

**The Aza-Silyl-Prins Reaction:  
Development and Application  
to the Total Synthesis of  
(±)-Pipelicolic Acid and (±)-Cannabisativine**

**Submitted by  
Robert James Parker**

**To the University of Exeter as a thesis for the degree of Doctor  
of Philosophy in Chemistry**

**September 2008**

This thesis is available for library use on the understanding that it is copyright material and no quotation from the thesis may be published without proper acknowledgement.

“I certify that all material in this thesis which is not my own work has been identified and no material is included for which a degree has previously been conferred upon me.

Signed \_\_\_\_\_”

## Abstract

The focus of this thesis is to develop new methods towards the synthesis of nitrogen-containing heterocycles. Chapter one contains a brief introduction into previous work by the Dobbs group, involving the optimisation of the silyl-Prins reaction and aza-silyl-Prins reaction, which afford substituted dihydropyrans and tetrahydropyridines respectively.

Chapter two initially provides a literature overview towards the synthesis of piperidines using this methodology. Following this, our results demonstrate that using different substitution patterns in the homoallylic amine precursors has quite a significant regiochemical effect on the reaction. These effects include the formation of pyrrolidine structures, which can be isolated and characterised.

Chapter three presents the utilization of the previously optimised silyl-Prins and aza-silyl-Prins reaction to obtain oxa- and aza-cycles containing a trifluoromethyl group, a functionality known to have significant effects on the lipophilicity of drug molecules. Next in chapter four, again the advantages of using the aza-silyl-Prins reaction to obtain high functionality in a simple coupling reaction are presented, with the formation of pipercolate and pipercolic acid analogues. Chapter five includes attempts to use the aza-silyl-Prins to form tetrasubstituted tetrahydropyridines using precedent from studies in the silyl-Prins reaction. However, although the similarities between these two coupling reactions are obvious, the differences in heteroatom in the substrates and products have a significant effect. Following previous attempts in the group to form nitrogen heterocycles in high enantiopurity with little success, chapter six discusses the optimisation of a new Lewis acid mediated imine-vinylsilane cyclisation reaction. The formation of 2-substituted free amine tetrahydropyridines was successful for racemic examples, but the studies into utilising this methodology towards an asymmetric synthesis are yet to be finalised. Finally, chapter seven investigates the use of the aza-silyl-Prins reaction into forming more complex natural products such as cannabistatine.

Part of this work has been published in:

- 1) A.P.Dobbs, R.J.Parker, J.Skidmore, *Tetrahedron Letters*, **2008**, 49, 827-831.

## Contents

<a href="#">Abstract.....</a>	<a href="#">2</a>
-------------------------------	-------------------

<b>Abbreviations.....</b>	<b>7</b>
<b>Acknowledgments.....</b>	<b>10</b>
<b>INTRODUCTION.....</b>	<b>11</b>
<b>CHAPTER ONE: Previous Work.....</b>	<b>14</b>
.I The Silyl-Prins Reaction.....	15
.II The Aza-Silyl-Prins Reaction.....	17
<b>CHAPTER TWO: The Aza-Prins Reaction.....</b>	<b>22</b>
.I Literature Review of Prins Methodology.....	23
.1 The Prins Reaction.....	23
.2 Iminium Ion-Olefin Cyclisation Reactions .....	26
.3 Synthesis of 4-Halopiperidines.....	31
.II Results and Discussion: Studies into the Aza-Prins Reaction.....	40
.4 Preliminary Studies: The Aza-Prins Reaction.....	40
.a Precursor Synthesis for the Aza-Prins Reaction I.....	40
.b Initial Screening for Aza-Prins Reaction.....	42
.c Solvent Effects of Acetonitrile.....	45
.d Stabilisation Effects .....	46
.5 Iron(III) Halide Mediated Aza-Prins Reaction.....	47
.a Precursor Synthesis for the Aza-Prins Reaction II.....	52
.b Aza-Prins Cyclisations: Effects of (Z)-Homoallyl Amine .....	53
.c Aza-Prins Cyclisations: Effects of (E)-Homoallyl Amine.....	59
.6 Studies into the Regiochemistry of the Aza-Prins Reaction.....	63
.a Precursor Synthesis for the Aza-Prins Reaction III.....	63
.b Aza-Prins Cyclisations: Effects of (Z)-Homoallyl Amine II.....	64
.7 Further Substituent Effects in the Aza-Prins Reaction.....	70
.a Precursor Synthesis for the Aza-Prins Reaction IV.....	70
.b Aza-Prins Cyclisations: Effects of Trisubstituted olefins.....	71

.c Aza-Prins Cyclisations: Effects of Other Olefins.....	73
.8 Effects of the C1 Position in Homoallyl Amines.....	75
.a Precursor Synthesis for the Aza-Prins Reaction V.....	75
.b Aza-Prins Cyclisations: Effects of the C1 Position in Homoallyl Amines.....	77
<b>CHAPTER THREE: Formation of 6-Trifluoromethyl-3,4-dihydropyrans and 6-Trifluoromethyl-3,4-tetrahydropyridines.....</b>	<b>81</b>
.I Literature Review for Formation of Trifluoromethyl Containing Heterocycles.....	82
.9 Literature Examples of Formation of Fluorinated Oxacycles.....	82
.10 Literature Review for the Formation of Fluorinated Azacycles.....	89
.II Results and Discussion: Studies into the Formation of Fluorinated Heterocycles..	99
.11 Synthesis of 6-Trifluoromethyl-3,4-dihydropyrans.....	99
.a Precursor Synthesis I- Formation of 1-CF <sub>3</sub> -Homoallylic Alcohol.....	100
.b Silyl-Prins Reactions of 1-CF <sub>3</sub> -Homoallylic Alcohol.....	100
.c Further Functionalisation of Dihydropyran olefin.....	102
.12 Synthesis of 6-Trifluoromethyl-3,4-tetrahydropyridines.....	104
.a Precursor Synthesis II- Formation of 1-CF <sub>3</sub> -Homoallylic Amine.....	104
.b Aza-silyl-Prins Reactions of 1-CF <sub>3</sub> -Homoallylic Amine.....	107
.c Further Functionalisation of Tetrahydropyridine Olefin.....	110
.d Precursor Synthesis III – Formation of 1-CF <sub>3</sub> -Homoallylic Tosylamine.....	111
<b>CHAPTER FOUR: Towards the Synthesis of Pipecolic Acid Analogues and Pipecolates.....</b>	<b>113</b>
.I Literature Review for Synthesis of Pipecolic Acid and Analogues.....	114
.13 Formation of 2-Substituted Pipecolic Acids .....	114
.14 Formation of 2,6-Disubstituted Pipecolic Acids and Other Analogues.....	116
.II Results and Discussion: Studies into the Formation of Pipecolic Acid Analogues and Pipecolates.....	120
.15 Precursor Synthesis – Formation of Silylated Homoallylic Amines.....	120
.16 Synthesis of 6-Methyl Pipecolic Acid.....	121
.17 Synthesis of 3,4-Dihydroxy Pipecolates.....	124

<b>CHAPTER FIVE: Formation of 1,2,5,6-Tetrasubstituted-3,4-tetrahydropyridines</b>	<b>126</b>
. I Literature Review on the Fomation of Multi-substituted Tetrahydropyridines	127
. II Results and Discussion: Studies into Synthesis of N,2,5,6-Tetrasubstituted-3,4-tetrahydropyridines	132
. 18 Precursor Synthesis I: Formation of $\alpha,\beta$ -Disubstituted Amines	132
. 19 Precursor Synthesis II- Zinc Bromide Mediated $\alpha,\beta$ -Dialkyl Amine Formation	135
<b>CHAPTER SIX: Towards the Synthesis of Enantiopure 2-Substituted-3,4-tetrahydropyridines</b>	<b>138</b>
. III Literature Review Towards Formation of Enantiopure Tetrahydropyridines	139
. 20 Vinylsilane Cyclisations: Formation of Racemic Tetrahydropyridines	139
. 21 Activation of Imines with Lewis Acids	142
. 22 Utilisation of Chiral Lewis Acids	143
. IV Results and Discussion: Studies Towards Asymmetric Imine-vinylsilane Reaction	148
. 23 Lewis Acid Mediated Imine-vinylsilane Cyclisations for Racemic Products	149
. a Precursor Synthesis: Synthesis of Imine-vinylsilanes	149
. b Cyclisations Reactions for Racemic Products	150
. 24 Imine-vinylsilane Reactions: Formation of Enantiopure Products	154
. a Chiral ligand Synthesis	155
. b Imine-vinylsilane Cyclisations: Towards Enantiopure Products	156
<b>CHAPTER SEVEN: Towards the Total Synthesis of Cannabisativine</b>	<b>161</b>
. I Literature Review for Total Synthesis of Cannabisativene and Spermidine Alkaloids	162
. II Results and Discussion: Studies Towards the Total Synthesis of Cannabisativine	177
. 25 Retrosynthetic Analysis of Literature Examples, Towards the Formal Synthesis of Spermidine Alkaloids	178

<u>.26 ROUTE 1.....</u>	<u>180</u>
<u>. a Retrosynthetic Analysis of Cannabisativine I.....</u>	<u>180</u>
<u>. b Amine Precursor Synthesis I.....</u>	<u>181</u>
<u>.27 ROUTE 2.....</u>	<u>183</u>
<u>. a Retrosynthetic Analysis of Cannabisativine II.....</u>	<u>183</u>
<u>. b Amine Precursor Synthesis II.....</u>	<u>184</u>
<u>. c Aldehyde Formation.....</u>	<u>187</u>
<u>. d Aza-silyl-Prins Screening.....</u>	<u>188</u>
<u>. e Imine-vinylsilane Cyclisation.....</u>	<u>188</u>
<b><u>CONCLUSION.....</u></b>	<b><u>193</u></b>
<b><u>EXPERIMENTAL.....</u></b>	<b><u>195</u></b>
<b><u>REFERENCES.....</u></b>	<b><u>302</u></b>

## Abbreviations

Ac	Acetyl
acac	Acetylacetonate
BINOL	1,1'-Bi-2-naphthol
bpy	2,2'-Bipyridine
Boc	<i>t</i> -Butoxycarbonyl
Bn	Benzyl
Cbz	Benzyloxycarbonyl
CI	Chemical ionisation
Cy	Cyclohexyl
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[4.3.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCM	Dichloromethane
DHQ	Hydroquinine
<i>Di</i> BAL	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
4-DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPPA	Diphenyl phosphorylazide
EI	Electronic ionisation
eq.	Equivalent
HIV	Human immunodeficiency virus
HMDS	Hexamethyldisilazide
Hmim	1-Hexyl-3-methylimidazolium
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
Im	Imidazole
IR	Infrared

LA	Lewis Acid
LAH	Lithium aluminium hydride
LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
MEM	methoxethoxymethyl
MHz	Mega-Hertz
MMPP	Magnesium monoperoxyphthalate
MOM	Methoxymethyl
M.p.	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
<i>m/z</i>	Mass to charge ratio
NMO	4-Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PG	Protecting group
PhF	9-Phenylfluorene
PMP	1-Phenyl-3-methyl-5-pyrazolone
PYBOX	2,6-Bis(4,5-dihydro-1,3-oxazol-2-yl)pyridine
RCM	Ring closing metathesis
rt	Room temperature
SAR	Structure activity relationship
TBAB	Tetrabutylammonium bromide
TBS	<i>t</i> -Butyldimethylsilyl
TBDPS	<i>t</i> -Butyldiphenylsilyl
TCC	<i>trans</i> -2-( $\alpha$ -Cumyl)cyclohexyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tr	Triphenylmethyl (Trityl)
Tp	Hydridotrispyrazolylborate
Troc	2,2,2-Trichloroethyloxycarbonyl
Ts	<i>para</i> -Toluenesulfonyl
UV	Ultra-violet

## **Acknowledgments**

I would like to thank Dr Adrian P. Dobbs, my academic supervisor, for all his encouragement and support over the last four years. Especially for being so supportive with regards to my family situation. Also I would like to thank the staff at the University of Exeter, past and present, for allowing the practical aspects of my degree to run smoothly. I would like to thank my industrial supervisor, Dr John Skidmore of GlaxoSmithKline for all the precious time he has given to the project and for his expert supervision while I spent my CASE placement in Harlow.

The work described in this thesis was funded by GlaxoSmithKline and EPSRC, this financial support is greatly appreciated. Also I would like to thank the EPSRC Mass Spectrometry service at Swansea and the EPSRC X-ray Crystallography Service at Southampton for analysis of samples.

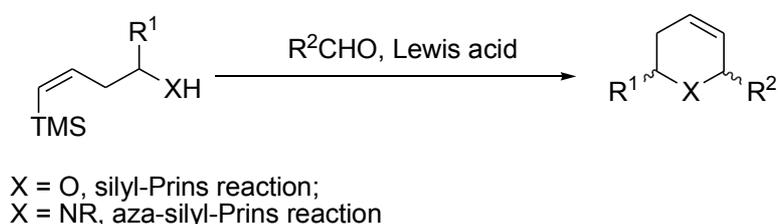
I would like to dedicate this thesis to my wife Dawn and children, Nathan and Darcey who have only ever encouraged me throughout my degree and have been very understanding when the majority of my time has been dedicated to this work. This is as much their achievement as it is mine.

Finally, I would like to thank my parents for being so supportive, to Dad for being there constantly during my write-up and to Mum for giving me everything I ever needed. So many people have encouraged me during my degree and I thank you all.

# **INTRODUCTION**

## Introduction

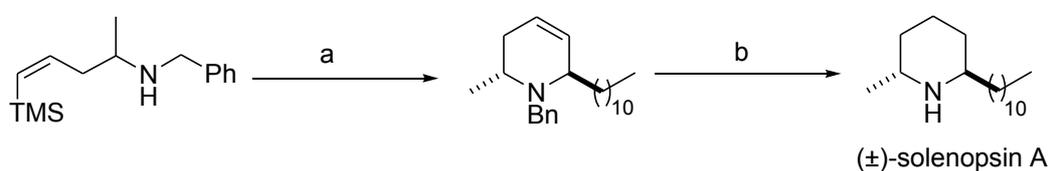
Research into novel routes for the synthesis of nitrogen-containing heterocycles is a common interest amongst organic chemists, mostly due to their presence in natural products such as piperidine alkaloids. Much success has been founded in producing the related oxygen-containing tetrahydropyrans *via* a Prins type cyclisation. It has long been an objective of synthetic chemists to develop a nitrogen or aza version of the Prins reaction. Work within our group has successfully investigated the silyl-Prins and the aza-silyl-Prins reactions, to afford dihydropyrans and tetrahydropyridines respectively, by coupling of silylated homo-allylic compounds and aldehydes in the presence of a Lewis acid catalyst (Scheme 1).



**Scheme 1. General scheme of silyl-Prins methodology.**

The terminal vinylsilane is vital not only for forming the olefin function but also for stabilisation of a cationic intermediate, therefore raising doubt when considering whether an aza-Prins reaction could be successful without the silicon function. It has been found that the vinylsilane is not essential in the oxygen series, for example, affording tetrahydropyrans *via* a Prins type cyclisation, which couples homoallylic alcohols to aldehydes using Lewis acids. Although mechanistically the Prins and aza-Prins reactions are potentially analogous, the difference in heteroatoms could alter the reaction rates significantly.

Piperidine synthesis has already been achieved within our group, using the aza-silyl-Prins reaction towards the total synthesis of (-)-solenopsin A (Scheme 2).

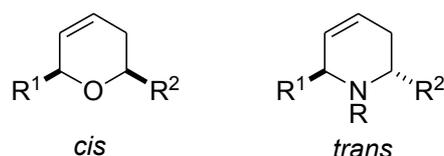


**Scheme 2. Reagents and conditions: (a) C<sub>11</sub>H<sub>23</sub>CHO, InCl<sub>3</sub>, CH<sub>3</sub>CN, reflux, 14h, 69%; (b) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, EtOH, rt, 4 h, quant.**

Use of the aza-silyl-Prins reaction afforded exclusively the *trans*-2,6-disubstituted tetrahydropyridine and subsequent hydrogenation of the olefin function with simultaneous removal of the protecting group gave the racemic piperidine alkaloid.

### Introduction

Studies on the formation of heterocycles in the group began by synthesizing dihydropyrans, using (*Z*)-trimethylsilyl homoallylic alcohols and commercially available aldehydes as precursors, *via* the silyl-Prins reaction. In order to avoid complex mixtures of products using Brønsted acids as promoters, Lewis acids were proposed and screened. Indium trichloride with DCM as solvent at room temperature was found to be optimal, initially giving simple 2-substituted tetrahydropyrans in high yields. This particular Lewis acid has benefits in that it is crystalline, easy to handle and reasonably moisture tolerant. Studies progressed to produce 2,6-disubstituted dihydropyrans also in high yields with exclusive *cis* stereochemistry observed across the oxygen (Figure 3). Similar precursors and conditions became transferable to the analogous nitrogen based aza-silyl-Prins reaction. This reaction progresses *via* a vinylsilane-iminium ion cyclisation using *N*-alkylated (*Z*)-silylated homoallylic amines. Again monosubstituted and disubstituted heterocycles were formed in high yields, with only a change in solvent to acetonitrile and a need for reflux conditions. Interesting however in this case, was the exclusive formation of *trans* disubstituted heterocycles (Figure 1).



**Figure 1. Relative stereochemistry in heterocycles synthesised from silyl-Prins methodology.**

The proposed aza-Prins reaction would presumably be identical in mechanism to the aza-silyl-Prins minus the stabilising effect and eventual elimination of the silane. The trapping of a cyclic carbocation by available nucleophiles in this case would terminate the reaction. The similarities between the two nitrogen-containing cyclisation reactions will be investigated fully in this report as well as comparisons to the oxygen associated Prins and silyl-Prins reactions. Also reported upon will be associated reactions which progress *via* other allylic-iminium ion intermediates.

## **CHAPTER ONE: Previous Work**

Piperidine cores are widespread in nature; the synthesis usually involves multi-step processes. Initially our group has focussed on the formation of dihydropyrans and tetrahydropyridines *via* the silyl-Prins and aza-silyl-Prins reactions respectively. Although both types of heterocycle are not as abundant as their saturated counterparts, they do serve as a useful handle towards analogues of piperidine alkaloids. In this chapter, both silylated reactions will be reviewed which will be beneficial when considering a non-silylated aza-Prins reaction.

### . IThe Silyl-Prins Reaction

This area of study seemed attractive when considering that basic Prins cyclisations involving Brønsted acids as catalysts, afforded a complex mixture of products. Studies by Li and co-workers suggested a Lewis acid mediated approach; however the use of tin and also two equivalents of aldehyde only afforded symmetrical dihydropyran substituents. Methods for the total synthesis of dihydropyrans included intramolecular Sakurai reactions, ring closing metathesis, or a hetero Diels-Alder approach but all have drawbacks.

Within the Dobbs group, the desired substrate for initial study was (*Z*)-4-trimethylsilyl-3-buten-1-ol **1**. When screened against simple aldehydes and a variety of Lewis acids, this homoallylic alcohol gave 2-substituted dihydropyrans **2** with a maximum yield of 90%. The reagents used in this instance were boron trifluoride etherate and phenylacetaldehyde in DCM at -78 °C. However comparable yields were obtained with indium trichloride at room temperature and so this Lewis acid was chosen for further study since it is crystalline, does not require strict anhydrous conditions, and can be used at room temperature as opposed to -78 °C (Table 1).

**Table 1. The silyl-Prins reaction between a homoallylic alcohol and aldehydes.**



Entry	R	% Yield
1	PhCH <sub>2</sub>	88

2	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	65
3	<i>c</i> -Hex	72
4	Ph <sub>2</sub> CH	85
5	Ph	39
6	<i>p</i> -NO <sub>2</sub> -Ph	86
7	<i>p</i> -CF <sub>3</sub> -Ph	54

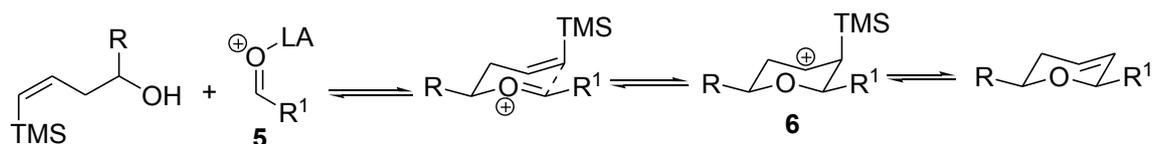
Indium trichloride gave high yields of products for a variety of aldehydes, with only benzaldehyde giving less than 50% yield (Table 1, entry 5). This observation does follow the pattern for aromatic aldehydes as previously reported, but yields were improved with *p*-NO<sub>2</sub> and *p*-CF<sub>3</sub> substituents, presumably due to electronic effects (Table 1, entries 6-7). It is interesting to observe that when sub-stoichiometric amounts of indium trichloride were used, the yield slightly declined, proving some catalytic activity, albeit presumably with low catalyst turnovers. Progression of this work continued with use of the C1 methylated alcohol substrate **3** with a range of aldehydes to provide 2,6-disubstituted-3,4-dihydropyrans **4** in good yields with exclusive *cis* stereochemistry as proven by nOe studies (Table 2).

**Table 2.** The silyl-Prins reaction between a methyl substituted homoallylic alcohol and aldehydes.



Entry	R <sup>1</sup>	%Yield
1	PhCH <sub>2</sub>	50
2	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	65
3	<i>c</i> -Hex	69
4	Ph <sub>2</sub> CH	78
5	<i>p</i> -NO <sub>2</sub> -Ph	60

The mechanism is assumed to progress *via* nucleophilic attack on the Lewis acid activated aldehyde **5**, followed by cationic cyclisation to give a six-membered secondary carbocation **6** stabilised by the  $\beta$ -effect from the silicon. Subsequent elimination of the silane moiety to form the olefin function gives the dihydropyrans. The stereochemistry is assumed to result from the favoured equatorial positions adopted in a chair-like transition state (Scheme 3). In comparison to an approach by Li, epoxides were used in place of the aldehyde and again dihydropyrans were afforded in good yields.

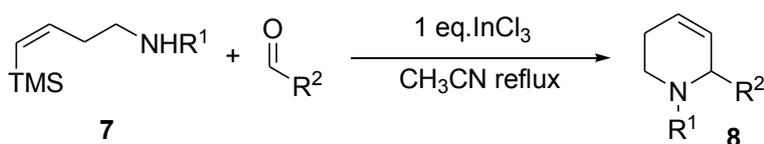


Scheme 3. The *cis* geometry across the heteroatom keeps the ring substituents equatorial.

## . II The Aza-Silyl-Prins Reaction

The idea for a nitrogen version of the silyl-Prins cyclisation stemmed from the success found in producing dihydropyrans. The comparable tetrahydropyridines are not so widespread in nature but their related piperidine alkaloids are found in a variety of natural products, e.g. (-)-solenopsin A. Examples of methods for piperidine synthesis include Ireland Claisen rearrangements, aza Diels Alder reactions and also aza[2,3]-Wittig reactions. Work carried out by Overman on acid catalysed vinylsilane-iminium ion cyclisations encouraged this field of study. Within the Dobbs group, the main precursors for initial study were *N*-substituted-*N*-(*Z*)-(4-trimethylsilylbut-3-enyl) amines **7**, formed from the amination of the associated tosylated alcohol by a series of primary amines. When initially screened with indium trichloride and hexanal or benzaldehyde in DCM at room temperature (as with the silyl-Prins reaction), only starting material remained. Raising the temperature only gave trace amounts of monosubstituted tetrahydropyridines **8** at reflux temperature. However when using the higher boiling solvent acetonitrile at reflux temperature, good yields were obtained for a variety of *N*-protected amines such as alkyl (e.g. *n*-Pr), aryl (e.g. Ph), and benzyl, as well as a number of Lewis acids and aldehydes. The maximum yield obtained using the preferred indium trichloride was 95% with the Bn protected amine, and either phenylacetaldehyde or hexanal (Table 3).

Table 3. The aza-silyl-Prins reaction between homoallylic amines and aldehydes.



Entry	R <sup>1</sup>	R <sup>2</sup>	Time(h)	%Yield
1	Ph	<i>n</i> -Pn	3	95
2		Bn	3	85
3	<i>n</i> -Pr	Ph	24	22
4		Bn	24	55
5	Bn	<i>n</i> -Pr	12	63
6		<i>n</i> -Pn	12	62
7		Ph	24	64
8		Bn	12	95

Aromatic aldehydes were again less successful as with the silyl-Prins reaction. Studies using the C2 methylated amines found that these afforded exclusively the *trans*-2,6-disubstituted tetrahydropyridines, shown by X-ray crystallography. This was further supported by nOe studies; a 2.2% enhancement of the C6 methyl group and a lack of enhancement of the C6 proton was observed on irradiation of the proton at C2 (Figure 2).

