, found 470.2483

93b

(S)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)propan-1-ol



Chemical Formula: $C_{22}H_{33}NO_2Si$
Exact Mass: 371.23
Molecular Weight: 371.59

Procedure **G** was followed using the following amounts:

L-alaninol (1 eq, 13.31 mmol, 1.00 g) in DCM (1 M, 13.30 mL)

Na_2SO_4 (1.02 eq, 13.58 mmol, 1.93 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 13.31 mmol, 4.16 g) in DCM (1.7 M, 8.00 mL)

$NaBH_4$ (1.5 eq, 19.97 mmol, 755 mg)

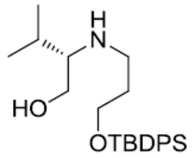
MeOH (1 M, 13.30 mL)

Yield: 3.27 g, 66 %, colourless oil.

R_f 0.34 (10 % MeOH in DCM); IR υ (cm^{-1}) 3299 (OH), 2930 (CH), 1589 (Ar), 1106 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (app dd, 4H (Ar*H*)), 7.46-7.35 (stack, 6H (Ar*H*)), 3.74 (t, 2H, *J* = 6.0 Hz (C*H₂*OSi)), 3.57 (dd, 1H, *J* = 4.0, 10.5 Hz (C*H*HOH)), 3.24 (dd, 1H, *J* = 7.0, 10.5 Hz (CH*H*OH)), 2.86 (dd, 1H, *J* = 7.0, 11.5 Hz (C*H*HN)), 2.81-2.71 (m, 1H (C*H*)), 2.66 (dd, 1H, *J* = 6.5, 11.5 Hz (CH*H*N)), 2.12 (brs, 2H (O*H*, N*H*)), 1.74 (ddt, 2H, *J* = 6.0, 6.5, 7.0 Hz (C*H₂*CH₂N)), 1.05 (s, 9H, (^{t}*Bu*)) 1.03 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6 (*Ar*H), 134.9, (ArH), 133.8 (*QAr*), 129.7 (*Ar*H), 129.5 (*Ar*H), 127.7 (*Ar*H), 65.4 (*C*H₂OH), 62.4 (*C*H₂OSi), 54.4 (*C*H), 44.1 (*C*H₂N), 32.9 (*C*H₂CH₂N), 26.9 (^{t}*Bu*), 19.2 (*Q*^{t}*Bu*), 17.2 (*C*H₃); m/z (ES) $[M+H]^+$ 372.3; $C_{22}H_{34}NO_2Si$ requires 372.2359, found 372.2346

93c

(*S*)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)-3-methylbutan-1-ol



Chemical Formula: $C_{24}H_{37}NO_2Si$
Exact Mass: 399.26
Molecular Weight: 399.64

Procedure **G** was followed using the following amounts:

L-valinol (1 eq, 9.69 mmol, 1.00 g) in DCM (1 M, 9.70 mL)

Na_2SO_4 (1.02 eq, 9.89 mmol, 1.40 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 9.69 mmol, 3.03 g) in DCM (1.7 M, 5.80 mL)

$NaBH_4$ (1.5 eq, 14.54 mmol, 550 mg)

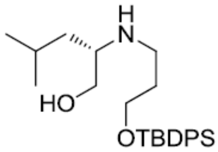
MeOH (1 M, 9.70 mL)

Yield: 1.80 g, 47 %, colourless oil.

R_f 0.40 (10 % MeOH in DCM); IR υ (cm^{-1}) 3348 (OH), 2931 (CH), 1105 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72-7.62 (stack, 4H (Ar*H*)), 7.52-7.35 (stack, 6H (Ar*H*)), 3.77 (t, 2H, *J* = 6.0 Hz (C*H₂*OSi)), 3.61 (dd, 1H, *J* = 4.5, 10.5 Hz (C*H*HOH)), 3.30 (dd, 1H, *J* = 7.5, 10.5 Hz (CH*H*OH)), 2.84 (dt, 1H, *J* = 7.0, 11.5 Hz (C*H*HN)), 2.70 (dt, 1H, *J* = 7.0, 11.5 Hz (CH*H*N)), 2.38 (ddd, 1H, *J* = 4.5, 7.0, 7.5 Hz (C*H*)), 2.12 (brs, 2H (O*H*, N*H*)), 1.80 (oct, 1H, *J* = 7.0 Hz (C*H*Me_2)), 1.74 (dt, 2H, *J* = 6.0, 7.0 Hz (C$H_2$$CH_2$N)), 1.07 (s, 9H, (^{t}*Bu*)) 0.97 (d, 3H, *J* = 7.0 Hz (*Me*)), 0.90 (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6 (*Ar*H), 134.9, (*Ar*H), 133.8 (*QAr*), 129.6 (*Ar*H), 127.7 (*Ar*H), 64.4 (*C*H), 62.3 (*C*H_2OSi), 60.4 (*C*H_2OH), 44.1 (*C*H_2N), 33.4 (*C*$H_2$$CH_2$N), 26.9 (^{t}*Bu*), 19.7 (*C*H_3), 19.2 (*Q*^{t}*Bu*), 17.2 (*C*H_3); m/z (ES) $[M+H]^+$ 400.3; $C_{24}H_{38}NO_2Si$ requires 400.2672, found 400.2679

93d

(S)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)-4-methylpentan-1-ol



Chemical Formula: $C_{25}H_{39}NO_2Si$
Exact Mass: 413.28
Molecular Weight: 413.67

Procedure **G** was followed using the following amounts:

L-leucinol (1 eq, 8.53 mmol, 1.00 g) in DCM (1 M, 8.50 mL)

Na_2SO_4 (1.02 eq, 8.70 mmol, 1.24 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 8.53 mmol, 2.67 g) in DCM (1.7 M, 5.0 mL)

$NaBH_4$ (1.5 eq, 12.80 mmol, 484 mg)

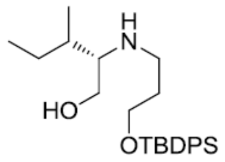
MeOH (1 M, 8.5 mL)

Yield: 2.22 g, 63 %, colourless oil.

R_f 0.46 (10 % MeOH in DCM); IR υ (cm^{-1}) 3301 (OH), 2953 (CH), 1106 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73-7.63 (stack, 4H (Ar*H*)), 7.49-7.35 (stack, 6H (Ar*H*)), 3.76 (t, 2H, *J* = 6.0 Hz (CH_2OSi)), 3.62 (dd, 1H, *J* = 4.0, 10.5 Hz (C*H*HOH)), 3.21 (dd, 1H, *J* = 6.5, 10.5 Hz (CH*H*OH)), 2.87-2.65 (stack, 3H (CH_2N, C*H*)), 1.94 (brs, 2H (O*H*, N*H*)), 1.74 (dt, 2H, *J* = 6.0, 6.5 Hz (CH_2CH_2N)), 1.64 (non, 1H, *J* = 7.0 Hz (C*H*Me_2)), 1.40-1.31 (m, 1H (C*H*HCH)), 1.28-1.14 (m, 1H (CH*H*CH)), 1.07 (s, 9H (^{t}*Bu*)) 0.93 (s, 3H (*Me*)), 0.91 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6 (*Ar*H), 134.9, (ArH), 133.8 (*QAr*), 129.6 (*Ar*H), 127.7 (*Ar*H), 63.2 (*C*H_2OH), 62.3 (*C*H_2OSi), 56.7 (*C*H), 43.9 (*C*H_2N), 41.4 (*C*H_2CH), 33.2 (*C*H_2CH_2N), 26.9 (^{t}*Bu*), 25.0 (*C*HMe_2), 23.1 (*Me*), 22.7 (*Me*) 19.2 (*Q*^{t}*Bu*); m/z (ES) $[M+H]^+$ 414.4; $C_{25}H_{40}NO_2Si$ requires 414.2828, found 414.2834

93e

(2S,3R)-2-(3-(tert-Butyldiphenylsilyloxy)propylamino)-3-methylpentan-1-ol



Chemical Formula: $C_{25}H_{39}NO_2Si$
Exact Mass: 413.28
Molecular Weight: 413.67

Procedure **G** was followed using the following amounts:

L-isoleucinol (1 eq, 8.53 mmol, 1.00 g) in DCM (1 M, 8.5 mL)

Na_2SO_4 (1.02 eq, 8.70 mmol, 1.24 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 8.53 mmol, 2.67 g) in DCM (1.7 M, 5.0 mL)

$NaBH_4$ (1.5 eq, 12.80 mmol, 484 mg)

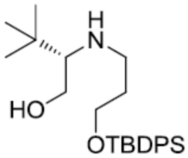
MeOH (1 M, 8.5 mL)

Yield: 2.86 g, 81 %, colourless oil.

R_f 0.40 (10 % MeOH in DCM); IR υ (cm^{-1}) 3336 (OH), 2958 (CH), 1106 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73-7.65 (stack, 4H (Ar*H*)), 7.46-7.35 (stack, 6H (Ar*H*)), 3.75 (t, 2H, *J* = 6.0 Hz (CH_2OSi)), 3.56 (dd, 1H, *J* = 4.5, 10.5 Hz (C*H*HOH)), 3.25 (dd, 1H, *J* = 8.0, 10.5 Hz (CH*H*OH)), 2.82 (dt, 1H, *J* = 7.0, 11.5 Hz (C*H*HN)), 2.63 (dt, 1H, *J* = 7.0, 11.5 Hz (CH*H*N)), 2.48 (ddd, 1H, *J* = 4.5, 7.0, 8.0 Hz (C*H*)), 1.91 (brs, 2H (O*H*, N*H*)), 1.71 (dt, 2H, *J* = 6.0, 7.0 Hz (CH_2CH_2N)), 1.62-1.53 (m, 1H, (C*H*CH_3)), 1.49-1.39 (m, 1H (C*H*HCH_3)), 1.26-1.10 (m, 1H (CH*H*CH_3)), 1.05 (s, 9H (^{t}*Bu*)) 0.91 (t, 3H, *J* = 7.5 Hz (CH_3CH_2)), 0.82 (d, 3H, *J* = 7.0 Hz (CH_3CH)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6 (*Ar*H), 134.8, (*Ar*H), 133.9 (*QAr*), 129.6 (*Ar*H), 127.7 (*Ar*H), 62.6 (*C*H), 62.3 (*C*H_2OSi), 60.2 (*C*H_2OH), 44.0 (*C*H_2N), 35.4 (*C*HCH_3), 33.4 (*C*H_2CH_2N), 26.9 (^{t}*Bu*), 26.4 (*C*H_2CH_3), 19.2 (*Q*^{t}*Bu*), 14.4 (*C*H_3CH), 11.8 (*C*H_3CH_2); m/z (ES) $[M+H]^+$ 414.3; $C_{25}H_{40}NO_2Si$ requires 414.2828, found 414.2823

93f

(S)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)-3,3-dimethylbutan-1-ol



Chemical Formula: $C_{25}H_{39}NO_2Si$
Exact Mass: 413.28
Molecular Weight: 413.67

Procedure **G** was followed using the following amounts:

L-*tert*-leucinol (1 eq, 8.53 mmol, 1.00 g) in DCM (1 M, 8.5 mL)

Na_2SO_4 (1.02 eq, 8.70 mmol, 1.24 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 8.53 mmol, 2.67 g) in DCM (1.7 M, 5.0 mL)

$NaBH_4$ (1.5 eq, 12.80 mmol, 484 mg)

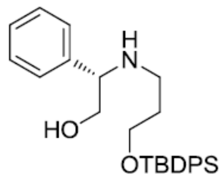
MeOH (1 M, 8.5 mL)

Yield: 2.09 g, 59 %, colourless oil.

R_f 0.44 (10 % MeOH in DCM); IR υ (cm^{-1}) 3353 (OH), 2931 (CH), 1106 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78-7.66 (stack, 4H (Ar*H*)), 7.52-7.38 (stack, 6H (Ar*H*)), 3.78 (t, 2H, *J* = 6.0 Hz (C*H₂*OSi)), 3.61 (dd, 1H, *J* = 4.5, 10.5 Hz (C*H*HOH)), 3.32 (dd, 1H, *J* = 7.0, 10.5 Hz (CH*H*OH)), 2.97 (dt, 1H, *J* = 7.0, 11.5 Hz (C*H*HN)), 2.77 (dt, 1H, *J* = 7.0, 11.5 Hz (CH*H*N)), 2.29 (dd, 1H, *J* = 4.5, 7.0 Hz (C*H*)), 1.80-1.70 (m, 2H (CH_2CH_2N)), 1.08 (s, 9H (^{t}*Bu*Si)), 0.95 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6 (*Ar*H), 134.8, (*Ar*H), 133.8 (*QAr*), 129.6 (*Ar*H), 127.7 (*Ar*H), 67.8 (*C*H), 62.2 (CH_2OSi), 59.9 (CH_2OH), 47.4 (CH_2N), 34.4 (Q^t*Bu*), 33.7 (CH_2CH_2N), 27.2 (^{t}*Bu*), 26.9 (^{t}*Bu*Si), 19.2 (Q^t*Bu*Si); m/z (ES) $[M+H]^+$ 414.3; $C_{25}H_{40}NO_2Si$ requires 414.2828, found 414.2825

93g

(S)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)-2-phenylethanol



Chemical Formula: $C_{27}H_{35}NO_2Si$
Exact Mass: 433.24
Molecular Weight: 433.66

Procedure **G** was followed using the following amounts:

L-phenylglycinol (1 eq, 7.29 mmol, 1.00 g) in DCM (1 M, 7.3 mL)

Na_2SO_4 (1.02 eq, 7.44 mmol, 1.06 g)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 7.29 mmol, 2.28 g) in DCM (1.7 M, 4.4 mL)

$NaBH_4$ (1.5 eq, 10.94 mmol, 414 mg)

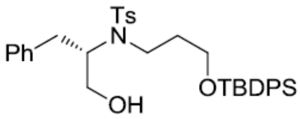
MeOH (1 M, 7.3 mL)

Yield: 2.05 g, 65 %, yellow oil.

R_f 0.50 (10 % MeOH in DCM); IR υ (cm^{-1}) 3302 (OH), 2930 (CH), 1106 (OSi); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73-7.62 (stack, 4H (Ar*H*)), 7.45-7.23 (stack, 11H (Ar*H*)), 3.87-3.66 (stack, 4H (CH, CH_2OSi, CHHOH)), 3.54-3.45 (m, 1H (CHHOH)), 2.71 (dt, 1H, J = 7.0, 11.5 Hz (CHHN)), 2.60 (dt, 1H, J = 6.5, 11.5 Hz (CHHN)), 2.11 (brs, 2H (O*H*, N*H*)), 1.72 (ddt, 2H, *J* = 6.0, 6.5, 7.0 Hz (C$H_2$$CH_2$N)), 1.02 (s, 9H, (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.0 (*Q*Ph), 135.6 (*Ar*H), 134.8, (*Ar*H), 133.9 (*QAr*), 129.6 (*Ar*H), 128.6 (*Ar*H), 127.7 (*Ar*H), 127.5 (*Ar*H), 127.1 (*Ar*H), 66.5 (*C*H_2OH), 64.6 (*C*H), 62.5 (*C*H_2OSi), 44.6 (*C*H_2N), 32.9 (*C*$H_2$$CH_2$N), 26.9 (^{t}*Bu*), 19.2 (*Q*^{t}*Bu*); m/z (ES) $[M+H]^+$ 434.3; $C_{27}H_{36}NO_2Si$ requires 434.2515, found 434.2522

95a

N-Tosyl-(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)propylamino)-3-phenylpropan-1-ol



Chemical Formula: $C_{35}H_{43}NO_4SSi$
Exact Mass: 601.27
Molecular Weight: 601.87

Procedure **B** was followed using the following amounts:

Amine **93a** (1 eq, 2.23 mmol, 1.00 g) in DCM (0.11 M, 20 mL)

Triethylamine (2 eq, 4.47 mmol, 623 μl)

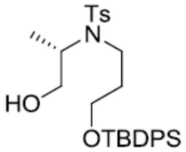
Tosyl chloride (1 eq, 2.23 mmol, 426 mg) in DCM (0.26 M, 8.50 mL)

The product was purified by column chromatography, eluting with 25 % EtOAc in hexane, to yield a green oil (564 mg, 42 %).

R_f 0.48 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3524 (OH), 2925 (CH), 1594 (Ar), 1326/1148 (SO_2N), 1086 (CO), 1103 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62-7.63 (stack, 6H (Ar*H*)), 7.47-7.36 (stack, 6H (Ar*H*)), 7.26-7.16 (stack, 5 H (Ar*H*)), 7.03-6.98 (stack, 2H (Ar*H*)), 4.06-3.97 (m, 1H (C*H*)), 3.76-3.65 (m, 2H (C*H₂*OSi)), 3.64-3.53 (m, 2H (C*H₂*OH)), 3.40 (dd, 2H, *J* = 7.5, 8.5 Hz (C*H₂*N)), 2.69 (dd, 1H *J* = 9.0, 13.5 Hz (C*H*HPh)), 2.58 (dd, 1H, *J* = 5.5, 13.5 Hz (CH*H*Ph)), 2.41 (s, 3H (ArC*H₃*)), 2.02 (dd, 1H, *J* = 5.5, 6.5 Hz (O*H*)), 1.98-1.87 (m, 2H (C*H₂*CH₂N)), 1.08 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3 (*QAr*), 137.7 (*QAr)*, 127.8 (*Ar*H), 127.3 (*Ar*H), 126.6 (*Ar*H), 62.5 (*C*H₂OH), 62.2 (*C*HN), 61.5 (*C*H₂OSi), 42.1 (*C*H₂N), 36.3 (*C*H₂Ph), 34.0 (*C*H₂CH₂N),27.0 (^{t}*Bu*), 21.5 (Ar*C*H₃), 19.3 (*Q*^{t}*Bu*); m/z (ES) $[M+Na]^+$ 624.5; $C_{35}H_{43}NO_4SiSNa$ requires 624.2580, found 624.2584

95b

N-Tosyl-(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)propylamino)propan-1-ol



Chemical Formula: $C_{29}H_{39}NO_4SSi$
Exact Mass: 525.24
Molecular Weight: 525.77

Procedure **B** was followed using the following amounts:

Amine **93b** (1 eq, 0.538 mmol, 200 mg) in DCM (0.1 M, 5.4 mL)

Triethylamine (2 eq, 1.08 mmol, 150 μl)

Tosyl chloride (2 eq, 1.08 mmol, 205 mg)

The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a colourless oil (196 mg, 69 %).

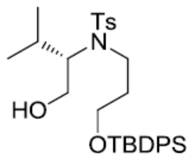
R_f 0.48 (15 % EtOAc in hexane); IR υ (cm^{-1}) 3516 (OH), 2930 (CH), 1598 (Ar), 1332/1151 (SO_2N), 1088 (CO), 1106 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62-7.63 (stack, 6H (Ar*H*)), 7.47-7.36 (stack, 4H (Ar*H*)), 7.26-7.16 (stack, 2 H (Ar*H*)), 7.03-6.98 (stack, 2H (Ar*H*)), 4.06-3.97 (m, 1H (C*H*)), 3.76-3.65 (m, 2H (CH_2OSi)), 3.64-3.53 (m, 2H (CH_2OH)), 3.40 (dd, 2H, *J* = 7.5, 8.5 Hz (CH_2N)), 2.58 (m, 3H (*Me*)), 2.41 (s, 3H (ArCH_3)), 2.02 (dd, 1H, *J* = 5.5, 6.5 Hz (O*H*)), 1.98-1.87 (m, 2H (CH_2CH_2N)), 1.08 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3 (*QAr*), 137.7 (*QAr)*, 135.6 (*Ar*H), 133.6 (QAr), 129.7 (*Ar*H), 129.7 (*Ar*H), 127.7 (*Ar*H), 127.2 (*Ar*H), 64.7 (*C*H_2OH), 61.5 (*C*H_2OSi), 55.8 (*C*HN), 40.9 (*C*H_2N), 34.3 (*C*H_2CH_2N), 26.9 (^{t}*Bu*), 21.5 (Ar*C*H_3), 19.2 (*Q*^{t}*Bu*), 14.3 (*C*H_3)

Further isolated was the doubly tosylated product:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78-7.61 (stack, 8H (Ar*H*)), 7.51-7.22 (stack, 10H (Ar*H*)), 4.19-4.10 (m, 1H (C*H*)), 4.05 (dd, 1H, *J* = 6.5, 9.5 Hz (C*H*HOTs)), 3.92 (dd, 1H, *J* = 6.5, 9.5 Hz (CH*H*OTs)), 3.62 (t, 2H, *J* = 5.5 Hz (C*H₂*OSi)), 3.24 (ddd, 1H, *J* = 3.5, 8.0, 10.0 (C*H*HN)), 3.15 (ddd, 1H, *J* = 3.5, 8.0, 15.0 (CH*H*N)), 2.45 (s, 3H (ArC*H₃*)), 2.43 (s, 3H (ArC*H₃*)), 1.87-1.66 (m, 2H (C*H₂*CH₂N)), 1.11 (d, 3H, *J* = 6.8 Hz (*Me*)), 1.06 (s, 9H (^{t}*Bu*))

95c

N-Tosyl-(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)propylamino)-3-methylbutan-1-ol



Chemical Formula: $C_{31}H_{43}NO_4SSi$
Exact Mass: 553.27
Molecular Weight: 553.83

Procedure **B** was followed using the following amounts:

Amine **93c** (1 eq, 0.50 mmol, 200 mg) in DCM (0.1 M, 5.0 mL)

Triethylamine (2 eq, 1.00 mmol, 140 μl)

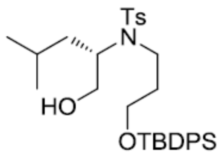
Tosyl chloride (2 eq, 1.00 mmol, 191 mg)

The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a colourless oil (163 mg, 59 %).

IR υ (cm^{-1}) 3535 (OH), 2931 (CH), 1598 (Ar), 1328/1148 (SO_2N), 1104 (SiO), 1086 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (app d, 2H (Ar*H*)), 7.68-7.61 (stack, 4H (*Ph*)), 7.51-7.31 (stack, 6H (*Ph*)), 7.28 (app d, 2H (Ar*H*)), 3.79 (ddd, 1H, *J* = 4.0, 6.0, 11.5 (C*H*HOH)), 3.67 (t, 2H, *J* = 5.4 Hz (C*H₂*OSi)), 3.60 (ddd, 1H, *J* = 4.0, 6.0, 11.5 Hz (CH*H*OH)), 3.46 (dt, 1H, *J* = 4.0, 10.0 Hz (C*H*)), 3.35 (dt, 1H, *J* = 7.5, 15.0 Hz (C*H*HN)), 3.31 (dt, 1H, *J* = 7.5, 15.0 Hz (CH*H*N)), 2.43 (s, 3H (ArC*H₃*)), 2.01 (t, 1H, *J* = 6.0 Hz (O*H*)), 1.98-1.87 (m, 2H (C*H₂*CH₂N)), 1.79 (dsept, 1H, *J* = 6.5, 10.0 Hz (C*H*Me$_2$)), 1.07 (s, 9H (^{t}*Bu*)), 0.93 (d, 3H, *J* = 6.5 Hz (*Me*)), 0.68 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 143.2 (*QAr*), 138.1 (*QAr)*, 135.5 (*Ar*H), 133.6 (*QAr*), 129.7 (*Ar*H), 129.5 (*Ar*H), 127.7 (*Ar*H), 127.4 (*Ar*H), 66.8 (*C*HN), 62.2 (*C*H$_2$OH), 61.6 (*C*H$_2$OSi), 42.3 (*C*H$_2$N), 33.6 (*C*H$_2$CH$_2$N), 28.5 (*C*HMe$_2$), 26.8 (^{t}*Bu*), 21.5 (Ar*C*H$_3$), 20.7 (*C*H$_3$), 20.2 (*C*H$_3$), 19.2 (*Q*^{t}*Bu*); m/z (ES) [M+Na]$^+$ 576.3; $C_{31}H_{43}NO_4SiSNa$ requires 576.2580, found 576.2589

95d

N-Tosyl-(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)propylamino)-4-methylpentan-1-ol



Chemical Formula: $C_{32}H_{45}NO_4SSi$
Exact Mass: 567.28
Molecular Weight: 567.85

Procedure **B** was followed using the following amounts:

Amine **93d** (1 eq, 0.48 mmol, 200 mg) in DCM (0.1 M, 4.8 mL)

Triethylamine (2 eq, 0.97 mmol, 140 μl)

Tosyl chloride (2 eq, 0.97 mmol, 184 mg)

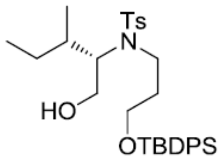
The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a colourless oil (219 mg, 80 %).