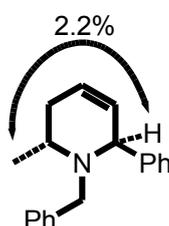
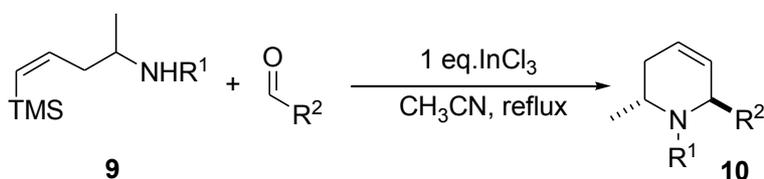


Figure 2. Exclusive stereochemistry proven by nOe studies.

The maximum yield for *trans*-2,6-disubstituted tetrahydropyridines **10** obtained from the C2 methylated precursors **9** was 85% with indium trichloride, the *n*-Pr substituted amine and phenylacetaldehyde (Table 4, entry 3).

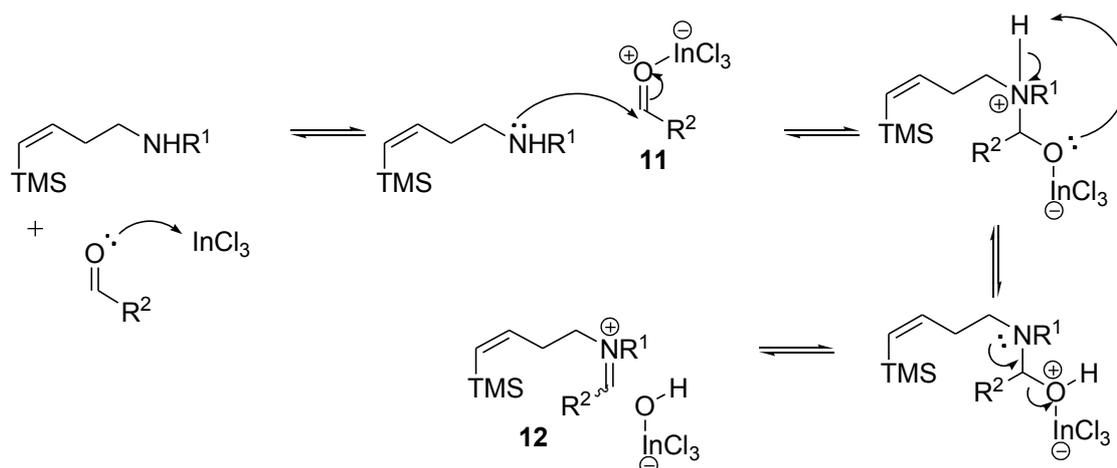
Table 4. The aza-silyl-Prins reaction between substituted homoallylic amines and aldehydes.



Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	%Yield
1	Ph	<i>n</i> -Pn	36	23
2	<i>n</i> -Pr	<i>n</i> -Pn	24	73
3		Bn	24	85
4		Ph	24	40

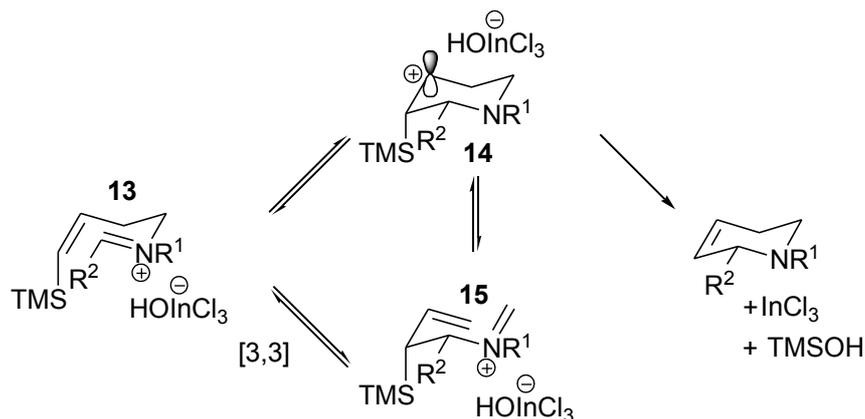
5	Bn	<i>n</i> -Pr	14	56
6		<i>n</i> -Pn	14	70
7		-(CH <sub>2</sub> ) <sub>10</sub> -CH <sub>3</sub>	24	70
8		Bn	24	60
9		Ph	12	69
10		<i>p</i> -Me-Ph	24	55
11		<i>p</i> -Br-Ph	16	65
12		<i>p</i> -NO <sub>2</sub> -Ph	14	70

The proposed mechanism is comparable to the silyl-Prins reaction except for the presence of an iminium ion intermediate **12** instead of an oxonium ion. Initially, formation of the iminium ion with an indium hydroxide counter-ion is achieved *via* condensation involving a Lewis acid activated aldehyde **11** or activated amine pathway (Scheme 4). On investigation, the activated aldehyde pathway which involves addition of the aldehyde before the amine substrate produced enhanced rates and yields. Also, introduction of the aldehyde before the amine was observed to aid the dissolution of the Lewis acid.



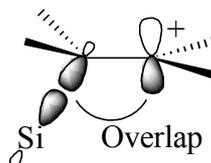
**Scheme 4.** Proposed mechanism for condensation of precursors in aza-silyl-Prins reaction.

The reaction proceeds *via* the cyclisation of the vinylsilane onto the iminium ion followed by elimination of the silane on to the formed cyclic carbocation **14**. It is proposed that the indium hydroxide species attacks the silane to give TMSOH and also to regenerate indium trichloride (Scheme 5). However catalytic turnovers have been found to be low suggesting this mechanistic rationale is not entirely accurate. Alternatively the iminium ionic pair **13** participates in a [3,3]-sigmatropic aza-Cope rearrangement to give the more reactive allyl silane **15**, which can cyclise to give the same silicon stabilised carbenium **14** (Scheme 5).



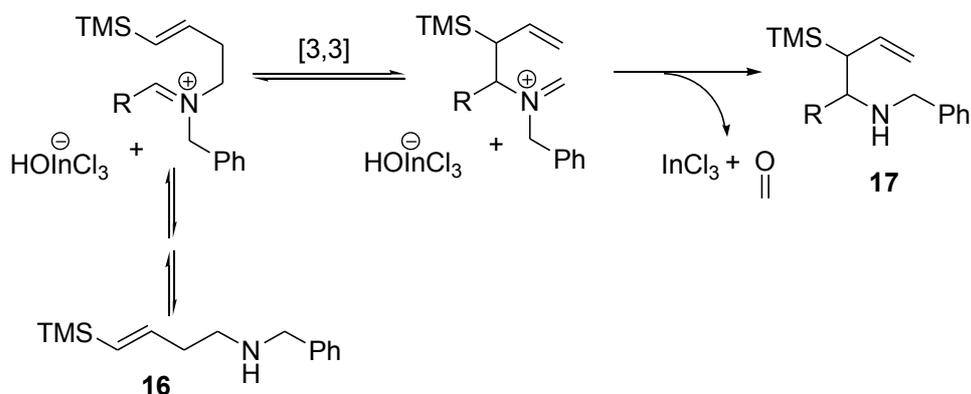
**Scheme 5. Proposed mechanism for cyclisation of intermediates in aza-silyl-Prins reaction.**

The vinylsilane moiety is key to a successful reaction: the silicon induced  $\beta$ -effect (overlap of the vacant p-orbital on the  $\beta$ -carbon and the polarised  $\sigma$ -orbital between the silicon and the  $\alpha$  carbon) offers stabilisation of the carbocation intermediate (Figure 3).



**Figure 3. Orbitals involved in the  $\beta$ -effect of silicon.**

The by-products from this procedure are minimal but may become important in monitoring the development of the aza-Prins cyclisation. One is the hydrolysed aza-Cope rearrangement adduct **17**. Also formed is the (*E*)-isomer of the silylated allylic amine **16** formed *via* the aza-Cope rearrangement, followed by the reversible reactions in the condensation pathway (Scheme 6). The latter is capable of cyclisation as reported by Overman.



**Scheme 6. Side-products from aza-silyl-Prins reaction.**

The stereochemical outcome of *trans* substituents across the ring nitrogen is presumably due to a minimisation of a phenomenon called  $A^{1,3}$  strain, which is based upon the steric interactions between the C-2, C-6 and N-substituents (Figure 4).

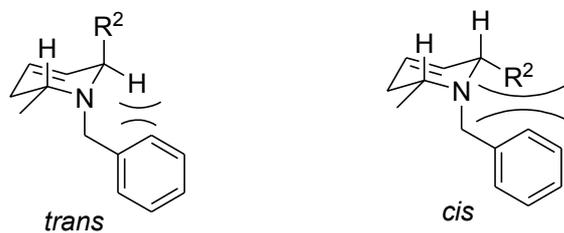


Figure 4. Minimisation of  $A^{1,3}$  strain leads to exclusive *trans* product.

## **CHAPTER TWO: The Aza-Prins Reaction**

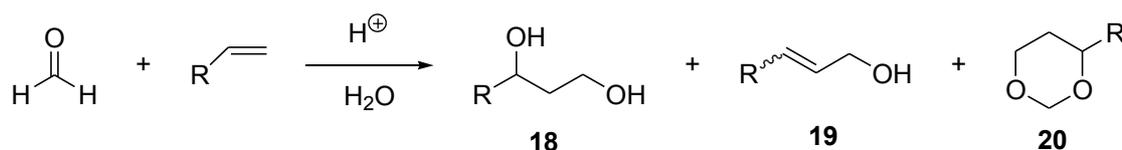
## . II Literature Review of Prins Methodology.

Previous studies by our group in forming substituted heterocycles, *via* the silyl-Prins and aza-silyl-Prins have been reviewed. The intention now is to introduce the Prins reaction, which will prove that the vinylsilane moiety is not essential for success in the oxygen series. The success found in forming tetrahydropyrans using this methodology encourages studies into forming piperidines *via* an aza-Prins reaction. However, the progression of the silyl-Prins reaction to the aza-silyl-Prins reaction showed that the latter requires more harsh conditions to achieve success. Therefore, it is likely that there will be similar contrasts between the Prins reaction and the aza-Prins reaction.

### . I The Prins

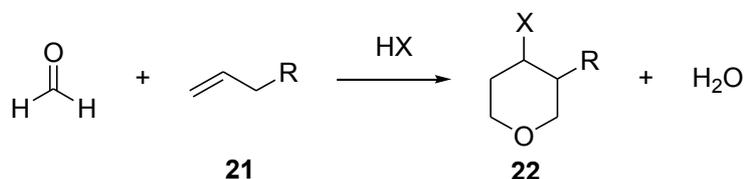
#### Reaction

Reported in 1899, the condensation of olefins with aldehydes under strongly acidic conditions is called the Prins reaction (Scheme 7).



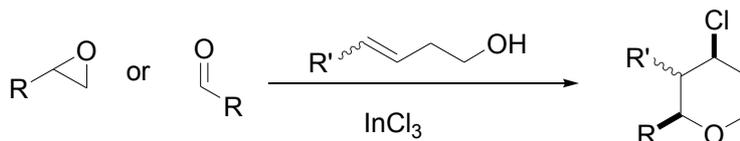
Scheme 7. The initial components involved in the Prins reaction.

The initial mixture of products consisted of 1,3-dioxanes **20**, 1,3-glycols **18** and unsaturated alcohols **19** but later the reaction was developed in the late 1960s by Stapp to form tetrahydropyran derivatives. This reaction proceeded in anhydrous media and involved the condensation of 1-olefins **21** with paraformaldehyde and hydrogen halides to give 3-alkyl-4-halotetrahydropyrans **22** (Scheme 8).



Scheme 8. The evolution of the Prins reaction to form tetrahydropyrans.

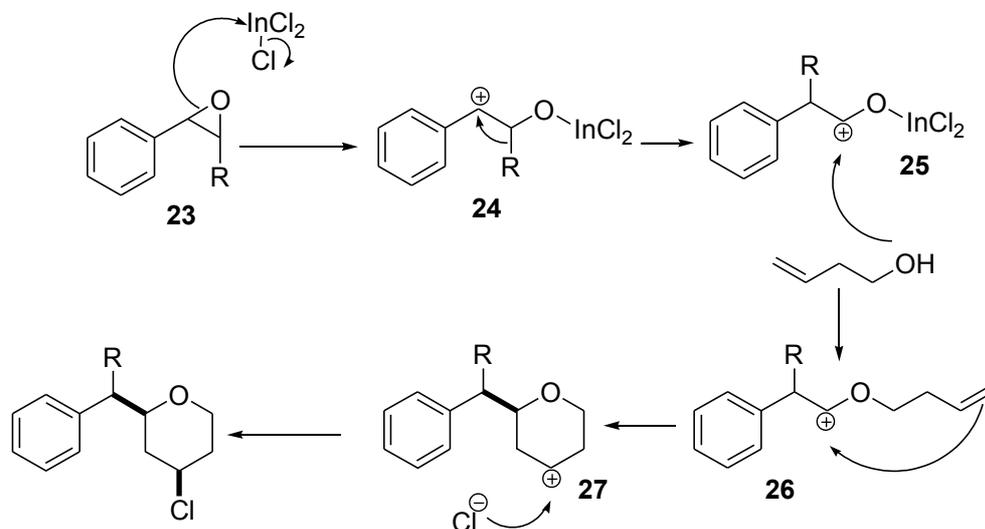
Recently Li has reported the indium trichloride-mediated cross-cyclization between epoxides or aldehydes and homoallylic alcohols. These condensation-cyclisation reactions, often mediated by Lewis acids, are the most modern evolution of the Prins reaction (Scheme 9).



**Scheme 9. Modern Prins reaction by Li utilised to form tetrahydropyrans.**

Their primary reaction involved the use of styrene epoxide and the homoallylic alcohol, 3-buten-1-ol. These were treated with indium trichloride in DCM at room temperature for 5 hours to yield 2-benzyl-4-chlorotetrahydropyran in 94% yield with a 3:1 *cis* to *trans* stereochemistry.

Cyclisations have also been performed with aldehydes (yields not published) in place of epoxides, also in high yields. Li has suggested a mechanism for the use of an epoxide, which should be highly similar to an aldehyde activated pathway. Firstly the epoxide **23** is activated by indium trichloride to afford a chloride anion. Then the migration of the R group **24** forms the carbenium ion **25** adjacent to the indium-oxy-anion leaving group. This allows substitution using the homoallylic alcohol, with the terminal olefin **26** cyclising onto the carbenium ion. This yields a six membered carbocation **27** (with no obvious aided stabilisation), which is trapped by the chloride anion, assumed to be produced from the Lewis acid (Scheme 10).

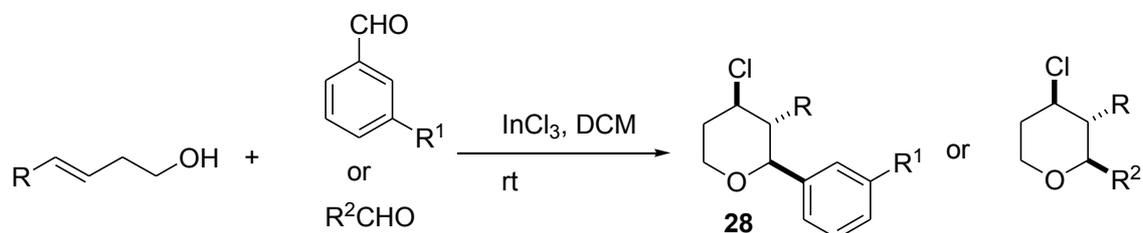


**Scheme 10. Li's proposed mechanism of Prins reaction.**

Li has also described the synthesis of polysubstituted tetrahydropyrans *via* an indium trichloride mediated Prins cyclisation. This introduces some intriguing regiochemical issues surrounding the Prins reaction. They demonstrate that variations in the geometry of the double bond of the homoallylic alcohol precursor can affect the diastereoselectivity of six-membered heterocyclic products. Assuming success can be found in optimising an

intermolecular aza-Prins reaction, then it is envisaged that similar stereochemical and regiochemical effects might be observed. Most of the homoallyl alcohols used in the cyclisations are commercially available. The treatment of *trans*-3-hexen-1-ol with benzaldehyde in the presence of indium trichloride afforded exclusively 2,3,4-trisubstituted tetrahydropyrans **28** with an *up-down-up* diastereoselectivity. Extending the chain length beyond the internal olefin as in *trans*-3-nonen-1-ol did not affect the stereoselectivity but the yield was decreased. This was assumed to be due to the increased steric hindrance in the transition state for the ring-closing step. A similar effect of decreasing yields was found when aliphatic aldehydes were used in comparison with the aromatic aldehydes (Table 5, entry 6 and 8).

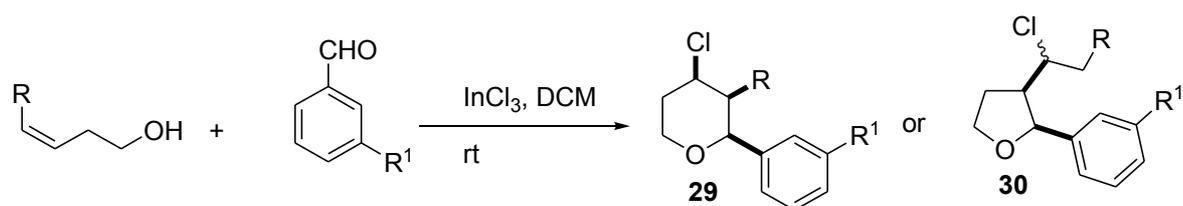
**Table 5.** Homoallylic alcohols coupled to aromatic aldehydes in the Prins reaction.



Entry	R	R <sup>1</sup>	R <sup>2</sup>	%Yield
1	Et	H	-	85
2	Et	F	-	90
3	Et	Cl	-	86
4	Et	Br	-	88
5	<i>n</i> -Pn	H	-	80
6	Et	-	Me	71
7	Et	-	<i>n</i> -Pn	81
8	Et	-	(CH <sub>2</sub> ) <sub>8</sub> (CH)CH <sub>2</sub>	46

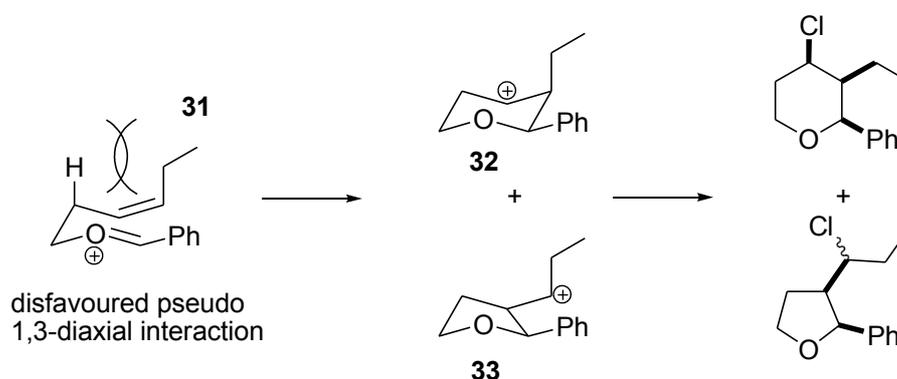
Next, changing the geometry of the double bond was investigated, with highly intriguing results. When the condensation of *cis*-3-hexen-1-ol to benzaldehyde was attempted, a mixture of (*up,up,up*)-2,3,4-trisubstituted tetrahydropyran **29** as the major product and *cis*-2,3-disubstituted tetrahydrofuran **30** as the minor product, was afforded. When the starting material was altered to *cis*-3-nonen-1-ol the ratio of 6-membered species to 5-membered increased to 1:1 (Table 6, entry 5).

Table 6. Regiochemical effects in Prins reaction.



Entry	R	R <sup>1</sup>	%Yield of 29	%Yield of 30
1	Et	H	54	13
2	Et	F	65	Trace
3	Et	Cl	50	9
4	Et	Br	69	9
5	<i>n</i> -Pn	H	23	28

A possible explanation behind the formation of the tetrahydrofuran product involves firstly envisaging the chair intermediate **31**. In the case of the *trans* homoallyl alcohol, all the substituents are equatorial whereas in the case of the *cis* homoallyl alcohol the disfavoured pseudo 1,3-diaxial interactions lead to a mixture of carbocations **32** and **33**. From here, subsequent nucleophilic attack from the chloride ion will either give the more stable tetrahydropyran or the tetrahydrofuran (Scheme 11).



Scheme 11. Possible explanation for the formation of tetrahydrofuran.

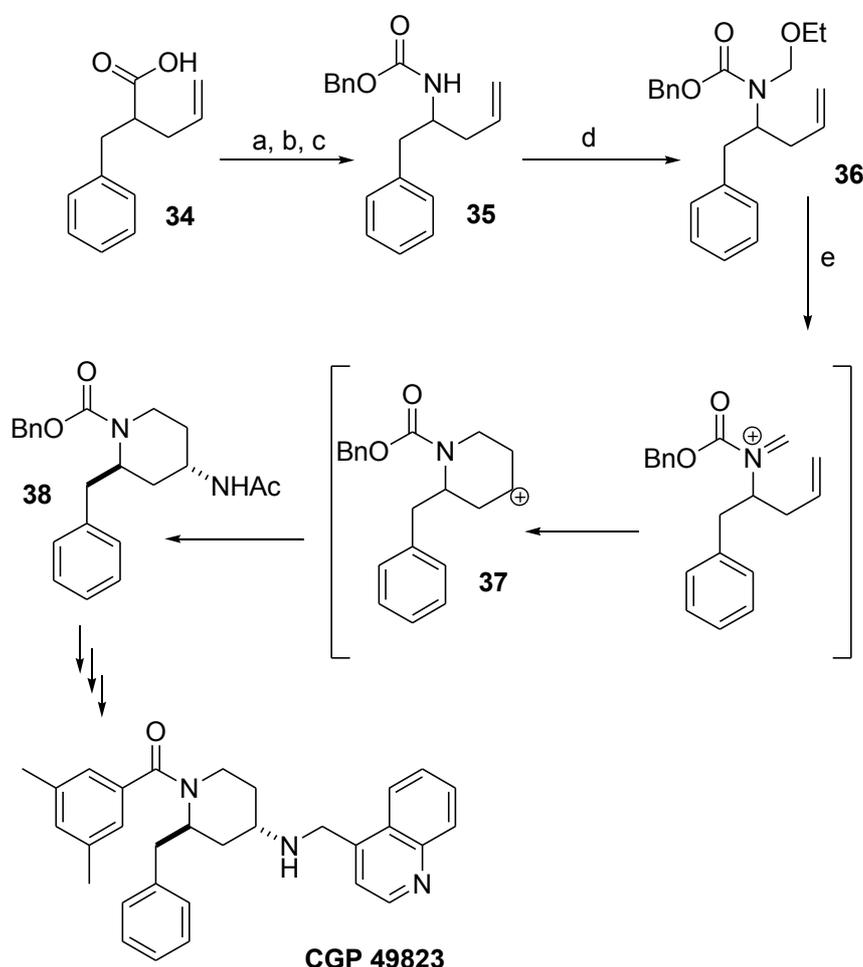
Thus, examples exist of Prins and related cyclisations, which occur, unlike the silyl-Prins reaction, without stabilisation of the intermediate carbocation. Therefore if amines are considered as nitrogen-analogues of alcohols (albeit less-reactive), an aza-Prins reaction may be possible.

A variety of methods for the synthesis of piperidines involve olefin cyclisations onto iminium ion intermediates, often lacking any stabilisation adjacent to the olefin function. These could offer a direct comparison to the proposed aza-Prins reaction. Even more

Reactions

promising is that Lewis acids have been employed in a few of these examples to activate the starting materials. These examples will be discussed briefly.