IR υ (cm^{-1}) 3536 (OH), 2932 (CH), 1599 (Ar), 1324/1146 (SO$_2$N), 1106 (SiO), 1088 (CO); ^{1}H-NMR (300 MHz, CDCl3) δ 7.92-7.00 (stack, 14H (Ar*H*)), 4.06-3.29 (stack, 5H (C*H*, C*H$_2$*OSi, C*H$_2$*OH)), 3.23-2.96 (m, 2H (C*H$_2$*N)), 2.41 (s, 3H (ArC*H$_3$*)), 2.14-1.56 (stack, 4H (C*H$_2$*CH$_2$N, C*H$_2$*CH)), 1.08 (s, 9H (^{t}*Bu*)), 0.93 (s, 6H (*Me*)), 0.85-0.64 (m, 1H (C*H*Me$_2$)); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 143.0 (*QAr*), 137.6 (*QAr*), 134.0 (*QAr*), 130.1 (*Ar*H), 130.0 (*Ar*H), 129.5 (*Ar*H), 129.3 (*Ar*H), 128.3 (*Ar*H), 63.3 (*C*H$_2$OH), 61.4 (*C*H$_2$OSi), 56.9 (*C*HN), 44.6 (*C*H$_2$N), 37.8 (*C*H$_2$CH), 31.7

(Q^tBu), 30.2 (CH_2CH_2N), 26.8 (^tBu), 25.1 ($CHMe_2$), 23.2 (Me), 21.3 ($ArCH_3$); m/z (ES) $[M+Na]^+$ 590.28

95e

N-Tosyl-(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)propylamino)-4-methylpentan-1-ol



Chemical Formula: $C_{32}H_{45}NO_4SSi$
Exact Mass: 567.28
Molecular Weight: 567.85

Procedure **B** was followed using the following amounts:

Amine **93e** (1 eq, 0.48 mmol, 200 mg) in DCM (0.1 M, 4.8 mL)

Triethylamine (2 eq, 0.97 mmol, 140 μl)

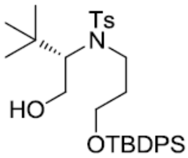
Tosyl chloride (2 eq, 0.97 mmol, 184 mg)

The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a colourless oil (219 mg, 80 %).

IR υ (cm^{-1}) 3499 (OH), 1603 (Ar), 1332/1158 (SO_2N), 1102 (SiO), 1082 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71-7.13 (stack, 14H (Ar*H*)), 3.73-3.15 (stack, 7H (C*H*, CH_2OSi, CH_2OH, CH_2N)), 2.33 (s, 3H ($ArCH_3$)), 1.95-1.17 (stack, 5H (CH_2CH_2N, CH_2CH_3, $CHCH_3$)), 0.97 (s, 9H (^tBu)), 0.80 (t, 3H, *J* = 6.0 Hz (CH_3CH_2)), 0.67 (d, 3H, *J* = 1.5 Hz (CH_3CH)). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.2 (*QAr*), 137.6 (*QAr*), 134.3 (*QAr*), 130.1 (*Ar*H), 129.7 (*Ar*H), 129.5 (*Ar*H), 129.2 (*Ar*H), 128.1 (*Ar*H), 64.1 (*C*HN), 61.4 (CH_2OSi) 60.6 (CH_2OH), 44.8 (CH_2N), 34.5 (*C*HMe), 31.7 (Q^tBu), 30.2 (CH_2CH_2N), 26.9 (^tBu), 26.1 (CH_2Me), 21.3 ($ArCH_3$), 18.3 (*Me*CH), 11.6 ($MeCH_2$); m/z (ES) $[M+Na]^+$ 590.3

95f

N-Tosyl-(*S*)-2-(3-(*tert*-butyldiphenylsilyloxy)propylamino)-3,3-dimethylbutan-1-ol



Chemical Formula: $C_{32}H_{45}NO_4SSi$
Exact Mass: 567.28
Molecular Weight: 567.85

Procedure **B** was followed using the following amounts:

Amine **93f** (1 eq, 0.48 mmol, 200 mg) in DCM (0.1 M, 4.8 mL)

Triethylamine (2 eq, 0.97 mmol, 140 μl)

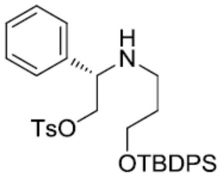
Tosyl chloride (2 eq, 0.97 mmol, 184 mg)

The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a colourless oil (61 mg, 22 %).

IR υ (cm^{-1}) 3498 (OH), 2859 (CH), 1599 (Ar), 1330/1153 (SO_2N), 1106 (SiO), 1086 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78-7.75 (stack, 2H (Ar*H*)), 7.66-7.64 (stack, 4H (Ar*H*)), 7.48-7.37 (stack, 6H (Ar*H*)), 7.30-7.28 (stack, 2H (Ar*H*)), 3.82-3.61 (stack, 5H (C*H*, C*H₂*OSi, C*H₂*OH)), 3.39-3.34 (m, 2H (C*H₂*N)), 2.44 (s, 3H (ArC*H₃*)), 2.15-1.99 (m, 2H (C*H₂*CH₂N)), 1.67 (brs, 1H (OH)), 1.05 (s, 9H (^{t}*Bu*Si)), 0.92 (s, 9H, (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.2 (*QAr*), 137.6 (*QAr*), 134.3 (*QAr*), 130.1 (*Ar*H), 129.6 (*Ar*H), 129.5 (*Ar*H), 129.2 (*Ar*H), 128.1 (*Ar*H), 74.4 (*C*HN), 61.6 (*C*H₂OSi) 57.7 (*C*H₂OH), 45.2 (*C*H₂N), 31.5 (*Q*^{t}*Bu*Si), 30.4 (*C*H₂CH₂N), 28.6 (*Q*^{t}*Bu*), 27.3 (^{t}*Bu),* 26.8 (^{t}*Bu*Si), 21.3 (Ar*C*H₃); m/z (ES) $[M+Na]^+$ 590.3

95g

(*S*)-2-(3-(*tert*-Butyldiphenylsilyloxy)propylamino)-2-phenylethyl-4-methylbenzene sulfonate



Chemical Formula: $C_{34}H_{41}NO_4SSi$
Exact Mass: 587.25
Molecular Weight: 587.84

Procedure **B** was followed using the following amounts:

Amine **93g** (1 eq, 0.46 mmol, 200 mg) in DCM (0.1 M, 4.6 mL)

Triethylamine (2 eq, 0.92 mmol, 129 μl)

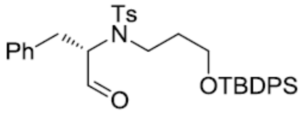
Tosyl chloride (2 eq, 0.92 mmol, 176 mg)

The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a colourless oil (44 mg, 16 %).

IR υ (cm^{-1}) 3521 (NH), 2929 (CH), 1596 (Ar), 1340/1155 (SO2N), 1109 (SiO), 1088 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (app d, 2H (Ar*H*)), 7.61-7.57 (stack, 4H (Ar*H*)), 7.48-7.35 (stack, 6H (Ar*H*)), 7.33-7.20 (stack, 5H (Ar*H*)), 7.01 (app d, 2H (Ar*H*)), 5.07 (dd, 1H, *J* = 6.5, 8.0 Hz (C*H*)), 4.07 (m, 2H, C*H₂*OTs)), 3.59 (ddd, 1H *J* = 4.5, 6.5, 11.0 Hz (CH*H*OSi)), 3.50 (ddd, 1H *J* = 4.5, 7.5, 11.0 Hz (CH*H*OSi)), 3.26 (dt, 2H, *J* = 5.5, 10.5 Hz (C*H*$_2$N)), 2.46 (s, 3H (ArC*H*$_3$)), 2.17 (brs, 1H (NH)), 1.84-1.59 (m, 2H (C*H*$_2$CH$_2$N)), 1.03 (s, 9H (^{t}*Bu*)). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.4 (*QAr*), 138.0 (*QAr*), 136.1 (*QAr*), 135.5 (*Ar*H), 133.6 (*QAr*), 133.5 (*QAr*), 129.7 (*Ar*H), 128.7 (*Ar*H), 128..2 (*Ar*H), 128.1 (*Ar*H), 127.7 (*Ar*H), 127.7 (*Ar*H), 127.4 (*Ar*H), 62.2 (*C*H$_2$OH), 62.2 (*C*H), 61.5 (*C*H$_2$OSi), 42.6 (*C*H$_2$N), 33.7 (*C*H$_2$CH$_2$N), 26.9 (^{t}*Bu*), 21.6 (*Ar*CH$_3$), 19.2 (*Q*^{t}*Bu*); m/z (ES) $[M+Na]^+$ 610.3 (no negative ion found therefore no free OH i.e. Ts on oxygen)

96a

N-Tosyl-(*S*)-2-((3-(*tert*-butyldiphenylsilyloxy)propyl)amino)-3-phenylpropanal



Chemical Formula: $C_{35}H_{41}NO_4SSi$
Exact Mass: 599.25
Molecular Weight: 599.85

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 2.89 mmol, 0.24 mL) in DCM (0.33 M, 8.00 mL)

DMSO (2.4 eq, 6.30 mmol, 0.45 mL)

Alcohol **95a** (1 eq, 2.63 mmol, 1.58 g) in DCM (1 M, 2.60 mL)

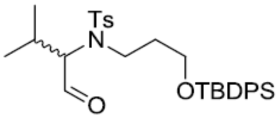
Triethylamine (5 eq, 13.13 mmol, 1.83 mL)

The product was purified by column chromatography, eluting with 15 % EtOAc in heptane, to yield a yellow oil (1.28 g, 81 %).

R_f 0.20 (15 % EtOAc in heptane); IR υ (cm^{-1}) 2927 (CHO), 1656 (Ar), 1326/1144 (SO_2N), 1110 (SiO), 1083 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H (C*H*O)), 7.64-7.58 (stack, 4H (Ar*H*)), 7.54-7.51 (stack, 2H (Ar*H*)), 7.46-7.33 (stack, 6H (Ar*H*)), 7.22-7.16 (stack, 5H (Ar*H*)), 7.09-7.04 (stack, 2H (Ar*H*)), 4.48 (dd, 1H, *J* = 6.5, 8.0 Hz (C*H*)), 3.68-3.54 (m, 2H (CH_2OSi)), 3.38 (dd, 1H, *J* = 6.0, 14.5 Hz (C*H*HPh)), 3.28 (ddt, 2H, *J* = 8.0, 10.0, 15.0 Hz (CH_2N)), 2.74 (dd, 1H, *J* = 8.0, 14.5 Hz (CH*H*Ph)), 2.40 (s, 3H (ArCH_3)), 1.79-1.63 (m, 2H (CH_2CH$_2$N)), 1.03 (s, 9H (^{t}*Bu*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.9 (*C*HO), 143.6 (*QAr*), 142.6 (*QAr*), 138.9 (*QAr*), 137.1 (*QAr*), 135.5 (*Ar*H), 129.8 (*Ar*H), 129.0 (*Ar*H), 128.6 (*Ar*H), 127.7 (*Ar*H), 127.4 (*Ar*H), 126.7 (*Ar*H), 68.1 (*C*HN), 61.1 (*C*H$_2$OSi), 44.0 (*C*H$_2$N), 33.2 (*C*H$_2$CH$_2$N), 32.9 (*C*H$_2$Ph), 26.9 (^{t}*Bu*), 21.5 (Ar*C*H$_3$), 19.0 (*Q*^{t}*Bu*); m/z (ES) $[M+Na]^+$ 622.1; $C_{35}H_{41}NO_4SiSNa$ requires 622.2423, found 622.2429

96c

N-Tosyl-2-((3-((*tert*-butyldiphenylsilyl)oxy)propyl)amino)-3-methylbutanal



Chemical Formula: $C_{31}H_{41}NO_4SSi$
Exact Mass: 551.25
Molecular Weight: 551.81

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 1.99 mmol, 0.17 mL) in DCM (0.33 M, 5.0 mL)

DMSO (2.4 eq, 4.33 mmol, 0.31 mL)

Alcohol **95c** (1 eq, 1.81 mmol, 1.0 g) in DCM (1 M, 2.2 mL)

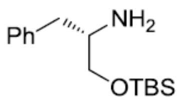
Triethylamine (5 eq, 9.03 mmol, 1.25 mL)

The product was purified by column chromatography, eluting with 20 % EtOAc in hexane, to yield a yellow oil (990 mg, >99 %).

R_f 0.57 (20 % EtOAc in hexane); IR υ (cm^{-1}) 2923 (CHO), 1646 (Ar), 1328/1139 (SO_2N), 1115 (SiO), 1081 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.53 (d, 1H, *J* = 1.0 Hz (C*H*O)), 7.71 (app d, 2H (Ar*H*)), 7.66-7.61 (stack, 4H (*Ph*)), 7.54-7.34 (stack, 6H (*Ph*)), 7.29 (app d, 2H (Ar*H*)), 3.94 (dd, 1H, *J* = 1.0, 10.0 Hz (C*H*)), 3.71-3.57 (m, 2H (CH_2O)), 3.30 (ddd, 2H, *J* = 6.0, 7.5, 10.5 Hz (CH_2N)), 2.44 (s, 3H (ArCH_3)), 2.19 (dsept, 1H, *J* = 6.5, 10.0 Hz (C*H*Me_2)), 1.99- 1.76 (m, 2H (CH_2CH_2N)), 1.07 (d, 3H, *J* = 6.5 Hz (*Me*)), 1.05 (s, 9H (^{t}*Bu*)), 0.92 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.9 (*C*HO), 143.5 (*QAr*), 142.6 (*QAr*), 137.3 (*Ar*H), 135.5 (*QAr*), 129.7 (*Ar*H), 127.7 (*Ar*H), 127.4 (*Ar*H), 72.0 (*C*HN), 61.3 (*C*H_2OSi), 44.3 (*C*H_2N), 33.4 (*C*H_2CH_2N), 27.2 (*C*HMe_2), 26.8 (^{t}*Bu*), 21.5 (Ar*C*H_3), 20.2 (*Me*), 19.9 (*Me*), 19.2 (*Q*^{t}*Bu*); m/z (ES) $[M+Na]^+$ 622.1; $C_{35}H_{41}NO_4SiSNa$ requires 622.2423, found 622.2429

97a

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-phenylpropan-2-amine[117]



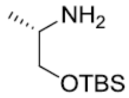
Chemical Formula: $C_{15}H_{27}NOSi$
Exact Mass: 265.19
Molecular Weight: 265.47

To a solution of alcohol **69a** (1 eq, 13.23 mmol, 2.00 g) and triethylamine (2 eq, 26.45 mmol, 3.69 mL) in DCM (1.65 M, 8 mL), was added TBSCl (1 eq, 13.23 mmol, 1.99 g) in DCM (1.65 M, 8 mL). The mixture stirred at RT for 48 hours then was diluted with sat. aq. ammonium chloride and extracted into DCM and washed with brine. Yield 3.46 g as a white solid (98 %).

R_f 0.64 (5 % MeOH in DCM); IR υ (cm^{-1}) 3370 (NH_2), 1251/833 (SiMe), 1093/774 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36-7.15 (stack, 5H (Ar*H*)), 3.58 (dd, 1H, *J* = 4.5, 9.5 (C*H*HO)), 3.43 (dd, 1H, *J* = 6.5, 9.5 Hz (CH*H*O)), 3.15-3.03 (m, 1H (C*H*)), 2.79 (dd, 1H, *J* = 8.5, 13.5 (C*H*HPh)), 2.51 (dd, 1H, *J* = 8.5, 13.5 (CH*H*Ph)), 1.63 (brs, 2H (N*H_2*)), 0.91 (s, 9H (*^{t}Bu*)), 0.06 (s, 3H (*Me*)), 0.06 (s, 3H (*Me*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.0 (*QAr*), 128.8 (*Ar*H), 128.1 (*Ar*H), 126.0 (*Ar*H), 70.8 (*C*H_2O), 54.9 (*C*HN), 39.6 (*C*H_2Ph), 30.6 (*Q^{t}Bu*), 25.9 (*^{t}Bu*), -2.3 (*Me*); m/z (ES) $[M+H]^+$ 266.1; $C_{15}H_{28}NOSi$ requires 266.1940, found 266.1934

97b

(*S*)-1-(*tert*-Butyldimethylsilyloxy)propan-2-amine



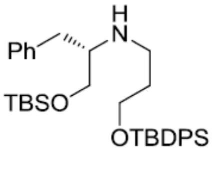
Chemical Formula: $C_9H_{23}NOSi$
Exact Mass: 189.15
Molecular Weight: 189.37

To a solution of alcohol **69b** (1 eq, 6.66 mmol, 500 mg) and triethylamine (2 eq, 13.31 mmol, 1.86 mL) in DCM (1.65 M, 4.0 mL), was added TBSCl (1 eq, 6.66 mmol, 1.00 g) in DCM (1.65 M, 4.0 mL). The mixture stirred at RT for 20 hours then was diluted with sat. aq. ammonium chloride and extracted into DCM and washed with brine. Yield 0.94 g as a colourless oil (75 %).

IR υ (cm^{-1}) 3321 (NH_2), 1258/831 (SiMe), 1090/775 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.53 (dd, 1H, *J* = 4.5, 9.5 Hz (C*H*HO)), 3.29 (dd, 1H, *J* = 7.5, 9.5 (CH*H*O)), 3.06-2.88 (m, 1H (C*H*)), 1.60 (brs, 2H (NH_2)), 1.03 (d, 3H, *J* = 6.5 Hz (CH_3)), 0.92 (s, 9H (^{t}*Bu*)), 0.07 (s, 6H (*Me*Si)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 69.9 (CH_2), 48.6 (*C*H), 25.9 (^{t}*Bu*), 19.3 (CH_3), 18.3 (*Q*^{t}*Bu*), -5.3 (CH_3Si); m/z (ES) $[M+H]^+$ 190.1; $C_9H_{24}NOSi$ requires 190.1627, found 190.1626

98a

(*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)-3-phenylpropan-2-yl)-3-(*tert*-butyldiphenylsilyloxy) propan-1-amine



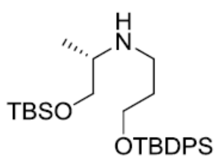
Chemical Formula: $C_{34}H_{51}NO_2Si_2$
Exact Mass: 561.35
Molecular Weight: 561.95

Alcohol **93a** (1 eq, 1.12 mmol, 500 mg) and triethylamine (2 eq, 2.23 mmol, 0.31 mL) were dissolved in DCM (1.67 M, 0.67 mL). *tert*-Butyldimethylsilyl chloride (1 eq, 1.12 mmol, 168 mg) in DCM (1.67 M, 0.67 mL) was added and the reaction mixture stirred at RT overnight. The reaction was quenched with aq. ammonium chloride, the products extracted into DCM and washed with brine to yield a purple oil. Yield 563 mg (89 %).

R_f 0.47 (20 % EtOAc in hexane); IR υ (cm^{-1}) 3071 (NH), 1590 (Ar), 1105 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (app dd, 4H (Ar*H*)), 7.49-7.38 (stack, 6H (Ar*H*)), 7.34-7.17 (stack, 5H (Ar*H*)), 3.71 (t, 2H, *J* = 6.5 Hz (CH_2OTBDPS)), 3.51 (dd, 2H, *J* = 1.0, 4.0 Hz (CH_2Ph)), 2.86 (dt, 1H, *J* = 4.0, 9.5 Hz (C*H*)), 2.81-2.73 (stack, 4H (CH_2N, CH_2OTBS)), 1.73 (quin, 2H, *J* = 6.5 Hz (CH_2 CH_2N)), 0.92 (s, 9H (^{t}*Bu*)), 0.06 (s, 3H (*Me*)), 0.04 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6 (*QAr*), 134.0 (*QAr*), 129.6 (*Ar*H), 129.3 (*Ar*H), 128.6 (*Ar*H), 128.3 (*Ar*H), 127.6 (*Ar*H), 126.1 (*Ar*H), 63.8 (*C*H_2Ph), 62.1 (*C*H_2OTBDPS), 60.9 (*C*H), 44.3 (*C*H_2N), 37.8 (*C*H_2OTBS), 33.3 (*C*$H_2$$CH_2$N), 26.9 (^{t}*Bu*), 25.9 (^{t}*Bu*), 19.2 (*Q*^{t}*Bu*), 18.3 (*Q*^{t}*Bu*); m/z (ES) $[M+Na]^+$ 584.4

98b

(*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-3-(*tert*-butyldiphenylsilyloxy)propan-1-amine



Chemical Formula: $C_{28}H_{47}NO_2Si_2$
Exact Mass: 485.31
Molecular Weight: 485.85

Procedure **G** was followed using the following amounts:

Amine **97b** (1 eq, 4.96 mmol, 939 mg) in DCM (1 M, 5.00 mL)

Na_2SO_4 (1.02 eq, 5.06 mmol, 718 mg)

3-(*tert*-butyldiphenylsilyloxy)propanal (1 eq, 4.96 mmol, 1.55 g) in DCM (1.75 M, 3.00 mL)

$NaBH_4$ (1.5 eq, 7.44 mmol, 281 mg)

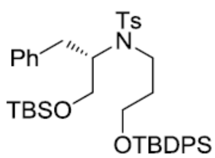
MeOH (1 M, 5.00 mL)

Yield: 2.01 g, 91 %, yellow oil.

R_f 0.05 (2.5 % MeOH in DCM); IR υ (cm^{-1}) 3071 (NH), 1088 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73-7.65 (stack, 4H (Ar*H*)), 7.49-7.32 (stack, 6H (Ar*H*)), 3.76 (t, 2H, *J* = 6.0 Hz (C*H₂*OTBDPS)), 3.49 (ddd, 2H, *J* = 6.0, 10.0, 16.5 Hz (CH_2N)), 2.88-2.64 (stack, 3H (C*H*, CH_2OTBS)), 1.89 (brs, 1H (N*H*)), 1.83-1.70 (m, 2H (CH_2CH_2N)), 1.07 (s, 9H (^{t}*Bu*)), 1.01 (d, 3H, *J* = 6.5 Hz (*Me*)), 0.91 (s, 9H (^{t}*Bu*)), 0.07 (s, 6H (*Me*Si)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.1 (*QAr*), 130.2 (*Ar*H), 130.0 (*Ar*H), 129.6 (*Ar*H), 72.4 (*C*HN), 71.2 (*C*H_2OTBS), 61.5 (*C*H_2OTBDPS), 43.2 (*C*H_2N), 33.9 (*C*H_2CH_2N), 31.4 (*Q*^{t}*Bu*), 30.4 (*Q*^{t}*Bu*), 26.7 (^{t}*Bu*), 25.4 (^{t}*Bu*), 17.4 (*Me*), -2.1 (*Me*Si); m/z (ES) $[M+Na]^+$ 508.3

99

N-Tosyl-(*S*)-*N*-(1-(*tert*-butyldimethylsilyloxy)-3-phenylpropan-2-yl)-3-(*tert*-butyldiphenylsilyloxy)propan-1-amine



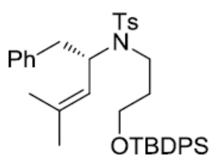
Chemical Formula: $C_{41}H_{57}NO_4SSi_2$
Exact Mass: 715.35
Molecular Weight: 716.13

Amine **98a** (1 eq, 8.85 mmol, 5.00 g), triethylamine (2 eq, 17.70 mmol, 2.47 mL) and tosyl chloride (1 eq, 8.85 mmol, 1.69 g) were mixed together in DCM (0.07 M, 130 mL) and stirred at RT overnight. The solvents were removed and the residue taken up into ethyl acetate. The white precipitate was removed by filtration under suction and the filtrate washed with $NaHCO_3$ and water. The product was purified by column chromatography, eluting with 5 % EtOAc in hexane, to yield a pale yellow oil (4.63 g, 73 %).

R_f 0.75 (25 % EtOAc in hexane); IR υ (cm^{-1}) 2929 (CH), 1733 (Ar), 1337/1154 (SO_2N), 1106 (Si); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71-7.10 (stack, 19H (Ar*H*)), 4.10-4.02 (m, 1H (C*H*)), 3.66 (dd, 2H, *J* = 4.0, 7.5 Hz (C*H₂*OTBDPS)), 3.59 (dd, 2H, *J* = 5.0, 10.5 (CH_2OTBS)), 3.52-3.29 (m, 2H (CH_2N)), 2.99 (dd, 1H, *J* = 8.0, 13.5 (C*H*HPh)), 2.77 (dd, 1H, *J* = 6.5, 13.5 (CH*H*Ph)), 2.40 (s, 3H (ArCH_3)), 1.96-1.84 (m, 2H (CH_2CH_2N)), 1.08 (s, 9H (^{t}*Bu*)), 0.85 (s, 9H (^{t}*Bu*)), -0.03 (s, 3H (*Me*)), -0.04 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.6 (*QAr*), 138.6 (*QAr*), 138.3 (*QAr*), 135.6 (*Ar*H), 133.7 (*QAr*), 129.7 (*Ar*H), 129.4 (*Ar*H), 129.2 (*Ar*H), 128.4 (*Ar*H), 127.7 (*Ar*H), 127.2 (*Ar*H), 126.3 (*Ar*H), 63.6 (*C*H_2OTBDMS), 61.8 (*C*H_2OTBDPS), 60.4 (*C*H), 42.6 (*C*H_2N), 36.5 (*C*H_2Ph), 34.0 (*C*H_2CH_2N), 26.9 (^{t}*Bu*), 25.9 (^{t}*Bu*), 21.4 (Ar*C*H_3), 19.2 (*Q*^{t}*Bu*), 18.2 (*Q*^{t}*Bu*), -5.6 (Si*Me*); m/z (ES) $[M+Na]^+$ 738.1; $C_{41}H_{57}NO_4SSi_2Na$ requires 738.3445, found 738.3442

100a

N-Tosyl-(*S*)-*N*-3-(*tert*-butyldiphenylsilyloxy)propyl-4-methyl-1-phenylpent-3-en-2-amine



Chemical Formula: $C_{38}H_{47}NO_3SSi$
Exact Mass: 625.30
Molecular Weight: 625.94

Procedure **H** was followed using the following amounts:

Isopropyltriphenylphosphonium iodide (3 eq, 11.0 mmol, 4.76 g) in THF (0.05 M, 70 mL) *n*-BuLi [1.6 M] (3 eq, 11.0 mmol, 6.88 mL)

aldehyde **96a** (1 eq, 3.67 mmol, 2.20 g) in THF (0.1 M, 40 mL)

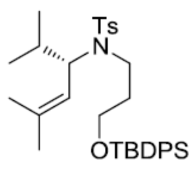
ylide colour: deep red

yield: 1.94 g (84 %) orange oil after column 10 % EtOAc in heptane.

R_f 0.80 (10 % EtOAc in heptane); IR υ (cm^{-1}) 1724 (Ar), 1599 (=), 1337/1156 (SO_2N), 1105 (SiO), 1089 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68-7.61 (stack, 6H (Ar*H*)), 7.46-7.34 (stack, 6H (Ar*H*)), 7.25-7.14 (stack, 5H (Ar*H*)), 7.11-7.07 (stack, 2 H (Ar*H*)), 5.05 (d, 1H, *J* = 9.5 Hz (=C*H*)), 4.71 (dt, 1H, *J* = 4.5, 9.5 Hz (C*H*)), 3.67 (t, 2H, *J* = 5.5 Hz (CH_2OSi)), 3.38-3.21 (m, 2H (CH_2N)), 2.91 (dd, 1H, *J* = 4.5, 13.0 Hz (C*H*HPh)), 2.67 (dd, 1H, *J* = 9.5, 13.0 Hz (CH*H*Ph)), 2.39 (s, 3H (ArCH_3)), 1.98-1.81 (m, 2H (CH_2CH_2N)), 1.51 (d, 3H, *J* = 1.0 Hz (=CH_3)), 1.17 (d, 3H, *J* = 1.0 Hz (=CH_3)), 1.07 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.2 (*QAr*), 137.7 (*QAr*), 136.9 (=*C*Me_2), 135.9 (*QAr*), 134.2 (*QAr*), 130.5 (*Ar*H), 130.2 (*Ar*H), 129.6 (*Ar*H), 129.1 (*Ar*H), 128.4 (*Ar*H), 128.1 (=*C*H), 128.0 (*Ar*H), 127.5 (*Ar*H), 125.4 (*Ar*H), 61.2 (*C*H_2O), 55.4 (*C*HN), 44.9 (*C*H_2N), 38.5 (*C*H_2Ph), 31.5 (*Q*^{t}*Bu*), 30.0 (*C*H_2CH_2N), 26.4 (^{t}*Bu*), 21.3 (Ar*C*H_3), 21.5 (*Me*=), 15.6 (*Me*=); m/z (ES) $[M+Na]^+$ 648.2; $C_{38}H_{47}NO_3SSiNa$ requires 648.2944, found 648.2941

100c

N-Tosyl-(*S*)-*N*-3-(*tert*-butyldiphenylsilyloxy)propyl-2,5-dimethylhex-4-en-3-amine



Chemical Formula: $C_{34}H_{47}NO_3SSi$
Exact Mass: 577.30
Molecular Weight: 577.89

Procedure **H** was followed using the following amounts:

Isopropyltriphenylphosphonium iodide (3 eq, 1.09 mmol, 470 mg) in THF (0.16 M, 7 mL) n-BuLi [1.6 M] (3 eq, 1.09 mmol, 0.68 mL)

aldehyde **96b** (1 eq, 0.36 mmol, 200 mg) in THF (0.27 M, 4 mL)

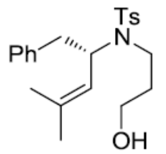
ylide colour: deep red

yield: 98 mg (47 %) orange oil after column 10 % EtOAc in hexane.

IR υ (cm^{-1}) 1727 (Ar), 1605 (=), 1332/1151 (SO_2N), 1107 (SiO), 1088 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73-7.58 (stack, 6H (Ar*H*)), 7.49-7.32 (stack, 6H (Ar*H*)), 7.21 (app d, 2H (Ar*H*)), 5.02 (dsept, 1H, *J* = 1.5, 10.5 Hz (=C*H*)), 4.19 (t, 1H, *J* = 10.5 (C*H*)), 3.66 (t, 1H, *J* = 5.5 Hz (C*H*HO)), 3.65 (t, 1H, *J* = 5.5 Hz (CH*H*O)), 3.27 (ddd, 1H, *J* = 5.5, 11.0, 22.0 (C*H*HN)), 3.16 (ddd, 1H, *J* = 5.5, 11.0, 15.0 (CH*H*N)), 2.41 (s, 3H (ArCH_3)), 2.07-1.90 (m, 1H (C*H*Me_2)), 1.89-1.71 (m, 2H (CH_2CH_2N)), 1.62 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.62 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.07 (s, 9H (^{t}*Bu*)), 1.03 (d, 3H, *J* = 6.5 Hz (*Me*)), 0.82 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.5 (*QAr*), 134.8 (*QAr*), 133.7 (*QAr*), 132.6 (=*C*Me_2), 129.7 (*Ar*H), 129.0 (*Ar*H), 127.7 (*Ar*H), 127.4 (*Ar*H), 121.8 (*Ar*H), 116.1 (=*C*H), 62.9 (*C*H), 61.8 (*C*H_2O), 42.1 (*C*H_2N), 33.8 (*C*H_2CH_2N), 31.7 (*C*HMe_2), 26.8 (^{t}*Bu*), 25.8 (=*Me*), 21.5 (Ar*C*H_3), 20.4 (*Me*), 19.9 (*Q*^{t}*Bu*), 19.5 (*Me*), 18.9 (=*Me*)

101a

N-Tosyl-(*S*)-3-((4-methyl-1-phenylpent-3-en-2-yl)amino)propan-1-ol



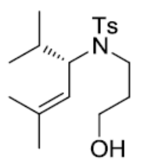
Chemical Formula: $C_{22}H_{29}NO_3S$
Exact Mass: 387.19
Molecular Weight: 387.54

To a solution of silyl ether **100a** (1 eq, 7.79 mmol, 4.87 g) in THF (0.1 M, 78 mL) was added TBAF [1 M/THF] (1.5 eq, 11.68 mmol, 11.68 mL). The mixture was stirred at room temperature overnight then water was added and the product extracted into ether. Purification by column chromatography, eluting with 30 % EtOAc in heptane, yielded an orange oil (1.98 g, 65 %).

R_f 0.22 (30 % EtOAc in heptane); IR υ (cm^{-1}) 3562 (OH), 2931 (CH), 1675 (Ar), 1598 (=), 1383/1153 (SO_2N), 1322 (CO); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (app d, 2H (Ar*H*)), 7.27- 7.13 (stack, 5H (Ar*H*)), 7.10 (app d, 2H (Ar*H*)), 5.05 (d, 1H, *J* = 9.5 Hz (=C*H*)), 4.64 (ddd, 1H, *J* = 4.5, 9.5, 10.0 Hz (C*H*)), 3.78-3.64 (m, 2H (CH_2N)), 3.36 (t, 2H, *J* = 7.0 Hz (CH_2OH)), 2.97 (dd, 1H, *J* = 4.5, 13.0 Hz (C*H*HPh)), 2.69 (dd, 1H, *J* = 10.0, 13.0 Hz (CH*H*Ph)), 2.39 (s, 3H (ArCH_3)), 2.31 (brs, 1H (O*H*)), 1.82 (dt, 2H, *J* = 5.5, 7.0 Hz (C$H_2$$CH_2$N)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.2 (*QAr*), 137.5 (*QAr*), 136.5 (=*C*Me_2), 136.1 (*QAr*), 129.7 (*Ar*H), 128.4 (*Ar*H), 128.3 (*Ar*H), 128.1 (=*C*H), 127.8 (*Ar*H), 125.2 (*Ar*H), 58.4 (*C*H_2O), 55.4 (*C*HN), 44.7 (*C*H_2N), 38.7 (*C*H_2Ph), 31.5 (*C*$H_2$$CH_2$N), 21.4 (Ar*C*$H_3$), 21.1 (*Me*=), 15.8 (*Me*=); m/z (ES) $[M+Na]^+$ 410.1; $C_{22}H_{29}NO_3SNa$ requires 410.1766, found 410.1773

101c

N-Tosyl-(*S*)-3-((2,5-dimethylhex-4-en-3-yl)amino)propan-1-ol



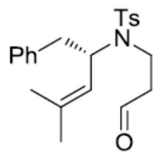
Chemical Formula: $C_{18}H_{29}NO_3S$
Exact Mass: 339.19
Molecular Weight: 339.49

To a solution of silyl ether **100c** (1 eq, 0.53 mmol, 305 mg) in THF (0.1 M, 5.50mL) was added TBAF [1 M/THF] (1.5 eq, 0.79 mmol, 0.80 mL). The mixture was stirred at room temperature overnight then water was added and the product extracted into ether. Purification by column chromatography, eluting with 25 % EtOAc in hexane, yielded a pale yellow oil (139 mg, 78 %).

IR υ (cm^{-1}) 3514 (OH), 2959 (CH), 1672 (=), 1384/1154 (SO_2N), 1326 (CO); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (app d, 2H (Ar*H*)), 7.22 (app d, 2H (Ar*H*)), 5.01 (dsept, 1H, *J* = 1.0, 10.5 Hz (=C*H*)), 4.09 (t, 1H, *J* = 10.5 Hz (C*H*)), 3.82-3.62 (m, 2H (CH_2N)), 3.26 (t, 2H, *J* = 7.0 Hz (CH_2OH)), 2.40 (s, 3H (ArCH_3)), 2.31 (brs, 1H (O*H*)), 1.98-1.67 (stack, 3H (C$H_2$$CH_2$N, C*H*$Me_2$)), 1.59 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.53 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.26 (d, 3H, *J* = 7.0 Hz (*Me*)), 0.99 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.7 (=*C*Me_2), 137.8 (*QAr*), 136.0 (*QAr*), 129.1 (*Ar*H), 127.4 (*Ar*H), 121.4 (=*C*H), 63.1 (*C*H), 59.7 (*C*H_2N), 41.4 (*C*H_2OH), 33.6 (*C*$H_2$$CH_2$N), 31.9 (*C*H$Me_2$), 25.7 (=*Me*), 21.1 (Ar*C*H_3), 20.4 (*Me*), 19.6 (*Me*), 18.9 (=*Me*); m/z (ES) $[M+Na]^+$ 362.2

102a

N-Tosyl-(*S*)-3-((4-methyl-1-phenylpent-3-en-2-yl)amino)propanal



Chemical Formula: $C_{22}H_{27}NO_3S$
Exact Mass: 385.17
Molecular Weight: 385.52

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 1.42 mmol, 0.12 mL) in DCM (0.33 M, 3.50 mL)

DMSO (2.4 eq, 3.10 mmol, 0.22 mL)

Alcohol **101a** (1 eq, 1.29 mmol, 0.50 g) in DCM (1 M, 1.50 mL)

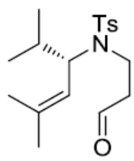
Triethylamine (5 eq, 6.45 mmol, 0.90 mL)

The product was purified by column chromatography, eluting with 15 % EtOAc in heptane, to yield a yellow oil (432 mg, 87 %).

R_f 0.21 (20 % EtOAc in heptane); IR υ (cm^{-1}) 3029 (CHO), 2928 (CH), 1719 (C=O), 1598 (Ar), 1453 (=), 1330/1153 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H (C*H*O)), 7.64 (app d, 2H (Ar*H*)), 7.26-7.15 (stack, 5H (Ar*H*)), 7.09 (app d, 2H (Ar*H*)), 4.97 (dt, 1H, *J* = 1.5, 9.5 Hz (=C*H*)), 4.74 (dt, 1H, *J* = 5.0, 9.5 Hz (C*H*)), 3.50-3.31 (m, 2H (CH_2N)), 2.96-2.79 (stack, 3H (CH_2CHO, C*H*HPh)), 2.64 (dd, 1H, *J* = 9.5, 13.0 Hz (CH*H*Ph)), 2.40 (s, 3H (ArCH_3)), 1.52 (s, 3H (=CH_3)), 1.26 (s, 3H (=CH_3)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.7 (*C*HO), 143.2 (=*C*Me_2), 137.7 (*QAr*), 137.6 (*QAr*), 137.3 (*QAr*), 129.4 (*Ar*H), 128.7 (*Ar*H), 128.3 (*Ar*H), 127.4 (*Ar*H), 126.4 (*Ar*H), 121.0 (=*C*H), 57.6 (*C*H), 46.2 (*C*H_2CHO), 41.0 (*C*H_2Ph), 37.7 (*C*H2N), 25.6 (*Me*), 21.5 (Ar*C*H_3), 18.1 (*Me*); m/z (ES) $[M+Na]^+$ 408.1; $C_{22}H_{27}NO_3SNa$ requires 408.1609, found 408.1618

102c

N-Tosyl-(*S*)-3-((2,5-dimethylhex-4-en-3-yl)amino)propanal



Chemical Formula: $C_{18}H_{27}NO_3S$
Exact Mass: 337.17
Molecular Weight: 337.48

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 0.42 mmol, 36 μl) in DCM (0.4 M, 1 mL)

DMSO (2.4 eq, 0.92 mmol, 65 μl)

Alcohol **101c** (1 eq, 0.38 mmol, 130 mg) in DCM (0.75 M, 0.5 mL)

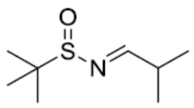
Triethylamine (5 eq, 1.91 mmol, 266 μl)

The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a yellow oil (55 mg, 43 %).

IR υ (cm^{-1}) 2921 (CH), 1720 (C=O), 1598 (=), 1330/1156 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H (C*H*O)), 7.63 (app d, 2H (Ar*H*)), 7.25 (app d, 2H (Ar*H*)), 4.95 (d, 1H, *J* = 10.0 Hz (=C*H*)), 4.19 (t, 1H, *J* = 10.0 Hz (C*H*)), 3.43 (ddd, 1H, *J* = 5.0, 9.5, 13.5 (C*H*HCHO)), 3.38 (ddd, 1H, *J* = 5.0, 9.5, 15.5 Hz (CH*H*CHO)), 3.10 (ddd, 1H, *J* = 5.0, 9.5, 18.5 (C*H*HN)), 2.89 (ddd, 1H, *J* = 5.0, 9.5, 18.5 (CH*H*N)), 2.42 (s, 3H (=*Me*)), 1.59 (s, 3H (=*Me*)), 0.99 (d, 3H, *J* = 6.5 Hz (*Me*)), 0.81 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.6 (*C*HO), 143.0 (=*C*Me_2), 137.2 (*QAr*), 136.4 (*QAr*), 129.2 (*Ar*H), 127.5 (*Ar*H), 121.0 (=*C*H), 62.9 (*C*HN), 45.8 (*C*H_2CHO), 37.4 (*C*H_2N), 31.6 (*C*HMe_2), 25.7 (=*Me*), 21.5 (Ar*C*H_3), 20.3 (*Me*) 19.4 (*Me*), 19.0 (=*Me*); m/z (ES) $[M+Na]^+$ 360.2; $C_{18}H_{27}NO_3SNa$ requires 360.1609, found 360.1613

112a

(*E*)-2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide[80]



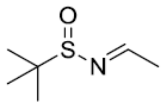
Chemical Formula: $C_8H_{17}NOS$
Exact Mass: 175.10
Molecular Weight: 175.29

(*R*)-*t*-butanesulfinamide (1 eq, 16.50 mmol, 2.00 g) was dissolved in DCM (1.7 M, 28 mL), then pyridinium tosylate (5 mol%, 0.83 mmol, 207 mg), anhydrous magnesium sulfate (5 eq, 82.51 mmol, 9.93 g) isobutyraldehyde (2 eq, 33.00 mmol, 3.0 mL) and 3 Å molecular sieves were added. The reaction mixture stirred at RT overnight then was filtered through Celite® and washed with DCM. The filtrate was concentrated and purified by column chromatography, eluting with 5 % hexane in DCM, to yield a yellow liquid (2.77 g, 95 %).

IR υ (cm^{-1}) 2969 (CH), 1704/1621 (C=N), 1063 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 4.5 Hz (N=C*H*)), 2.67 (dsept, 1H, *J* = 4.5, 7.0 Hz (C*H*Me_2)), 1.17 (s, 9H, (^{t}*Bu*)), 1.12 (s, 6H (*Me*)) [lit. agreement] ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7 (*C*=N), 59.8 (*Q^{t}Bu*), 32.4 (*C*HMe_2), 27.1 (^{t}*Bu*), 19.4 (*Me*); m/z (ES) $[M+Na]^+$ 198.1; $C_8H_{17}NOSNa$ requires 198.0929, found 198.0936

112b

(*E*)-*N*-Ethylidene-2-methylpropane-2-sulfinamide[118]



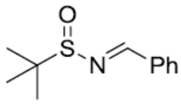
Chemical Formula: $C_6H_{13}NOS$
Exact Mass: 147.07
Molecular Weight: 147.24

(*R*)-*t*-butanesulfinamide (1 eq, 8.25 mmol, 1.00 g) was dissolved in DCM (1.7 M, 14 mL), then pyridinium tosylate (5 mol%, 0.41 mmol, 104 mg), anhydrous magnesium sulfate (5 eq, 41.25 mmol, 4.97 g) acetaldehyde (2 eq, 16.50 mmol, 0.92 mL) and 3 Å molecular sieves were added. The reaction mixture stirred at RT overnight then was filtered through Celite® and washed with DCM. The filtrate was concentrated and purified by column chromatography, eluting with 5 % hexane in DCM, to yield a yellow liquid (1.95 g, 95 %).

IR υ (cm^{-1}) 3233 (N=C), 2977 (CH), 1413/1030 (S=O), 886 (SN); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (q, 1H *J* = 5.1 Hz (N=C*H*)), 2.24 (d, 3H, *J* = 5.1 Hz (*Me*)), 1.18 (s, 9H, (^{t}*Bu*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.2 (N=*C*H), 59.8 (Q^t*Bu*), 25.6 (^{t}*Bu*), 14.9 (*Me*); m/z (ES) $[M+Na]^+$ 170.1

112c

(*E*)-*N*-Benzylidene-2-methylpropane-2-sulfinamide[80]



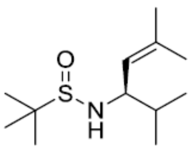
Chemical Formula: $C_{11}H_{15}NOS$
Exact Mass: 209.09
Molecular Weight: 209.31

To a solution of (*R*)-*t*-butanesulfinamide (1 eq, 8.25 mmol, 1.00 g) in DCM (0.5 M, 16.5 mL) was added freshly dried and ground copper sulfate (2.2 eq, 18.15 mmol, 2.90 g) followed by benzaldehyde (1.1 eq, 9.08 mmol, 1.68 mL). The reaction mixture stirred at RT overnight before filtering through Celite® and washing with DCM. The filtrate was reduced to half its volume then dried with $MgSO_4$ and concentrated fully, the product was purified by column chromatography, eluting with DCM, to yield a clear oil (1.09 g, 63 %).

IR υ (cm^{-1}) 1605 (N=C), 1572 (Ar), 1082 (S=O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H (N=C*H*)), 7.87 (app dd, 2H (Ar*H*)), 7.56-7.45 (stack, 3H (Ar*H*)), 1.27 (s, 9H (^{t}*Bu*)) [lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.8 (N=*C*H), 134.1 (Q*Ar*), 132.4 (*Ar*H), 129.4 (*Ar*H), 128.9 (*Ar*H), 57.8 (Q^t*Bu*), 22.6 (^{t}*Bu*); m/z (ES) $[M+Na]^+$ 232.0; $C_{11}H_{15}NOSNa$ requires 232.0772, found 232.0773

114a

N-((*R*)-2,5-Dimethylhex-4-en-3-yl)-2-methylpropane-2-sulfinamide



Chemical Formula: $C_{12}H_{25}NOS$
Exact Mass: 231.17
Molecular Weight: 231.40

Procedure **I** was followed using the following amounts:

Imine **112a** (1 eq, 5.67 mmol, 1.00 g)

DCM (0.2 M, 28 mL)

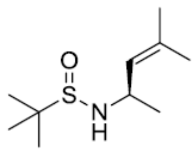
2-Methyl-1-propenylmagnesium bromide [0.5 M/THF] (2 eq, 11.34 mmol, 22.70 mL)

Yield: 1.11 g, 85 %, yellow liquid [31:69 isomers]

R_f 0.32 (1 % MeOH in DCM); IR υ (cm^{-1}) 3228 (NH), 2959 (CH), 1674 (=), 1039 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.06 [4.90] (dsept, 1H, *J* = 1.5, 9.5 Hz (=C*H*)), 3.75 [3.83] (ddd, 1H, *J* = 1.0, 5.5, 9.5 Hz (C*H*)), 2.90 [3.15] (d, 1H, *J* = 5.5 Hz (N*H*)), 1.78 (dsept, 1H, *J* = 1.0, 7.0 Hz (C*H*Me_2)), 1.69 [1.72] (d, 3H *J* = 1.5 Hz (*Me*)), 1.66 [1.66] (d, 3H *J* = 1.5 Hz (*Me*)), 1.16 [1.15] (s, 9H (^{t}*Bu*)), 0.87 [0.88] (d, 3H, *J* = 7.0 Hz (*Me*)), 0.84 [0.86] (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.8 (=*C*Me_2), 123.8 (=*C*H), 58.8 (*C*H), 55.7 (*Q*^{t}*Bu*), 33.0 (*C*H), 26.0 (*Me*), 22.7 (^{t}*Bu*), 19.0 (*Me*), 18.5 (*Me*), 17.5 (*Me*); m/z (EI) $[M]^+$ 231.2; $C_{12}H_{25}NOS$ requires 231.1657 found 231.1658

114b

2-Methyl-*N*-((*R*)-4-methylpent-3-en-2-yl)propane-2-sulfinamide



Chemical Formula: $C_{10}H_{21}NOS$
Exact Mass: 203.13
Molecular Weight: 203.34

Procedure **I** was followed using the following amounts:

Imine **112b** (1 eq, 8.15 mmol, 1.20 g)

DCM (0.2 M, 40 mL)

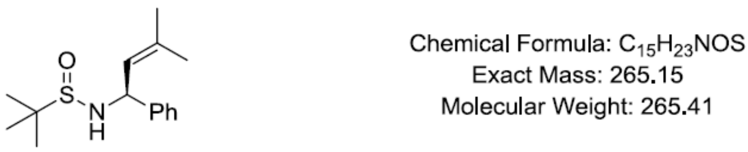
2-Methyl-1-propenylmagnesium bromide [0.5 M/THF] (2 eq, 16.30 mmol, 32.6 mL)

Yield: 1.13 g, 68 %, yellow oil [25:75 isomers]

IR υ (cm^{-1}) 3430 (NH), 2977 (CH), 1626 (=), 1026 (S=O), 870 (SN); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.09 [4.97] (dsept, 1H, *J* = 1.5, 9.0 Hz (=C*H*)), 4.18-4.06 (m, 1H (C*H*)), 2.92 [2.97] (brs, 1H, (N*H*)) 1.67 (s, 3H (=*Me*)), 1.63 (s, 3H (=*Me*)), 1.15 (s, 3H (*Me*)), 1.10 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 180.0 (=*C*Me_2), 127.7 (=*C*H), 48.3 (*C*H), 55.7 (*Q*^{t}*Bu*), 25.7 (=*Me*), 22.5 (^{t}*Bu*), 21.8 (*Me*), 18.2 (=*Me*); m/z (ES) $[M+Na]^+$ 226.2; $C_{10}H_{21}NOSNa$ requires 226.1242 found 226.1228

114c

2-Methyl-*N*-((*S*)-3-methyl-1-phenylbut-2-en-1-yl)propane-2-sulfinamide



Procedure **I** was followed using the following amounts:

Imine **112c** (1 eq, 0.96 mmol, 200 mg)

DCM (0.2 M, 4.8 mL)

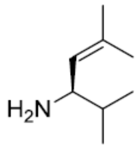
2-Methyl-1-propenylmagnesium bromide [0.5 M/THF] (2 eq, 1.91 mmol, 3.82 mL)

Yield: 208 mg, 82 %, yellow oil [10:90 isomers]

IR υ (cm^{-1}) 3398 (NH), 29.59 (CH), 1453 (=), 1052 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (stack, 5H (ArH)), 5.37 (dsept, 1H, *J* = 1.5, 9.0 Hz (=C*H*)), 5.21 (dd, 1H, *J* = 2.5, 9.0 Hz

(C*H*)), 3.34 (brs, 1H, (N*H*)) 1.82 (d, 3H, J = 1.5 Hz (=*Me*)), 1.74 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.22 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.2 (=*C*Me_2), 135.4 (*QAr*), 128.6 (*Ar*H), 127.4 (*Ar*H), 126.9 (*Ar*H), 126.3 (=*C*H), 56.6 (*C*H), 55.6 (*Q*^{t}*Bu*), 25.8 (=*Me*), 22.6 (^{t}*Bu*), 18.4 (=*Me*); m/z (ES) $[M+Na]^+$ 288.2; $C_{15}H_{23}NOSNa$ requires 288.1398, found 288.1386

(*R*)-2,5-Dimethylhex-4-en-3-amine

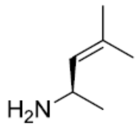


Chemical Formula: $C_8H_{17}N$
Exact Mass: 127.14
Molecular Weight: 127.23

To a solution of **114a** (1 eq, 4.32 mmol, 1.00 g) in methanol (2 M, 2.20 mL) at 0 °C, was added anhydrous HCl [1 M/Et_2O] (2 eq, 8.64 mmol, 8.60 mL). The mixture was stirred at room temperature for 30 minutes then was reduced in volume by half. Anhydrous ether was added and the white precipitate collected. The filtrate was concentrated then further triturated with ether. Yield 348 mg, off-white solid (49 %).