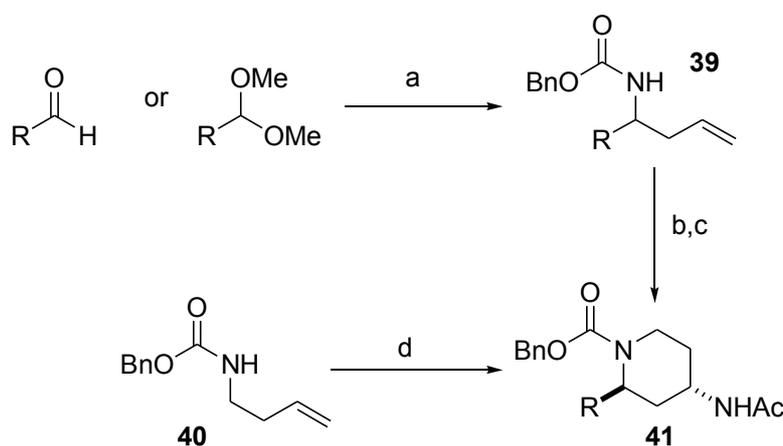
The potent NK<sub>1</sub> antagonist CGP 49823, contains a 2-benzyl-4-aminopiperidine moiety and has been prepared by Veenstra. The synthesis included production of a benzyl carbamate protected allylic amine **35**, derived from the associated carboxylic acid **34** using Hofmann conditions. This was readily alkylated with a chloromethyl ethyl ether to afford an acyl iminium ion **36** capable of undergoing cyclisation with the unactivated olefin in acetonitrile and in the presence of two equivalents of chlorosulfonic acid. The cyclic carbenium ion **37** provided was trapped by the solvent acetonitrile, which on aqueous work-up produced the *trans*-2-benzyl-4-acetamidopiperidine **38** in adequate yield of 73% (Scheme 12).



**Scheme 12.** Reagents and conditions: (a) i) SOCl<sub>2</sub>; ii) aq. NH<sub>3</sub>; (b) Br<sub>2</sub>, NaOH; (c) ClCO<sub>2</sub>Bn, aq. NaHCO<sub>3</sub>, 68% for 3 steps; (d) ClCH<sub>2</sub>OEt, 50% aq. NaOH, DCM, benzyltributylammonium chloride, 5-10 °C, 80%; (e) ClSO<sub>3</sub>H, CH<sub>3</sub>CN, -20 °C, 30 min, 73%.

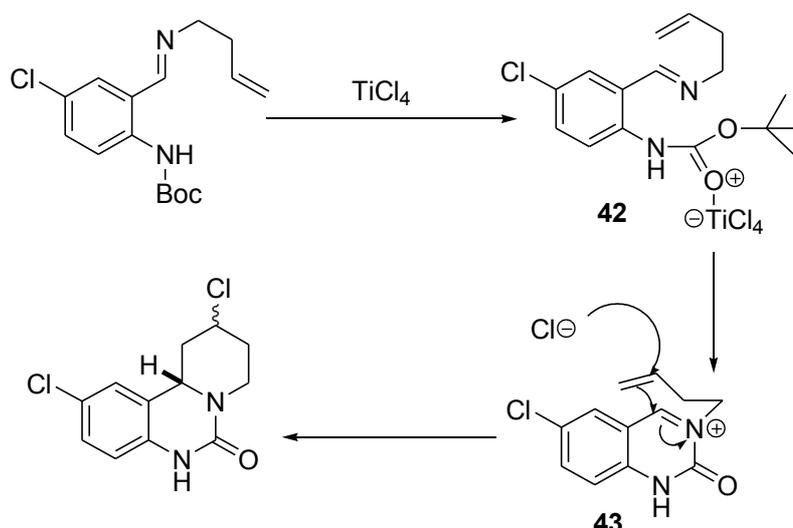
It was assumed that the *trans* diastereoselectivity dominated because *N*-acylated 2-alkylpiperidines have strong preference for axial conformations; therefore it is sterically

favourable for acetonitrile to attack from the opposite side of the ring. Debate on whether acetonitrile would be favoured for carbocation trapping in the presence of a Lewis acid was answered in the SAR studies of the substituent on C2. Introduction of varied substituents into this position was achieved either *via* the allylic carboxylic acid or *via* a novel one-pot synthesis to a CBZ-protected homoallylic amine **39**. This involved the use of equimolar amounts of aldehyde or acetal, benzylcarbamate, allyltrimethylsilane, and boron trifluoride diethyletherate. The *trans*-2-substituted-acetamidopiperidine **41** could also be synthesised using the unsubstituted CBZ-protected allylic amine **40** *via* a one-pot aza-Prins cyclisation reaction. This was limited to aromatic aldehydes however and required the presence of acetic anhydride. Reagents for this step also included tin tetrachloride in acetonitrile at -20 °C. Interestingly only acetonitrile trapped products were obtained unlike examples of other Prins methodology where the anions of Lewis acid salts quench the cation (Scheme 13).



**Scheme 13. Reagents and conditions:** (a) BnOCONH<sub>2</sub>, allyltrimethylsilane, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>3</sub>CN, 0–25 °C; (b) ClCH<sub>2</sub>OEt, 50% aq. NaOH, DCM, benzyltributylammonium chloride; (c) CF<sub>3</sub>SO<sub>3</sub>H, CH<sub>3</sub>CN, -20 °C, 30 min; (d) PhCHO, SnCl<sub>4</sub>, Ac<sub>2</sub>O, CH<sub>3</sub>CN, -20 °C.

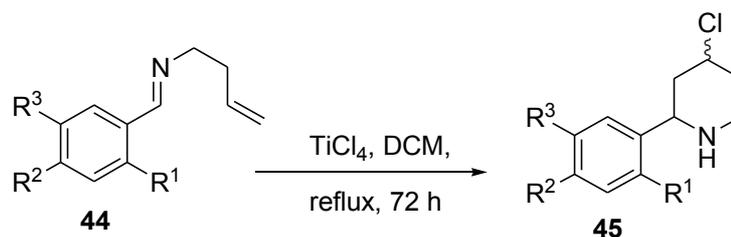
Iminium ion-olefin cyclisations have been utilised by Aubé in studies towards the tricyclic core of a group of bradykinin antagonists called Martinellines. These possess a pyrroloquinoline ring system. This system was targeted using an unusual imine-olefin cyclization *via* an acyl iminium ion intermediate **43**. This intermediate is formed *via* intramolecular attack from the imine **42** on to a Lewis acid activated *t*-butyl carbamate function. This publication then suggests that a concerted process occurs involving the chloride attacking the olefin, which in turn cyclises onto the iminium ion (Scheme 14).



**Scheme 14.** Proposed mechanism for iminium ion-olefin cyclisation.

Reactions involving imines **44** without the *N*-protected aniline function and with a variety of groups of differing electronic effects on the aryl system only gave moderate yields of 2-substituted-4-chloropiperidines **45** and these could not be isolated cleanly (Table 7).

**Table 7.** Imine-olefin cyclisation reaction mediated by titanium(IV) chloride.

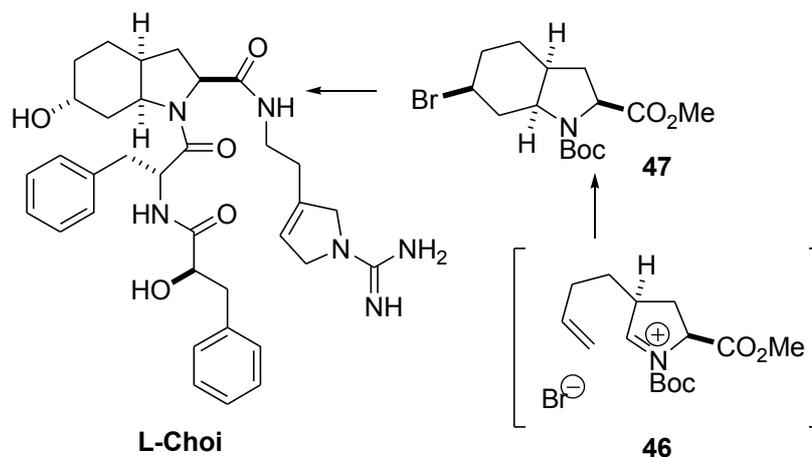


Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	%Yield
1	H	H	H	25
2	H	OMe	H	18
3	H	NO <sub>2</sub>	H	31
4	H	CO <sub>2</sub> Me	H	52
5	NO <sub>2</sub>	H	Cl	21

In conclusion, in the imines containing the *o*-NHBoc aromatic substituent, the yields were consistently higher and with cleaner products.

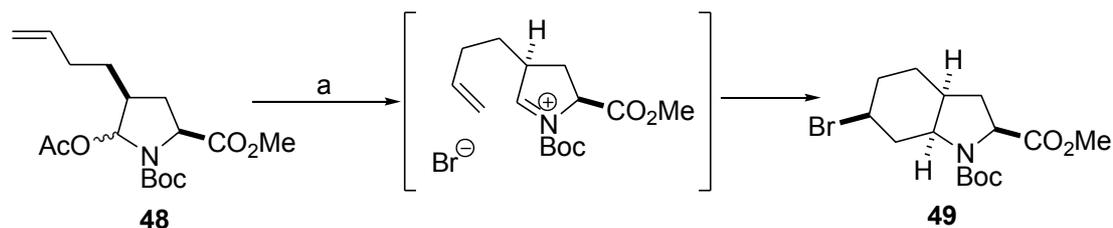
Hanessian has employed an iminium ion-olefin cyclisation with carbocation trapping in the total synthesis of Oscillarín, a member of the aeruginosin family. These secondary metabolites are produced by blue-algal species of prokaryotic aquatic microorganisms and are linear peptides that possess serine protease inhibitory properties. This family shares a common 1-aza[4.3.0]-bicyclic core, which in the case of oscillarin is more specifically a (2*S*,3*aS*,6*R*-hydroxy,7*aS*) octahydroindole 2-carboxylic acid core (L-Choi). To access the

bicyclic core, an approach involving an *N*-acyloxyiminium ion **46** aza-Prins cyclization to form 6-halo-octahydroindole 2-carboxylates **47** was chosen (Scheme 15).



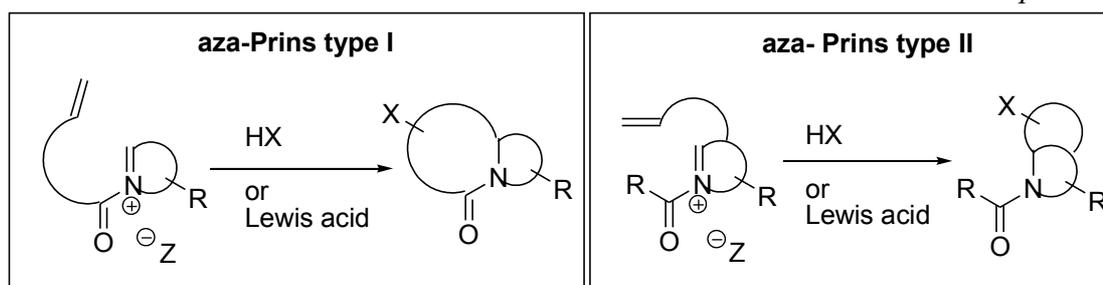
**Scheme 15. Summary of intramolecular cyclisation to form L-Choi.**

The intramolecular cyclizations take place between a hemiaminal acetate **48** and an olefinic tether by treatment with tin tetrabromide in DCM, at  $-78\text{ }^{\circ}\text{C}$  for approximately 5 minutes to form product **49** in 78% yield (Scheme 16).



**Scheme 16. Reagents and conditions: (a)  $\text{SnBr}_4$ , DCM,  $-78\text{ }^{\circ}\text{C}$ , 78%.**

The stereochemistry at C6 was confirmed by X-ray crystallography of an advanced intermediate. The authors go on to classify intramolecular aza-Prins cyclizations involving *N*-acyliminium ions. It is reported that there are many examples of nucleophilic attack of the *N*-olefinic tether on to an endocyclic iminium cation. These *endo* aza-Prins cyclizations, which lead to the nitrogen atom at the junction of the bicyclic unit such as with pyrrolizidinones or indolizidinones, are said to be Type I. There are however fewer examples of intramolecular cyclizations in which the olefinic tether is attached to a distal carbon and cyclises onto an incipient endocyclic *N*-acyliminium ion (Type II) (Scheme 17).



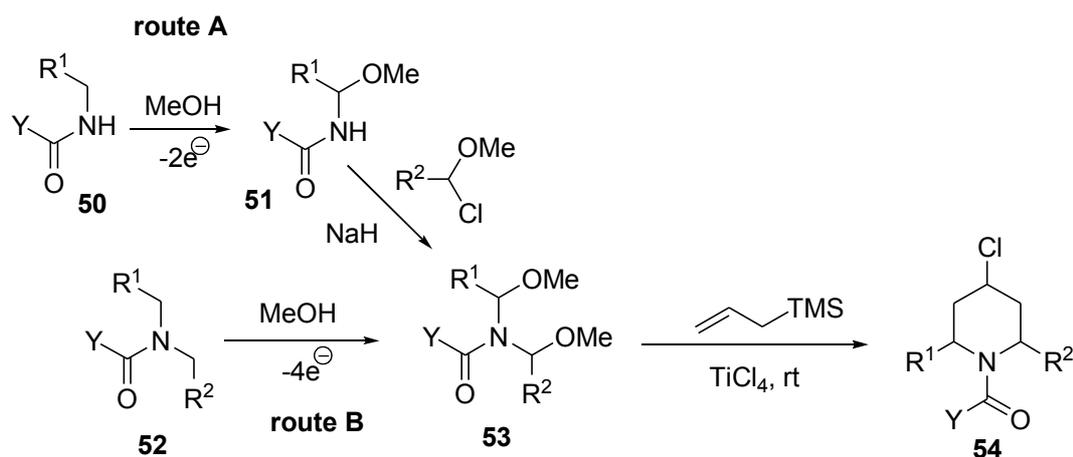
Scheme 17. Types of aza-Prins reaction.

### . 3 Synthesis of 4-

#### Halopiperidines.

The use of Prins methodology to perform iminium ion-olefin cyclisations and so form nitrogen-containing heterocycles has been reviewed. In the proposal for the aza-Prins reaction, the aim was to form specifically 4-halopiperidines, as it was felt that these would have significant value in pharmaceuticals or become useful intermediates in total synthesis of natural products. The literature precedent for the formation of these heterocycles by a variety of different routes will now be reviewed.

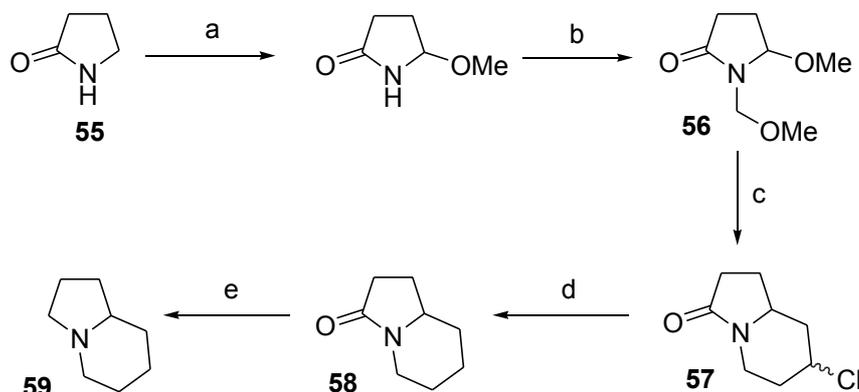
Liotta has reported the synthesis of 4-halopiperidines from the [3+3] annelation between  $\alpha,\alpha'$ -dimethoxylated amides **53** and allyltrimethylsilane. The  $\alpha,\alpha'$ -dimethoxylated amides were prepared by one of two routes, route A, involving the anodic  $\alpha$ -monomethoxylation of *N*-monoalkylamides **50** followed by methoxyalkylation of the product **51**. The second route, route B, involves the anodic  $\alpha,\alpha'$ -dimethoxylation of *N,N*-dialkylamides **52**. The typical procedure for the synthesis of the 4-chloropiperidines **54** involves the treatment of  $\alpha,\alpha'$ -dimethoxylated amides **53** and allyltrimethylsilane with titanium(IV) chloride in moderate to excellent yields (Table 8).

Table 8. Formation of 4-chloropiperidines *via* [3+3]-type annelation.

Entry	$\alpha,\alpha'$ -Dimethoxylated amide	4-Chloropiperidine	% Yield
1			75
2			83
3			50
4			62
5			77
6			85

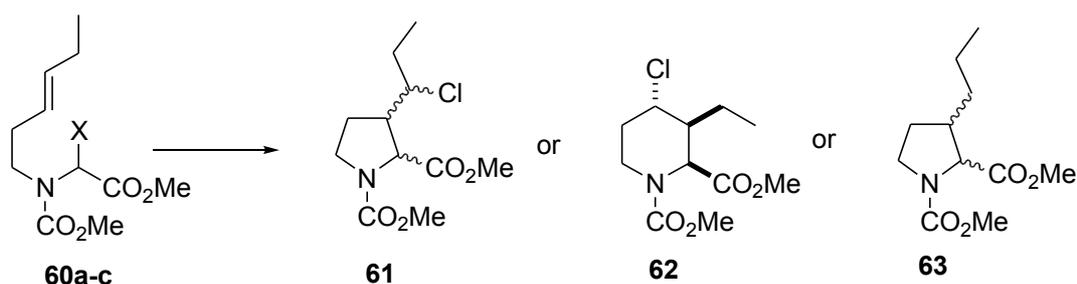
This methodology has been applied to the synthesis of ( $\pm$ )- $\delta$ -coniceine **59**, which is a bicyclic nitrogen heterocycle. The synthesis began with a lactam **55**, which after using route A, furnished the desired [3+3]-type annelation precursor **56**. Treatment under standard conditions afforded the indolizidine **57**, which was then hydrogenated over

Raney Nickel to give **58** followed by hydride reduction to give the desired bicycle **59** (Scheme 18).



**Scheme 18.** Synthesis of (±)- $\delta$ -coniceine. *Reagents and conditions:* (a) MeOH,  $-2e^-$ , 67%; (b) ClCH<sub>2</sub>OMe, NaH, 71%; (c) TiCl<sub>4</sub>, rt, 77%; (d) H<sub>2</sub>, Raney Ni, KOH, 85%; (e) NaBH<sub>4</sub>, AcOH, 34%.

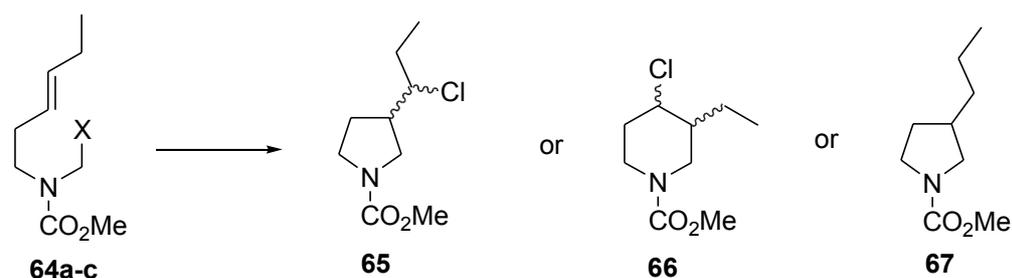
Speckamp and Hiemstra describe the Lewis acid mediated transformation of *N*-(chloromethyl)alk-3-enylcarbamates into 4-chloropiperidines *via* a cationic ring-closure. These conditions were then compared to a radical transfer process which involved a comparable alkenylcarbamate precursor treated with tributyltin hydride to afford the corresponding pyrrolidine. The initial conditions that were screened involved the treatment of a *N*-(chloromethyl-carboxylate)alk-3-enylcarbamate **60a** with a copper(I) chloride/2,2'-bipyridine complex, secondly treatment of the *N*-(thiophenyl-carboxylate) derivative **60b** with tributyltin hydride and thirdly the treatment of the *N*-(acetyloxy-carboxylate) derivative **60c** with tin tetrachloride. The copper complex mediated reaction led to formation of the 2-carboxylate-3-(1-chloropropyl)pyrrolidine **61** (5-*exo* product) exclusively (Table 9, entry 1) and the tributyltin hydride treated reaction led to the unchlorinated proline derivative **63** (Table 9, entry 2). However, the tin tetrachloride and also the un-catalysed control reaction only led to 4-chloropiperidine **62** (6-*endo* product), although the Lewis acid mediated reaction produced much higher yields (Table 9, entries 3 and 4).

Table 9. Piperidine and pyrrolidine formation *via* radical or cationic processes.

Entry	X	Promoter	%Yield of 61	%Yield of 62	%Yield of 63
1	Cl ( <b>60a</b> )	Cu(bpy)Cl	78 (20:80; cis:trans)	2	0
2	SPh ( <b>60b</b> )	Bu <sub>3</sub> SnH	0	0	93 (35:65; cis:trans)
3	OAc ( <b>60c</b> )	SnCl <sub>4</sub>	0	80	0
4	Cl ( <b>60a</b> )	Blank	0	33	0

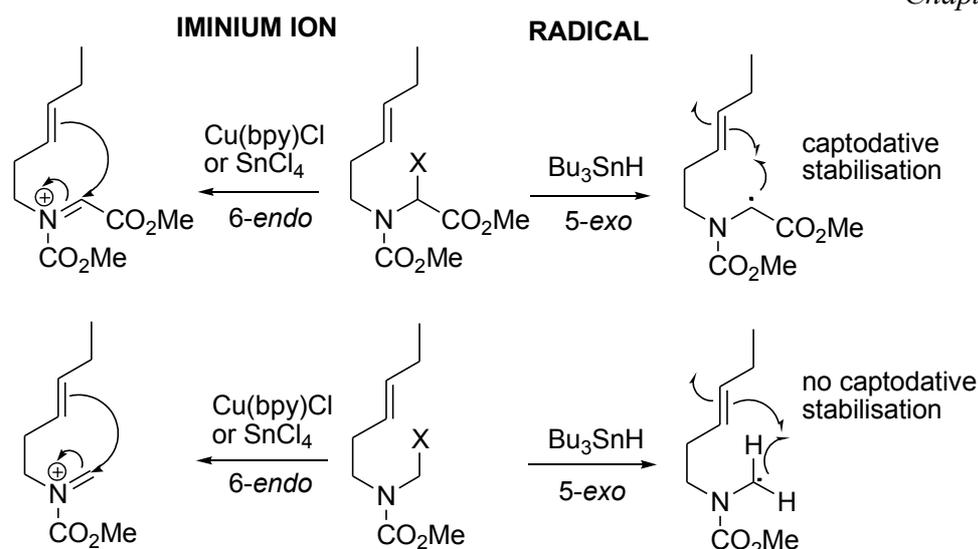
Interestingly, when the alkenylcarbamate precursor was altered for carbamates that did not possess the methylcarboxylate function **64a-c**, the outcome was quite different. For the copper complex, tin tetrachloride and blank control, the 4-chloropiperidine **66** was the sole product with excellent yields in all cases, albeit slightly lower in the un-catalysed control (Table 10, entries 1,3 and 4). The diastereoselectivity of all three cases was different, in the control the *cis* diastereomer was favoured, whilst in the tin tetrachloride mediated reaction the *trans* diastereomer was almost exclusively favoured. However in the copper complex mediated reaction, a 1:1 mixture of diastereomers was observed. When the carbamate precursor was treated with tributyltin hydride, the un-chlorinated pyrrolidine **67** was the only product to be observed, albeit in low yields (Table 10, entry 2).

Table 10. Piperidine and pyrrolidine formation minus carboxylate stabilisation of substrate.



Entry	X	Promoter	%Yield of 65	%Yield of 66	%Yield of 67
1	Cl ( <b>64a</b> )	Cu(bpy)Cl	0	82 (46:54; <i>cis:trans</i> )	0
2	SPh ( <b>64b</b> )	Bu <sub>3</sub> SnH	0	0	30
3	OMe ( <b>64c</b> )	SnCl <sub>4</sub>	0	95 (5:95; <i>cis:trans</i> )	0
4	Cl ( <b>64a</b> )	blank	0	66 (87:13; <i>cis:trans</i> )	0

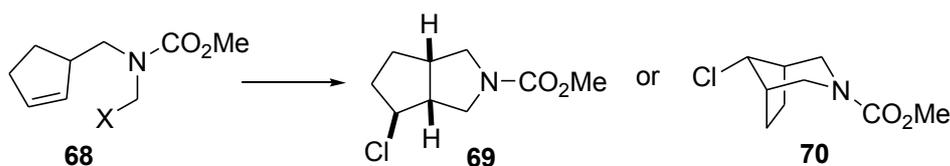
These results may be explained by the Lewis acid-mediated reaction proceeding *via* an iminium ion-olefin cyclisation which is terminated *via* the nucleophilic trapping with chloride ions, while the tributyltin hydride reaction involves a radical-olefin cyclisation. On use of the *N*-(thiophenyl-carboxylate)alk-3-enylcarbamate precursor **64b**, the intermediate radical formed is stabilised by the adjacent ester function. The so-called captodative radical stabilisation is absent in the second precursor and thus detrimental to the yields of the pyrrolidine product (Scheme 19).