IR υ (cm^{-1}) 2890 (br) (NH), 2032 (NH_3^+), 1600 (=); ^{1}H-NMR (300 MHz, MeOD) δ 5.15 (dt, 1H, *J* = 1.5, 10.0 Hz (=C*H*)), 3.77 (dd, *J* = 7.0, 10.0 Hz (C*H*)), 1.91 (sept, 1H, *J* = 7.0 Hz (C*H*Me_2)), 1.84 (d, 3H, *J* = 1.5 Hz (*Me*)), 1.77 (d, 3H, *J* = 1.5 Hz (*Me*)), 1.02 (d, 3H, *J* = 7.0 Hz (*Me*)), 0.96 (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.8 (=*C*Me_2), 119.9 (=*C*H), 56.2 (*C*HN), 33.1 (*C*HMe_2), 26.1 (*Me*), 19.3 (*Me*), 18.7 (*Me*), 17.9 (*Me*); m/z (ES) $[M+Na]^+$ 150.1

(*R*)-4-Methylpent-3-en-2-amine



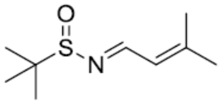
Chemical Formula: $C_6H_{13}N$
Exact Mass: 99.10
Molecular Weight: 99.17

To a solution of **114b** (1 eq, 5.55 mmol, 1.13 g) in methanol (2 M, 3.0 mL) at 0 °C, was added anhydrous HCl [1 M/Et_2O] (2 eq, 11.11 mmol, 11.1 mL). The mixture stirred at room temperature for 30 minutes then was concentrated to a brown oil. Anhydrous ether was added and the white precipitate collected. The filtrate was concentrated then further triturated with ether. Yield 279 mg, white solid (37 %).

IR υ (cm^{-1}) 3118/3025/2806 (NH_3^+), 1756 (=), 1392 (CH); ^{1}H-NMR (300 MHz, MeOD) δ 5.17 (dsept, 1H, *J* = 1.5, 9.5 Hz (=C*H*)), 4.14 (dq, 1H, *J* = 6.5, 9.5 Hz (C*H*)), 1.80 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.77 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.33 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.8 (=*C*Me_2), 125.9 (=*C*H), 53.2 (*C*HN), 26.2 (*Me*), 21.3 (=*Me*), 15.9 (=*Me*); m/z (ES) $[M]^+$ 100.1; $C_6H_{14}N$ requires 100.1126, found 100.1125

115

(*E*)-2-Methyl-*N*-(3-methylbut-2-en-1-ylidene)propane-2-sulfinamide



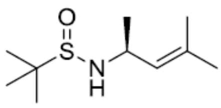
Chemical Formula: $C_9H_{17}NOS$
Exact Mass: 187.10
Molecular Weight: 187.30

(*R*)-*t*-butanesulfinamde (1 eq, 4.13 mmol, 500 mg) and 3-methylbut-2-enal (2 eq, 8.25 mmol, 0.79 mL) were dissolved in toluene (0.1 M, 40 mL) and potassium bisulfate (2 eq, 8.25 mmol, 1.12 g) was added. The reagents were stirred at 45 °C for 24 hours then the solids were removed and the filtrate concentrated to yield a yellow liquid in quantitative yield. The product required no further purification.

IR υ (cm^{-1}) 2868 (CH), 1639 (N=C), 1570 (C=), 1078 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 1H, *J* = 10.0 Hz (N=C*H*)), 6.26 (dsept, 1H, *J* = 1.5, 10.0 Hz (=C*H*)), 2.07 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.99 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.22 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.5 (N=*C*H), 153.7 (=*C*Me_2), 124.1 (C=*C*H), 57.1 (*Q*^{t}*Bu*), 27.0 (=*Me*), 22.5 (^{t}*Bu*), 19.3 (=*Me*); m/z (ES) $[M+Na]^+$ 210.1; $C_9H_{17}NOSNa$ requires 210.0929, found 210.0926

116a

2-Methyl-*N*-((*S*)-4-methylpent-3-en-2-yl)propane-2-sulfinamide



Chemical Formula: $C_{10}H_{21}NOS$
Exact Mass: 203.13
Molecular Weight: 203.34

Procedure **I** was followed using the following amounts:

Imine **115** (1 eq, 13.24 mmol, 2.48 g)

DCM (0.2 M, 65 mL)

Methylmagnesium bromide [3 M/Et_2O] (2 eq, 26.48 mmol, 8.83 mL)

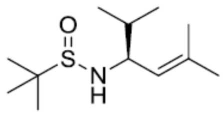
Yield: 2.01 g, 75 %, yellow liquid [13:87 isomers]

IR υ (cm^{-1}) 3215 (NH), 2928 (CH), 1673 (=), 1028 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.91 [5.03] (dsept, 1H, *J* = 1.5, 9.0 Hz (=C*H*)), 4.21 (m, 1H (C*H*)), 2.98 [2.93] (d, 1H, *J* = 2.0 Hz (N*H*)), 1.65 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.63 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.15 (d, 3H, *J* = 6.5 Hz (*Me*)), 1.13

(s, 9H (^tBu)); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 134.7 (=CMe$_2$), 127.7 (=CH), 55.1 (Q^tBu), 48.5 (CH), 25.7 (Me), 23.2 (Me), 22.6 (^tBu), 18.2 (Me); m/z (EI) $[M]^+$ 203.1; $C_{10}H_{21}NOS$ requires 203.1344, found 203.1342

116b

N-((*S*)-2,5-Dimethylhex-4-en-3-yl)-2-methylpropane-2-sulfinamide



Chemical Formula: $C_{12}H_{25}NOS$
Exact Mass: 231.17
Molecular Weight: 231.40

Isopropylmagnesium bromide was produced following the procedure set out by Harwood and Moody.[83]

Procedure **I** was followed using the following amounts:

Imine **115** (1 eq, 2.67 mmol, 0.50 g)

DCM (0.2 M, 10 mL)

Isopropylmagnesium bromide [1.25 M/Et_2O] (2 eq, 5.34 mmol, 4.27 mL)

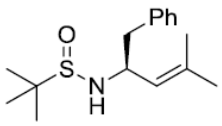
Yield: 468 mg, 76 %, yellow oil [20:80 isomers]

IR υ (cm^{-1}) 3209 (NH), 2935 (CH), 1457 (=), 1049 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.88 [5.04] (dsept, 1H, J = 1.5, 9.0 Hz (=CH)), 3.81 [3.73] (ddd, 1H, J = 3.0, 6.0, 9.0 Hz (CH)), 3.12 [2.86] (brs, 1H (NH)), 1.70 (d, 3H, J = 1.5 Hz (=Me)), 1.68-1.65 (m, 1H (CHMe$_2$)), 1.64 (d, 3H, J = 1.5 Hz (=Me)), 1.13 (s, 9H (^tBu)), 0.85 (d, 3H, J = 6.0 Hz (Me)), 0.82 (d, 3H, J = 6.0 Hz (Me)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.8 (=CMe$_2$), 122.7 (=CH), 57.3 (CH), 55.4 (Q^tBu), 34.1

(CHMe$_2$), 26.0 (=*Me*), 22.7 (^{t}*Bu*), 19.1 (*Me*), 18.6 (=*Me*), 17.5 (*Me*); m/z (EI) $[M]^+$ 231.2; $C_{12}H_{25}NOS$ requires 231.1657, found 231.1660

116c

2-Methyl-*N*-((*S*)-4-methyl-1-phenylpent-3-en-2-yl)propane-2-sulfinamide



Chemical Formula: $C_{16}H_{25}NOS$
Exact Mass: 279.17
Molecular Weight: 279.44

Benzylmagnesium bromide was produced following the procedure set out by Harwood and Moody.[83]

Procedure **I** was followed using the following amounts:

Imine **115** (1 eq, 50.34 mmol, 9.43 g)

DCM (0.2 M, 250 mL)

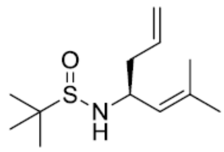
Benzylmagnesium bromide [1.25 M/Et_2O] (2 eq, 100.69 mmol, 80.6 mL)

Yield: 7.83 g, 59 %, yellow oil after column chromatography (10 % EtOAc in Hexane).

IR υ (cm^{-1}) 3212 (NH), 2975 (CH), 1454 (=), 1049 (S=O), 749/698 (Ph); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36-7.12 (stack, 5H (Ar*H*)), 5.00 (dsept, 1H, *J* = 1.0, 9.0 Hz (=C*H*)), 4.28 (dddd, 1H, *J* = 1.5, 6.0, 7.5, 9.0 Hz (C*H*)), 3.27 (d, 1H, *J* = 1.5 Hz (N*H*)), 2.85 (dd, 1H, *J* = 6.0, 13.0 Hz (C*H*HPh)), 2.75 (dd, 1H, *J* = 7.5, 13.0 Hz (CH*H*Ph)), 1.74 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.59 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.15 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 136.7 (=*C*Me$_2$), 136.5 (*QAr*), 128.7 (=*C*H), 128.6 (*Ar*H), 127.4 (*Ar*H), 125.4 (*Ar*H), 61.1 (*Q*^{t}*Bu*), 52.5 (*C*HN), 41.8 (*C*H$_2$Ph), 26.6 (^{t}*Bu*), 21.6 (=*Me*), 15.2 (=*Me*); m/z (ES) $[M+Na]^+$ 302.2

116d

2-Methyl-*N*-((*S*)-6-methylhepta-1,5-dien-4-yl)propane-2-sulfinamide



Chemical Formula: $C_{12}H_{23}NOS$
Exact Mass: 229.15
Molecular Weight: 229.38

Allylmagnesium bromide was produced following the procedure set out by Harwood and Moody.[83]

Procedure **I** was followed using the following amounts:

Imine **115** (1 eq, 5.34 mmol, 1.00 g)

DCM (0.2 M, 16 mL)

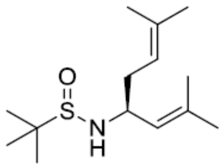
Allylmagnesium bromide [1.25 M/Et_2O] (3 eq, 16.02 mmol, 12.80 mL)

Yield: 862 mg, 71 %, yellow oil after column chromatography (10 % EtOAc in Hexane).

Rf 0.10 (25 % EtOAc in hexane); IR υ (cm^{-1}) 3215 (NH), 2979 (CH), 1640 (=), 1572 (=), 1050 (S=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.77 (dddd, 1H, *J* = 6.0, 8.5, 11.0, 17.0 Hz (=C*H*CH_2)), 5.14 (d, 1H, *J* = 17.0 Hz (=C*H*H)), 5.13 (d, 1H, *J* = 11.0 Hz (=CH*H*)), 4.96 (dsept, 1H, *J* = 1.5, 8.0 Hz (=C*H*CH)), 4.17-4.06 (m, 1H (C*H*)), 3.36 (brs, 1H (N*H*)), 2.33 (ddd, 1H, *J* = 6.0, 8.5, 14.0 Hz (C*H*HCH)), 2.22 (ddd, 1H, *J* = 7.5, 8.5, 14.0 Hz (CH*H*CH)), 1.76 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.73 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.20 (s, 9H (^{t}*Bu*)); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 135.7 (=*C*Me_2), 132.7 (=*C*HCH_2), 128.4 (=*C*HCH), 116.7 (=*C*H_2), 60.1 (*Q*^{t}*Bu*), 51.5 (*C*HN), 40.9 (*C*H_2), 26.7 (^{t}*Bu*), 21.2 (=*Me*), 15.8 (=*Me*); m/z (ES) $[M+Na]^+$ 252.2

116e

N-((*S*)-2,7-Dimethylocta-2,6-dien-4-yl)-2-methylpropane-2-sulfinamide



Chemical Formula: $C_{14}H_{27}NOS$
Exact Mass: 257.18
Molecular Weight: 257.44

Prenylmagnesium bromide was produced following the procedure set out by Harwood and Moody.[83]

Procedure **I** was followed using the following amounts:

Imine **115** (1 eq, 2.67 mmol, 500 mg)

DCM (0.2 M, 14 mL)

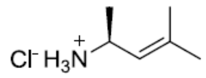
Prenylmagnesium bromide [1 M/Et_2O] (3 eq, 8.01 mmol, 8.01 mL)

Yield: 12 mg, <2 % after column chromatography (10 % EtOAc in Hexane).

R_f 0.05 (10 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.86 (t, 1H, *J* = 8.5 Hz (=C*H*CH_2)), 4.14-3.89 (m, 1H (=C*H*CH)), 3.26 (t, 1H, *J* = 12.5 Hz (C*H*)), 1.93 (d, 3H, *J* = 1.0 Hz (*Me*)), 1.85 (d, 3H, *J* = 1.0 Hz (*Me*)), 1.71 (dt, 2H, *J* = 8.5, 12.5 Hz (C*H₂*)), 1.67 (brs, 1H (N*H*)), 1.33 (s, 3H (*Me*)), 1.29 (s, 9H (^{t}*Bu*)), 1.29 (s, 3H (*Me*)); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 136.7 (=*C*Me_2), 132.0 (=*C*Me_2), 127.9 (=*C*HCH), 123.8 (=*C*HCH_2), 60.1 (*Q*^{t}*Bu*), 51.5 (*C*HN), 34.1 (*C*H_2), 27.1 (^{t}*Bu*), 24.1 (=*Me*), 21.5 (=*Me*), 18.2 (=*Me*), 15.1 (=*Me*); m/z (ES) $[M+Na]^+$ 280.2

117a

(S)-4-Methylpent-3-en-2-aminium chloride[128]



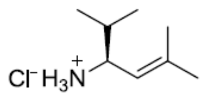
Chemical Formula: $C_6H_{14}ClN$
Exact Mass: 135.08
Molecular Weight: 135.64

Sulfinamide **116a** (1 eq, 68.9 mmol, 14.0 g) was dissolved in methanol (2 M, 35 mL) and chilled to 0 °C. HCl [4 M/dioxane] (2 eq, 137.7 mmol, 34 mL) was added slowly before the reaction mixture stirred at RT for 30 minutes. The solvents were removed and the product used without further purification. NB full data not collected.

IR υ (cm^{-1}) 3412/2973 (br) (NH_3^+), 2917 (CH), 1613 (=); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (brs, 3H (NH_3^+)), 5.24 (d, 1H, J = 9.5 Hz (=C*H*)), 4.18-4.03 (m, 1H (C*H*)), 1.72 (d, 6H, J = 2.0 Hz (=*Me*)), 1.42 (d, 3H, J = 6.5 Hz (*Me*)).

117b

(S)-2,5-Dimethylhex-4-en-3-aminium chloride

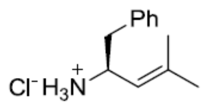


Chemical Formula: $C_8H_{18}ClN$
Exact Mass: 163.11
Molecular Weight: 163.69

Sulfinamide **116b** (1 eq, 25.06 mmol, 5.8 g) was dissolved in methanol (2 M, 12.5 mL) and chilled to 0 °C. HCl [4 M/dioxane] (2 eq, 50.13 mmol, 12.5 mL) was added slowly before the reaction mixture stirred at RT for 30 minutes. The solvents were removed and the product used without further purification. NB data not collected.

117c

(*S*)-4-Methyl-1-phenylpent-3-en-2-aminium chloride

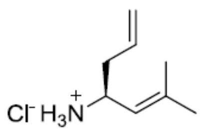


Chemical Formula: $C_{12}H_{18}ClN$
Exact Mass: 211.11
Molecular Weight: 211.73

Sulfinamide **116c** (1 eq, 29.50 mmol, 7.83 g) was dissolved in methanol (2 M, 14.80 mL) and chilled to 0 °C. HCl [4 M/dioxane] (2 eq, 59.00 mmol, 14.80 mL) was added slowly before the reaction mixture stirred at RT for 30 minutes. The solvents were removed and the product used without further purification. NB data not collected.

117d

(*S*)-6-Methylhepta-1,5-dien-4-aminium chloride

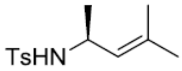


Chemical Formula: $C_8H_{16}ClN$
Exact Mass: 161.10
Molecular Weight: 161.67

Sulfinamide **116d** (1 eq, 25.07 mmol, 5.75 g) was dissolved in methanol (2 M, 12.5 mL) and chilled to 0 °C. HCl [4 M/dioxane] (2 eq, 50.14 mmol, 12.5 mL) was added slowly before the reaction mixture stirred at RT for 30 minutes. The solvents were removed and the product used without further purification. NB data not collected.

118a

(*S*)-2-Toluenesulfonamid-4-methylpent-3-ene



Chemical Formula: $C_{13}H_{19}NO_2S$
Exact Mass: 253.11
Molecular Weight: 253.36

General procedure **B** was followed with the following amounts used:

Amine **117a** hydrochloride (1 eq, 28.89 mmol, 3.92 g)

DCM (0.1 M, 290 mL)

Triethylamine (3 eq, 86.67 mmol, 12.08 mL)

p-Toluene sulfonyl chloride (3 eq, 86.67 mmol, 16.52 g)

DMAP (10 mol%, 2.89 mmol, 353 mg)

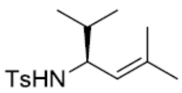
Heated at reflux for 20 hours

Crude product was purified by column chromatography, eluting with 5 % EtOAc in hexane, yielding a yellow liquid (5.27 g, 72 %).

R_f 0.09 (10 % EtOAc in hexane); IR υ (cm^{-1}) 3267 (NH), 2973 (CH), 1598 (Ph), 1321/1149 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (app d, 2H (Ar*H*)), 7.27 (app d, 2H (Ar*H*)), 4.78 (dsept, 1H, *J* = 1.0, 9.0 Hz (=C*H*)), 4.66 (d, 1H, *J* = 6.5 Hz (N*H*)), 4.08 (dp, 1H, *J* = 6.5, 9.0 Hz (C*H*)), 2.41 (s, 3H (ArCH_3)), 1.48 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.43 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.14 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.0 (*QAr*), 138.3 (*QAr*), 134.1 (=*C*Me_2), 129.3 (*Ar*H), 127.2 (*Ar*H), 126.2 (=*C*H), 48.2 (*C*H), 24.5 (Ar*C*H_3), 22.5 (=*Me*), 21.5 (*Me*), 17.8 (=*Me*); m/z (ES) $[M+Na]^+$ 276.1

118b

N-Tosyl-(*S*)-2,5-dimethylhex-4-en-3-amine



Chemical Formula: $C_{15}H_{23}NO_2S$
Exact Mass: 281.14
Molecular Weight: 281.41

General procedure **B** was followed with the following amounts used:

Amine **117b** hydrochloride (1 eq, 25.04 mmol, 4.10 g)

DCM (0.1 M, 250 mL)

Triethylamine (3 eq, 75.12 mmol, 10.50 mL)

p-Toluene sulfonyl chloride (3 eq, 75.12 mmol, 14.32 g)

DMAP (10 mol%, 2.50 mmol, 306 mg)

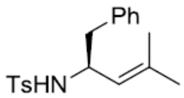
Heated at reflux for 20 hours

Crude product was purified by column chromatography, eluting with 5 % EtOAc in hexane, to give a white solid.

R_f 0.20 (10 % EtOAc in hexane); IR υ (cm^{-1}) 3262 (NH), 2973 (CH), 1716 (Ar), 1597 (=), 1331/1154 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (app d, 2H (Ar*H*)), 7.17 (app d, 2H (Ar*H*)), 4.60 (dsept, 1H, *J* = 1.5, 10.0 Hz (=C*H*)), 4.30 (d, 1H, *J* = 7.5 Hz (N*H*)), 3.69 (ddd, 1H, *J* = 7.5, 10.0, 13.5 Hz (C*H*N)), 2.34 (s, 3H (ArC*H₃*)), 1.64 (dsept, 1H, *J* = 7.0, 13.5 Hz (C*H*Me_2)), 1.38 (s, 3H (=*Me*)), 1.31 (s, 3H (=*Me*)), 0.79 (d, 3H, *J* = 7.0 Hz (*Me*)), 0.76 (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.0 (*QAr*), 137.9 (*QAr*), 135.1 (=*C*Me_2), 129.7 (*Ar*H), 128.2 (*Ar*H), 128.1 (=*C*H), 50.2 (*C*HN), 35.4 ($CHMe_2$), 22.5 (Ar*C*H_3), 22.3 (=*Me*), 19.5 (*Me*), 15.8 (=*Me*); m/z (ES) $[M+Na]^+$ 304.1; $C_{15}H_{23}NO_2SNa$ requires 304.1347, found 304.1342

118c

N-Tosyl-(*S*)-4-methyl-1-phenylpent-3-en-2-amine



Chemical Formula: $C_{19}H_{23}NO_2S$
Exact Mass: 329.14
Molecular Weight: 329.46

General procedure **B** was followed with the following amounts used:

Amine **117c** hydrochloride (1 eq, 29.48 mmol, 6.24 g)

DCM (0.1 M, 290 mL)

Triethylamine (3 eq, 88.44 mmol, 12.30 mL)

p-Toluene sulfonyl chloride (3 eq, 88.44 mmol, 16.86 g)

DMAP (10 mol%, 2.95 mmol, 360 mg)

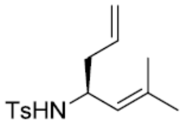
Heated at reflux for 20 hours

Crude product was purified by column chromatography, eluting with 5 % EtOAc in hexane, to give a white solid (9.13 g, 94 %).