**Scheme 19.** Iminium ion and radical pathways.

To test the Lewis acid strength of the copper complex, a carbamate **68** with a cyclopentenyl function and an alkyl chloride was introduced to the conditions containing tin tetrachloride, the blank control and also the copper complex. When the carbamate was introduced to the copper complex, a mixture of a bridged bicyclic system **69** (6-endo product) and a bicyclic pyrrolidine **70** (5-exo product) was formed with equal quantities of each. A similar ratio of products was formed on use of tin tetrachloride, whereas in the un-promoted reaction, no cyclisation products were formed (Table 11). This suggests that since the regioselectivities of the copper promoted cyclisation and the tin tetrachloride mediated cyclisation are essentially the same, the cuprous chloride/2,2'-bipyridine complex functions as a Lewis acid promoter. Interestingly, the tin tetrachloride mediated conditions in the first two examples (Table 9, entry 3 and Table 10, entry 3) only produced 6-membered piperidine whereas in the last example, a mixture with 5-membered pyrrolidine was obtained (Table 11, entry 2).

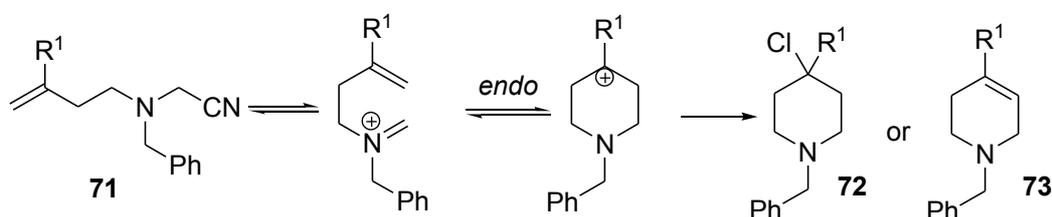
Table 11. Formation of bicyclic systems on use of copper and tin promoters.



Entry	X	Catalyst	%Yield of 69	%Yield of 70
1	Cl	Cu(bpy)Cl	30	32
2	Cl	SnCl <sub>4</sub>	37	32
3	Cl	blank	0	0

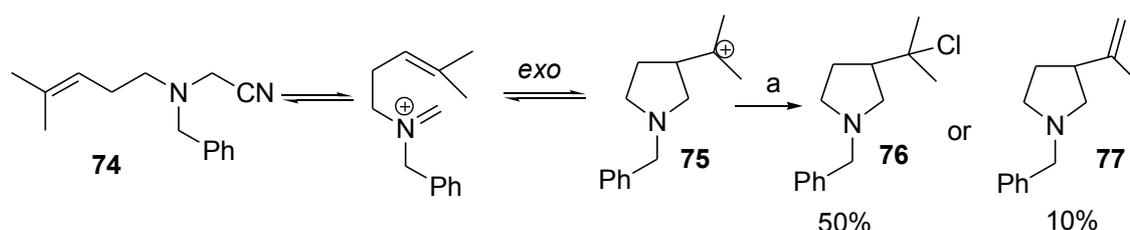
Yang described the titanium(IV) chloride-induced iminium ion cyclisations of  $\alpha$ -cyanoamines. This report showed examples where iminium ion-olefin cyclisations lead to 6 or 5-membered heterocycles. The prerequisite tertiary cyanoamine cyclisation precursors **71** were all prepared by the alkylation of primary amines with alkyl halides and 2-chloroacetonitrile in the presence of triethylamine. The cyclisations were induced by the treatment of the cyanoamines **71** with 3-4 equivalents of titanium(IV) chloride. Use of the but-3-enyl cyanoamine in the presence of 3 equivalents of Lewis acid at  $-78\text{ }^{\circ}\text{C}$  to room temperature yielded a 4-chloropiperidine **72** as the single product (Table 12, entry 1). The precursor was then altered to the 3-methylbut-3-enyl derivative and with the same conditions but with a constant temperature of  $0\text{ }^{\circ}\text{C}$ , a mixture of the 4-chloropiperidine product **72** and a tetrahydropyridine **73** was afforded (Table 12, entry 2). The tetrahydropyridine product is most likely formed by the E1 elimination of the 4-chloropiperidine product *via* a stable intermediate tertiary carbocation.

Table 12. Formation of azacycles on use of titanium(IV) chloride.



Entry	R <sup>1</sup>	Temp.	%Yield of 72	%Yield of 73
1	H	$-78\text{ }^{\circ}\text{C}$ to rt	70	0
2	Me	$0\text{ }^{\circ}\text{C}$	35	50

When the precursor was altered to the 4-methylpent-3-enyl cyanoamine **74** and the reaction was carried out at room temperature, formation of a mixture of 3-(2-chloropropan-2-yl)pyrrolidine **76** as the major product and an associated eliminated pyrrolidine **77** as the minor product was observed. It is most likely that the explanation for the formation of the 5-membered species over the 6-membered piperidine is that the latter was formed *via* a secondary carbocation, whereas the former *via* a tertiary one **75** (Scheme 19).



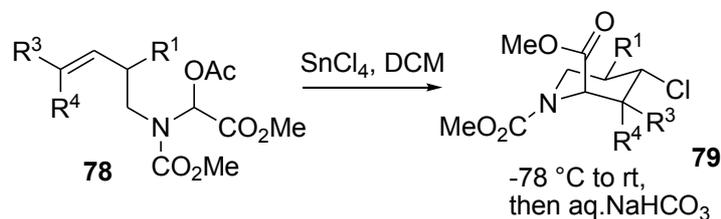
**Scheme 19. Reagents and conditions: (a) 3 equiv. TiCl<sub>4</sub>, rt.**

Speckamp and Hiemstra used aza-Prins methodology in the formation of pipercolic acid analogues. The cyclisations of homoallyl tertiary amines are again promoted by tin tetrachloride with the regioselectivity and stereoselectivity of these reactions being highly variable. The precursors to these reactions are *N,O*-acetals **78** that were prepared from homoallyl carbamates or 2-pyrrolidinones.

The cyclisation of these precursors was effected by treatment with 2 equivalents of tin tetrachloride in DCM at  $-78\text{ }^{\circ}\text{C}$ , followed by warming to room temperature. On use of the but-3-enyl carbamate, a (*up-down*)-2-carboxylate-4-chloropiperidine **79** was afforded in good yields (Table 13, entry 1). When the precursor was altered to the hex-(3*E*)-enyl derivative, the 2,4-*trans* geometry was maintained in the formed (*up-up-down*)-2-carboxylate-3-ethyl-4-chloropiperidine product (Table 13, entry 2). With a simple alteration in the olefin geometry to the hex-(3*Z*)-enyl carbamate, the ethyl substituent becomes axial in the (*up-down-down*)-2-carboxylate-3-ethyl-4-chloropiperidine product, but in much lower yield (Table 13, entry 3). An interesting result occurred when the precursor was changed to the 2-methylbut-3-enyl carbamate with firstly the formation of the (*up-down-up*)-2-carboxylate-4-chloro-5-methylpiperidine as the major product. However, the 2-carboxylate-4-(1-chloroethyl)pyrrolidine **80** was also formed as a minor product (Table 13, entry 4, side product yield in brackets). It was presumed that an

intermediate rearrangement of a primary carbocation to a secondary carbocation was the reason behind the production of the 4-(1-chloroethyl) substituent.

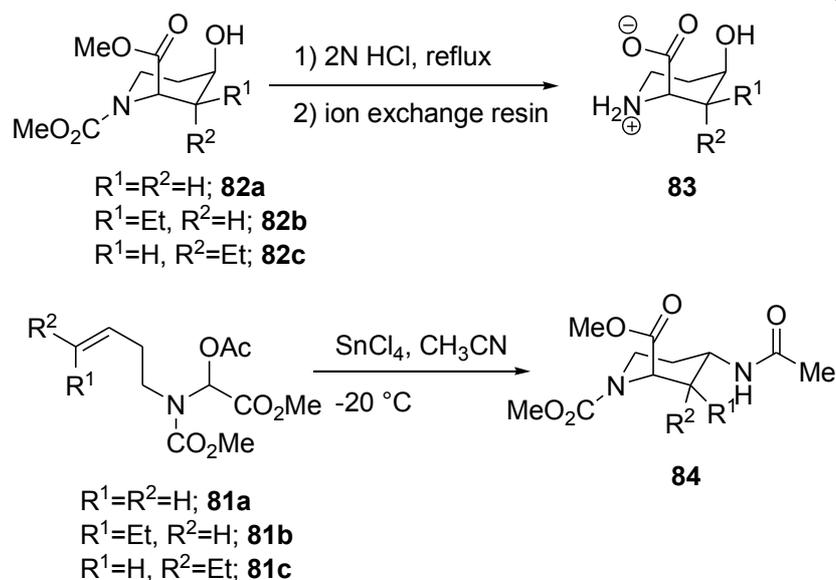
**Table 13. Formation of piperidine in tin mediated aza-Prins type reactions.**



Entry	R <sup>1</sup>	R <sup>3</sup>	R <sup>4</sup>	%Yield of 79
1	H	H	H	77
2	H	Et	H	80
3	H	H	Et	33
4	Me	H	H	44

**80**  
CO<sub>2</sub>Me  
CO<sub>2</sub>Me  
(12)

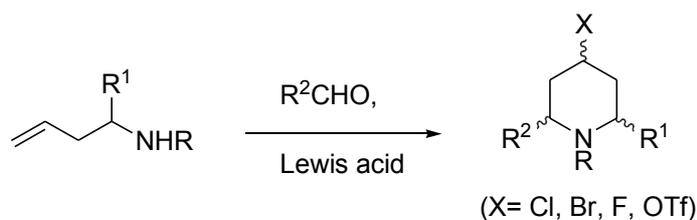
In all the examples involving homoallyl carbamates, a separate series of reactions was studied where the reaction was quenched at  $-78\text{ }^{\circ}\text{C}$  with aqueous sodium hydrogen carbonate (instead of warming to room temperature). In each case, a 2-carboxylate-4-hydroxypiperidine was formed rather than the 4-chloropiperidine. The geometry of the other ring substituents was the same in both series. However, the hydroxy function was always found to be axial on comparison to the equatorial chlorine found in the earlier examples. The 4-hydroxypiperidines **82a-c** that were isolated from the reaction of tin tetrachloride with but-3-enyl (**81a**), hex-(3*E*)-enyl (**81b**) and hex-(3*Z*)-enyl carbamate (**81c**) precursors, were treated with hydrochloric acid at reflux. After isolation from an ion-exchange resin, the 4-hydroxy piperidic acid analogues **83** were afforded (Scheme 20). Interestingly, when the same carbamate precursors **81a-c** were treated with tin tetrachloride in acetonitrile at  $-20\text{ }^{\circ}\text{C}$ , the 4-chloropiperidine species were not formed. Instead the solvent acetonitrile trapped the intermediate carbocation and after aqueous work-up, a *trans*-2-carboxylate-4-(acetylamino)piperidine **84** was formed which is highly comparable with the work by Veenstra (Scheme 20).



Scheme 20. Synthesis of pipercolic acid analogues and cyclisations in acetonitrile.

### . II Results and Discussion: Studies into the Aza-Prins Reaction

Having successfully achieved the synthesis of dihydropyrans and tetrahydropyridines in the group, it was proposed to afford the piperidine skeleton *via* an intermolecular aza-Prins reaction (Scheme 21). This would involve the coupling of homoallylic *N*-substituted amines to aldehydes in the presence of a Lewis acid. By further substituting the amine starting material, it would be possible to afford multiply substituted piperidines, which would further our study on the diastereoselectivity of the reaction. The successful conditions found from the aza-silyl-Prins reaction were used as a starting point.



Scheme 21. Proposed scheme for an intermolecular aza-Prins reaction

### . 4 Preliminary Studies: The Aza-Prins

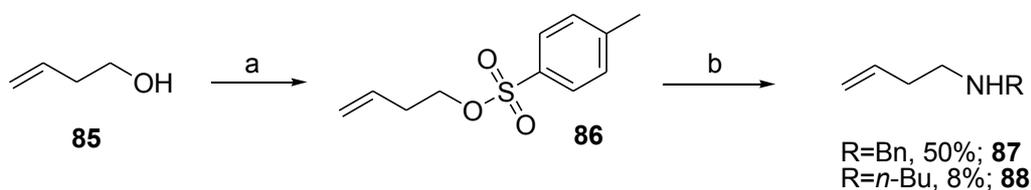
#### Reaction

### . a Precursor Synthesis for the Aza-Prins

#### Reaction I

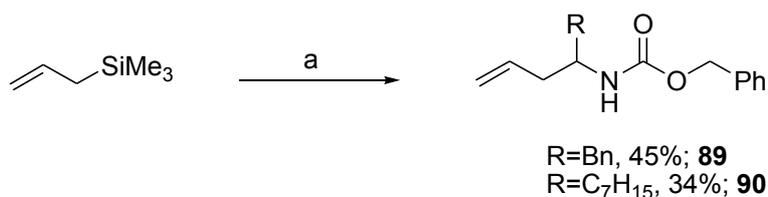
By applying the same methodology used to investigate the aza-silyl-Prins reaction, the desired precursors were synthesised in order to afford both *N*,2,4-substituted piperidine alkaloids and also *N*,2,4,6-substituted analogues. The *N*,2,4-substituted piperidines would

require the coupling of commercially available aldehydes, under Lewis acid mediated conditions with *N*-substituted-*N*-(3-butenyl) amines (Scheme 22). These were obtained in 2 steps starting from the commercially available homoallylic alcohol, 3-buten-1-ol **85**. In order to displace the hydroxyl function to yield the secondary amines, the alcohol was first converted to the corresponding tosylate to provide a better leaving group using a literature method. Thus, *p*-toluenesulfonyl chloride, 4-dimethylaminopyridine and triethylamine in DCM were mixed at 0 °C to afford the tosyl-substituted alcohol **86** in 78% yield. Simple amination of the tosyl-substituted alcohol **86** using primary amines in ethanol at reflux temperature gave the secondary amines in poor yields using a modified literature method. This included formation of the *N*-benzyl-*N*-(3-butenyl) amine **87** using benzyl amine, in a moderate 50% yield, and formation of a *N*-alkyl analogue **88** using *n*-butylamine in a very poor 8% yield (Scheme 22).



**Scheme 22. Reagents and conditions:** (a) TsCl, Et<sub>3</sub>N, 4-DMAP, DCM, 0 °C, 22 h, 78%; (b) EtOH, RNH<sub>2</sub>, 110 °C, R=Bn, benzylamine, 20 h, 50%, R=*n*-Bu, *n*-butylamine, 22 h, 8%.

In order to obtain the *N*,2,4,6-substituted piperidines and thus investigate the diastereoselectivity of the aza-Prins reaction, the synthesis of *N*-substituted-1-substituted but-3-enylamines was required. These were obtained *via* an iodine-catalysed one-pot multi-component reaction, described in the literature. Stoichiometric quantities of aldehyde, benzyl carbamate, and allyltrimethylsilane were combined with 10 mol% of iodine in acetonitrile at room temperature to afford CBz-protected-1-substituted homoallylic amines in moderate yields. The use of phenylacetaldehyde gave the protected secondary amine **89** in 45% yield, while use of octanal to give **90** gave a lower yield of 34% (Scheme 23).

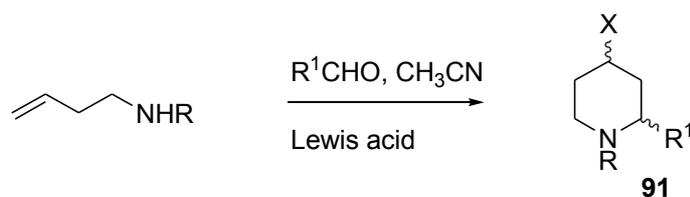


**Scheme 23.** *Reagents and conditions:* (a) RCHO, CBzNH<sub>2</sub>, I<sub>2</sub> (10 mol%), CH<sub>3</sub>CN, rt, R=CH<sub>2</sub>Ph, 20 h, 45%, R=*n*-C<sub>7</sub>H<sub>15</sub>, 20 h, 34%.

### . bInitial Screening for Aza-

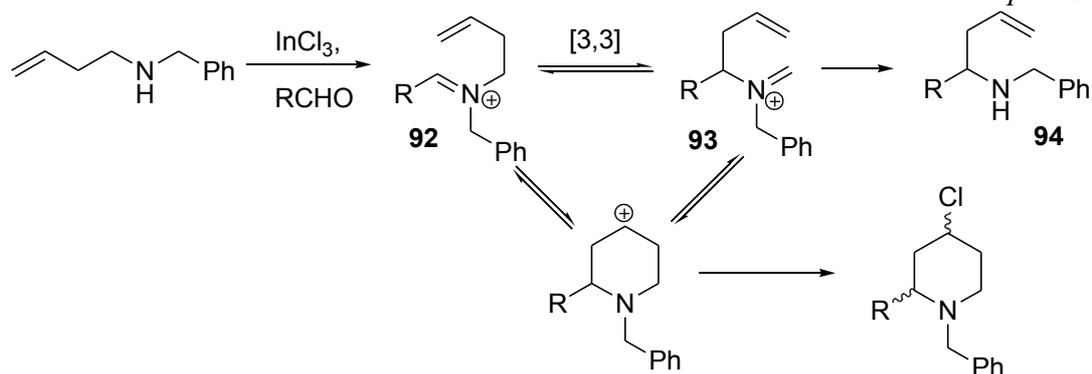
#### Prins Reaction

A typical procedure for the aza-silyl-Prins reaction involved treatment of an *N*-protected silylated homoallylic amine and an aldehyde in the presence of a Lewis acid in a 1:1:1 ratio in acetonitrile at reflux, with reaction times ranging from 3-36 hours. Previous work towards optimising the aza-silyl-Prins reaction showed that the use of phenylacetaldehyde or hexanal with benzyl *N*-protection of the homoallylic amine precursor gave good yields. Therefore our initial screening for the aza-Prins cyclisation towards the synthesis of *N*,2,4-substituted piperidine alkaloids **91** involved mostly these substrates. These were utilised in conjunction with a range of Lewis acids that had found success in promoting the aza-silyl-Prins reaction and also other Prins-type cyclisations in the literature. The solvent of choice was acetonitrile as this gave optimal yields in the aza-silyl-Prins reaction and it was assumed that the high boiling temperature would enhance the chances of success in the aza-Prins reaction. This solvent also allowed full dissolution of the Lewis acids (Table 14).

Table 14. Initial screening towards the aza-Prins reaction; synthesis of *N*,2,4-substituted piperidines.

Entry	Lewis Acid	R	R <sup>1</sup>	X	Temp.	Time (h)	%Yield of 91	
1	InCl <sub>3</sub>	<i>n</i> -Bu	CO <sub>2</sub> Et	Cl	reflux	48	0	
2			Bn			48	0	
3			Bn			CO <sub>2</sub> Et	48	0
4	In(OTf) <sub>3</sub>		Bn	OTf		72	0	
5			<i>n</i> -C <sub>5</sub> H <sub>11</sub>			72	0	
6	AlCl <sub>3</sub>		Bn	Cl		24	0	
7			<i>n</i> -C <sub>5</sub> H <sub>11</sub>			24	0	
8	TiCl <sub>4</sub>		Bn	Cl		24	0	
9			<i>n</i> -C <sub>5</sub> H <sub>11</sub>			24	0	
10	TMSOTf		Bn	OTf		-30°C	72	0
11	BF <sub>3</sub> .OEt <sub>2</sub>		<i>n</i> -C <sub>5</sub> H <sub>11</sub>				F	to rt

After workup, GCMS and <sup>1</sup>H NMR analysis of the crude reaction material, in all cases showed mostly amine starting material, which was recovered in quantitative yields, also with small amounts of aldehyde (Table 14, entry 1-11). Most of the Lewis acids screened had found success in promoting the aza-silyl-Prins reaction (Table 14, entries 1-7 and 10-11). Also screened was titanium(IV) chloride, which had proven successful for the synthesis of piperidine alkaloids by Aubé by utilising imine-olefin cyclisations. Use of boron trifluoride etherate and trimethylsilyl triflate was only compatible at sub-zero to room temperatures. All other Lewis acids were screened at room temperature and when no positive progress was observed, the temperature was raised to reflux. In some instances, use of the *N*-alkyl homoallylic amine substrate and also highly reactive ethyl glyoxylate also produced negative results (Table 14, entries 1-3). Although mostly starting material was recovered, an additional compound was also detected in trace quantities by GCMS and <sup>1</sup>H NMR analysis in a few examples (Table 14, entries 4-5). This compound is the hydrolysis product of the aza-Cope rearrangement. This aza-Cope adduct **94** proves that iminium-ion **92** formation does occur from the condensation of aldehydes and the benzyl protected amine and that it subsequently undergoes a [3,3]-sigmatropic rearrangement to another iminium species **93** (Scheme 24).

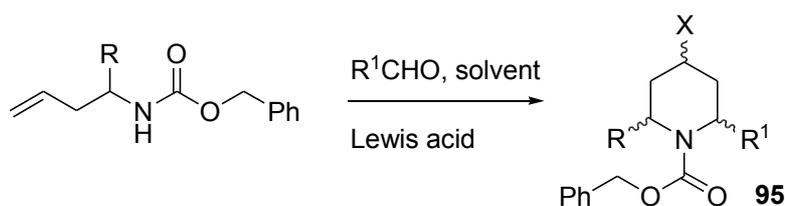


**Scheme 24.** Aza-Cope rearrangement leading to hydrolysis product.

These initial results suggest that iminium ion formation does occur but that the cyclisation of the olefin onto the iminium ion is unfavourable, presumably due to the instability of the cyclic carbocation formed. This suggests that the extra stability provided by the  $\beta$ -effect from the silane function present in the aza-silyl-Prins reaction may be a necessity for these cyclisations to proceed.

The screening of the aza-Prins reaction towards the synthesis of *N*,2,4,6-substituted piperidines **95** was run in parallel to the first data set (Table 14) and the results are presented (Table 15). In this case, the amine precursor contains an *N*-carbamate function and this functionality found success in the aza-silyl-Prins reaction. It was expected that the *N*-carbamate function would reduce the nucleophilicity of the nitrogen lone pair by delocalisation. However this group would be expected to enhance the reactivity of the intermediate iminium ion and so promote the cyclisation step.

**Table 15.** Further screening of aza-Prins reaction, towards the synthesis of 1,2,4,6-substituted piperidine alkaloids.



Entry	Lewis Acid	R	R <sup>1</sup>	X	Temp.	Time (h)	Solvent	%Yield of 95

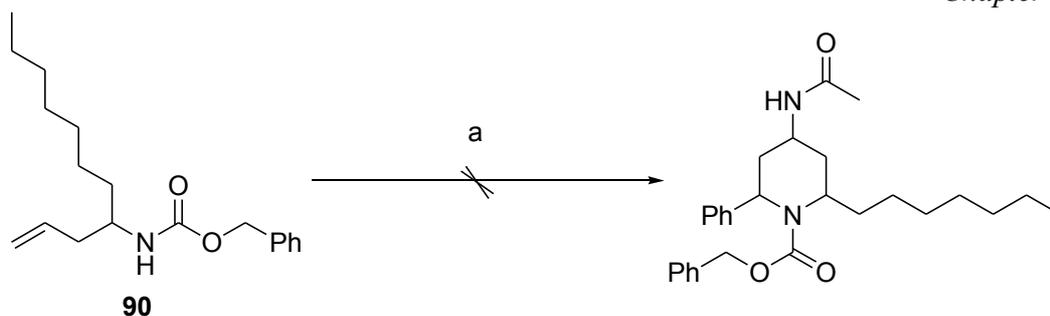
1	InCl <sub>3</sub>	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	Cl	reflux	48	CH <sub>3</sub> CN	0
2		Bn	Bn			72		0
3						72		0
4	In(OTf) <sub>3</sub>		<i>n</i> -C <sub>5</sub> H <sub>11</sub>	OTf		72		0
5			Bn			72		0
6	BF <sub>3</sub> .OEt <sub>2</sub>		<i>n</i> -C <sub>5</sub> H <sub>11</sub>	F	-30°C to rt	72		0
7			Bn			72		0
8	TMSOTf		<i>n</i> -C <sub>5</sub> H <sub>11</sub>	OTf		72		0
9			Bn			72		0
10	SnBr <sub>4</sub>		<i>n</i> -C <sub>5</sub> H <sub>11</sub>	Br	-78°C to reflux	48	DCM	0
11			CO <sub>2</sub> Et			48		0

Again after workup, GCMS and <sup>1</sup>H NMR analysis of the crude reaction material in all instances showed mostly amine starting material, recovered in quantitative yields. Acetonitrile was preferred as solvent in most cases due to past success. Studies by Hanessian, which involved an intramolecular aza-Prins cyclisation of an olefin tethered onto an iminium ion, included the use of tin tetrabromide at -78 °C in DCM. These conditions were applied to our studies and again no positive results were obtained (Table 15, entries 10-11). Again it was assumed that the instability of the intermediate carbocation contributes significantly to the failures observed.