IR υ (cm^{-1}) 3253 (NH), 2978 (CH), 1716 (Ar), 1598 (=), 1331/1157 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65-7.60 (stack, 2H (Ar*H*)), 7.28-7.07 (stack, 5H (Ar*H*)), 7.10-7.04 (stack, 2H (Ar*H*)), 4.76 (dsept, 1H, *J* = 1.5, 9.5 Hz (=C*H*)), 4.37 (d, 1H, *J* = 6.5 Hz (N*H*)), 4.22-4.14 (m, 1H (C*H*)), 2.82 (dd, 1H, *J* = 6.0, 13.5 Hz (C*H*HPh)), 2.69 (dd, 1H, *J* = 7.0, 13.5 Hz (CH*H*Ph)), 2.40 (s, 3H (ArC*H*$_3$)), 1.47 (s, 3H (*Me*)), 1.26 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.0 (*QAr*), 136.8 (*QAr*), 135.3 (*QAr*), 134.6 (=*C*Me$_2$), 129.6 (*Ar*H), 129.3 (*Ar*H), 128.4 (*Ar*H), 126.6 (=CH), 124.0 (*Ar*H), 53.2 (*C*HN), 42.5 (*C*H$_2$Ph), 25.4 (Ar*C*H$_3$), 21.5 (=*Me*), 17.8 (=*Me*); m/z (ES) $[M+Na]^+$ 352.1; $C_{19}H_{23}NO_2SNa$ requires 352.1347, found 352.1358

118d

N-Tosyl-(*S*)-6-methylhepta-1,5-dien-4-amine



Chemical Formula: $C_{15}H_{21}NO_2S$
Exact Mass: 279.13
Molecular Weight: 279.40

General procedure **B** was followed with the following amounts used:

Amine **111d** hydrochloride (1 eq, 25.05 mmol, 4.05 g)

DCM (0.1 M, 250 mL)

Triethylamine (2 eq, 50.10 mmol, 7.00 mL)

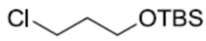
p-Toluene sulfonyl chloride (2 eq, 50.10 mmol, 9.55 g)

DMAP (10 mol%, 2.51 mmol, 306 mg)

Heated at reflux for 20 hours

Crude product was purified by column chromatography, eluting with 5 % EtOAc in hexane, to give a colourless crystalline solid (6.35 g, 91 %).

R_f 0.22 (10 % EtOAc in hexane); IR υ (cm^{-1}) 3270 (NH), 2980 (CH), 1641 (Ar), 1599(=), 1496 (=), 1323/1157 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (app d, 2H (Ar*H*)), 7.28 (app d, 2H (Ar*H*)), 5.65 (ddt, 1H, *J* = 6.5, 10.5, 17.5 Hz (=C*H*CH_2)), 5.12-5.07 (m, 1H (=C*H*H)), 5.12-5.04 (m, 1H (=CH*H*)), 4.78 (dsept, 1H, *J* = 1.5, 9.5 Hz (=C*H*CH)), 4.38 (d, 1H, *J* = 6.5 Hz (N*H*)), 4.06 (dq, 1H, *J* = 6.5, 9.5 Hz (C*H*)), 2.44 (s, 3H (ArC*H_3*)), 2.31-2.15 (m, 2H (C*H_2*)), 1.52 (d, 3H, *J* = 1.5 Hz (*Me*)), 1.48 (d, 3H, *J* = 1.5 Hz (*Me*)) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.1 (*QAr*), 138.2 (*QAr*), 135.2 (=*C*Me_2), 133.3 (RH*C*=CH_2), 129.3 (*Ar*H), 127.3 (*Ar*H), 124.2 (RH*C*=CMe_2), 118.7 (=*C*H_2), 51.5 (*C*H), 40.5 (*C*H_2), 25.5 (*Me*), 21.5 (Ar*C*H_3), 18.0 (*Me*) *tert*-Butyl(3-chloropropoxy)dimethylsilane[119]

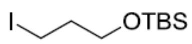


Chemical Formula: $C_9H_{21}ClOSi$
Exact Mass: 208.11
Molecular Weight: 208.80

3-Chloro-1-propanol (1 eq, 52.92 mmol, 5.00g) was dissolved in DMF (1 M, 50 mL), before imidazole (1.1 eq, 58.21 mmol, 3.96 g) and *tert*-butylsilyl chloride (1.1 eq, 58.21 mmol, 8.77 g) were added. The mixture was stirred at room temperature overnight before quenching with sat. aq. ammonium chloride. The product was extracted into ether and washed with water and brine to yield a clear oil (10.35 g, 94 %).

R_f 0.60 (10 % MeOH in DCM); IR υ (cm^{-1}) 2955/2858 (CH), 1255/833 (SiMe), 1101/774 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.68 (t, 2H, *J* = 6.0 Hz (CH_2Cl)), 3.59 (t, 2H, *J* = 6.0 Hz (CH_2OSi)), 1.88 (quin, 2H, *J* = 6.0 Hz (CH_2CH_2)), 0.83 (s, 9H (^{t}*Bu*)), 0.00 (s, 6H (*Me*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 59.4 (CH_2OSi), 41.8 (CH_2Cl), 35.4 (CH_2CH_2), 25.9 (^{t}*Bu*), 18.3 (*Q*^{t}*Bu*), -5.4 (*Me*); m/z (EI) [^{35}Cl] $[M-H]^+$ 207

tert-Butyl(3-iodopropoxy)dimethylsilane[120]



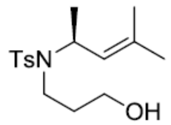
Chemical Formula: $C_9H_{21}IOSi$
Exact Mass: 300.04
Molecular Weight: 300.25

tert-Butyl(3-chloropropoxy)dimethylsilane (1 eq, 49.58 mmol, 10.35 g) was dissolved in freshly distilled acetone (1 M, 50 mL). Sodium iodide (2.5 eq, 123.95 mmol, 18.58 g) was added and stirred until completely dissolved. The apparatus was covered to exclude all light and the reaction mixture heated at reflux overnight. The mixture was diluted with ether and the precipitate removed. The solvents were removed to yield a yellow oil in quantitative yield that was used without further purification. NB. Product requires dark storage.

R_f 0.54 (40 % EtOAc in hexane); IR υ (cm^{-1}) 2953/2884 (CH), 1252/856 (SiMe), 1050/832 (SiO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.68 (t, 2H, J = 5.5 Hz (CH_2O)), 3.30 (t, 2H, J = 6.5 Hz (CH_2I)), 2.06-1.95 (m, 2H, (CH_2CH$_2$)), 0.91 (s, 9H (^{t}*Bu*)), 0.09 (s, 6H (*Me*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 62.3 (*C*H$_2$OSi), 36.2 (*C*H$_2$CH$_2$), 25.9 (^{t}*Bu*), 18.3 (*Q*^{t}*Bu*), 3.6 (*C*H$_2$I), -5.3 (*Me*); m/z (EI) [M-^{t}Bu]$^+$ 243.0; C5H12OSi^{127}I requires 242.9702, found 242.9703

119a

N-Tosyl-(*S*)-3-((4-methylpent-3-en-2-yl)amino)propan-1-ol



Chemical Formula: $C_{16}H_{25}NO_3S$
Exact Mass: 311.16
Molecular Weight: 311.44

Procedure **E** was followed using the following amounts:

Amine **118a** (1 eq, 8.88 mmol, 2.25 g) in DMF (0.1 M, 90 mL)

Cesium carbonate (1.5 eq, 13.32 mmol, 4.34 g)

tert-Butyl(3-iodopropoxy)dimethylsilane (1.5 eq, 13.32 mmol, 4.00 g)

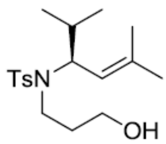
yield: pale yellow oil (1.97 g, 71 %)

R_f 0.06 (25 % EtOAc in hexane); IR υ (cm^{-1}) 2954/2856 (CH), 1471 (=), 1462/1153 (NSO_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (app d, 2H (Ar*H*)), 7.26 (app d, 2H (Ar*H*)), 4.98 (dsept, 1H, J = 1.5, 9.0 Hz (=C*H*)), 4.66 (dq, 1H, J = 7.0, 9.0 Hz (C*H*)), 3.75 (m, 2H (CH_2N)), 3.29 (t, 2H, J = 6.5

Hz (CH_2O)), 2.41 (s, 3H (ArCH_3)), 1.81 (dt, 2H, *J* = 6.5, 13.5 (CH_2CH_2N)), 1.70 (brs, 1H (O*H*)), 1.59 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.55 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.12 (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.5 (*QAr*), 137.4 (*QAr*), 136.4 (=*C*Me_2), 129.4 (*Ar*H), 128.4 (*Ar*H), 128.2 (=*C*H), 58.9 (*C*H_2O), 49.5 (*C*HN), 44.7 (*C*H_2N), 31.4 (*C*H_2CH_2N), 21.8 (Ar*C*H_3), 21.5 (=*Me*), 19.2 (*Me*), 15.4 (=*Me*); m/z (ES) $[M+Na]^+$ 334.3; $C_{16}H_{25}NO_3SNa$ requires 334.1453, found 334.1443

119b

N-Tosyl-(*S*)-3-((2,5-dimethylhex-4-en-3-yl)amino)propan-1-ol



Chemical Formula: $C_{18}H_{29}NO_3S$
Exact Mass: 339.19
Molecular Weight: 339.49

Procedure **E** was followed using the following amounts:

Amine **118b** (1 eq, 0.89 mmol, 250 mg) in DMF (0.1 M, 9 mL)

Cesium carbonate (1.5 eq, 1.33 mmol, 434 mg)

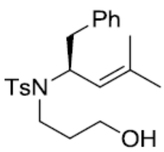
tert-Butyl(3-iodopropoxy)dimethylsilane (1.5 eq, 1.33 mmol, 400 mg)

yield: pale yellow oil (116 mg, 38 %)

R_f 0.08 (20 % EtOAc in hexane); IR υ (cm^{-1}) 3520 (OH), 2872 (CH), 1725 (Ar), 1673 (=), 1327/1154 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66-7.60 (m, 2H (Ar*H*)), 7.25-7.19 (m, 2H (Ar*H*)), 5.01 (dsept, 1H, *J* = 1.5, 10.5 Hz (=C*H*)), 4.09 (t, 1H, *J* = 10.5 Hz (C*H*)), 3.82-3.65 (m, 2H (CH_2N)), 3.26 (t, 2H, *J* = 7.0 Hz (CH_2O)), 2.40 (s, 3H (ArCH_3)), 1.93-1.70 (stack, 3H (C*H*Me_2, CH_2CH_2N)), 1.63 (brs, 1H (O*H*)), 1.57 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.54 (d, 3H, *J* = 1.5 Hz (=*Me*)), 0.99 (d, 3H, *J* = 6.5 Hz (*Me*)), 0.79 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.5 (*QAr*), 137.4 (*QAr*), 136.4 (=*C*Me_2), 129.4 (*Ar*H), 128.4 (*Ar*H), 132.2 (=*C*H), 58.9 (*C*H_2O), 59.5 (*C*HN), 45.7 (*C*H_2N), 32.6 (*C*HMe_2), 31.4 (CH_2CH_2N), 21.8 (ArCH_3), 21.5 (=*Me*), 19.2 (*Me*), 15.4 (=*Me*); m/z (ES) $[M+Na]^+$ 362.2

119c

N-Tosyl-(*S*)-3-((4-methyl-1-phenylpent-3-en-2-yl)amino)propan-1-ol



Chemical Formula: $C_{22}H_{29}NO_3S$
Exact Mass: 387.19
Molecular Weight: 387.54

Procedure **E** was followed using the following amounts:

Amine **118c** (1 eq, 15.17 mmol, 5.00 g) in DMF (0.1 M, 150 mL)

Cesium carbonate (1.5 eq, 22.75 mmol, 7.41 g)

tert-Butyl(3-iodopropoxy)dimethylsilane (1.5 eq, 22.75 mmol, 6.83 g)

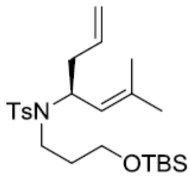
yield: pale yellow oil (2.66 g, 45 %)

IR υ (cm^{-1}) 3515 (OH), 2929 (CH), 1742 (Ar), 1598 (=), 1327/1154 (SO_2N), 1256 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70-7.63 (stack, 2H (Ar*H*)), 7.27-7.13 (stack, 5H (Ar*H*)), 7.12-7.08 (stack, 2H (Ar*H*)), 5.05 (dsept, 1H, *J* = 1.5, 9.5 Hz (=C*H*)), 4.64 (dt, 1H, *J* = 4.5, 9.5 Hz (C*H*)), 3.72 (ddd, 1H, *J* = 5.5, 11.5, 17.0 Hz (C*H*HN)), 3.70 (ddd, 1H, *J* = 5.5, 11.5, 17.0 Hz (CH*H*N)), 3.36 (t, 2H, *J* = 7.0 Hz (C*H₂*O)), 2.96 (dd, 1H, *J* = 4.5, 13.0 Hz (C*H*HPh)), 2.69 (dd, 1H, *J* = 4.5, 13.0 Hz (CH*H*Ph)), 2.52 (brs, 1H (O*H*)), 2.39 (s, 3H (ArC*H₃*)), 1.83 (dt, 2H, *J* = 5.5, 7.0 Hz (CH_2CH_2N)), 1.50 (d, 3H, *J* = 1.5 Hz (*Me*)), 1.12 (d, 3H, *J* = 1.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.1 (*QAr*), 138.0 (*QAr*), 137.7 (*QAr*), 137.5 (=*C*Me_2), 59.1 (*C*H_2N), 58.0 (*C*H), 42.0 (*C*H_2Ph), 41.4

(CH_2O), 33.7 (CH_2CH_2N), 25.6 (*Me*), 21.5 (ArCH_3), 17.9 (*Me*); m/z (ES) $[M+Na]^+$ 410.1; $C_{22}H_{29}NO_3SNa$ requires 410.1766, found 410.1765

119d(i)

N-Tosyl-(*S*)-*N*-(3-(*tert*-butyldimethylsilyloxy)propyl)-6-methylhepta-1,5-dien-4-amine



Chemical Formula: $C_{24}H_{41}NO_3SSi$
Exact Mass: 451.26
Molecular Weight: 451.74

Procedure **E** was followed using the following amounts:

Amine **118d** (1 eq, 21.47 mmol, 6.0 g) in DMF (0.1 M, 215 mL)

Cesium carbonate (1.5 eq, 32.21 mmol, 10.50 g)

tert-Butyl(3-iodopropoxy)dimethylsilane (1.5 eq, 32.21 mmol, 9.67 g)

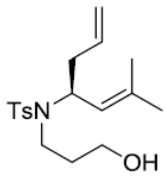
yield: pale yellow oil (9.04 g, 93 %)

IR υ (cm^{-1}) 2928 (CH), 1641 (=), 1599 (=), 1339/1159 (SO_2N), 1254 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (app d, 2H (Ar*H*)), 7.25 (app d, 2H (Ar*H*)), 5.65 (dsept, 1H, *J* = 1.0, 9.0 Hz (=C*H*)), 5.15-4.94 (stack, 3H (=C*H*)), 4.58 (td, 1H, *J* = 6.0, 9.0 Hz (C*H*)), 3.63 (t, 1H, *J* = 5.5 Hz (C*H*HN)), 3.59 (t, 1H, *J* = 5.5 Hz (CH*H*N)), 3.22 (dd, 1H, *J* = 6.5, 9.5 Hz (C*H*HO)), 3.15 (dd, 1H, *J* = 6.0, 15.0 Hz (CH*H*O)), 2.42 (s, 3H (ArCH_3)), 2.36-2.16 (stack, 2H (CH_2C=)), 1.96-1.75 (stack, 2H (C$H_2$$CH_2$O)), 1.63 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.59 (d, 3H, *J* = 1.0 Hz (=*Me*)), 0.91 (s, 9H (^{t}*Bu*)), 0.09 (s, 3H (Si*Me*)), 0.06 (s, 3H (Si*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.7 (*QAr*), 138.1 (*QAr*), 136.3 (=*C*Me_2), 134.6 (H*C*=CH_2), 129.2 (*Ar*H), 127.4 (*Ar*H), 122.3 (H*C*=Me_2), 117.1 (=CH_2), 60.7 (CH_2N), 56.1 (*C*H), 41.9 (CH_2O), 39.2 (CH_2CH), 34.4 (CH_2CH_2N), 25.9 (^{t}*Bu*), 25.7 (=*Me*), 21.5

(ArCH_3), 18.5 (=*Me*), 18.2 (Q^tBu), -5.4 (Si*Me*); m/z (ES) $[M+Na]^+$ 475.4; $C_{24}H_{41}NO_3SSiNa$ requires 474.2474, found 474.2459

119d(ii)

N-Tosyl-(*S*)-3-(6-methylhepta-1,5-dien-4-yl)aminopropan-1-ol



Chemical Formula: $C_{18}H_{27}NO_3S$
Exact Mass: 337.17
Molecular Weight: 337.48

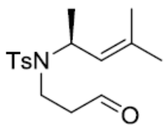
Silyl ether **119d(i)** (1 eq, 1.42 mmol, 640 mg) was dissolved in THF (0.1 M, 14 mL) and TBAF [1 M] (1.5 eq, 2.13 mmol, 2.20 mL) added slowly. The mixture was stirred at room temperature overnight then diluted with water and the products extracted into ether. Purification by column chromatography, eluting with 20 % EtOAc in hexane yielded a yellow oil.

IR υ (cm^{-1}) 3418 (OH), 2931 (CH), 1663 (Ar), 1598 (=), 1331/155 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.63 (app d, 2H (Ar*H*)), 7.21 (app d, 2H (Ar*H*)), 5.60 (dsept, 1H, *J* = 1.0, 8.5 Hz (=C*H*)), 5.24-4.86 (stack, 3H (=C*H*)), 4.46 (dt, 1H, *J* = 6.0, 8.5 Hz (C*H*)), 3.52 (t, 1H, *J* = 6.0 Hz (C*H*HN)), 3.62 (t, 1H, *J* = 6.0 Hz (CH*H*N)), 3.51 (brs, 1H (O*H*)), 3.13 (dd, 1H, *J* = 6.5, 9.5 Hz (C*H*HO)), 3.10 (dd, 1H, *J* = 6.5, 15.0 Hz (CH*H*O)), 2.40 (s, 3H (ArCH_3)), 2.31-2.11 (stack, 2H (CH_2C=)), 1.87-1.69 (stack, 2H (C$H_2$$CH_2$O)), 1.58 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.56 (d, 3H, *J* = 1.0 Hz (=*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.7 (*QAr*), 138.1 (*QAr*), 136.3 (=*C*Me_2), 134.6 (H*C*=CH_2), 129.2 (*Ar*H), 127.4 (*Ar*H), 122.3 (H*C*=Me_2), 117.1 (=*C*H_2), 60.7 (*C*H_2N), 56.1 (*C*H), 39.9 (*C*H_2O), 39.2

(CH_2CH), 35.4 (CH_2CH_2N), 25.7 (=*Me*), 21.5 ($ArCH_3$), 18.5 (=*Me*); m/z (ES) $[M+Na]^+$ 360.3; $C_{18}H_{27}NO_3SNa$ requires 360.1609, found 360.1599

120a

N-Tosyl-(*S*)-3-(4-methylpent-3-en-2-yl)aminopropanal



Chemical Formula: $C_{16}H_{23}NO_3S$
Exact Mass: 309.14
Molecular Weight: 309.42

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 1.77 mmol, 149 μl) in DCM (0.4 M, 4.50 mL)

DMSO (2.4 eq, 3.85 mmol, 274 μl)

Alcohol **119a** (1 eq, 1.61 mmol, 500 mg) in DCM (0.75 M, 2.00 mL)

Triethylamine (5 eq, 8.03 mmol, 1.12 mL)

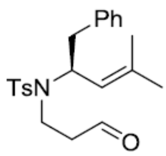
The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a pale yellow oil (418 mg, 84 %).

R_f 0.71 (50 % EtOAc in hexane); IR υ (cm^{-1}) 2930 (CHO), 1721 (C=O), 1648 (=), 1597 (Ar), 1329/1152 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H (C*H*O)), 7.69 (app d, 2H (Ar*H*)), 7.28 (app d, 2H (Ar*H*)), 4.92 (dsept, 1H, *J* = 1.5, 8.5 Hz (=C*H*)), 4.74 (dq, 1H, *J* = 7.0, 8.5 Hz (C*H*N)), 3.53-3.28 (m, 2H (CH_2N)), 2.95 (t, 2H, *J* = 7.5 Hz (CH_2CHO)), 2.43 (s, 3H ($ArCH_3$)), 1.64 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.62 (d, 3H, *J* = 1.5 Hz (=*Me*)), 1.06 (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.7 (*C*HO), 141.2 (*QAr*), 137.7 (*QAr*), 136.3 (=CMe_2), 129.4 (*Ar*H), 128.4

(ArH), 128.0 (=CH), 49.6 (CHN), 43.2 (CH_2N), 39.4 (CH$_2$CH$_2$N), 21.5 (ArCH_3), 21.4 (=Me), 18.5 (Me), 15.4 (=Me); m/z (ES) $[M+Na]^+$ 332.1

120c

N-Tosyl-(*S*)-3-(4-methyl-1-phenylpent-3-en-2-yl)aminopropanal



Chemical Formula: $C_{22}H_{27}NO_3S$
Exact Mass: 385.17
Molecular Weight: 385.52

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 7.10 mmol, 600 μl) in DCM (0.4 M, 18.00 mL)

DMSO (2.4 eq, 15.48 mmol, 1.10 mL)

Alcohol **119c** (1 eq, 6.45 mmol, 2.50 g) in DCM (0.75 M, 8.00 mL)

Triethylamine (5 eq, 32.25 mmol, 4.50 mL)

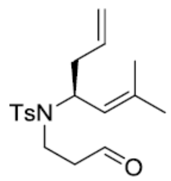
The product was purified by column chromatography, eluting with 25 % EtOAc in hexane, to yield a pale yellow liquid (1.67 g, 67 %).

IR υ (cm^{-1}) 2932 (CHO), 1723 (C=O), 1639 (=), 1592 (Ar), 1336/1149 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H (C*HO*)), 7.66 (app d, 2H (Ar*H*)), 7.32-7.17 (stack, 5H (*Ph*)), 7.11 (app d, 2H (Ar*H*)), 4.98 (dsept, 1H, *J* = 1.0, 9.0 Hz (=C*H*)), 4.77 (dt, 1H, *J* = 9.0, 9.5 Hz (C*H*)), 3.54 (ddd, 1H, *J* = 5.0, 9.5, 12.5 Hz (C*H*HN)), 3.42 (ddd, 1H, *J* = 5.0, 9.5, 12.5 Hz (CH*H*N)), 3.03-2.78 (stack, 3H (CH_2CHO, C*H*HPh)), 2.65 (dd, 1H, *J* = 9.5, 13.0 (CH*H*Ph)), 2.42 (s, 3H (ArCH_3)), 1.53 (d, 3H, *J* = 1.0 Hz (=*Me*)), 1.28 (d, 3H, *J* = 1.0 Hz (=*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.7 (*C*HO), 143.2 (*QAr*), 137.7 (*QAr*), 137.6 (*QAr*), 137.3 (=CMe$_2$), 129.4 (*Ar*H), 129.4 (*Ar*H), 128.3

(*Ar*H), 127.4 (*Ar*H), 126.4 (*Ar*H), 121.0 (=*C*H), 57.6 (*C*H), 46.2 (*C*H_2O), 41.0 (*C*H_2Ph), 37.7 (*C*H_2N), 25.6 (*Me*), 21.5 (Ar*C*H_3), 18.1 (*Me*); m/z (ES) $[M+Na]^+$ 408.2

120d

N-Tosyl-(*S*)-3-(6-methylhepta-1,5-dien-4-yl)aminopropanal



Chemical Formula: $C_{18}H_{25}NO_3S$
Exact Mass: 335.16
Molecular Weight: 335.46

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 6.52 mmol, 552 μl) in DCM (0.4 M, 16.50 mL)

DMSO (2.4 eq, 14.22 mmol, 1.00 mL)

Alcohol **119d(ii)** (1 eq, 5.93 mmol, 2.00 g) in DCM (0.75 M, 7.00 mL)

Triethylamine (5 eq, 29.63 mmol, 4.10 mL)

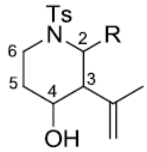
The product was purified by column chromatography, eluting with 15 % EtOAc in hexane, to yield a pale yellow oil (1.12 g, 56 %).

R_f 0.21 (15 % EtOAc in hexane); IR υ (cm^{-1}) 2916 (CHO), 1730 (C=O), 1646 (=), 1598 (Ar), 1324/1157 (SO_2N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H (C*H*O)), 7.65 (app d, 2H (Ar*H*)), 7.25 (app d, 2H (Ar*H*)), 5.66-5.53 (m, 1H (=C*H*CH_2)), 5.03-4.95 (stack, 2H (=C*H_2*)), 4.91 (dsept, 1H, *J* = 1.5, 9.0 Hz (=C*H*CH)), 4.58 (dt, 1H, *J* = 6.5, 9.0 Hz (C*H*)), 3.43 (ddd, 1H, *J* = 6.0, 8.5, 15.5 Hz (C*H*HN)), 3.36 (ddd, 1H, *J* = 6.0, 8.5, 15.5 Hz (CH*H*N)), 2.96 (ddd, 1H, *J* = 6.0, 8.5, 18.5 Hz (C*H*HCHO)), 2.89 (ddd, 1H, *J* = 6.0, 8.5, 18.5 Hz (CH*H*CHO)), 2.39 (s, 3H (ArC*H_3*)), 2.22-2.09 (m, 2H (C*H_2*CH)), 1.59 (d, 6H, *J* = 1.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.7 (*C*HO), 143.2

(*QAr*), 137.3 (*QAr*), 134.2 (=*C*H), 129.4 (*Ar*H), 127.4 (*Ar*H), 121.6 (=*C*H), 117.4 (=CH_2), 117.3 (*Q*=*C*Me_2), 55.9 (*C*H), 46.2 (CH_2CHO), 38.7 (CH_2CH), 37.4 (CH_2N), 25.6 (*Me*), 21.4 (ArCH_3), 18.5 (*Me*); m/z (ES) $[M+Na]^+$ 358.2

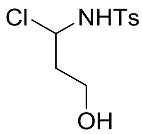
Data from cyclisations

Where protons and carbons have been assigned as numbered atoms, they refer to those in the piperidine ring, numbered as follows:



121

N-Tosyl-3-amino-3-chloropropan-1-ol



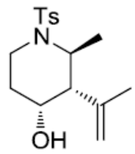
Chemical Formula: $C_{10}H_{14}ClNO_3S$
Exact Mass: 263.04
Molecular Weight: 263.74

Produced from the reaction of compounds **114a-c** with HCl gas as a pale yellow residue.