#### . cSolvent Effects of

##### Acetonitrile

Veenstra successfully accomplished piperidine synthesis *via* aza-Prins coupling of CBz-protected homoallylic amines to aromatic aldehydes, but the formation required the use of acetic anhydride and tin tetrachloride. No yields were published and Veenstra suggests that the solvent acetonitrile traps the carbenium ion, as opposed to the leaving group from the Lewis acid. This procedure was attempted using equimolar amounts of reagents at -20 °C. Two trials were attempted, one following the literature procedure precisely with 16 hours at -20 °C, the other slowly warming from -20 °C to room temperature and then an additional 7 days at room temperature. The literature procedure yielded mostly starting material, but the longer run gave a complex mixture of unwanted products, which even after chromatography, were impossible to characterise (Scheme 25). Based on this literature precedent, all our previous studies on the aza-Prins cyclisation were reviewed to identify acetonitrile-trapped piperidines, but again no positive results were found.

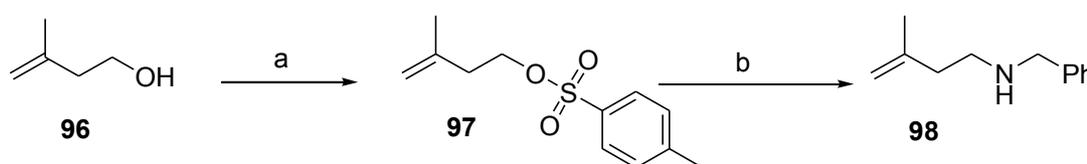


Scheme 25. *Reagents and conditions:* (a)  $\text{SnCl}_4$ ,  $\text{Ac}_2\text{O}$ ,  $\text{PhCHO}$ ,  $\text{CH}_3\text{CN}$  (i)  $-20\text{ }^\circ\text{C}$ , 16 h, 0%; (ii)  $-20\text{ }^\circ\text{C}$ , 5 h, rt, 178 h, 0%.

### . dStabilisa

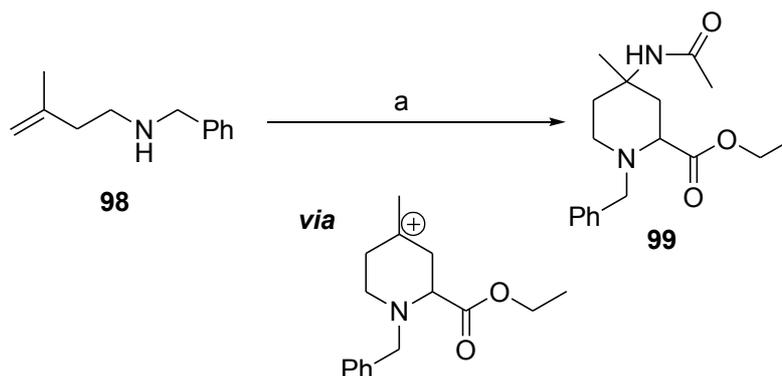
#### tion Effects

Since the major difference between the aza-Prins and the cyclisations involving silylated precursors is the stabilisation of the intermediate carbocation, it was proposed to induce stabilisation by using 3-alkylated homoallylic amines, which have a more substituted alkene function. The cyclisation should be more favourable due to the formation of a tertiary carbocation over a secondary one. To obtain the more substituted homoallylic amine, procedures as previously described were used, starting with commercially available 3-methyl-3-buten-1-ol **96**. Again the action of *p*-toluenesulfonyl chloride afforded the crude tosyl-protected alcohol **97** in 75% yield. Amination of the tosylate **97** using benzylamine gave *N*-benzyl-3-methyl-3-butenamine **98** in 97% yield (Scheme 26).



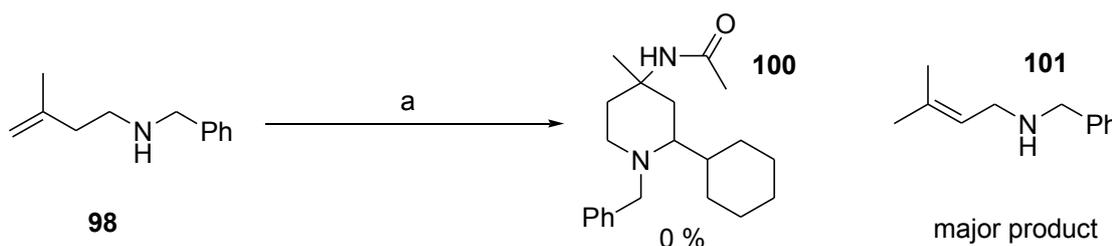
Scheme 26. *Reagents and conditions:* (a)  $\text{TsCl}$ , 4-DMAP,  $\text{Et}_3\text{N}$ ,  $\text{DCM}$ ,  $0\text{ }^\circ\text{C}$ , 48 h, 75%; (b)  $\text{BnNH}_2$ ,  $\text{EtOH}$ ,  $110\text{ }^\circ\text{C}$ , 18 h, 97%.

After coupling of this amine **98** with the highly reactive ethyl glyoxylate in the presence of indium trichloride after 3 days at reflux, TLC showed complete consumption of the amine substrate. After flash chromatography a product **99** obtained in trace quantities was positively identified as the acetonitrile trapped piperidine by GC-MS analysis, however  $^1\text{H}$  NMR data were inconclusive due to the small quantities obtained (Scheme 27).



**Scheme 27. Reagents and conditions:** (a)  $\text{InCl}_3$ ,  $(\text{CO}_2\text{Et})\text{CHO}$ ,  $\text{CH}_3\text{CN}$ ,  $75^\circ\text{C}$ , 72 h, trace.

The substituted homoallylic amine was also screened with cyclohexanecarbaldehyde and indium trichloride or trimethylsilyl triflate. After 20 hours at reflux both attempts showed complete consumption of starting material **98** but after analysis by  $^1\text{H}$  NMR, it seemed that no piperidine **100** was formed in either case. Instead it seemed that the allylic amine had isomerised to the more substituted amine **101** by double bond migration, proven by  $^1\text{H}$  NMR analysis (Scheme 28).



**Scheme 28. Reagents and conditions:** (a)  $\text{InCl}_3$  or  $\text{TMSOTf}$ , *c*-HexCHO,  $\text{CH}_3\text{CN}$ ,  $75^\circ\text{C}$ , 20 h.

Based on these studies it would again seem that the enhanced stabilisation present in a tertiary carbocation does not promote the vital cyclisation step of the olefin function onto the intermediate iminium ion. On condensation of the highly reactive ethyl glyoxylate and the amine substrate, it seemed that perhaps piperidine **99** formation was present, albeit in trace quantities. Perhaps, this is a result of the enhanced reactivity of the intermediate iminium ion caused by the neighbouring carboxylate function.

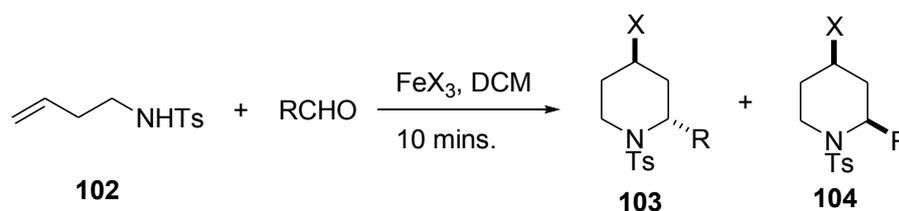
### . 5Iron(III) Halide Mediated Aza-Prins

#### Reaction

Concurrent with our studies, Martin and Padron published details of a study of an intermolecular aza-Prins reaction between homoallyl amines and aldehydes in the presence of a Lewis acid promoter. This work was a direct progression from their previous work on the Prins cyclisation of homopropargylic alcohols and aldehydes to give

halo-dihydropyrans in the presence of iron trihalides. Here, the use of iron trihalides to generate  $\gamma,\delta$ -unsaturated-iminium ion intermediates, which further cyclise to six-membered azacycles, was explored. They were able to form *trans*-2-alkyl-4-halo-1-tosylpiperidines from homoallyl tosylamines **102** and 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines from homopropargyl tosylamines *via* the aza-Prins reaction. Both iron trichloride and tribromide-based Lewis acids produced good yields of *trans*-2-alkyl-4-halo-*N*-tosylpiperidines **103**, although iron tribromide enhanced the yield in most cases. The aza-Prins cyclisation worked well with both aliphatic and aromatic aldehydes, with the *trans*-diastereomer being formed as the exclusive product, although the diastereoselectivity is reduced in aldehydes containing an aromatic substituent (Table 16, entries 4-5 and 10-11).

**Table 16.** The aza-Prins reaction of *N*-tosyl homoallylamine and aldehydes by Martin and Padron.

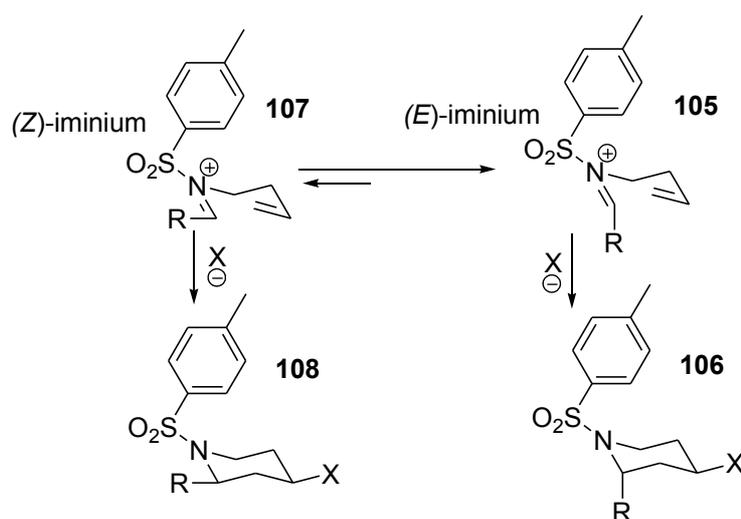


Entry	R	X	<i>Trans:cis</i>	Total % Yield of 103 and 104
1	<i>c</i> -Hex	Cl	98:2	68
2	<i>i</i> -Bu	Cl	99:1	82
3	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Cl	97:3	88
4	Ph	Cl	90:10	46
5	PhCH <sub>2</sub>	Cl	83:17	78
6	H	Cl	-	91
7	<i>c</i> -Hex	Br	98:2	82
8	<i>i</i> -Bu	Br	97:3	96
9	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Br	98:2	90
10	Ph	Br	92:8	82
11	PhCH <sub>2</sub>	Br	86:14	94
12	H	Br	-	90

The stereochemical outcome of these reactions was studied by *ab initio* calculations of the *trans*-2-alkyl-4-halo-tosylpiperidine products and their *N*-sulfonyl iminium ion intermediates. The calculations showed that in the cases of aliphatic aldehydes, the (*E*)-iminium ion **105**, which leads to *trans*-piperidine **106**, is more stable than the (*Z*)-iminium ions **107** that lead to *cis*-isomers **108**. In one instance, with an aldehyde bearing an aromatic ring, the (*Z*)-iminium ion was more stable (Table 17). They suggest that this could account for the fact that in cases where an aryl aldehyde was used, the

diastereoselectivity of the aza-Prins reactions was less selective. It must be said at this point that the authors make no comment on the Curtin-Hammett principle which dictates that the product ratio depends only on the difference in the activation energy of the transition state going to each product (and therefore, reaction rate), and not on the equilibrium constant between the intermediates. Another interesting comment made by the authors was that in both *cis*- and *trans*-isomers, where aliphatic aldehydes were used, the most stable conformer has the *N*-tosyl group *endo* over the piperidine ring. However, in the case where the aldehyde bore an aromatic ring, then the *N*-tosyl group had an *exo* disposition and this was evident in the X-ray crystallographic structures.

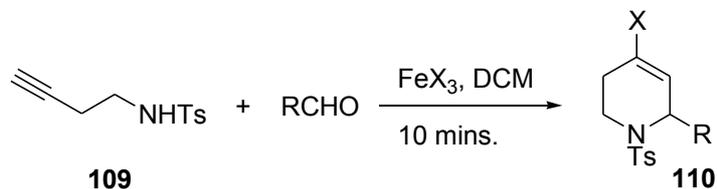
Table 17. Stability of (*E*)-iminium ions from *ab initio* calculations by Martin and Padron.



Entry	R	$E_E$ -iminium- $E_Z$ -iminium (kcal/mol)	$E_{106}$ - $E_{108}$ (kcal/mol)
1	Me	-0.78	-1.25
2	Et	-1.77	-2.12
3	<i>i</i> -Pr	-1.25	-0.41
4	<i>s</i> -Bu	-1.56	-0.74
5	CH <sub>2</sub> Ph	+0.37	-2.12

Next their work proceeded towards an alkyne aza-Prins reaction where homopropargylic amines were coupled to a range of aldehydes in the presence of iron trihalides as promoters. The precursor *N*-(but-3-ynyl)-4-methylbenzenesulfonamide **109** gave 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines **110** in good yields, albeit on reaction with benzaldehyde. Again the Lewis acid of choice was iron tribromide as it gave higher yields in most cases (Table 18).

Table 18. Alkyne aza-Prins reaction between homopropargylic amines and aldehydes.



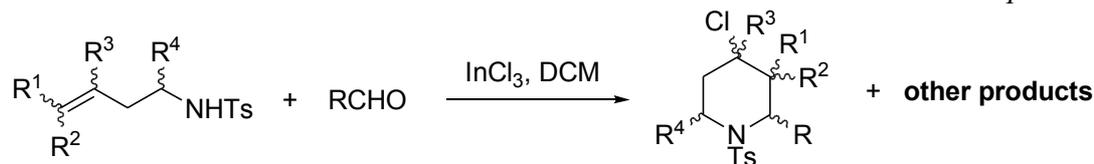
Entry	R	X	%Yield of 110
1	<i>c</i> -Hex	Cl	74
2	<i>i</i> -Bu	Cl	85
3	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Cl	91
4	Ph	Cl	29
5	PhCH <sub>2</sub>	Cl	63
6	H	Cl	83
7	<i>c</i> -Hex	Br	84
8	<i>i</i> -Bu	Br	85
9	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Br	90
10	Ph	Br	38
11	PhCH <sub>2</sub>	Br	67
12	H	Br	96

DCM or 1,2-dichloroethane as solvent gave the greatest yields. When iron tribromide was used as a promoter and DCM as solvent, a mixture of chlorovinyl and bromovinyl derivatives was isolated. This was assumed to be a result of halide exchange between the halogenated solvent and the Lewis acid metal, as well as capture of the solvent halogen by the vinyl cation intermediate. The advantage of using iron trihalides over other metal halides was proven when indium trihalides were screened in the alkyne aza-Prins reaction in the presence of *iso*-butyraldehyde. Although both indium Lewis acids promoted this reaction, it was with detriment to both yields of product and time of reaction. The indium trichloride mediated reaction produced 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridine product **110** in 32% yield after 96 hours at room temperature, *c.f.* iron trichloride (85% yield in 10 minutes). Indium tribromide mediated reaction produced the 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridine product **110** in an improved 42% yield and after 24 hours at room temperature, a contrast to the use of iron tribromide which gave the product in 85% yield after only 10 minutes.

It is interesting to observe that success was found with high yields and in very short reaction times in Martin and Padron's studies, begging the question of why did our

cyclisations show so little success? The first difference between our screening and this study is that the homoallyl amine is *N*-tosyl protected as opposed to benzyl, butyl, or CBz in our examples. It is noted by Martin and Padron that the sulfonamide nitrogen is of similar chemical reactivity to an alcohol moiety, which have found success in the Prins reaction. More specifically, it was believed that the benefit of the *N*-tosyl group is the enhancement of the electrophilicity of the iminium ion, which would aid the cyclisation step. The next difference between our research is the use of iron(III) halides over indium trichloride. In Martin and Padron's studies on the alkyne aza-Prins and the oxa-Prins reactions they found that iron(III) halides promote these cyclisations in 10 minutes and in very good yields, whereas indium trichloride required much longer reaction times and produced low yields of product in some examples. The final difference between the studies is the use of DCM and at room temperature, whereas our studies have used acetonitrile at harsher reflux temperatures. Based on their studies of alternating halogenated solvents and iron(III) halides in the alkyne aza-Prins and the oxa-Prins reactions, they found that the solvent could contribute to the trapping of the intermediate cyclic carbocation. A disadvantage of the use of acetonitrile is that it could compete as a Lewis base with the aldehyde for the Lewis acid catalyst. It was found that the advantages of using acetonitrile were the solubility of the Lewis acid in this solvent as well as its high boiling point.

It is believed that indium trichloride can still have success in promoting aza-Prins reactions based on our initial studies and the success found by Martin and Padron in the alkyne aza-Prins reaction. In their examples they required anhydrous iron(III) halides, which are moisture-sensitive crystalline solids. Success has been found with both silyl-Prins and aza-silyl-Prins when using indium trichloride, which is a crystalline solid, is easily handled in air, and has even promoted these reactions in the presence of water. Next the Dobbs group's success in adopting indium trichloride in the aza-Prins reaction will be reported. Also reported will be the effect on the diastereoselectivity and the regioselectivity of the reaction when using substituted *N*-tosyl homoallyl amines (Scheme 29).

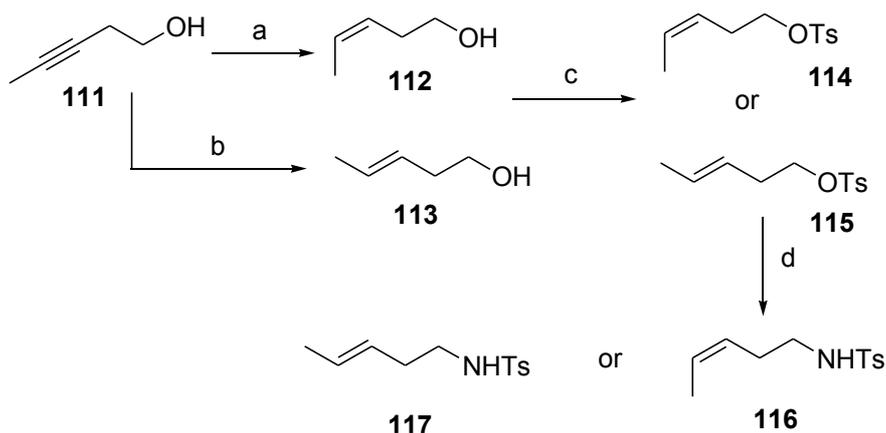


Scheme 29. Proposed scheme for indium trichloride-mediated aza-Prins reaction.

### . a Precursor Synthesis for the Aza-Prins

#### Reaction II

For the initial investigations it was decided to focus on synthesising homoallyl tosylamines that contained an internal olefin function instead of a terminal alkene. It was postulated that this would allow us to form 2,3,4-trisubstituted piperidines. By varying the geometry of the double bond, perhaps this would have a controlling effect on the diastereoselectivity of the aza-Prins reaction. The simple *N*-(pent-3-enyl)-4-methylbenzenesulfonamides were obtained in 3 steps from commercially available pent-3-yn-1-ol **111** (Scheme 30).



Scheme 30. *Reagents and conditions:* (a)  $\text{H}_2$ , Lindlar's catalyst, MeOH, rt, 17 h, 79%; (b) LAH, triglyme, THF, 85 °C, 72 h, 65%; (c) TsCl, DMAP, Et<sub>3</sub>N, DCM, 0 °C, 17 h, (*Z*)=88% or (*E*)=57%; (d) NaI, *p*-TsNH<sub>2</sub>, KOH, DMSO, 50 °C, 20 h, (*Z*)=94% or (*E*)=97%.

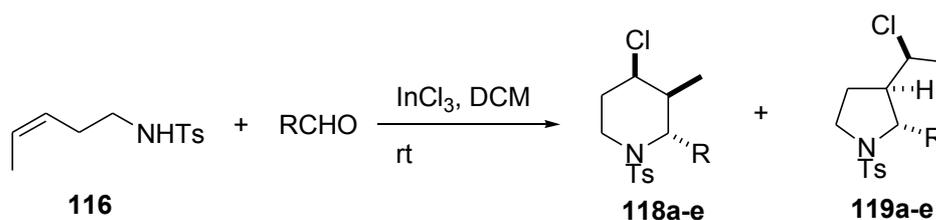
The (*Z*)-pent-3-en-1-ol **112** was obtained by a literature method, catalytic hydrogenation over Lindlar's catalyst affording the homoallylic alcohol as a 10:1 (*Z*:*E*) inseparable mixture of geometric isomers in 79% yield. This ratio of isomers was maintained at each step in the precursor synthesis, even after flash column chromatography. The (*E*)-alkene **113** was exclusively formed in 65% yield, again by a known procedure, by LAH reduction in triglyme and THF at 85 °C. The alcohol was fully characterised as its tosylate because even after distillation it remained a mixture with triglyme. Both homoallylic alcohols were then transformed to the tosylates, each under the same conditions by the

action of tosyl chloride to afford the (*Z*)-alkenyl tosylate **114** in 88% yield, but disappointingly the (*E*)-alkenyl tosylate **115** in 54% yield. Lastly, the homoallyl tosylamines were generated by the substitution of the tosylates with 4-methylbenzenesulfonamide in the presence of catalytic quantities of sodium iodide, using a modified literature procedure. Action of potassium hydroxide deprotonates the sulfonamide and the tosylate is transformed *in situ* to the iodide by sodium iodide. Overall the substitution reaction gave (*Z*)-homoallyl tosylamine **116** in 94% yield and (*E*)-homoallylamine **117** in an excellent 97% yield. The geometry of the double bond in both homoallyl tosylamines was confirmed by NOESY experiments with enhancements of 3.2% and 2.1% between alkenyl protons in the (*Z*)-homoallylamine **116** and smaller enhancements of 2.4% and 0.5% in the (*E*)-homoallylamine **117**. The synthesis of the (*Z*)-isomer **116** was completed in 65% overall yield and the (*E*)-isomer **117** completed in 36% overall yield, both over 3 steps.

### . bAza-Prins Cyclisations: Effects of (*Z*)-

#### Homoallyl Amine

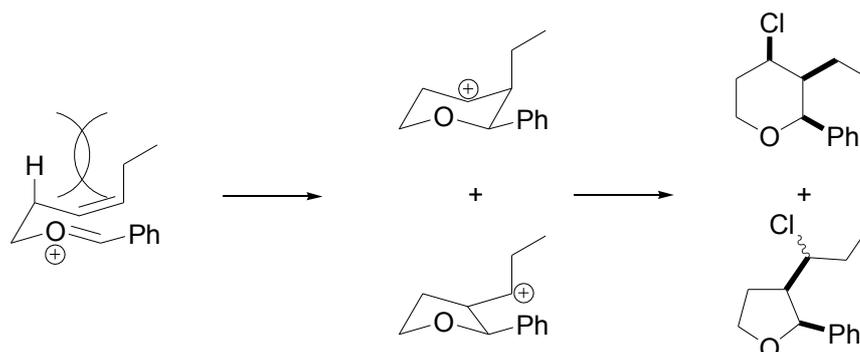
Here the success of using homoallyl tosylamines with internal olefin functions in indium trichloride mediated aza-Prins reactions is reported. Small-scale reactions were performed to test the batch of indium trichloride and <sup>1</sup>H NMR and GCMS data showed positive results for piperidine formation. Another Lewis acid, scandium triflate, which has been shown to be recyclable from an aqueous work-up, was screened with the same substrates with less success. With the positive result for indium trichloride in hand, a collection of aldehydes were screened with *N*-(pent-(3*Z*)-enyl)-4-methylbenzenesulfonamide **116**. Success was found by Martin and Padron when using a stoichiometry of 1:1.5:1.5 for amine: Lewis acid: aldehyde, so these quantities were followed. The (*Z*)-homoallyl tosylamine **116** was screened with aliphatic and aromatic aldehydes as well as the highly reactive ethyl glyoxylate on <0.7 mmol scale and all reactions went to completion (Table 19).