R_f 0.80 (25 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (app d, 2H (Ar*H*)), 7.30 (app dd, 2H (Ar*H*)), 5.21 (t, 1H, *J* = 4.5 Hz (C*H*Cl)), 3.70 (dt, 1H, *J* = 5.5, 14.0 Hz (C*H*HOH), 3.31 (dt, 1H, *J* = 5.5, 14.0 Hz (CH*H*OH)), 2.31 (s, 3H (ArC*H₃*)), 1.92 (m, 2H (O*H*, N*H*)), 1.85 (ddt, 1H, *J* = 4.5, 5.5, 14.0 Hz (C*H*HCH)), 1.64 (ddt, 1H, *J* = 4.5, 5.5, 14.0 Hz (CH*H*CH)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.0 (*QAr*), 135.7 (*QAr*), 129.9 (*Ar*H), 127.5 (*Ar*H), 77.1 (*C*H), 37.8 (*C*H_2), 28.9 (*C*H_2), 21.6 (Ar*C*H_3); m/z (ES) [^{35}Cl] $[M+Na]^+$ 286.0

122a

(2*S*,3*S*,4*R*)-2-Methyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



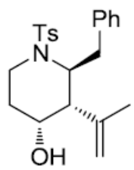
Chemical Formula: $C_{16}H_{23}NO_3S$
Exact Mass: 309.14
Molecular Weight: 309.42

Formed as the **major** product from the reaction of precursor **120a** in procedure **K** as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62 (app d, 2H (Ar*H*)), 7.22 (app d, 2H (Ar*H*)), 4.99 (d, 1H, *J* = 1.0 Hz (=C*H*)), 4.85 (d, 1H, *J* = 1.0 Hz (=C*H*)), 4.09 (dq, 1H, *J* = 4.5, 7.0 Hz (H_2)), 3.89 (q, 1H, *J* = 7.0 Hz (H_4)), 3.59 (dt, 1H, *J* = 4.5, 9.5 Hz (H_{6e})), 3.09 (dt, 1H, *J* = 7.0, 13.0 Hz (H_{6a})), 2.35 (s, 3H (ArCH_3)), 2.28 (dd, 1H, *J* = 4.5, 7.0 Hz (H_3)), 1.84 (s, 3H (*Me*)), 1.82-1.74 (m, 2H (H_{5e}, H_{5a})), 1.00 (d, 3H, *J* = 7.0 Hz (Me))

122c

(2*S*,3*S*,4*R*)-2-Benzyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



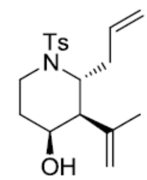
Chemical Formula: $C_{22}H_{27}NO_3S$
Exact Mass: 385.17
Molecular Weight: 385.52

Formed as the **major** product from the reaction of precursor **120c** in procedure **K** as a colourless crystalline solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (app d, 2H (Ar*H*)), 7.28-7.11 (stack, 7H (Ar*H*)), 4.90 (t, 1H, *J* = 1.5 (=C*H*)), 4.85 (app s, 1H (=C*H*)), 4.69 (brs, 1H (OH)), 4.17 (ddd, 1H, *J* = 4.5, 7.0, 8.0 Hz (H_2)), 3.53 (ddd, 1H, *J* = 2.0, 7.5, 14.0 Hz (H_{6e})), 3.47 (ddd, 1H, *J* = 2.0, 7.0, 7.5 Hz (H_4)), 3.11 (dd, 1H, *J* = 8.0, 13.5 Hz (C*H*HPh)), 2.92 (ddd, 1H, *J* = 5.5, 11.0, 14.0 Hz (H_{6a})), 2.64 (dd, 1H, *J* = 4.5, 13.5 Hz (CH*H*Ph)), 2.33 (s, 3H (ArCH_3)), 2.13 (t, 1H, *J* = 7.0 Hz (H_3)), 2.08-1.95 (m, 1H (H_{5e})), 1.57 (s, 3H (*Me*)), 1.36-1.25 (m, 1H (H_{5a})); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.6 (*QAr*), 142.2 (*QAr*), 138.0 (*QAr*), 136.6 (*C*=), 128.8 (*Ar*H), 128.3 (*Ar*H), 127.6 (*Ar*H), 126.1 (*Ar*H), 125.4 (*Ar*H), 114.9 (=*C*H2), 65.0 (C_4), 55.3 (C_2), 49.0 (C_3), 37.3 (CH_2Ph), 36.7 (C_6), 28.7 (C_5), 20.5 ($ArCH_3$), 19.5 (*Me*)

122d

(2*S*,3*S*,4*R*)-2-Allyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



Chemical Formula: $C_{18}H_{25}NO_3S$
Exact Mass: 335.16
Molecular Weight: 335.46

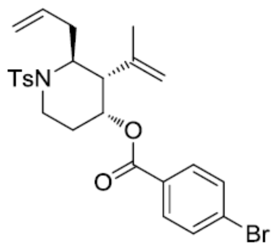
Formed as the **major** product from the reaction of precursor **120d** in procedure **K** as a yellow residue.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (app d, 2H (Ar*H*)), 7.22 (app d, 2H (Ar*H*)), 5.62 (dddd, 1H, *J* = 6.0, 8.0, 10.0, 16.5 Hz (=C*H*)), 5.02-4.89 (stack, 4H (4x =CH*H*)), 4.15 (dt, 1H, *J* = 3.5, 10.5 Hz (H_2)), 3.90 (dd, 1H, *J* = 6.0, 13.5 Hz (H_4)), 3.72 (ddt, 1H, *J* = 1.0, 4.0, 14.0 Hz (H_{6e})), 2.90 (ddd, 1H, *J* = 6.0, 7.5, 14.0 Hz (H_{6a})), 2.51 (dd, 1H, *J* = 3.5, 6.0 Hz (H_3)), 2.35 (s, 3H (ArCH_3)), 2.31-

2.18 (m, 1H (H_{5a})), 1.99-1.88 (m, 1H (H_{5e})), 1.84 (s, 3H (*Me*)), 1.82-1.73 (m, 1H (C*H*HCH=)), 1.63-1.47 (m, 1H (CH*H*CH=))

der-122d

(2*S*,3*S*,4*R*)-2-Allyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-yl 4-bromobenzoate



Chemical Formula: $C_{25}H_{28}BrNO_4S$
Exact Mass: 517.09
Molecular Weight: 518.46

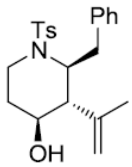
Piperidine **122d** (1 eq, 1.40 mmol, 470 mg), DMAP (0.5 eq, 0.70 mmol, 86 mg) and triethylamine (2 eq, 2.80 mmol, 0.39 mL) were dissolved in DCM (0.1 M, 14 mL) at 0 °C. 4-bromobenzoyl chloride (1 eq, 1.40 mmol, 308 mg) in minimal DCM was added dropwise and the reaction stirred at RT for 6 hours. After aqueous workup the product was purified by column chromatography, eluting with 20 % ethyl acetate in hexane to give a white crystalline solid, 580 mg (80 %).

R_f 0.70 (30 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87 (app d, 2H (ArH_ε)), 7.73 (app d, 2H (ArH_{Ts})), 7.59 (app d, 2H (ArH_ε)), 7.28 (app d, 2H ((ArH_{Ts})), 5.82-5.63 (m, 1H (=C*H*)), 5.40 (dt, 1H, *J* = 5.0, 10.0 Hz (H_4)), 5.16-5.06 (stack, 2H (=CH_2)), 5.09- 4.99 (stack, 2H (=CH_2)), 4.38 (dt, 1H, *J* = 3.5, 9.5 Hz (H_2)), 3.89 (dd, 1H, *J* = 5.0, 13.5 Hz (H_{6e})), 3.08 (dt, 1H, *J* = 3.5, 13.0 Hz (H_{6a})), 2.79 (dd, 1H, *J* = 3.5, 5.0 Hz (H_3)), 2.49-2.37 (m, 1H (H_{5e})), 2.42 (s, 3H (ArCH_3)), 2.22 (tdd, 1H, *J* = 6.0, 10.0, 13.0 Hz (C*H*HC=)), 2.13-2.01 (m, 1H (H_{5a})), 2.01- 1.91 (m, 1H (CH*H*C=)), 1.86 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.1 (*C*=O), 143.3 (=*C*R_2), 142.8 (*QTs*), 138.0

(*QTs*), 133.8 (=*C*H), 131.8 (*Ar*H$_\varepsilon$), 131.2 (*Ar*H$_\varepsilon$), 129.7 (*Ar*H$_{Ts}$), 129.1 (*Q*ε), 128.2 (*Q*ε), 127.1 (*Ar*HTs), 118.7 (=CH_2), 115.4 (=CH_2), 69.8 (C_2), 56.3 (C_4), 44.2 (C_3), 39.7 (C_6), 35.1 (C_5), 27.6 (CH_2C=), 24.4 (*Me*), 21.5 (ArCH_3)

123c

(2*S*,3*S*,4*S*)-2-Benzyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



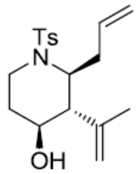
Chemical Formula: $C_{22}H_{27}NO_3S$
Exact Mass: 385.17
Molecular Weight: 385.52

Formed as the **minor** product from the reaction of precursor **120c** in procedure **K** as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (app d, 2H (Ar*H*)), 7.29-7.17 (stack, 5H (Ar*H*)), 7.12 (app d, 2H (Ar*H*)), 4.95 (t, 1H, *J* = 1.5 Hz (=C*H*)), 4.83 (s, 1H (=C*H*)), 4.44 (dt, 1H, *J* = 3.0, 10.5 Hz (H_2)), 4.03 (dt, 1H, *J* = 5.5, 7.5 Hz (H_4)), 3.80 (dt, 1H, *J* = 3.0, 13.5 Hz (H_{6e})), 2.93 (ddd, 1H, *J* = 7.5, 13.0, 13.5 Hz (H_{6a})), 2.76 (dd, 1H, *J* = 10.5, 13.5 Hz (C*H*HPh)), 2.57 (dd, 1H, *J* = 3.0, 13.5 Hz (CH*H*Ph)), 2.38 (dd, 1H, *J* = 3.0, 5.5 Hz (H_3)), 2.37 (s, 3H (ArCH_3)), 1.84-1.79 (stack, 2H (H_{5e}, H_{5a})), 1.74 (s, 3H (*Me*)), 1.67 (brs, 1H (O*H*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.6 (*QAr*), 143.3 (*QAr*), 143.2 (*QAr*), 137.7 (*C*=), 130.9 (*Ar*H), 129.8 (*Ar*H), 128.7 (*Ar*H), 127.0 (*Ar*H), 126.7 (*Ar*H), 115.9 (=CH_2), 65.5 (C_4), 57.6 (C_2), 45.8 (C_3), 39.1 (C_6), 36.2 (CH_2Ph), 30.3 (C_5), 24.6 (*Me*), 21.5 (ArCH_3)

123d

(2*S*,3*S*,4*S*)-2-Allyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



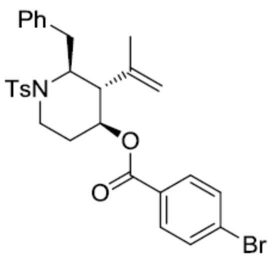
Chemical Formula: $C_{18}H_{25}NO_3S$
Exact Mass: 335.16
Molecular Weight: 335.46

Formed as the **trace** product from the reaction of precursor **120d** in procedure **K** as a yellow residue.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (app d, 2H (Ar*H*)), 7.31 (app d, 2H (Ar*H*)), 5.72 (ddt, 1H, *J* = 6.0, 8.5, 12.0 Hz (=C*H*)), 5.25 (dt, 1H, *J* = 5.0, 10.0 Hz (H_2)), 5.14-4.98 (stack, 4H (4x =C*H*)), 4.25 (dt, 1H, *J* = 3.5, 9.5 Hz (H_4)), 3.88 (dd, 1H, *J* = 5.5, 13.0 Hz (H_{6e})), 3.06 (dd, 1H, *J* = 4.0, 12.5 Hz (H_{6a})), 2.68 (dd, 1H, *J* = 3.5, 5.0 Hz (H_3)), 2.51-2.34 (m, 1H (H_{5a})), 2.44 (s, 3H (ArCH_3)), 2.12-1.98 (m, 1H (H_{5e})), 1.95-1.85 (m, 1H (C*H*HCH=)), 1.84 (s, 3H (*Me*)), 1.79-1.57 (m, 1H (CH*H*CH=))

der-123c

(2*S*,3*S*,4*S*)-2-Benzyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-yl 4-bromobenzoate



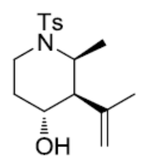
Chemical Formula: $C_{29}H_{30}BrNO_4S$
Exact Mass: 567.11
Molecular Weight: 568.52

Piperidine **123c** (1 eq, 0.31 mmol, 120 mg), DMAP (0.5 eq, 0.16 mmol, 19 mg) and triethylamine (2 eq, 0.62 mmol, 87 μl) were dissolved in DCM (0.1 M, 3 mL) at 0 °C. 4-bromobenzoyl chloride (1 eq, 0.31 mmol, 68 mg) in minimal DCM was added dropwise and the reaction stirred at RT for 2 ½ hours. After aqueous workup the product was purified by column chromatography, eluting with 20 % ethyl acetate in hexane to give a white solid, 151 mg (86 %).

R_f 0.75 (30 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (app d, 2H (Ar*H*)), 7.74 (app d, 2H (Ar*H*)), 7.63 (app d, 2H (Ar*H*)), 7.31 (app d, 2H (Ar*H*)), 7.25-7.13 (stack, 5H (*Ph*)), 5.26 (q, 1H, *J* = 4.0 Hz (H_4)), 5.03 (s, 1H (=CH*H*)), 4.93 (s, 1H (=C*H*H)), 4.49 (ddd, 1H, *J* = 3.0, 3.5, 10.5 Hz (H_2)), 3.75 (ddd, 1H, *J* = 2.0, 5.5, 13.5 Hz (H_{6a})), 3.30 (dt, 1H, *J* = 3.5, 13.0 Hz (H_{6e})), 3.19 (dd, 1H, *J* = 10.5, 13.5 Hz (CH*H*Ph)), 2.83 (dd, 1H, *J* = 3.5, 13.5 Hz (C*H*HPh)), 2.49-2.42 (m, 1H (H_3)), 2.44 (s, 3H (ArCH_3)), 2.27-2.11 (m, 1H (H_{5e})), 1.79 (dddd, 1H, *J* = 2.0, 3.5, 4.0, 14.5 Hz (H_{5a})), 1.66 (s, 3H (*Me*))

124a

(2*S*,3*R*,4*R*)-2-Methyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



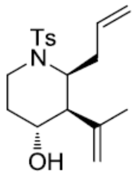
Chemical Formula: $C_{16}H_{23}NO_3S$
Exact Mass: 309.14
Molecular Weight: 309.42

Formed as the **minor** product from the reaction of precursor **120a** in procedure **K** as a yellow residue.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (app d, 2H (Ar*H*)), 7.30 (app d, 2H (Ar*H*)), 5.08 (s, 1H (=C*H*)), 4.83 (d, 1H, *J* = 1.0 Hz (=C*H*)), 4.29 (dq, 1H, *J* = 5.0, 7.0 Hz (H_2)), 3.97 (td, 1H, *J* = 5.0, 11.0 Hz (H_4)), 3.86 (dt, 1H, *J* = 5.0, 14.0 Hz (H_{6e})), 3.07 (dt, 1H, *J* = 2.5, 14.0 Hz (H_{6a})), 2.42 (s, 3H (ArCH_3)), 2.03 (dd, 1H, *J* = 5.0, 11.0 Hz (H_3)), 1.96 (ddt, 1H, *J* = 2.5, 5.0, 12.5 (H_{5e})), 1.76 (s, 3H (*Me*)), 1.39 (m, 2H (H_{5a})), 0.95 (d, 3H, *J* = 7.0 Hz (Me)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.3 (*QAr*), 142.3 (*QAr*), 138.1 (*C*=), 129.8 (*Ar*H), 126.9 (*Ar*H), 113.0 (=CH_2), 64.8 (C_4), 54.3 (C_2), 50.8 (C_3), 38.8 (C_6), 32.9 (C_5), 23.1 (*Me*=), 21.5 (*ArCH$_3$*), 12.3 (*Me*)

124d

(2*S*,3*R*,4*R*)-2-Allyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol



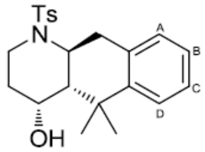
Chemical Formula: $C_{18}H_{25}NO_3S$
Exact Mass: 335.16
Molecular Weight: 335.46

Formed as the **minor** product from the reaction of precursor **120d** in procedure **K** as a yellow residue.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (app d, 2H (Ar*H*)), 7.31 (app d, 2H (Ar*H*)), 5.79 (ddt, 1H, *J* = 7.0, 11.0, 16.5 Hz (=C*H*)), 5.12-5.05 (stack, 2H (2x =CH*H*)), 5.04-4.95 (stack, 2H (2x =CH*H*)), 3.92 (dt, 1H, *J* = 5.0, 7.0 Hz (H_2)), 3.64 (dddd, 1H, *J* = 0.5, 3.0, 7.5, 14.0 Hz (H_4)), 3.48 (dt, 1H, *J* = 7.0, 9.0 Hz (H_{6e})), 3.32 (ddd, 1H, *J* = 6.0, 9.0, 14.0 Hz (H_{6a})), 2.64 (dd, 1H, *J* = 7.0, 14.0 Hz (H_3)), 2.44 (s, 3H (ArCH_3)), 2.33-2.06 (stack, 3H (1 of H_5, CH_2CH=)), 1.74 (s, 3H (*Me*)), 1.50-1.39 (m, 1H (1 of H_5, CH_2CH=))

126

(4*R*,4a*S*,10a*S*)-5,5-Dimethyl-1-tosyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-4-ol



Chemical Formula: $C_{22}H_{27}NO_3S$
Exact Mass: 385.17
Molecular Weight: 385.52

Formed as a by-product during derivatization of piperidine **122c**, or during extended reaction of precursor **120c** in procedure **K** as a white solid. (NB piperidine stereochemistry: 2*S*,3*S*,4*R*).

IR υ (cm^{-1}) 3612 (OH), 1593 (Ar), 1363/1181 (SO_2N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93-7.73 (m, 2H (Ar*H*)), 7.36 (app dd, 1H (ArH_A)), 7.37-7.32 (m, 2H (Ar*H*)), 7.20 (app dt, 1H (ArH_C)), 7.12 (app dt, 1H (ArH_B)), 7.00 (app dd, 1H (ArH_D)), 4.42-4.28 (stack, 2H (H_2, H_4)), 3.78 (app dt, 1H, *J* = 5.0, 14.5 Hz (H_{6e})), 3.22 (dt, 1H, *J*= 9.0, 14.5 Hz (H_{6a})), 3.04 (dd, 1H, *J* = 5.5, 15.5 Hz (C*H*HAr)), 2.97 (dd, 1H, *J* = 10.0, 15.5 Hz (CH*H*Ar)), 2.46 (s, 3H (ArCH_3)), 2.05-1.98 (stack, 2H (H_5)), 1.85 (d, 1H, *J* = 8.5 Hz (O*H*)), 1.65 (d, 1H, *J* = 11.5 Hz (H_3)), 1.42 (s, 3H (*Me*)), 1.39 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.7 (*QAr*), 143.6 (*QAr*), 137.7 (*QAr*), 132.9 (*QAr*), 129.8 (*Ar*H), 129.5 (*Ar*H_D), 127.3 (*Ar*H), 126.6 (*Ar*H_A), 126.5 (*Ar*H_C), 125.6 (*Ar*H_B), 63.6 (C_4), 50.1 (C_3), 48.3 (C_2), 39.3 (*C*Me_2), 36.5 (C_6), 36.0 (*C*H_2Ar), 35.2 (C_5), 29.5 (*Me*), 28.5 (*Me*), 21.6 (Ar*C*H_3); m/z (ES) $[M+Na]^+$ 408.2; $C_{22}H_{27}NO_3SNa$ requires 408.1609, found 408.1622

Unknown stereochemistry ^{i}Pr piperidine isomers

Isomer A

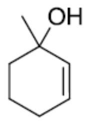
R_f 0.37 (40 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (app d, 2H (Ar*H*)), 7.27 (app d, 2H (Ar*H*)), 4.95 (quin, 1H, *J* = 1.5 Hz (=C*H*H)), 4.82 (s, 1H (=CH*H*)), 3.77 (dt, 1H, *J* = 1.0, 7.0 Hz (H_2)), 3.68 (dddd, 1H, *J* = 1.0, 3.5, 9.0, 14.5 Hz (H_{6e})), 3.38 (tt, 1H, *J* = 5.5, 8.5 Hz (H_4)), 3.24 (ddd, 1H, *J* = 7.5, 8.5, 14.5 Hz (H_{6a})), 2.41 (s, 3H (ArCH_3)), 2.22 (dd, 1H, *J* = 7.0, 8.5 Hz (H_3)), 2.16-2.00 (stack, 2H (H_{5e}, C*H*Me_2)), 1.78 (d, 3H, *J* = 0.5 Hz (*Me*C=)), 1.37 (dddd, 1H, *J* = 5.5, 7.5, 9.0, 13.5 Hz (H_{5a})), 1.01 (d, 3H, *J* = 7.0 Hz (*Me*)), 0.91 (d, 3H, *J* = 7.0 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.4 (*QAr*), 143.1 (*QAr*), 138.0 (*C*=), 129.5 (*Ar*H), 127.4 (*Ar*H), 115.7 (H_2*C*=), 66.0 (C_4), 61.0 (C_2), 52.8 (C_3), 38.4 (C_6), 32.9 (*C*HMe_2), 29.1 (C_5), 21.5 (Ar*C*H_3), 20.3 (*Me*), 20.1 (*Me*=), 19.5 (*Me*).

Isomer B

R_f 0.29 (15 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.71 (app d, 2H (Ar*H*)), 7.25 (app d, 2H (Ar*H*)), 4.93 (quin, 1H, *J* = 1.0 Hz (=C*H*H)), 4.84 (s, 1H (=CH*H*)), 4.06-3.96 (m, 1H (H_4)), 3.93 (dt, 1H, *J* = 2.5, 9.5 Hz (H_2)), 3.74 (dddd, 1H, *J* = 1.5, 2.5, 6.0, 14.0 Hz (H_{6e})), 2.97 (ddd, 1H, *J* = 4.5, 11.5, 14.0 Hz (H_{6a})), 2.59 (dd, 1H, *J* = 2.5, 5.0 Hz (H_3)), 2.41 (s, 3H (ArCH_3)), 1.98 (dsept, 1H, *J* = 6.5, 9.5 Hz (C*H*Me_2)), 1.94-1.87 (m, 1H (H_{5e})), 1.85 (s, 3H (*Me*C=)), 1.83-1.71 (m, 1H (H_{5a})), 1.60 (s, 1H (OH)), 1.02 (d, 3H, *J* = 6.5 Hz (*Me*)), 0.84 (d, 3H, *J* = 6.5 Hz (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.9 (*QAr*), 142.7 (*QAr*), 138.5 (*C*=), 129.3 (*Ar*H), 127.4 (*Ar*H), 114.6 (H_2*C*=), 66.5 (C_4), 62.3 (C_2), 47.1 (C_3), 39.5 (C_6), 30.2 (C_5), 29.5 (*C*HMe_2), 24.6 (*Me*=), 21.5 (Ar*C*H_3), 20.8 (*Me*), 20.2, (*Me*)

128

1-Methylcyclohex-2-enol[121]



Chemical Formula: $C_7H_{12}O$
Exact Mass: 112.09
Molecular Weight: 112.17

Methyllithium:

Cerium chloride heptahydrate (1.5 eq, 30.03 mmol, 11.20 g) was dehydrated under high vacuum then ground and re-dried before suspending in THF (0.3 M, 100 mL) at 0 °C. The suspension was sonicated for 30 minutes then cooled to -78 °C. Methyllithium [1.6 M] (1.5 eq, 30.06 mmol, 18.8 mL) was added slowly then the mixture stirred for 30 minutes allowing a pale yellow colour to develop. Cyclohexenone (1 eq, 20.00 mmol, 1.92 g) in THF (1 M, 20 mL) was added and the mixture stirred at -78 °C for 3 hours before quenching with sat. aq. ammonium chloride. The aqueous portion was washed with ether to yield a colourless oil (1.81 g, 81 %).

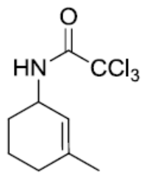
Methyl Grignard:

Methylmagnesium bromide [3 M] (1.5 eq, 78.02 mmol, 26.00 mL) was added dropwise to a solution of cyclohexenone (1 eq, 52.01 mmol, 5.00 g) in THF (0.3 M, 175 mL) at 0 C. The mixture was allowed to warm to RT and stirred overnight before quenching with sat. aq. ammonium chloride. The product was extracted with ether to yield a colourless oil (4.42 g, 76 %).

R_f 0.35 (20 % EtOAc in hexane); IR υ (cm^{-1}) 3351 (br)(OH), 2933/2867 (CH), 1651 (=); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.75 (d, 1H, *J* = 3.5, 10.0 Hz (=C*H*C)), 5.63 (dt, 1H, *J* = 10.0 Hz (=C*H*CH_2)), 2.11-1.85 (stack, 2H (CH_{2ring})), 1.81-1.57 (stack, 4H (CH_2CH_{2ring})), 1.49 (brs, 1H (O*H*)), 1.28 (s, 3H (*Me*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.8 (=*C*H), 129.0 (=*C*H), 67.9 (*C*OH), 37.9 (*C*H_2COH), 29.3 (*Me*), 25.0 (*C*H_2), 19.5 (*C*H_2); m/z (ES) $[C_6H_8]^+$ 79.0, $[C_6H_8CH_3]^+$ 94.1

129

2,2,2-Trichloro-*N*-(3-methylcyclohex-2-en-1-yl)acetamide[121]



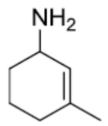
Chemical Formula: $C_9H_{12}Cl_3NO$
Exact Mass: 255.00
Molecular Weight: 256.56

Potassium hydride [25 %] (0.15 eq, 6.16 mmol, 988 mg) was washed in anhydrous ether several times before ether (2 M, 20 mL) was added and the suspension cooled to -5 °C. Alcohol **128** (1 eq, 41.04 mmol, 4.60 g) in ether (1.6 M, 25 mL) was added slowly and the mixture stirred for 30 minutes before adding to a solution of trichloroacetonitrile (1 eq, 41.04 mmol, 4.11 mL) in ether (1 M, 40 mL) at -5 °C. The reaction stirred at RT overnight then was diluted with ether and washed with water. The product was recrystallized from hexane to give a pale yellow solid. (4.74 g, 45 %)

R_f 0.20 (20 % EtOAc in hexane); IR υ (cm^{-1}) 3255 (NH), 2940/2859 (CH), 1685 (C=O), 1536 (=); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.55 (brs, 1H (N*H*)), 5.36 (dq, 1H, *J* = 1.5, 2.0 Hz (=C*H*)), 4.42 (dddd, 1H, *J* = 2.0, 3.5, 5.5, 8.5 Hz (C*H*NH)), 2.04-1.81 (stack, 3H (CH_2CH_{ring})), 1.75-1.54 (stack, 3H (CH_2CH_{ring})), 1.70 (s, 3H (*Me*)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.7 (*C*=O), 133.5 (=*C*Me), 118.5 (=*C*H), 92.8 (*C*Cl_3), 45.2 (*C*HN), 30.5 (*C*H_2C=), 29.8 (*C*H_2CH), 22.4 (*Me*), 18.5 (CH_2CH_2CH); m/z (ES) $[M+Na]^+$ 278.0; $C_9H_{12}NO^{35}Cl_3Na$ requires 277.9882, found 277.9889

130

3-Methylcyclohex-2-enamine[121]



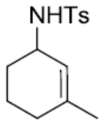
Chemical Formula: $C_7H_{13}N$
Exact Mass: 111.10
Molecular Weight: 111.18

Acetamide **129** (1 eq, 15.60 mmol, 4.00 g) was dissolved in ethanol (0.7 M, 22 mL) at 0 °C then sodium hydroxide (5 eq, 77.98 mmol, 3.12 g) in water (2 M, 15.60 mmol, 1.73 g) was added dropwise. After stirring at RT overnight the product was extracted with petrol/ether (1:4) and washed with water. After careful concentration (bp 58-64 °C/30 mbar) the product was purified by Kugelrohr distillation to yield a clear oil (572 mg, 33 %).

IR υ (cm^{-1}) 3265 (NH), 1528 (=); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.40-5.32 (m, 1H, (=C*H*)), 3.38-3.26 (m, 1H, (C*H*N)), 2.00-1.18 (stack, 6H ($CH_2CH_2CH_{2ring}$)), 1.66 (s, 3H, (CH_3)), 1.42 (s, 2H, (NH_2)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.5 (=*C*Me), 118.7 (=*C*H), 47.8 (*C*HN), 30.4 (*C*H_2C=), 22.3 (*Me*), 20.6 (*C*H_2CH), 18.4 (*C*H_2CH_2CH); m/z (ES) $[M+Na]^+$ 134.1

131

N-Tosyl-3-methylcyclohex-2-en-1-amine



Chemical Formula: $C_{14}H_{19}NO_2S$
Exact Mass: 265.11
Molecular Weight: 265.37

General procedure **B** was followed with the following amounts used:

Amine **130** (1 eq, 2.70 mmol, 300 mg)

DCM (0.1 M, 27 mL)

Triethylamine (2 eq, 5.40 mmol, 0.75 mL)

p-Toluene sulfonyl chloride (2 eq, 5.40 mmol, 1.03 g)

DMAP (10 mol%, 0.27 mmol, 33 mg)

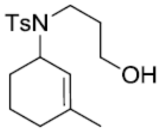
Time: 20 hours

Crude product was purified by column chromatography, eluting with 5 % EtOAc in hexane to yield a pale yellow oil (320 mg, 45 %)

R_f 0.28 (10 % EtOAc in hexane); IR υ (cm^{-1}) 3256 (NH), 1531 (=); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 (app d, 2H (Ar*H*)), 7.30 (app d, 2H (Ar*H*)), 5.09 (dq, 1H, *J* = 1.5, 3.5 Hz (=C*H*)), 4.81 (d, 1H, *J* = 8.0 Hz (N*H*)), 3.81-3.68 (m, 1H (C*H*)), 2.43 (s, 3H (ArCH_3)), 1.89-1.43 (stack, 6H (CH_2CH_2CH_{2ring})), 1.57 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.8 (QAr), 137.5 (QAr), 133.6 (=CMe), 129.7 (ArH), 128.7 (ArH), 118 (=CH), 52.9 (CHNH), 30.7 (CH_2C=), 28.1 (CH_2CH), 22.4 (Me), 21.3 ($ArCH_3$), 18.2 (CH_2CH_2CH); m/z (ES) $[M+Na]^+$ 288.1

132

N-Tosyl-3-(3-methylcyclohex-2-en-1-yl)aminopropan-1-ol



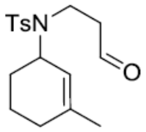
Chemical Formula: $C_{17}H_{25}NO_3S$
Exact Mass: 323.16
Molecular Weight: 323.45

Amine **131** (1 eq, 1.13 mmol, 300 mg), cesium carbonate (1.5 eq, 1.70 mmol, 553 mg) and *tert*-butyl(3-iodopropoxy)dimethylsilane (1.5 eq, 1.70 mmol, 509 mg) were dissolved in DMF (0.1 M, 11 mL) and stirred in the dark at RT overnight. 1 M HCl was added and the reaction stirred for a further hour before dilution with water and extraction into ether. Column chromatography (5-25 % EtOAc in hexane) yielded desilylated product as a pale yellow oil (219 mg, 60 %).

IR υ (cm^{-1}) 3642 (OH), 1352/1173 (SO_2N); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74 (app d, 2H (Ar*H*)), 7.31 (app d, 2H (Ar*H*)), 4.82-4.79 (m, 1H (=C*H*)), 4.49-4.39 (m, 1H (C*H*)), 3.87- 3.68 (stack, 2H (C*H₂*N)), 3.31 (dt, 1H, *J* = 7.0, 16.0 Hz (C*H*HO)), 3.20 (dt, 1H, *J* = 6.5, 16.0 Hz (CH*H*O)), 2.45 (s, 3H (ArC*H₃*)), 1.99-1.23 (stack, 8H ($CH_2CH_2CH_{2ring}$, CH_2CH_2N)), 1.59 (s, 3H (C*H₃*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.1 (*QAr*), 140.0 (*QAr*), 137.9 (=*C*Me), 129.7 (*Ar*H), 127.1 (*Ar*H), 121.7 (=*C*H), 59.4 (CH_2N), 55.8 (*C*H), 40.6 (CH_2O), 34.4 (CH_2CH_2N), 29.4 (CH_{2ring}), 28.5 (CH_{2ring}), 23.6 (*Me*), 21.9 (CH_{2ring}), 21.5 ($ArCH_3$); m/z (ES) $[M+Na]^+$ 346.2

133

N-Tosyl-3-(3-methylcyclohex-2-en-1-yl)aminopropanal



Chemical Formula: $C_{17}H_{23}NO_3S$
Exact Mass: 321.14
Molecular Weight: 321.43

Procedure **F** was followed using the following amounts:

Oxalyl chloride (1.1 eq, 0.73 mmol, 62 μl) in DCM (0.4 M, 1.8 mL)

DMSO (2.4 eq, 1.56 mmol, 113 μl)

Alcohol **132** (1 eq, 0.66 mmol, 215 mg) in DCM (0.8 M, 0.8 mL)

Triethylamine (5 eq, 3.32 mmol, 463 μl)

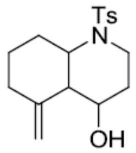
The product (yellow oil) was purified by column chromatography (20 % EtOAc in hexane) to yield piperidine **134**.

Title compound data:

IR υ (cm^{-1}) 2884 (CH), 1744 (C=O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H (C*H*O)), 7.64 (app d, 2H (Ar*H*)), 7.23 (app d, 2H (Ar*H*)), 4.66 (d, 1H, *J* = 1.0 Hz (=C*H*)), 4.42-4.31 (m, 1H (C*H*N)), 3.39-3.16 (m, 2H (CH_2N)), 2.36 (s, 3H (ArCH_3)), 1.89-1.59 (stack, 6H (CH_2CHN, CH_2CHO, CH_2C=)), 1.49 (s, 3H (=CCH_3)), 1.38-1.23 (m, 2H (C$H_2$$CH_2$C=)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.9 (*C*HO), 140.5 (*QAr*), 137.5 (*QAr*), 133.9 (*QC*=), 129.7 (*Ar*H), 127.1 (*Ar*H), 121.3 (=*C*H), 56.0 (*C*HN), 45.9 (*C*H_2N), 37.4 (*C*H_2CHO), 29.3 (*C*H_2C=), 28.4 (*C*H_2CH), 23.6 (*C*H_3), 21.7 (Ar*C*H_3), 21.5 (*C*$H_2$$CH_2$C=); m/z (ES) $[M+Na]^+$ 344.2

134

N-Tosyl-5-methylenedecahydroquinolin-4-ol



Chemical Formula: $C_{17}H_{23}NO_3S$
Exact Mass: 321.14
Molecular Weight: 321.43

A solution of aldehyde **133** (0.22 mmol) in DCM (4.36 mL) was cooled to -78 °C and $MeAlCl_2$ (1M, 0.436 mL) was added dropwise. After 1 hour the reaction was quenched with water (15 mL) then the organic phase extracted with DCM and washed with brine to yield a yellow oil (61 mg, 87 %).

IR υ (cm^{-1}) 3558 (OH), 2922 (CH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (app d, 2H (Ar*H*)), 7.21 (app d, 2H (Ar*H*)), 5.62 (d, 2H, *J* = 1.0 Hz (=C*H*)), 4.00 (app. dt, 2H, *J* = 2.5, 6.0 Hz (C*H*N, C*H*OH)), 3.64-3.60 (m, 1H (C*H*HN)), 3.30 (dt, 1H, *J* = 5.5, 13.5 Hz (CH*H*N)), 2.35 (s, 3H (ArCH_3)), 2.13-2.08 (m, 1H (C*H*C=)), 1.96-2.02 (m, 2H (CH_2CHN)), 1.82 (dd, 1H, *J* = 2.5, 5.5 Hz (C*H*HCHOH)), 1.78 (dd, 1H, *J* = 2.5, 5.5 Hz (CH*H*CHOH)), 1.61 (brs, 1H (O*H*)), 1.42-1.32 (m, 2H (CH_2C=), 1.33-1.23 (m, 2H (CH_2CH$_2$C=)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.9 (*QAr*), 138.8 (=*C*R$_2$), 131.4 (*QAr*), 129.7 (*Ar*H), 127.1 (*Ar*H), 126.7 (=CH$_2$), 63.5 (*C*HOH), 51.9 (*C*HNH), 43.8 (*C*HC=), 35.0 (*C*H$_2$N), 30.7 (*C*H$_2$C=), 24.6 (*C*H$_2$CHOH), 22.8 (*C*H$_2$CHN), 21.5 (*C*H$_2$CH$_2$C=), 21.0 (Ar*C*H$_3$); m/z (ES) $[M+Na]^+$ 344.2

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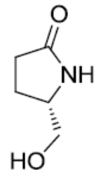
(*S*)-5-(Hydroxymethyl)pyrrolidin-2-one[122]



Chemical Formula: $C_5H_9NO_2$
Exact Mass: 115.06
Molecular Weight: 115.13

(*S*)-methyl 5-oxopyrrolidine-2-carboxylate (1 eq, 6.99 mmol, 1.0 g) and sodium borohydride (1.25 eq, 8.73 mmol, 330 mg) in ethanol (0.7 M, 10 mL) were stirred at 0 °C for 1 hour 45 minutes before conc. HCl was added dropwise until fuming ceased. The solvent was removed and the residue taken into 20 % MeOH in EtOAc, filtered through Celite® and the product purified by column chromatography to yield a white solid (670 mg, 83 %).

R_f 0.38 (20 % MeOH in EtOAc); IR υ (cm^{-1}) 3189 (amide) 3088/1260 (OH), 2975/1439 (NH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.00 (brs, 1H (N*H*)), 4.30 (brs, 1H (O*H*)), 3.85-3.74 (m, 1H (C*H*)), 3.69 (dd, 1H, *J* = 3.5, 11.5 Hz (C*H*HOH)), 3.47 (dd, 1H, *J* = 7.0, 11.5 Hz (CH*H*OH)), 2.45-1.74 (stack, 4H (CH_2CH_2)) [Lit. agreement]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.3 (*C*=O), 65.9 (*C*H_2OH), 56.4 (*C*H), 30.2 (*C*H_2C=O), 22.6 (*C*H_2CH); m/z (EI) $[M]^+$ 115.0

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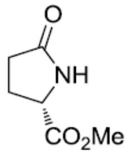
(*S*)-Methyl-5-oxopyrrolidine-2-carboxylate

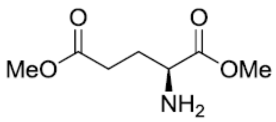


Chemical Formula: $C_6H_9NO_3$
Exact Mass: 143.06
Molecular Weight: 143.14

To a solution of (*S*)-pyroglutamic acid (1 eq, 232.3 mmol, 30.00 g) in methanol (0.8 M, 300 mL) at 0 °C was added thionyl chloride (2 eq, 464.7 mmol, 33.90 mL). After two hours the solvents were removed and the residue taken up into DCM. The organic extract was washed with sat. aq. $NaHCO_3$ and the product extracted into DCM to yield a colourless oil (22.20 g, 67 %).

R_f 0.57 (20 % MeOH in EtOAc); IR υ (cm^{-1}) 3308 (NH), 3170 (NC=O), 1736 (ester), 1671 (C=O), 1480 (NH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H (N*H*)), 4.24 (dd, 1H, *J* = 5.0, 8.5 Hz (C*H*)), 3.74 (s, 3H (O*Me*)), 2.53-2.13 (stack, 4H (C*H₂*C*H₂*)); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.6 (N*C*=O), 172.7 (O*C*=O), 55.5 (*C*H), 52.4 (*C*H3), 29.3 (*C*H2C=O), 24.7 (*C*H2CH); m/z (EI) $[M]^+$ 143.0; $C_6H_9NO_3$ requires 143.0582, found 143.0580

(*S*)-Dimethyl-2-aminopentanedioate



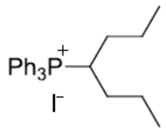
Chemical Formula: $C_7H_{13}NO_4$
Exact Mass: 175.08
Molecular Weight: 175.18

To a solution of glutamic acid (1 eq, 3.40 mmol, 500 mg) in methanol (0.7 M, 5 mL) at 0 °C was added thionyl chloride (1 eq, 3.40 mmol, 0.7 mL). The reaction mixture stirred at RT for 36 hours before an aqueous work up to yield a pale yellow oil in quantitative yield.

R_f 0.66 (10 % MeOH in DCM); IR υ (cm^{-1}) 3407 (NH), 2955 (CH), 1733 (CO_2Me), 1507 (NH_2), 1219 (CO); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.42 (brs, 2H, (N*H₂*)), 4.24 (dd, 1H, *J* = 5.0, 8.5 Hz (C*H*)), 3.70 (s, 3H (O*Me*)), 3.64 (s, 3H (O*Me*)), 2.49-1.78 (stack, 4H (C*H₂*C*H₂*)); ^{13}C-NMR (75

MHz, $CDCl_3$) δ 172.9 (*C*=OCH_2), 169.6 (*C*=OCH), 53.4 (*Me*), 52.6 (*Me*), 52.0 (*C*H), 29.3 (*C*H_2C=O), 25.3 (*C*H_2CH); m/z (CI) $[M+H]^+$ 176.1; $C_7H_{14}NO_4$ requires 176.0923, found 176.0921

Heptan-4-yltriphenylphosphonium iodide[124]



Chemical Formula: $C_{25}H_{30}IP$
Exact Mass: 488.11
Molecular Weight: 488.38

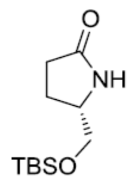
To butyltriphenylphosphonium bromide (1 eq, 2.35 mmol, 940 mg) in THF (0.1 M, 24 mL) at 0 °C was added KO^tBu (1.25 eq, 2.94 mmol, 330 mg). After 30 minutes iodopropane (1.25 eq, 2.94 mmol, 500 mg) was added and the reaction stirred at RT overnight inducing loss of the yellow ylide colour. The mixture was diluted with water then treated with 1M HCl until the solution was just acidic then the product extracted into EtOAc.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90-7.75 (stack, 15H (Ar*H*)), 4.70-4.53 (m, 1H (C*H*)), 1.50-1.40 (m, 4H (CH_2)), 1.32-1.19 (m, 4H (CH_2)), 0.70 (t, 6H, *J* = 7.0 Hz (CH_3)) [Lit. agreement]; m/z (ES) $[M]^+$ 361.2

The conditions were optimised by reaction with benzaldehyde to give the mono substituted Z-alkene and the disubstituted alkene:

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.8-7.0 (Ar*H*), 6.24 (d, 1H, *J* = 11.5 Hz (=C*H*Ph_{mono})), 6.09 (s, 1H (=CH_{di})), 5.49 (dt, 1H, *J* = 7.0, 11.5 Hz (=C*H*CH_{2mono})), 2.40-0.65 (Alk); m/z (EI) $[M_{mono}]^+$ 146.1, $[M_{di}]^+$ 188.2

(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)pyrrolidin-2-one[125]

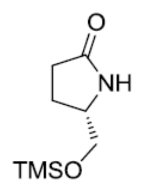


Chemical Formula: $C_{11}H_{23}NO_2Si$
Exact Mass: 229.15
Molecular Weight: 229.39

(*S*)-5-(hydroxymethyl)pyrrolidin-2-one (1 eq, 8.69 mmol, 1.00 g), imidazole (1.5 eq, 13.03 mmol, 887 mg) and *tert*-butylsilyl chloride (1 eq, 8.69 mmol, 1.31 g) were dissolved in DMF (1.5 M, 6 mL) at 0 °C. After 15 minutes the reaction mixture was warmed to RT and stirred overnight. The mixture was diluted with water and the products extracted into EtOAc and washed with brine to yield 1.81g as a colourless oil (91 %).

R_f 0.82 (10 % MeOH in DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.12 (brs, 1H (N*H*)), 3.75 (ddt, 1H, *J* = 4.0, 7.5, 12.5 Hz (C*H*)), 3.62 (dd, 1H, *J* = 4.0, 10.0 Hz (C*H*HOSi)), 3.45 (dd, 1H, *J* = 7.5, 10.0 Hz (CH*H*OSi)), 2.41-2.01 (stack, 3H (CH_2CH_{2ring})), 1.89-1.60 (m, 1H (CH_2CH_{2ring}), 0.88 (s, 9H (*tBu*)), 0.05 (s, 6 (*Me*)) [Lit. agreement].

(*S*)-5-((Trimethylsilyloxy)methyl)pyrrolidin-2-one[126]



Chemical Formula: $C_8H_{17}NO_2Si$
Exact Mass: 187.10
Molecular Weight: 187.31

(*S*)-5-(hydroxymethyl)pyrrolidin-2-one (1 eq, 4.34 mmol, 500 mg), freshly distilled trimethylsilyl chloride (1.5 eq, 6.51 mmol, 0.83 mL), triethylamine (1.2 eq, 5.21 mmol, 0.73 mL) and DMAP (20 mol%, 0.87 mmol, 106 mg) were dissolved in DCM (0.3 M, 15 mL) and stirred at RT for 24 hours. Sat. Aq. NH_4Cl was added and the product extracted into DCM then washed with brine to yield a colourless oil, which solidified on cold storage, in quantitative yield.

R_f 0.79 (10 % MeOH in DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.30 (brs, 1H (N*H*)), 3.70-3.57 (m, 1H (C*H*)), 3.56-3.43 (m, 1H (C*H*HO)), 3.40-3.25 (m, 1H (CH*H*O)), 2.38-1.54 (stack, 4H (C*H₂*C*H₂*)), 0.11 (s, 9H (*Me*)) [Lit. agreement].

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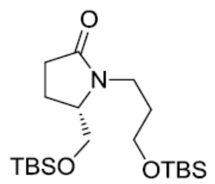
(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(3-(*tert*-butyldimethylsilyloxy)propyl) pyrrolidin-2-one



Chemical Formula: $C_{20}H_{43}NO_3Si_2$
Exact Mass: 401.28
Molecular Weight: 401.73

To a solution of (*S*)-5-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidin-2-one (1 eq, 0.44 mmol, 100 mg) in DMF (0.9 M, 0.50 mL) at 0 °C was added sodium hydride [60 %] (0.2 eq, 0.52 mmol, 21 mg). After 15 minutes the reaction was diluted with DMF (0.45 M, 1.00 mL) then *tert*-butyl(3-iodopropoxy)dimethylsilane (1.2 eq, 0.52 mmol, 157 mg) was added dropwise. The reaction mixture stirred at RT for 4 hours then was quenched with water and product extracted into EtOAc then purified by column chromatography, eluting with 20 % EtOAc in hexane.