Table 19. The aza-Prins reactions of (*Z*)-homoallyl tosylamine.

Entry	R	Time (h)	%Yield of 118a-e	%Yield of 119a-e
1	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	17	35 (a)	35 (a)
2	Ph	144	15 (b)	0 (b)
3	Ph(CH <sub>2</sub> ) <sub>2</sub>	17	40 (c)	36 (c)
4	<i>c</i> -Hex	144	26 (d)	50 (d)
5	CO <sub>2</sub> Et	1	20 (e)	0 (e)

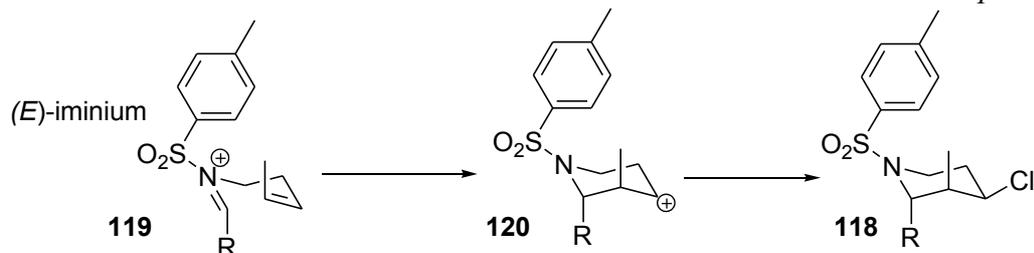
Performing these reactions with the (*Z*)-homoallyl tosylamine **116** formed the 4-chloropiperidine products **118**, but in some cases also produced unexpected side-products of 3-(1-chloroethyl)pyrrolidines **119**. It is important to mention that since the starting material contained a 10:1(*Z*:*E*) mixture of geometric isomers, the product therefore contained trace quantities of other cyclised products, the stereochemistry of which proved impossible to determine. These trace quantities were identified as 4-chloropiperidines and were inseparable after chromatography from the major diastereomer. Low yields of 4-chloropiperidine **118** were observed on use of benzaldehyde or ethyl glyoxylate (Table 19, entries 2 and 5) and perhaps this is why no pyrrolidine product **119** was isolated. It was expected that the yields for benzaldehyde would be low, in accordance with previous examples of the aza-silyl-Prins reaction and also the examples reported by Martin and Padron. As with previous studies, ethyl glyoxylate seems highly reactive based on the short reaction time. However the low yields suggest the products formed are unstable. The high overall yield for cyclised material formed on the use of the three aliphatic aldehydes (Table 19, entries 1,3 and 4) was expected based on previous studies. The reactivity of hydrocinnamaldehyde and octanal (Table 19, entries 1 and 3) in these reactions seems comparable based on the overall cyclised yields and reaction times. The reactivity of cyclohexanecarboxaldehyde (Table 19, entry 4) seems low based on reaction times, although the yield of cyclised material is high. The formation of 3-(1-chloroethyl)pyrrolidine **119** in these reactions can be explained based on previous oxa-Prins cyclisations by Li. When homoallylic alcohols with internal double bonds were cyclised under Lewis acid-catalysed Prins conditions, then a mixture of tetrahydropyran or tetrahydrofuran products was observed. Li only observed this when the internal olefin

had a *cis* geometry and not when *trans* double bonds were utilised. A possible explanation behind the formation of the tetrahydrofuran product is to first envisage the usual chair intermediate. In the case of the *trans* homoallyl alcohol, all the substituents are equatorial whereas in the case of the *cis* homoallyl alcohol the disfavoured pseudo 1,3-diaxial interaction leads to a mixture of carbocations. From here, subsequent nucleophilic attack from the chloride ion will either give the tetrahydropyran or the tetrahydrofuran (Scheme 31).



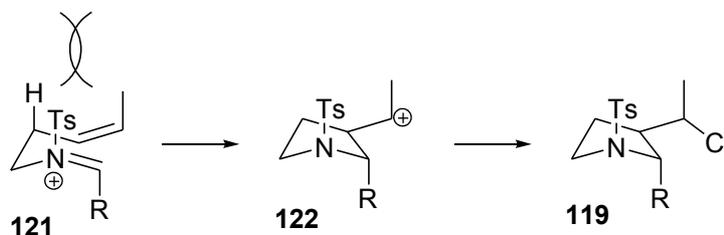
**Scheme 31. Outcome of disfavoured pseudo 1,3-diaxial interaction.**

There are examples in the literature on the formation of pyrrolidines on the use of internal olefin functions in iminium-olefin cyclisation reactions. It was believed that the reason for the formation of pyrrolidines **119** in our examples is based upon the disfavoured pseudo 1,3-diaxial interactions. The reactions involving octanal or hydrocinnamaldehyde (Table 19, entry 1 and 3) produced a 1:1 mixture of 6-membered **118** and 5-membered species **119**. This is a significant increase in the amount of 5-membered species **119** compared to Li's examples. In the case of cyclohexanecarboxaldehyde the ratio further increased to 1:2 and it was believed that this is based on further steric interactions from the cyclohexane ring. The stereochemistry observed in both 4-chloropiperidine products and 3-(1-chloroethyl)pyrrolidine could be explained based on *ab initio* calculations that the intermediate (*E*)-iminium ion is more stable than the (*Z*)-iminium ion. However, again it must be stated that according to the Curtin-Hammett principle, the ratio between different isomers of the products are reliant only on the free energy of the transition states and not on the equilibrium constant between the intermediates. The observation that the (*E*)-iminium ion is more stable does however allow us to explain the stereochemistry of the aza-Prins reactions.



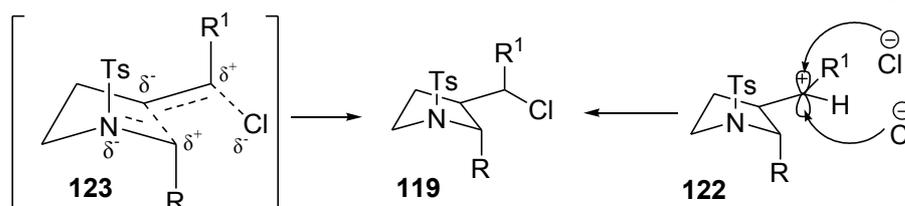
**Scheme 32.** Effect of *(E)*-iminium geometry on stereochemistry in 4-chloropiperidines.

In the case of 4-chloropiperidine syntheses, the *(E)*-iminium ion **119** allows the C2 substituent of the forming piperidine to adopt a pseudo-axial conformation and so leads to an axial substituent in the product **118**. The *cis* geometry of the internal olefin allows the C3 substituent to again adopt a pseudo-axial conformation and overall a *down-up-up* configuration. The intermediate secondary carbocation **120** is then trapped by a chloride anion from the least hindered opposite face to the C2 substituent (Scheme 32).



**Scheme 33.** Effect of *(E)*-iminium ion geometry on stereochemistry in 3-(1-chloroethyl)pyrrolidine.

In the case of forming a 3-(1-chloroethyl)pyrrolidine **119** the *(E)*-iminium ion **121** again forces an axial C2 substituent (Scheme 33). Based on the chair transition state, it is visible that the  $sp^2$  carbon of the alkene allows a pseudo-axial conformation of the C3 substituent. It is debatable how the configuration of the third stereocentre is controlled. If the chloride anion traps the trigonal planar carbocation **122**, then this could occur equally from either face. Possibly, neighbouring groups could hinder the attack of the carbocation **122** by the chloride anion. Alternatively a transition state **123** can be envisaged where the chloride ion attacks the  $sp^2$  alkene carbon at the point of cyclisation and so the geometry of the olefin is important (Scheme 34).



**Scheme 34. Contrast of carbocation formation and its effect on stereochemistry.**

Overall the stereochemistry of the 3-(1-chloroethyl)pyrrolidine **119** is *cis* across the C2 and C3 substituents which is the opposite of the *trans* geometry observed in the tetrahydrofuran analogues in Li's work. The difference observed is based on the pseudo-axial conformation related to the (*E*)-iminium ion and the pseudo equatorial conformation of the oxonium ion.

The stereochemistry and the configuration of both 6-membered and 5-membered species were supported by NOESY experiments and X-ray crystallography. In the trisubstituted piperidine **118b** derived from the coupling of the (*Z*)-homoallylamine **116** and benzaldehyde there is firstly a *trans* relationship between C2 and C3 substituents. This is proven by the 1.6% enhancement of the methyl hydrogens in the C3 position on irradiation of the hydrogen in the C2 position. There is a *cis* relationship between C2 and C3 substituents proven by the 1.4 and 1.1% enhancement on irradiation of each hydrogen at those positions. Similar nOe effects are observed in all piperidines derived from the (*Z*)-homoallylamine **118a-e** (Figure 5).

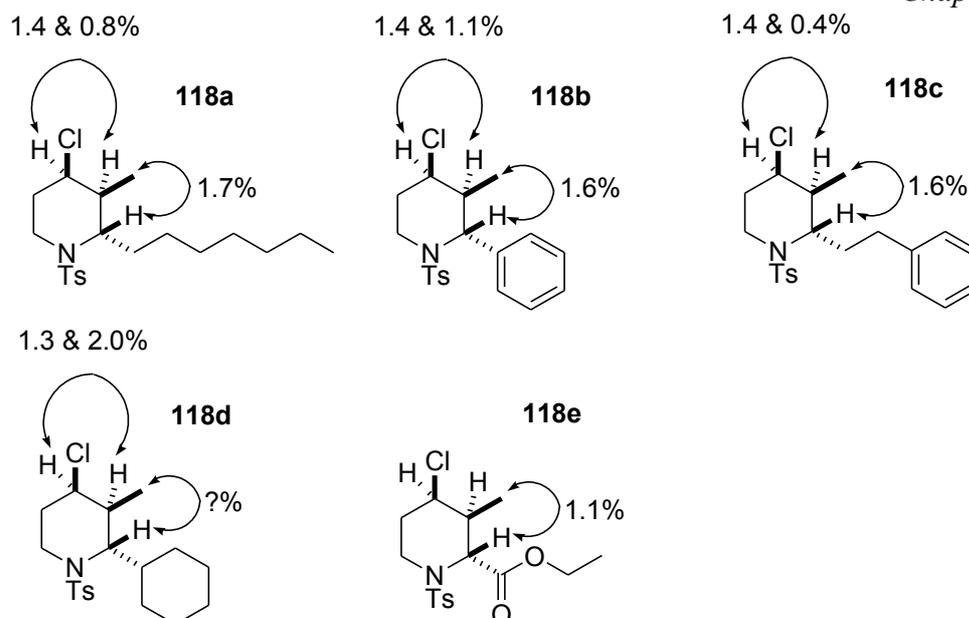


Figure 5. The nOe effects of 2,3,4-trisubstituted piperidines.

In the disubstituted pyrrolidine derived from the coupling of the (*Z*)-homoallylamine **116** and hydrocinnamaldehyde **119c** there is firstly a *trans* relationship between C2 and C3 substituents. This is proven by the small 0.5% enhancement of the C3 hydrogen on irradiation of the C2 hydrogen. This is further supported by the 1.3 and 1.4% enhancements between the C2 hydrogen and the C1 hydrogen of the 1-chloroethyl substituent. There is also a 1.1% enhancement of the C3 hydrogen on irradiation of the C1 hydrogen in the 1-chloroethyl substituent, although it is difficult to use this value to accurately determine the relative stereochemistry at these positions. Again all disubstituted pyrrolidines derived from the (*Z*)-homoallylamine **116** showed similar nOe effects (Figure 6).

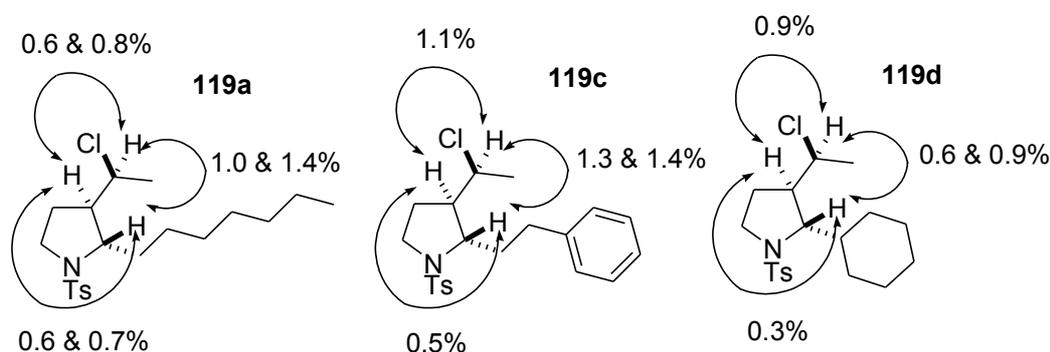
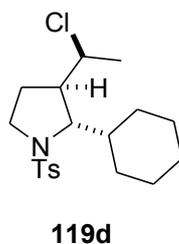


Figure 6. The nOe effects of 2,4-disubstituted pyrrolidines.

It was not possible to determine which substituents were orientated axially or equatorially in these compounds. Fortunately the X-ray structure for 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine **119d** was obtained (Figure 7). However an X-ray structure could not be

obtained for the 4-chloro-2-substituted-3-methyl-1-tosylpiperidines **118a-e** derived from the (*Z*)-homoallylamine **116**, although it was possible for a highly comparable compound, which will be discussed later.



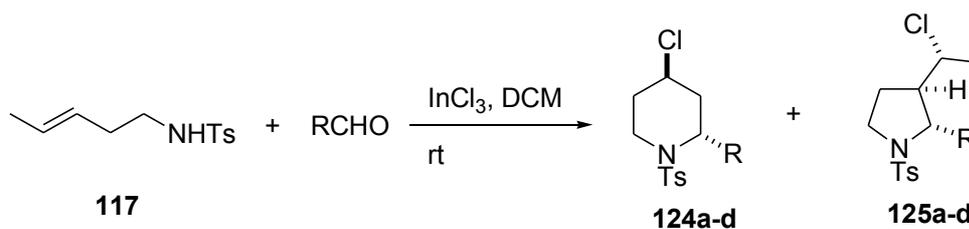
**Figure 7. X-ray structure of 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine.**

This clearly supports the NOESY experiments previously described, and also confirms the relative configuration of the compound. Here it can be seen that the cyclohexyl substituent adopts an axial conformation and the 1-chloroethyl substituent also adopts an axial conformation on the opposite face. It is interesting to observe that the *N*-tosyl group is *endo* over the pyrrolidine ring like a “sunshade”, comparable with the piperidine examples shown by Martin and Padron.

#### **. cAza-Prins Cyclisations: Effects of (*E*)-**

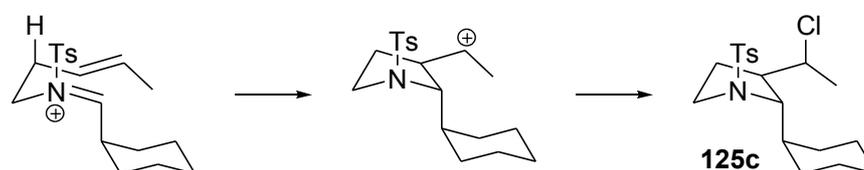
#### **Homoallyl Amine**

Now described are the results of the aza-Prins cyclisation on coupling *N*-(pent-(3*E*)-enyl)-4-methylbenzenesulfonamides **117** with different aldehydes. The same aldehydes were screened as previously, albeit without an aromatic example and all reactions went to completion on <0.7 mmol scale (Table 20).

Table 20. The aza-Prins reactions of (*E*)-homoallyl tosylamine.

Entry	R	Time (h)	%Yield of 124a-d	%Yield of 125a-d
1	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	17	66 (a)	0 (a)
2	(CH <sub>2</sub> ) <sub>2</sub> Ph	17	64 (b)	0 (b)
3	<i>c</i> -Hex	240	0 (c)	70 (c)
4	CO <sub>2</sub> Et	1	21 (d)	0 (d)

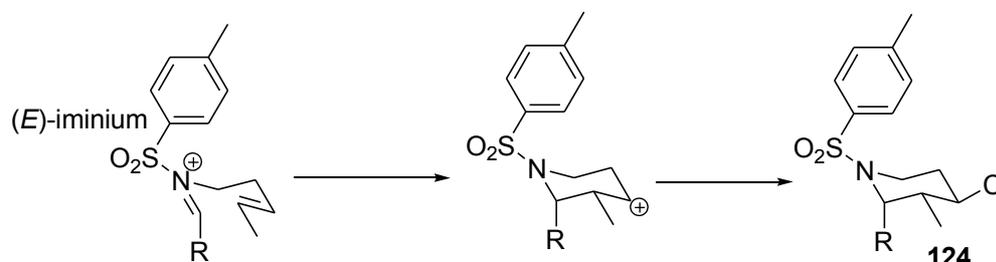
Performing these reactions with the (*E*)-homoallyl tosylamine **117** formed the 4-chloropiperidine product **124**, exclusively in all but one case. In this other example the side-product of 3-(1-chloroethyl)pyrrolidine **125** was formed exclusively. The use of ethyl glyoxylate (Table 20, entry 4) is comparable with the example involving the (*Z*)-amine precursor **116**, since the reaction time was very short but the yield was disappointingly low. Again the aliphatic aldehydes produced good yields in reasonably short reaction times (Table 20, entries 1-3) with a slight depreciation against the overall yields of cyclised product for the (*Z*)-amine precursor **116**. As expected, no 3-(1-chloroethyl)pyrrolidine product **125** was seen in three of the four examples due to the absence of the disfavoured pseudo 1,3-diaxial interaction in the chair transition state. This is consistent with the absence of tetrahydrofuran product in Li's examples when using (*E*)-homoallylic alcohols. However, most surprisingly the formation of only 3-(1-chloroethyl)pyrrolidine **125c** was observed in good yields on use of cyclohexanecarboxaldehyde (Table 20, entry 3). Again the actual reaction times were very long for use of this aldehyde (Scheme 35).



Scheme 35. Unexpected pyrrolidine formation on use of cyclohexanecarboxaldehyde.

Again the stereochemistry observed in both 4-chloropiperidine products and 3-(1-chloroethyl)pyrrolidine can be explained based on *ab initio* calculations that the intermediate (*E*)-iminium ion is more stable than the (*Z*)-iminium ion. The axial conformation of the C2 substituent in both products is based on the pseudo-axial

conformation resulting from the more stable (*E*)-iminium. The only difference in the 4-chloropiperidine products **124** is that the (*E*)-alkene allows the C3 methyl group to adopt a pseudo-equatorial conformation (Scheme 36). The only difference in the *trans*-disubstituted pyrrolidine **125** is that the third stereocentre is inverted based on the geometry of the double bond.



**Scheme 36. Iminium ion and olefin geometry effects in 4-chloropiperidine formation.**

The stereochemistry was confirmed again by use of NOESY experiments and also analysis of the X-ray crystallography data. The nOe effects show that in the 4-chloro-2-substituted-3-methyl-1-tosylpiperidines **124a-d**, the relationship between the C2 and C3 substituents is *cis*. This is based on the 4.1% enhancement of the C3 hydrogen on irradiation of the C2 hydrogen in the example **124b** taken from hydrocinnamaldehyde. In the same example there were enhancements of 1.4 and 1.8% between the C3 methyl hydrogens and the C4 hydrogen. This proves that there is a *trans* relationship between C3 and C4 substituents. Similar nOe effects were observed in other examples of 4-chloro-2-substituted-3-methyl-1-tosylpiperidines **124a-d** obtained from the (*E*)-homoallyl amine **117** (Figure 8). In the <sup>1</sup>H NMR spectra of the single example of 3-(1-chloroethyl)pyrrolidine **125c** occurring from the (*E*)-amine precursor **117**, the signals were too close together and so NOESY experiments are essentially inaccurate.

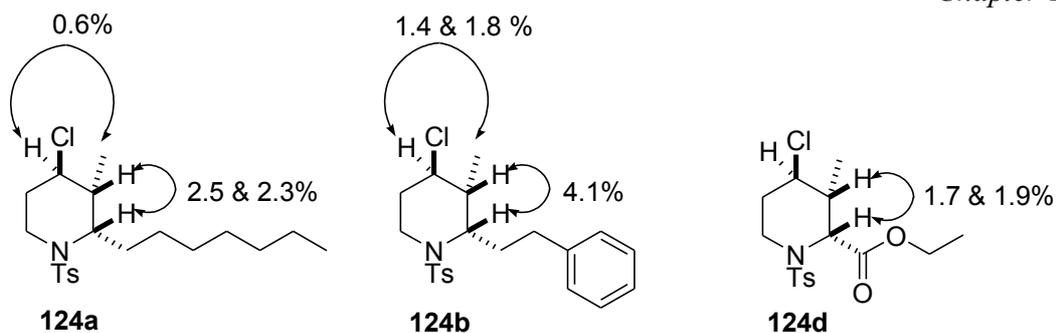


Figure 8. The nOe of 2,3,4-trisubstituted piperidines.

The configuration of 4-chloro-2-phenethyl-3-methyl-1-tosylpiperidine **124b** and 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine **125c** were confirmed on analysis of the X-ray data (Figure 9).

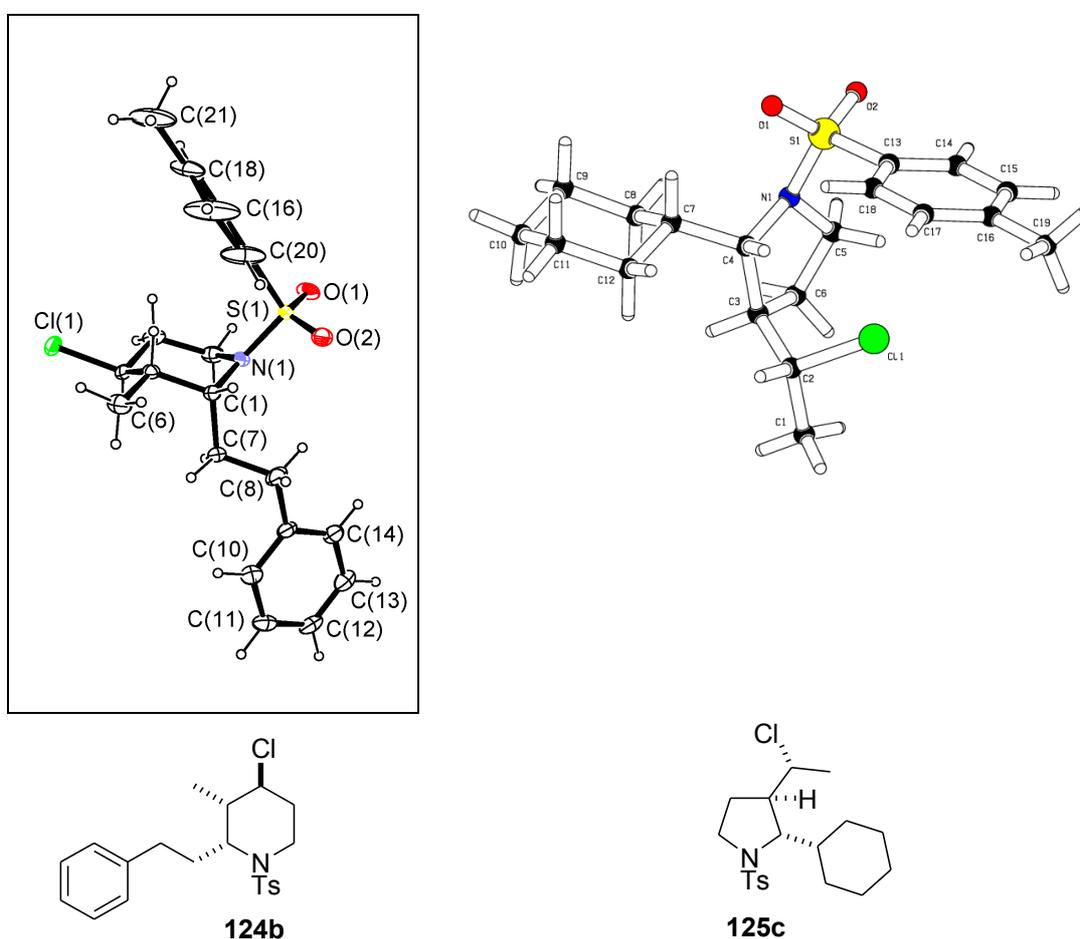


Figure 9. X-ray structure of 4-chloro-2-phenethyl-3-methyl-1-tosylpiperidine and 3-(1-chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine.