R_f 0.42 (20 % EtOAc in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.79 – 3.70 (m, 1H (C*H*)), 3.65 (t, 2H, *J* = 6.0 Hz (CH_2Cl)), 3.61 (dd, 1H, *J* = 4.0, 10.0 Hz (C*H*HOSi)), 3.54 (t, 2H, *J* = 6.0 Hz (CH_2OSi)), 3.44 (dd, 1H, *J* = 7.5, 10.0 Hz (CH*H*OSi)), 2.35 – 2.08 (stack, 3H (CH_2CH_{2ring})), 1.89 (quin, 2H, *J* = 6.0 Hz (C$H_2$$CH_2$)), 1.83 – 1.74 (m, 1H (CH_2CH_{2ring}), 0.86 (s, 9H (^{t}*Bu*)), 0.82 (s, 9H (*tBu*)), 0.03 (s, 6H (*Me*)), 0.01 (s, 6 (*Me*))

3-Iodo-1,1-dimethoxypropane[127]

Sodium iodide (1.2 eq, 44.70 mmol, 6.70 g) was suspended in acetonitrile (0.35 M, 100 mL) at 0 °C then acrolein (1 eq, 37.42 mmol, 2.50 mL) was added dropwise. Freshly distilled trimethylsilyl chloride (1.2 eq, 43.81 mmol, 5.60 mL) was added over 10 minutes and after stirring for 15 minutes the mixture was poured into a mixture of pentane (150 mL) and 5 % $NaHCO_3$ (50 mL) to produce 3 layers. The lower aqueous layer was removed and the organic phases washed with 5 % $Na_2S_2O_3$ (50 mL). The aqueous layer was again removed and the organic layers washed with brine (50 mL). The brine wash was repeated until no acetonitrile remained then the pentane layer was dried, filtered and concentrated to yield a pale yellow oil (4.89 g, 57 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.49 (t, 1H, *J* = 5.5 Hz (C*H*)), 3.38 (s, 6H (O*Me*)), 3.19 (t, 2H, *J* = 7.0 Hz (CH_2I)), 2.14 (td, 2H, *J* = 5.5, 7.0 Hz (CH_2CH)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 104.6 (*C*H), 53.7 (O*Me*), 36.6 (*C*H_2CH), 0.0 (*C*H_2I); m/z (EI) [^{127}I] $[M]^+$ 229.0

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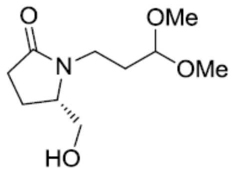
(*S*)-1-(3,3-Dimethoxypropyl)-5-(hydroxymethyl)pyrrolidin-2-one[104]



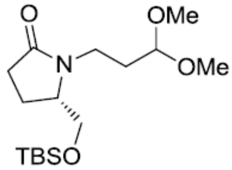
Chemical Formula: $C_{10}H_{19}NO_4$
Exact Mass: 217.13
Molecular Weight: 217.26

Sodium hydride [60 %] (1.5 eq, 0.80 mmol, 32 mg) was suspended in DMF (1.5 M, 0.35 mL) then (*S*)-5-(((trimethylsilyl)oxy)methyl)pyrrolidin-2-one (1 eq, 0.53 mmol, 100 mg) in DMF (1.5 M, 0.35 mL) was added slowly. The mixture was heated to 70 °C then 3-iodo-1,1-dimethoxypropane (1.5 eq, 0.80 mmol, 184 mg) in DMF (0.9 M, 0.60 mL) was slowly added. The reaction was stirred at this temperature for 30 hours before cooling, diluting with water and extracting the product into EtOAc to yield 110 mg as a yellow liquid (71 %).

R_f 0.55 (10 % MeOH in DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.43 (t, 1H, *J* = 5.5 Hz (C*H*(OMe)$_2$)), 3.85-3.47 (stack, 2H (C*H$_2$*OH)), 3.64-3.54 (m, 1H (C*H*N)), 3.35 (t, 2H, *J* = 7.0 Hz (C*H$_2$*N)), 3.29 (s, 3H (C*H$_3$*)), 3.24 (s, 3H (C*H$_3$*)), 2.50-1.80 (stack, 6H (C*H$_2$*C*H$_{2\text{ring}}$*, C*H$_2$*CH$_2$N)), 1.63 (brs, 1H (O*H*))

144

(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(3,3-dimethoxypropyl)pyrrolidin-2-one



Chemical Formula: $C_{16}H_{33}NO_4Si$
Exact Mass: 331.22
Molecular Weight: 331.52

Sodium hydride [60 %] (1.5 eq, 3.27 mmol, 131 mg) and 4 Å molecular seives were suspended in DMF (2.4 M, 0.90 mL) then (*S*)-5-((trimethylsilyloxy)methyl)pyrrolidin-2-one (1 eq, 2.18 mmol, 500 mg) in DMF (1.7 M, 1.30 mL) was added slowly. The mixture was heated to 70 °C then 3-iodo-1,1- dimethoxypropane (1.5 eq, 3.27 mmol, 752 mg) in DMF (1.5 M, 1.50 mL) was slowly added. The reaction was stirred at this temperature for 20 hours before cooling and removing the sieves, diluting with water and extracting the product into EtOAc to yield a yellow liquid (469 mg, 69 %).

R_f 0.43 (1 % MeOH in DCM); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.37 (t, 1H, *J* = 5.5 Hz (C*H*$(OMe)_2$)), 3.78-3.66 (m, 1H (C*H*)), 3.65-3.63 (m, 1H (C*H*HN)), 3.61 (dd, 1H, *J* = 4.0, 10.0 Hz (CH*H*OSi)), 3.45 (dd, 1H, *J* = 7.5, 10.0 Hz (C*H*HOSi)), 3.32 (s, 3H (O*Me*)), 3.29 (s, 3H (O*Me*)), 3.12-2.98 (m, 1H (CH*H*N)), 2.48-1.67 (stack, 6H (CH_2CH_{2ring}, CH_2CHMe_2)), 0.82 (s, 9H (*tBu*)), 0.00 (s, 6H (*Me*))

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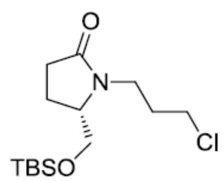
(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(3-chloropropyl)pyrrolidin-2-one



Chemical Formula: $C_{14}H_{28}ClNO_2Si$
Exact Mass: 305.16
Molecular Weight: 305.92

(*S*)-5-(((trimethylsilyl)oxy)methyl)pyrrolidin-2-one (1 eq, 0.13 mmol, 30 mg), 1-bromo-3-chloropropane (2 eq, 0.26 mmol, 41 mg) TBAI (2 eq, 0.26 mmol, 97 mg) and powdered KOH (3 eq, 0.39 mmol, 22 mg) were added to a microwave tube with THF (0.25 M, 0.5 mL). The tube was subjected to microvave radiation with the following settings: normal absorbance, 5 s pre-stir, time hold on, 120 °C, 10 min.

The products were isolated by HPLC. N.B. title compound is a minor product, major product is alkene **146**.

Title compound data: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.74 (dd, 1H, *J* = 3.5, 10.5 Hz (C*H*HOSi)), 3.70-3.63 (m, 1H (C*H*)), 3.62-3.50 (stack, 4H (CH*H*OSi, C*H*HN, C*H_2*Cl)), 3.24 (dt, 1H, *J* = 7.0, 14.0 (C*H*HN)), 2.45 (ddd, 1H, *J* = 7.5, 9.5, 17.0 Hz (C*H*HC=O)), 2.29 (ddd, 1H, *J* = 5.0, 10.0, 17.0 Hz (CH*H*C=O)), 2.14-2.04 (stack, 2H (C*H*HCH_2Cl, C*H*HCH)), 1.99 (quin, 1H, *J* = 7.0 Hz (CH*H*CH_2Cl)), 1.89-1.81 (m, 1H (CH*H*CH)), 0.88 (s, 9H (^{t}*Bu*)), 0.06 (s, 6H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.9 (*C*=O), 64.0 (*C*H_2OSi), 59.9 (*C*H), 42.6 (*C*H_2N), 30.6 (*C*H_2C=O), 30.4 (*C*H_2CHCl), 25.8 (^{t}*Bu*), 21.6 (*C*H_2CH), 18.1 (*Q*^{t}*Bu*), -5.0 (Si*Me*); m/z (ES) $[M+Na]^+$ 328.1/330.1; $C_{14}H_{28}NO_2NaSi^{35}Cl$ requires 328.1476, found 328.1468

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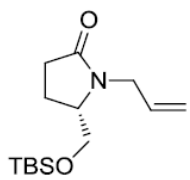
(*S*)-1-Allyl-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-2-one



Chemical Formula: $C_{14}H_{27}NO_2Si$
Exact Mass: 269.18
Molecular Weight: 269.46

(*S*)-5-(((trimethylsilyl)oxy)methyl)pyrrolidin-2-one (1 eq, 3.27 mmol, 750 mg), allyl bromide (2 eq, 6.54 mmol, 566 μl) and powdered KOH (3 eq, 9.81 mmol, 550 mg) were added to a microwave tube with THF (0.25 M, 13 mL). The tube was subjected to microwave radiation with the following settings: normal absorbance, 10 s pre-stir, time hold on, 120 °C, 10 min. The product was isolated by HPLC to yield a yellow liquid (802 mg, 91 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.74 (dddd, 1H, J = 5.0, 7.0, 10.0, 17.0 Hz (=C*H*)), 5.18 (dd, 1H, J = 1.5, 10.0 Hz (=C*H*H)), 5.15 (m, 1H (=CH*H*)), 4.30 (dd, 1H, J = 1.5, 5.0 Hz (C*H*HN)), 3.71- 3.55 (stack, 4H (CH*H*N, C*H₂*OSi, C*H*)), 2.52-2.43 (m, 2H (C*H₂*C=O)), 2.31 (m, 1H (C*H*HCH)), 1.88 (m, 1H (CH*H*CH)), 0.88 (s, 9H (^{t}*Bu*)), 0.04 (s, 3H (*Me*)), 0.04 (s, 3H (*Me*)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.4 (*C*=O), 133.1 (=*C*H), 117.3 (=*C*H_2), 63.6 (*C*H_2OSi), 58.8 (*C*H), 43.5 (*C*H_2N), 30.4 (*C*H_2CH_2), 25.8 (^{t}*Bu*), 21.6 (*C*H_2CH_2), 18.2 (*Q*^{t}*Bu*), -5.0 (*Me*); m/z (ES) $[M+Na]^+$ 292.1; $C_{14}H_{27}NO_2NaSi$ requires 292.1709, found 292.1702

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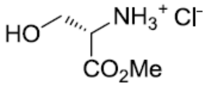
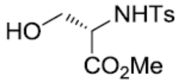
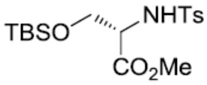
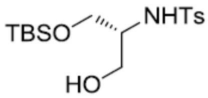
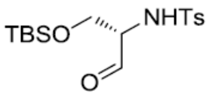
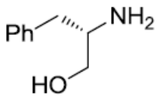
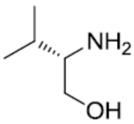
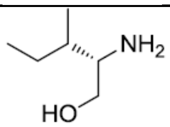
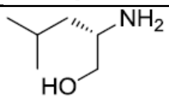
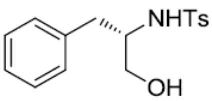
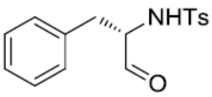
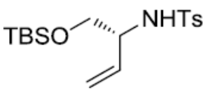
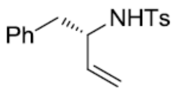
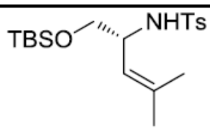
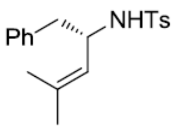
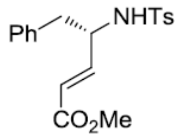
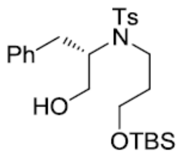
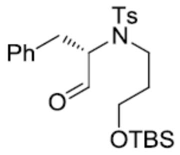
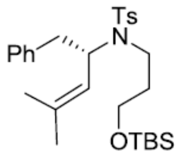
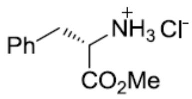
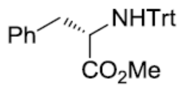
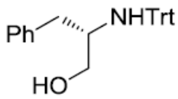
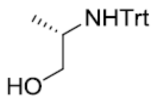
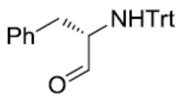
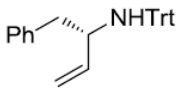
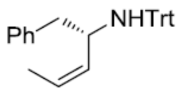
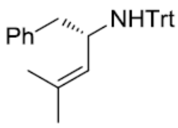
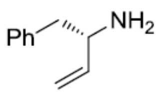
Compound number	Sketch	Page (text)	Page (experimental)	Reference
57		24	91	40
58		24	92	41
59		25	93	44
60		26	95	44
61		26	96	X
69a		31	97	109
69c		51	98	110
69d		51	-	74
69e		51	-	111
70		31	99	58
71		32	100	X
72		33	101	X
73		33	102	112
74		33	-	novel
75		33	103	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
76		33	104	novel
79		36	105	novel
80		36	106	novel
81		36	-	novel
83		37	107	113
84		37	107	114
85a		37	108	114
85b		-	109	X
86a		38	110	114
87		38	111	114
89		39	112	novel
90		39	112	novel
91		42	113	115
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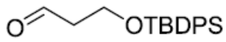
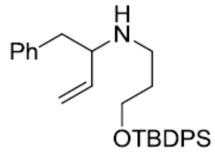
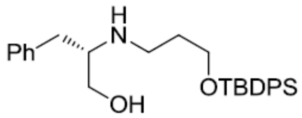
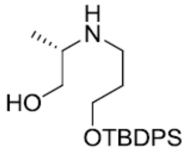
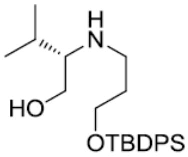
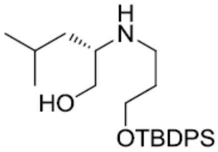
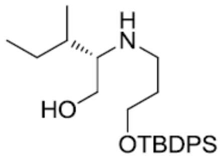
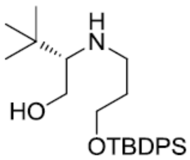
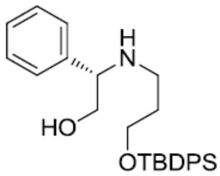
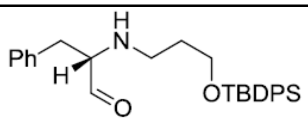
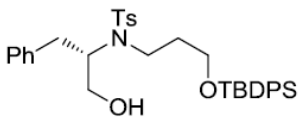
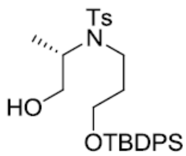
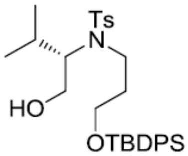
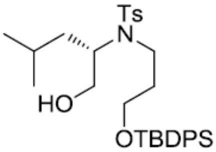
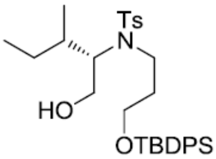
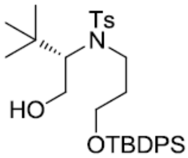
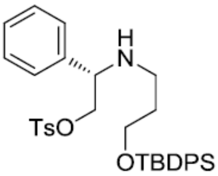
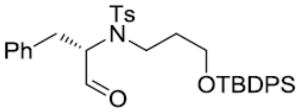
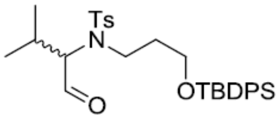
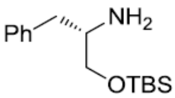
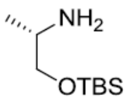
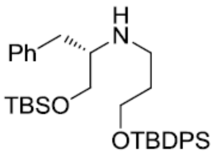
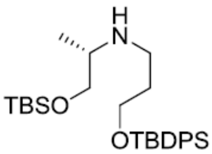
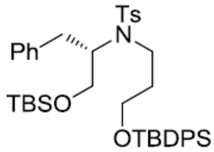
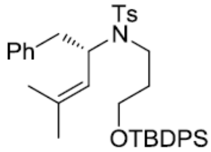
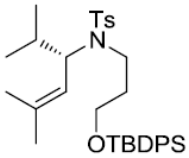
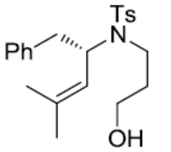
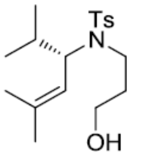
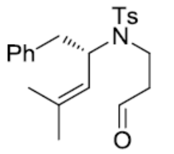
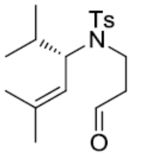
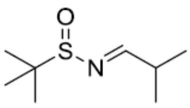
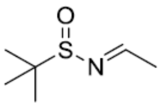
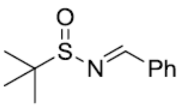
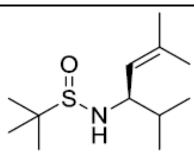
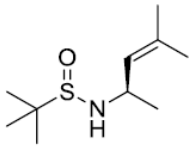
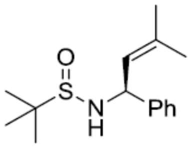
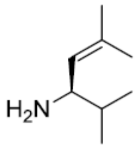
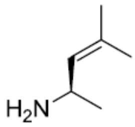
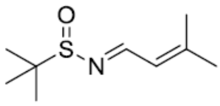
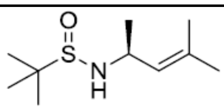
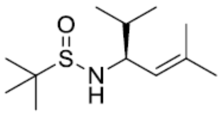
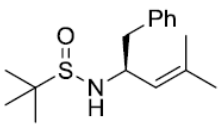
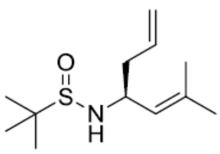
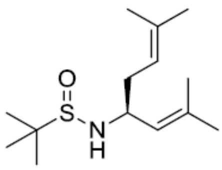
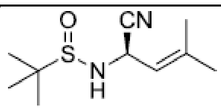
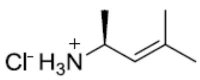
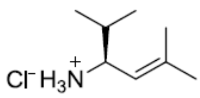
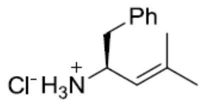
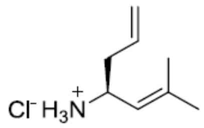
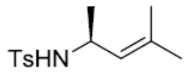
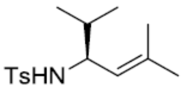
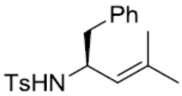
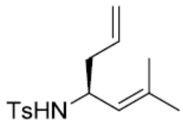
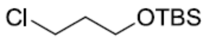
-		43	115	116

Compound number	Sketch	Page (text)	Page (experimental)	Reference
92a		43	116	novel
93a		44	117	novel
93b		51	118	novel
93c		51	119	novel
93d		51	120	novel
93e		51	121	novel
93f		51	122	novel
93g		51	123	novel
94		44	-	novel
95a		44	124	novel
95b		51	125	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
95c		51	126	novel
95d		51	127	novel
95e		51	128	novel
95f		51	129	novel
95g		51	130	novel
96a		44	131	novel
96c		51	132	novel
97a		45	133	117
97b		-	134	X
98a		45	134	novel
98b		-	135	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
99		45	136	novel
100a		47	137	novel
100c		51	138	novel
101a		47	139	novel
101c		51	140	novel
102a		47	141	novel
102c		51	142	novel
112a		54	143	80
112b		54	144	118
112c		54	145	80
114a		55	146	X

Compound number	Sketch	Page (text)	Page (experimental)	Reference
114b		55	147	novel
114c		55	147	X
-		-	148	novel
-		-	149	X
115		55	150	X
116a		55	150	novel
116b		55	151	novel
116c		55	152	novel
116d		55	153	novel
116e		55	154	novel
-		59	-	novel
117a		57	155	128
117b		57	155	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
117c		57	156	novel
117d		57	156	novel
118a		57	157	X
118b		57	158	novel
118c		57	159	novel
118d		57	160	novel
-		57	161	119
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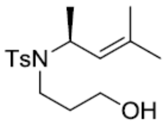
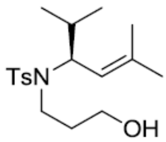
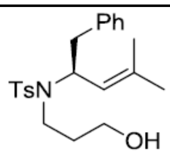
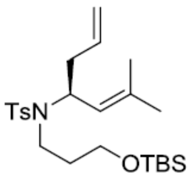
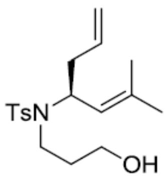
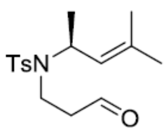
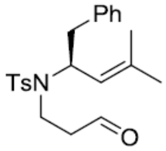
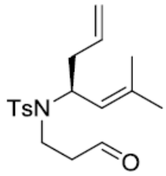
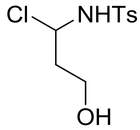
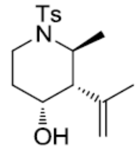
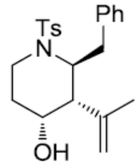
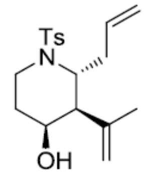
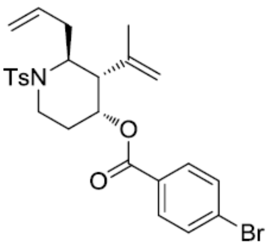
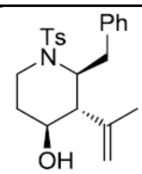
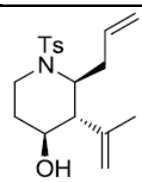
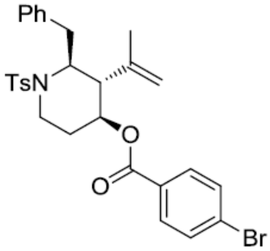
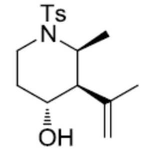
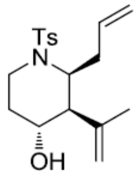
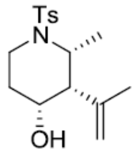
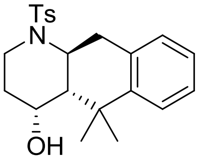
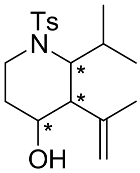
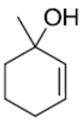
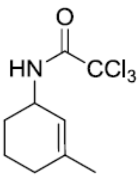
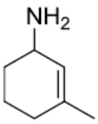
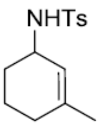
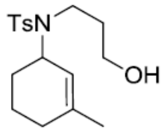
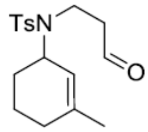
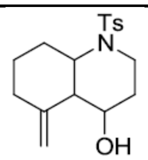
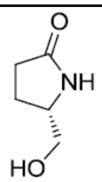
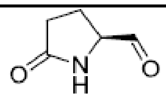
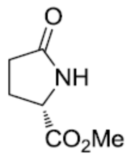
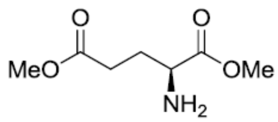
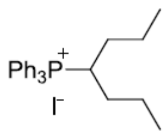
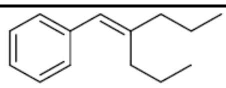
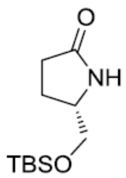
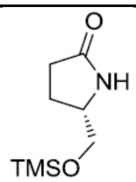
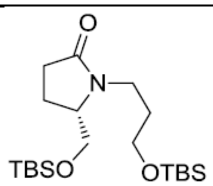
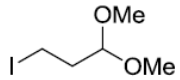
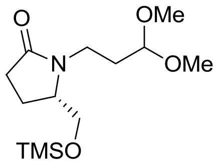
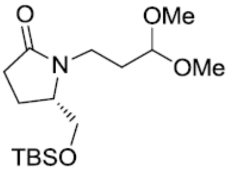
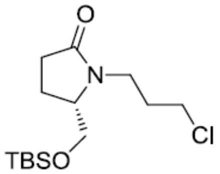
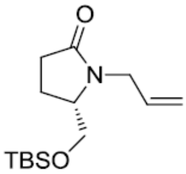
119a		57	162	novel
119b		57	163	novel
119c		57	164	novel
119d(i)		57	165	novel
119d(ii)		57	166	novel
120a		57	167	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
120c		57	168	novel
120d		57	169	novel
121		63	171	novel
122a		64	172	novel
122c		64	172	novel
122d		64	173	novel
Der-122d		69	174	novel
123c		64	175	novel
123d		64	176	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
der-123c		66	176	novel
124a		64	177	novel
124d		64	178	novel
125		69	-	novel
126		68	179	novel
-		68	180	novel
128		73	181	121
129		73	182	121
130		73	183	121
131		73	184	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
132		73	185	novel
133		73	186	novel
134		73	187	novel
138		78	188	122
139		78	-	123
141		79	188	X
-		79	189	X
-		81	190	124
-		81	190	X
-		81	191	125
-		81	191	126
142		83	192	novel

Compound number	Sketch	Page (text)	Page (experimental)	Reference
-		83	193	127
143		83	194	novel
144		83	194	novel
145		83	195	novel
146		83	196	novel

X indicates a compound that is known in the literature but for which no data is available. This was usually because it was referenced back many times to old articles with incomplete data or the only literature reference was in a language other than English.

Data tables for **122c**, **der-123c**, **der-122d** and **126**