Again, for both heterocycles, the axial conformation of the C2 substituent is shown, a result of the intermediate (*E*)-iminium ion. For the 4-chloropiperidine **124b** derivative the C3 methyl group adopts an equatorial position, a result from the geometry of the double

bond of the (*E*)-amine precursor. The equatorial chlorine in the C4 position is a result of attack on the intermediate carbocation from the least hindered face. The only difference for the pyrrolidine product **125c** is that the third stereocentre is the opposite configuration to that observed in examples taken from the (*Z*)-amine precursor **116**. This could be a result of the geometry of the olefin in the starting material. Interestingly, it was also observed in these X-ray structures that the *N*-tosyl group is *endo* over the ring in both cases, consistent with observations by Martin and Padron (Figure 9).

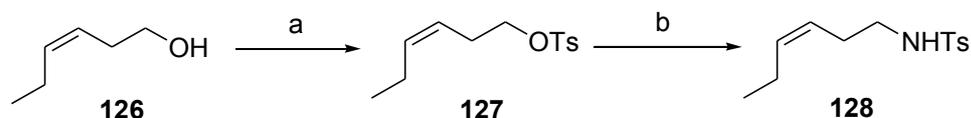
There are a few comparisons that can be drawn when comparing the aza-Prins reaction mediated by indium trichloride or iron(III) halides. Firstly, it would appear that the iron(III) halides are better promoters of these cyclisations, with regards to the much shorter reaction times and the greater yields of product. This however must be taken into context as different amine precursors were used. Conversely, perhaps the use of indium trichloride has allowed us to witness the formation of the 5-membered pyrrolidines.

## . 6Studies into the Regiochemistry of the Aza-Prins

### Reaction

#### . aPrecursor Synthesis for the Aza-Prins Reaction III

Here, an attempt will be made to support the observation that the formation of pyrrolidines from the indium trichloride-mediated aza-Prins reaction was reliant on disfavoured pseudo 1,3-diaxial interactions in the chair transition state. It was planned to achieve this by increasing the chain length of the external (*Z*)-olefin associated group from methyl to ethyl, so (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide **128** was prepared in two steps from commercially available (*Z*)-hex-3-en-1-ol **126** (Scheme 37).



**Scheme 37. Reagents and conditions:** (a) TsCl, DMAP, Et<sub>3</sub>N, DCM, 0 °C, 20 h, 84%; (d) NaI, *p*-TsNH<sub>2</sub>, KOH, DMSO, 50 °C, 17 h, 62%.

(*Z*)-Hex-3-en-1-ol **126** was treated with tosyl chloride to give the tosylate **127** in 84% yield using previous methods. The sodium iodide-catalysed amination procedure was used to generate the (*Z*)-homoallylic tosylamine **128** in 62% yield on treatment of the tosylate **127** with 4-methylbenzenesulfonamide. The yield of this substitution reaction was disappointing in comparison to the previous examples although it was performed on a 26 mmol scale instead of 4 mmol. To confirm that the geometry of the double bond was

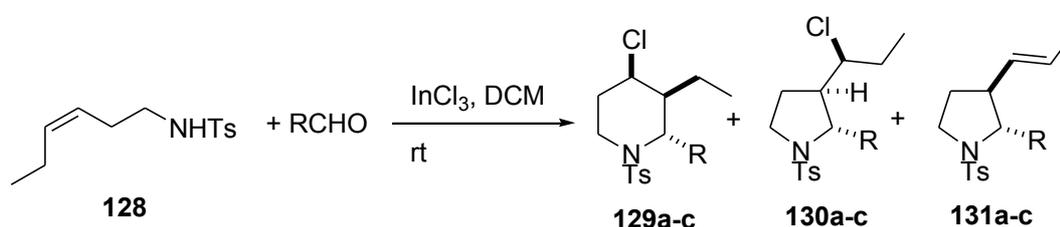
retained from the commercially available starting material, NOESY experiments were completed on the (*Z*)-homoallylic tosylamine **128**. A 1.4 and 2.7% enhancements between the two olefinic hydrogens on irradiation of each, confirmed the *cis* geometry.

### . b Aza-Prins Cyclisations: Effects of (*Z*)-

#### Homoallyl Amine II.

With the (*Z*)-homoallylic tosylamine in hand, the indium trichloride-mediated aza-Prins reaction was performed with the three aliphatic aldehydes that gave a mixture of six and five-membered products on reaction with (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116** (Table 21).

Table 21. Further aza-Prins reactions of (*Z*)-homoallyl tosylamines.



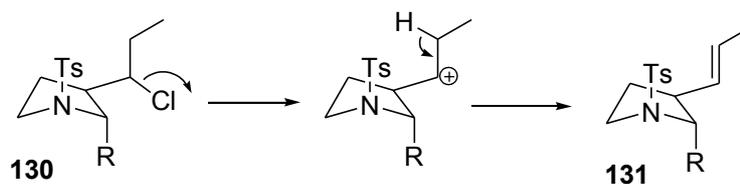
Entry	R	Time(h)	%Yield of <b>129a-c</b>	%Yield of <b>130a-c</b>	%Yield of <b>131a-c</b>	Ratio 6:5*	Ratio 6:5 <sup>#</sup>
1	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	17	34 (a)	43 (a)	7 (a)	17:25	1:1
2	(CH <sub>2</sub> ) <sub>2</sub> Ph	17	31 (b)	49 (b)	10 (b)	31:59	10:9
3	<i>c</i> -Hex	72	14 (c)	62 (c)	10 (c)	7:36	13:25

\*= ratio of 6-membered product to 5 membered product, includes 5 membered eliminated product.

# = previous example using (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116**.

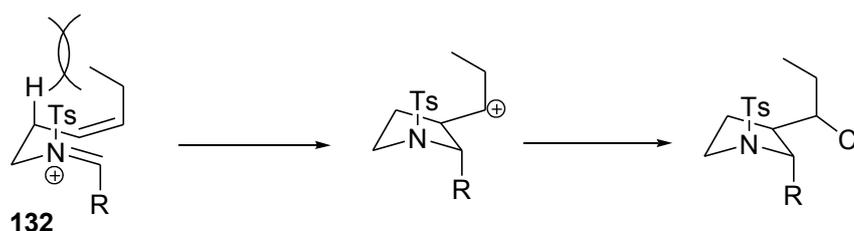
Each aliphatic aldehyde gave a mixture of 4-chloropiperidine **129**, 3-(1-chloropropyl)pyrrolidine **130** and a previously not observed, eliminated pyrrolidine **131**. The total yield for cyclised material in each case increased on comparison to the reactions performed with (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116**. Again the reactions performed with octanal or hydrocinnamaldehyde (Table 21, entries 1-2) led to the amine substrate being consumed within a day. Also as before, longer reaction times were observed on use of cyclohexanecarboxaldehyde (Table 21, entry 3). However the reaction of this tosylamine substrate with the cyclic aliphatic aldehyde was completed in a significantly shorter time compared to the use of (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116**. The first major difference to be observed in these examples was the formation of an unsaturated pyrrolidine **131**, which was assumed to be a reaction by-product of the 3-(1-chloropropyl)pyrrolidine **130**. It was assumed that the 3-

(1-chloropropyl)pyrrolidine **130** underwent an E1 elimination, based on the fact there was an absence of a strong base as found in E2 eliminations (Scheme 38).



**Scheme 38.** E1 elimination of 3-(1-chloropropyl)pyrrolidine.

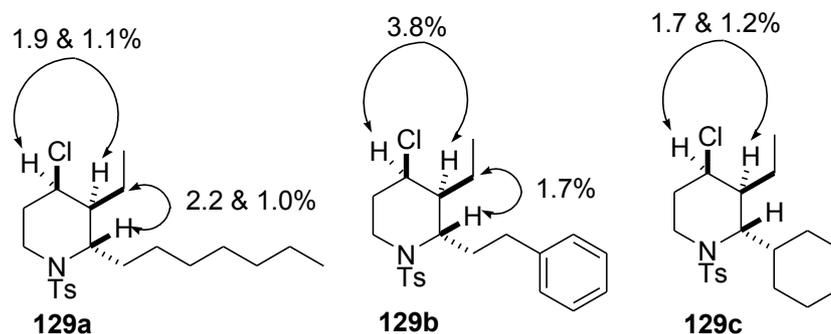
In each case the eliminated species **131** was a minor reaction product and was inseparable from the 4-chloropiperidine **129** by chromatography. Only in the example using cyclohexanecarboxaldehyde (Table 21, entry 3) was this species accurately characterised by  $^1\text{H}$  NMR. It is clear from this study that the quantity of 5-membered product was enhanced compared to the six membered product, a result of the chain elongation. It was assumed that the disfavoured pseudo 1,3-diaxial interactions in the chair intermediate **132** were more prominent with the ethyl group and so the increased yield of 5-membered product was observed (Scheme 39). The reactions performed with octanal or hydrocinnamaldehyde with the methyl substituent (Table 21, entries 1-2) produced a ratio of 1:1 for six membered to five membered products. However using the ethyl substituent improves the ratio to approximately 3:5 for octanal and 1:2 for hydrocinnamaldehyde. The biggest enhancement in pyrrolidine production was on use of cyclohexanecarboxaldehyde where the ratio improves from approximately 1:2 to 1:6.



**Scheme 39.** Enhancement of disfavoured pseudo 1,3-diaxial interactions by chain elongation.

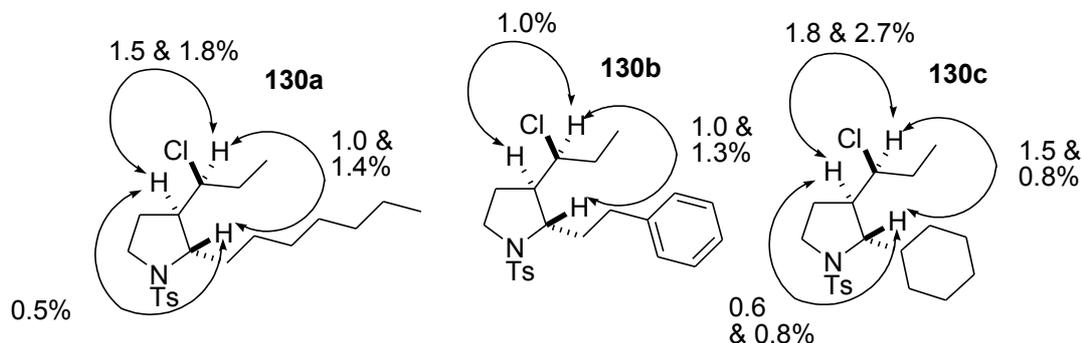
The relative stereochemistry of the 4-chloropiperidine **129** and the 3-(1-chloropropyl)pyrrolidine products **130** was confirmed by NOESY experiments. This relative stereochemistry was the same as observed on use of the (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide precursor **116**. In the 4-chloro-2-substituted-3-ethyl-1-tosylpiperidine **129b** derived from the use of hydrocinnamaldehyde (Table 21, entry 2), the relationship between the substituents at C2 and C3 is *trans*. This was supported by the 1.7% enhancement of the C3 methylene hydrogens on irradiation of the C2 hydrogen. The relationship between the C3 and C4 substituents in the same piperidine was *cis*, proven by

the 3.8% enhancement of the C3 hydrogen on irradiation of the C4 hydrogen. Similar nOe effects were observed for the other 4-chloropiperidines **129a-c** (Figure 10).



**Figure 10.** The nOe of 2,3,4-trisubstituted piperidines.

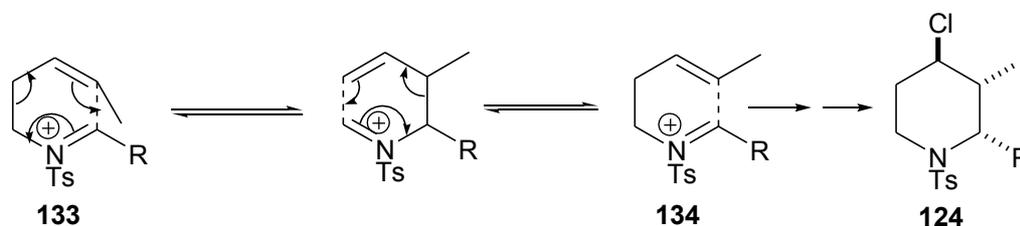
In the 3-(1-chloropropyl)pyrrolidine **130a**, derived from octanal, the relationship between C2 and C3 substituents was *trans* in keeping with previous examples. This relationship was proven by the small 0.5% enhancement of the C3 hydrogen on irradiation of the C2 hydrogen. This was further supported by the 1.0 and 1.4% enhancements between the C2 hydrogen and the hydrogen on the third stereocentre, on irradiation of each (Figure 11). It is difficult to comment on the configuration of the third stereocentre based on nOe effects.



**Figure 11.** The nOe of 2,4-disubstituted pyrrolidines.

It is believed that since the stereochemistry of the 4-chloropiperidine is exclusive and no trace of other stereoisomers was found, little or no aza-Cope [3,3] sigmatropic rearrangement occurs in these aza-Prins reactions. This is in contrast to the aza-silyl-Prins reaction where evidence of this rearrangement was found when a silylated (*E*)-homoallylic amine **16** was isolated from the (*Z*)-starting material. Initially in these reactions, a silylated (*Z*)-homoallylic amine was coupled to a Lewis acid activated aldehyde to form an iminium-vinylsilane intermediate. This intermediate can undergo a [3,3] sigmatropic rearrangement and so the geometry of the vinylsilane is lost. When the retro-[3,3] sigmatropic rearrangement occurs, the more stable (*E*)-vinylsilane is likely to be formed, and the subsequent reverse reactions lead to the silylated (*E*)-homoallylic

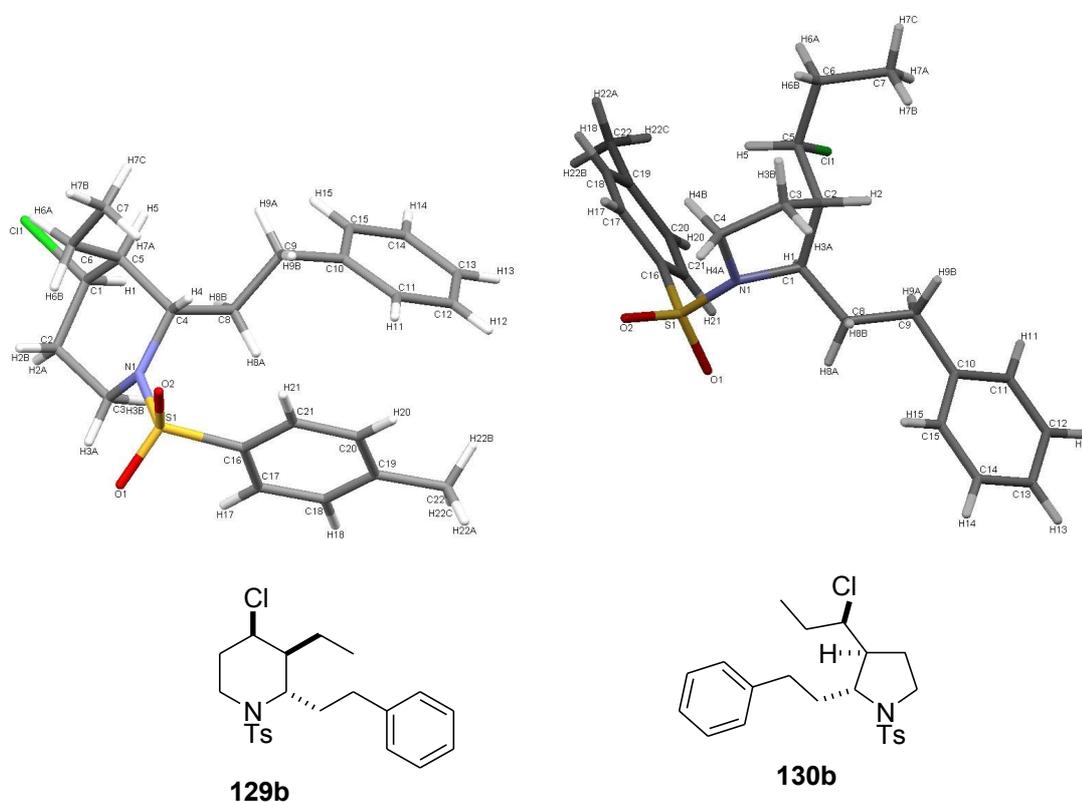
amine. If this explanation is applied to this example of the aza-Prins reaction, then the (*Z*) geometry of the iminium ion-olefin intermediate **133** could be altered to the (*E*) form **134** via the rearrangement. If this were the case, it would be expected to observe a stereochemistry in the piperidine product **135** comparable with the examples involving an (*E*)-homoallylic tosylamine **117** (Scheme 40).



**Scheme 40.** The aza-Cope rearrangement in the aza-Prins reaction, not observed.

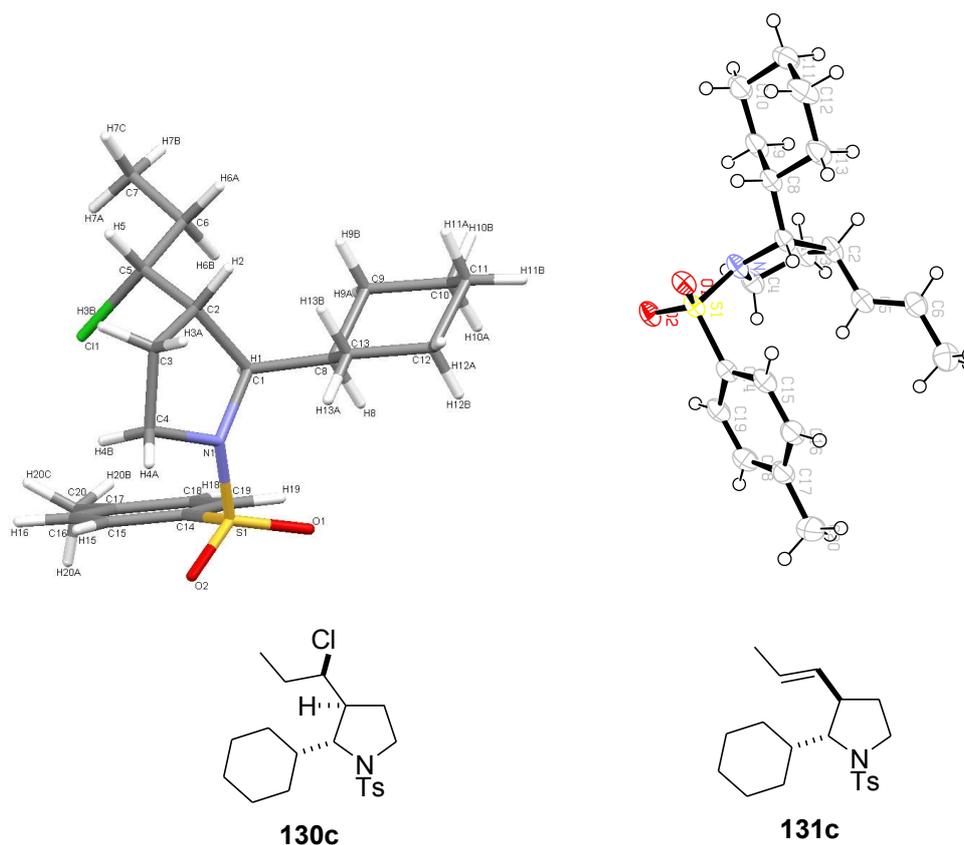
Previously it has been observed that aza-Cope rearrangement does occur in the aza-Prins reaction based on the recovery of an aza-Cope hydrolysis product **94** (Table 14, entry 4-5). It is assumed that in the examples involving homoallyl tosylamines, the cyclisation occurs rapidly and so little or no aza-Cope rearrangement can occur.

The configuration of 4-chloro-3-ethyl-2-phenethyl-1-tosylpiperidine **129b** and its 5-membered counterpart, 3-(1-chloropropyl)-2-phenethyl-1-tosylpyrrolidine **130b** were proven on analysis of the X-ray crystallographic data (Figure 12).



**Figure 12.** X-ray structure of 4-chloro-3-ethyl-2-phenethyl-1-tosylpiperidine and 3-(1-chloropropyl)-2-phenethyl-1-tosylpyrrolidine.

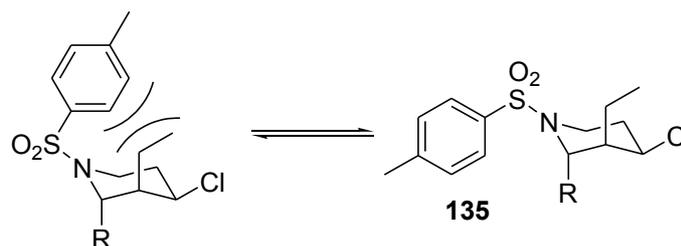
The configuration of products derived from the reaction with cyclohexanecarboxaldehyde (Table 21, entry 3) is also obtained from the X-ray data. These are the structures of the 5-membered 3-(1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine **130c** and also the eliminated by-product, 2-cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine **131c** (Figure 13).



**Figure 13.** X-ray structure of 3-(1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine and 2-cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine.

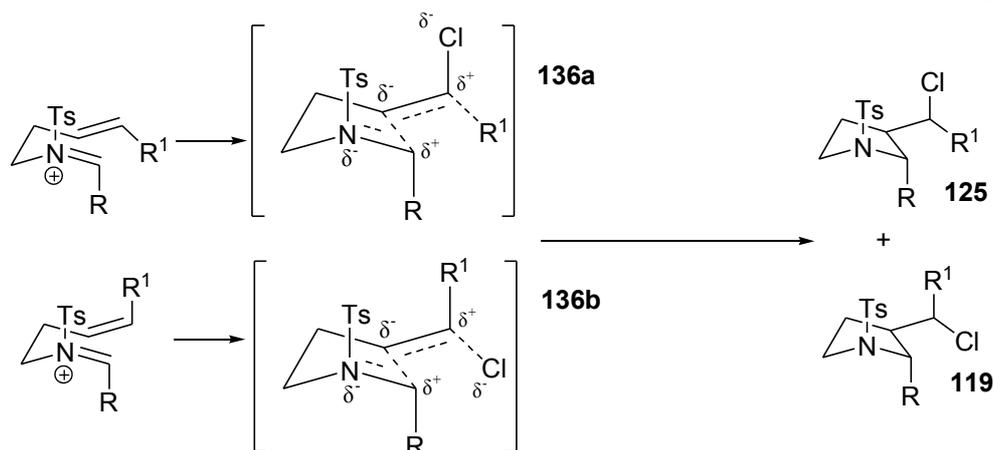
Once again, the C2 substituents adopt an axial conformation, a result of the intermediate (*E*)-iminium ion. In the 4-chloro-3-ethyl-2-phenethyl-1-tosylpiperidine structure **129b**, the axial conformation of the C3 ethyl group and also the *trans* relationship between itself and the C2 substituent can be seen. This is in contrast to the *cis* geometry witnessed between C2 and C3 in the same product **124b** derived from the (*E*)-homoallyl tosylamine **117**, highlighting the effect of the geometry of the double bond in the starting material. This X-ray analysis supports the stereochemical assignments previously made from NOESY experiments. The 4-chloro group adopts an equatorial conformation, a result of trapping the intermediate carbocation from the least hindered face. The most surprising

observation from this X-ray crystal structure is that the *N*-tosyl group does not adopt an *endo* conformation over the piperidine ring as in other examples (Figure 12).



**Scheme 41.** Steric effects between *N*-tosyl and C3 substituent.

It is assumed that this is due to the steric hindrance caused by the axial C3 ethyl group, which means that the *N*-tosyl group instead faces away from the piperidine ring **135** (Scheme 41). In all three pyrrolidines **130b-c** and **131c**, the *trans* relationship between the C2 and C3 substituents is highlighted by an axial C2 group and an axial C3 group (Figures 12 and 13). In both pyrrolidines that contain a 1-chloropropyl group **130b-c**, the chlorine in the third stereocentre is introduced to same vertical face as the large C2 substituent. This is in keeping with the previous examples **119a,c,d** derived from the (*Z*)-homoallyl tosylamine **116** and in contrast to the example **125c** derived from the (*E*)-homoallyl tosylamine **117**, which is incorporated from the opposite face. It is felt that this supports the observation that the geometry of the double bond in the precursor has an effect on this third stereocentre. It is hypothesised that the chlorine attacks at the point of cyclisation and so can be included in a proposed transition state **136a-b** (Scheme 42).

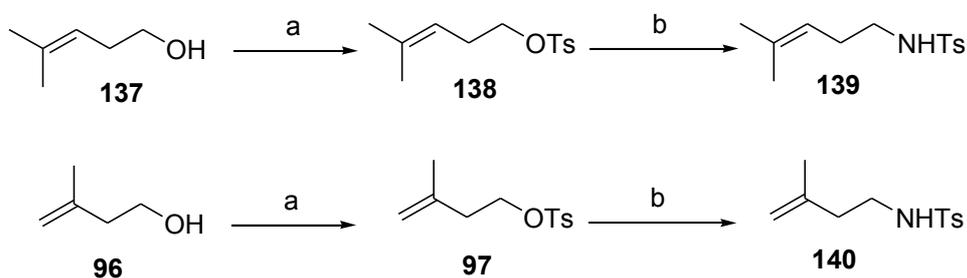


Scheme 42. Proposed transition states for 3-(1-chloropropyl)-2-substituted-1-tosylpyrrolidine formation.

### . 7 Further Substituent Effects in the Aza-Prins Reaction

#### . a Precursor Synthesis for the Aza-Prins Reaction

Based on the regiochemical outcome of the indium trichloride-mediated aza-Prins reaction when altering the olefin geometry, the effects of other substituents were studied, for example, using a tri-substituted double bond. Therefore 4-methyl-*N*-(4-methylpent-3-enyl)benzenesulfonamide **139** was prepared in two steps, starting from commercially available 4-methylpent-3-en-1-ol **137**. For completeness, 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide **140** was also synthesised from commercially available 3-methylbut-3-en-1-ol **96** in two steps (Scheme 43).



Scheme 43. Reagents and conditions: (a) TsCl, DMAP, Et<sub>3</sub>N, DCM, 0 °C, 17 h & 48 h, 99% & 75%; (d) NaI, *p*-TsNH<sub>2</sub>, KOH, DMSO, 50 °C, 20 h & 18 h, 50% & 68%.

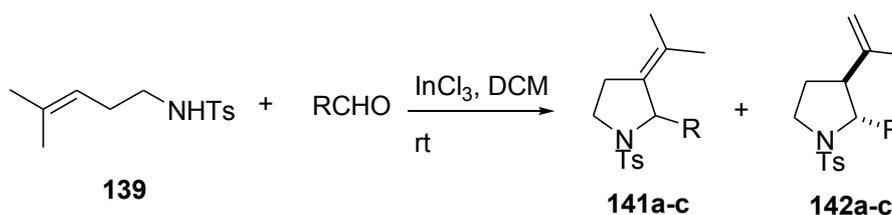
The tosylate derivatives were obtained by the action of tosyl chloride on the commercially available alcohols **137** and **96**. Each tosylate was prepared in excellent yield, 99% for **138** and 75% for **97**. Each tosylate was submitted to the sodium iodide-catalysed amination

conditions as used previously to give moderate yields of the homoallylic tosylamines; 50% for **139** and 68% for **140**.

### . b Aza-Prins Cyclisations: Effects of Trisubstituted olefins.

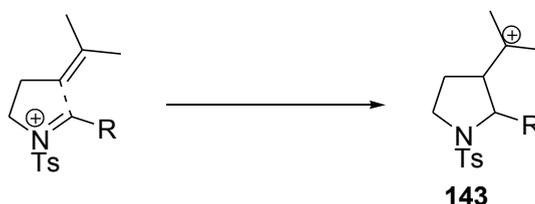
With the precursor **139** containing a tri-substituted double bond now available, the indium trichloride mediated aza-Prins reactions were performed on three aliphatic aldehydes. Surprisingly only two of these produced positive results (Table 22).

Table 22. Further aza-Prins reactions involving tri-substituted olefin.



Entry	R	Time (h)	%Yield of 141 and 142	Ratio
1	(CH <sub>2</sub> ) <sub>2</sub> Ph	6	75 (a)	52:48
2	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	6	60 (b)	58:42
3	<i>c</i> -Hex	144	Trace (c)	50:50

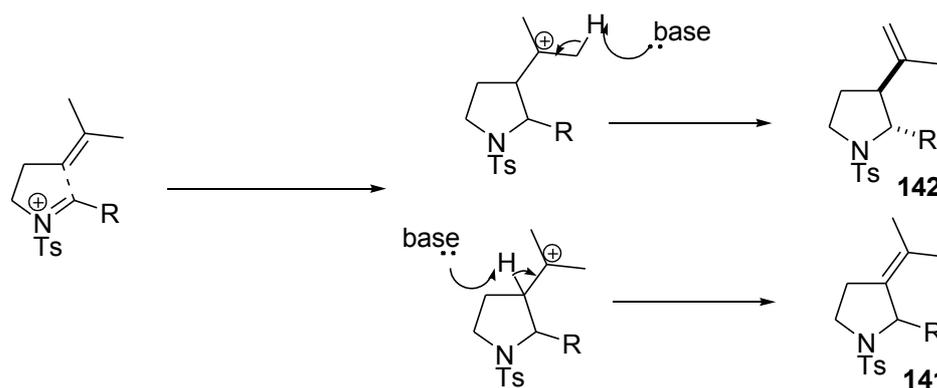
In each reaction, the tosylamine precursor was consumed and produced a mixture of pyrrolidine isomers **141** and **142**, which were inseparable by flash column chromatography. As in previous examples, the use of hydrocinnamaldehyde and octanal (Table 22, entry 1-2) produced good yields in short reaction times. The reaction times for these two aldehydes have been cut significantly on comparison to previous examples. It was assumed that the production of an intermediate tertiary carbocation **143** drives these reactions (Scheme 44).



Scheme 44. Formation of stable tertiary carbo cation.

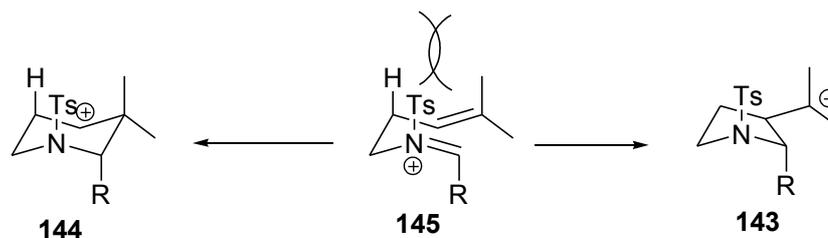
However, on use of cyclohexanecarboxaldehyde, only trace quantities of cyclised pyrrolidine were identified on analysis of the GCMS and <sup>1</sup>H NMR data (Table 22, entry 3). Even though the reaction eventually went to completion, the majority of the product was unidentifiable material, both before and after flash column chromatography.

Interestingly, the product ratio of olefinic regioisomers was close to 1:1 in all cases and this ratio was maintained after chromatography. This is somewhat surprising, as the more substituted olefinic product **141** would be expected to be a major product. It was suggested that the olefinic products were formed directly from elimination of the intermediate tertiary carbocation **143** and not from a chlorinated product, since no evidence for the presence of these products was observed. It seems that the reasoning for the mixture of regioisomers is based on steric effects and stability of reaction intermediates. Even though the fully substituted double bond would probably be the most stable product **141**, any base-catalysed elimination is more sterically viable from the unsubstituted position (Scheme 45). The competition between these pathways at room temperature leads to approximately a 1:1 mixture. Since it was assumed that this is an E1 elimination process, a strong base is not required. Another hypothesis could be that the  $sp^2$  centre of the fully substituted double bond **141** produces ring strain in the pyrrolidine core.



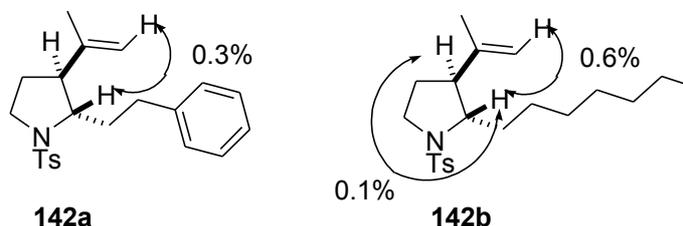
**Scheme 45.** Steric and stability effects in E1 elimination.

The next question to be answered is why 5-membered pyrrolidines are formed exclusively and not 6-membered piperidines. The explanation could be based upon the formation of a more stable tertiary carbocation **143** in a 5-membered intermediate against the formation of a less stable secondary carbocation in a 6-membered intermediate **144**. It is also presumed that since a tri-substituted double bond was used, the disfavoured pseudo 1,3-diaxial interactions in the chair transition state **145** are present leading to the 5-membered product (Scheme 46).



**Scheme 46. Stability effects in carbocations.**

The relative stereochemistry of the 2-substituted-3-(prop-1-en-2-yl)-1-tosylpyrrolidines **142a-b** was suggested by NOESY experiments. This suggestion was not entirely accurate however, because of overlapping signals in the  $^1\text{H}$  NMR spectrum. The configuration of these products could not be confirmed since no X-ray crystallographic data could be obtained. It was assumed that the relationship between the C2 and C3 substituents in the pyrrolidine products **142a-b** was *trans*, based on previous examples. Only small nOe effects could be obtained and so this cannot accurately describe the relative configuration. However for the pyrrolidine **142b** obtained from octanal, the *trans* relationship could be supported based on the small 0.1% enhancement of the C2 hydrogen on irradiation of the C3 hydrogen. This is further supported by the 0.6% enhancement of one of the olefinic hydrogens on irradiation of the C2 hydrogen (Figure 14).



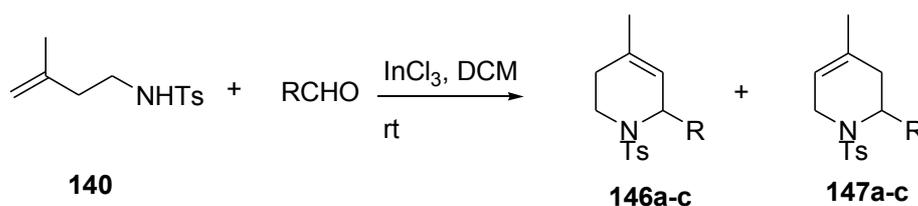
**Figure 14. The nOe in 2-substituted-3-(prop-1-en-2-yl)-1-tosylpyrrolidines.**

### . c Aza-Prins Cyclisations: Effects of

#### Other Olefins

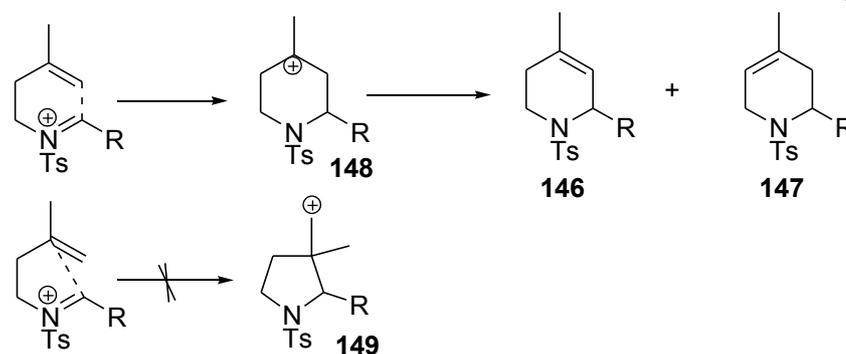
Now it was decided to perform indium trichloride-mediated aza-Prins reactions between two aliphatic aldehydes, ethyl glyoxylate and a homoallylic tosylamine **140** containing an external olefin. It was proposed that the positioning of this methyl group in the amine precursor would have a major affect on the stability of the intermediate carbocation and so possibly on the regiochemical outcome of the reaction (Table 23).

Table 23. Further aza-Prins reactions involving di-substituted olefin.



Entry	R	Time(h)	%Yield of 146 and 147	Ratio
1	(CH <sub>2</sub> ) <sub>2</sub> Ph	2	90 (a)	53:47
2	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	2	73 (b)	53:47
3	CO <sub>2</sub> Et	1	0 (c)	N/A

On use of the two aliphatic aldehydes (Table 23, entry 1-2), a mixture of regioisomers (**146** and **147**) of 4-methyltetrahydropyridine was formed, which was inseparable by flash column chromatography. The ratio of regioisomers was determined by analysing the integration of olefinic protons in the <sup>1</sup>H NMR spectrum. The separation problem is highlighted by the fact that the gas chromatograph showed only one peak. Unfortunately when using ethyl glyoxylate, no products could be identified, although the amine substrate was consumed. Again use of the aliphatic aldehydes, octanal and hydrocinnamaldehyde, have produced good yields of cyclised material and short reaction times (Table 23, entry 1-2). For these two aldehydes, this is the shortest time recorded for an indium trichloride mediated aza-Prins reaction. The ratio of regioisomers was approximately 1:1 in each case and this ratio was maintained after flash column chromatography. Again no traces of chlorinated species were identified by GCMS or <sup>1</sup>H NMR analysis. It was assumed that the formation of a stable tri-substituted double bond formed *via* elimination from the intermediate tertiary carbocation **148** is more rapid than the trapping by chloride anions. The formation of this tertiary carbocation can also explain the regiochemical outcome of the reaction. The stability of this carbocation is much greater than a primary carbocation **149** that would be present if a five-membered intermediate had been produced (Scheme 47).



**Scheme 47. Stability of tertiary carbo-cation.**

The success found on use of 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide **140** is unsurprising. This is based on the fact that the comparable *N*-benzyl substituted precursor **98** screened in the initial studies (Scheme 27) was the only amine to produce positive results. Following this study our initial GCMS and <sup>1</sup>H NMR data was reviewed so as to identify any tetrahydropyridine products formed on use of the *N*-benzyl precursor. However, no positive results were identified and so it would seem that the *N*-tosyl group has a significant effect on the success of the aza-Prins reaction. It would seem that indium trichloride has less success on promoting the aza-Prins reaction in comparison with iron(III) halides with regards to yields and reaction times. However the mild nature of indium trichloride does have benefits with regards to handling. Also, perhaps the effect on reaction rates on use of this Lewis acid could affect the regiochemical outcome of the aza-Prins reaction.

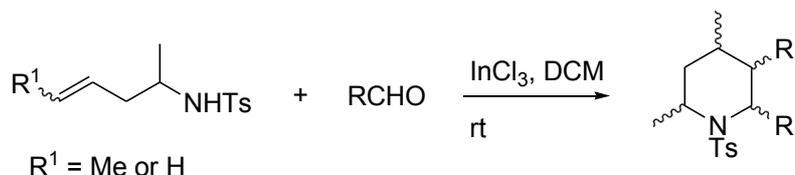
## . 8Effects of the C1 Position in Homoallyl

### Amines

#### . aPrecursor Synthesis for the Aza-Prins

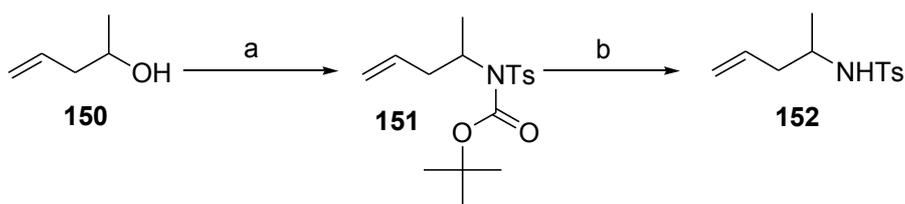
### Reaction V

It is important to be able to utilise the aza-Prins reaction to form heterocycles substituted in all possible ring positions. With this in mind, it was proposed to synthesise homoallylic tosylamines that contained a C1 methyl group in order to functionalise the C6 position in the target piperidines (Scheme 47).



**Scheme 47.** Proposed scheme for aza-Prins reaction of C1 substituted tosylamines.

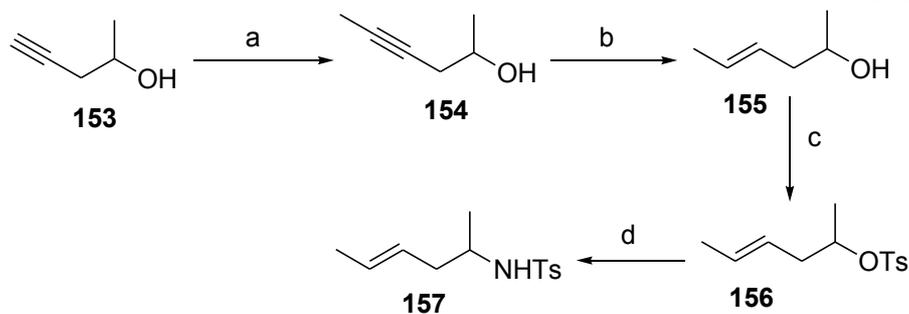
In the past, utilising this position has allowed us to explore the diastereoselectivity of the silyl-Prins and aza-silyl-Prins reaction across the heteroatom in the formed heterocycle. In studies on the aza-silyl-Prins reaction it was shown that the 2,6-disubstituted tetrahydropyridines formed had exclusive *trans* geometry across the heteroatom. It has been proposed in previous work that the large *N*-substituent contributes to a steric effect known as A<sup>1,3</sup> strain. It was believed that the same effect would be present in examples of the aza-Prins reaction where methyl substituted tosylamines are utilised. Firstly synthesised was 4-methyl-*N*-(pent-4-en-2-yl)benzenesulfonamide **152** in two steps from the commercially available pent-4-en-2-ol **150** (Scheme 48).



**Scheme 48.** Reagents and conditions: (a) *N*-Boc-TsNH, PPh<sub>3</sub>, DIAD, THF, rt, 17h, 69%. (b) TFA, DCM, rt, 17h, quantitative.

Attempts to obtain this tosylamine *via* the sodium iodide-catalysed amination methodology were unsuccessful. Success was found following a literature procedure for two steps. Firstly pent-4-en-2-ol **150** was treated with *t*-butyl tosylcarbamate under Mitsunobu conditions to form the homoallylic tertiary amine **151** in 69% yield. The carbamate function was then cleaved by the action of TFA in DCM to give the required homoallylic tosylamine **152** in quantitative yield.

To explore once again the regioselectivity of the aza-Prins reaction and introduce multiple substituents into the cyclised products, it was attempted to synthesise tosylamines with internal olefins and a C1 methyl group. Therefore (*E*)-*N*-(hex-4-en-2-yl)-4-methylbenzenesulfonamide **157** was synthesised in 4 steps from commercially available pent-4-en-2-ol **153** (Scheme 49). The synthesis of the corresponding (*Z*)-*N*-(hex-4-en-2-yl)-4-methylbenzenesulfonamide was unsuccessful.



**Scheme 49.** *Reagents and conditions:* (a) *n*-BuLi, MeI, THF, -78 °C to rt, 53%. (b) LAH, triglyme, THF, 85 °C, 60%. (c) TsCl, Et<sub>3</sub>N, DMAP, 0 °C, 40 h, 25%. (d) TsNH<sub>2</sub>, KOH, NaI, DMSO, 50 °C, 20 h, 31%.

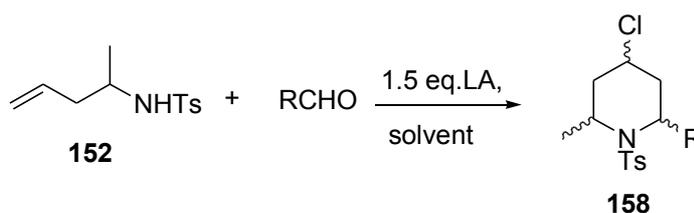
To synthesise the appropriate (*E*)-olefin, the alkyne methylation of pent-4-yn-2-ol **153** was required. Deprotonation of the alkyne hydrogen with *n*-butyllithium followed by treatment with iodomethane gave the methyl substituted alkyne **154** in a disappointing 53% yield. To access the (*E*)-homoallylic alcohol, the alkyne **154** was treated with LAH in a mixture of triglyme and THF to give the required geometric isomer **155** in 60% yield. The alcohol was fully characterised as its tosyl activated alcohol **156** because even after distillation, it remains a mixture with triglyme. The homoallylic alcohol was transformed into the tosyl activated alcohol by the action of tosyl chloride in the presence of triethylamine and 4-dimethylaminopyridine to give (*E*)-hex-4-en-2-yl 4-methylbenzenesulfonate **156** in 25% yield. As in previous examples, this tosylate **156** underwent sodium iodide catalysed amination to give the required (*E*)-homoallylic tosylamine **157** in 31% yield.

#### . bAza-Prins Cyclisations: Effects of the C1 Position in

##### Homoallyl Amines

Next, aza-Prins reactions with 4-methyl-*N*-(pent-4-en-2-yl)benzenesulfonamide **152** were attempted with an aim to synthesise 2,4,6-trisubstituted piperidines **158**. Various different aldehydes were screened, with various temperatures, solvents and Lewis acid being employed, but unfortunately, no positive results were found for generation of cyclised material (Table 24).

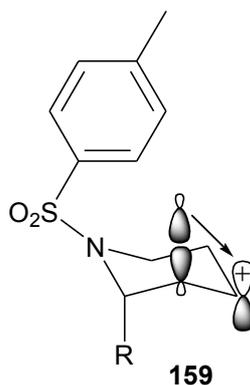
Table 24. The aza-Prins reactions involving a C1 substituted tosylamine.



Entry	R	LA	solvent	Temp.	Time	Comment
1	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	InCl <sub>3</sub>	DCM	Rt and reflux	48 h, then 24 h reflux	No reaction, SM remained
2	(CH <sub>2</sub> ) <sub>2</sub> Ph					
3	<i>c</i> -Hex					
4	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	TMSOTf		Rt	48 h	“ “
				Rt	48 h	“ “
5	(CH <sub>2</sub> ) <sub>2</sub> Ph	InCl <sub>3</sub>	CH <sub>3</sub> CN	Rt and reflux	48 h, then 72 h reflux	“ “
6	(CH <sub>2</sub> ) <sub>2</sub> Ph	FeCl <sub>3</sub> anhydrous	DCM	Rt	70 h	90% SM consumed, product trace

When the three aliphatic aldehydes that had brought the most success in previous examples were screened in the presence of indium trichloride and DCM at room temperature, no reaction was observed (Table 24, entry 1-3). Even when more forcing conditions were attempted with DCM at reflux, still only starting material remained. Also when trimethylsilyl triflate was screened in comparative conditions, again the results were negative. When the solvent was altered for the higher boiling acetonitrile and reflux conditions attempted, still only starting material remained and no trace of any type of cyclised product was observed. Finally it was decided to screen iron(III) chloride and after 70 hours at room temperature, most of the starting material was consumed. However, only trace quantities of product were detected on analysis by GCMS and the rest of the crude mass was unidentifiable. It is highly disappointing that no success was found when this C1 methyl substituted tosylamine was screened as this potentially limits the use of the aza-Prins reaction in other fields such as pharmaceuticals.

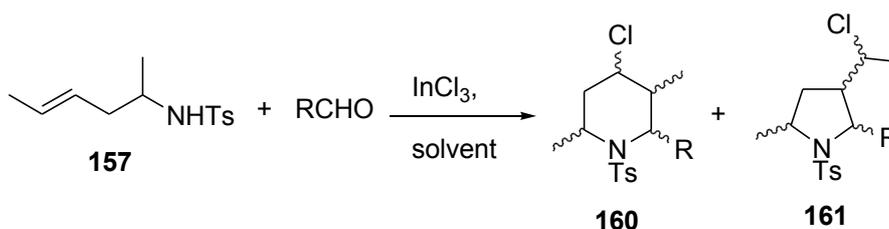
Next to be attempted were aza-Prins reactions with (*E*)-*N*-(hex-4-en-2-yl)-4-methylbenzenesulfonamide **157**. Even though it appears that the C1 methyl group hinders these cyclisation reactions, it was hoped that the internal olefin function would enhance the stability of reaction intermediates. If the six-membered carbocation intermediate **159** is considered, then the adjacent methyl substituent would enhance the stability of the adjacent empty p-orbital *via* hyperconjugation and so promote the cyclisation step (Figure 15).



**Figure 15. Stabilisation of intermediate carbo cation by hyperconjugation.**

This is comparable with the  $\beta$ -effect of silicon where there is sufficient overlap between the empty p-orbital and the polarised carbon-silicon  $\sigma$ -orbital to stabilise the intermediate. Our screening studies included alterations in temperature and solvents but no positive results for generation of cyclised material **160** and **161** were observed (Table 25).

**Table 25. The aza-Prins reactions involving C1 substituted tosylamine and other substituents.**



Entry	R	Solvent	Temp.	Time	Comment
1	(CH <sub>2</sub> ) <sub>2</sub> Ph	DCM	Rt and reflux	72 h, then 72 h reflux	No reaction, SM remained
2	(CH <sub>2</sub> ) <sub>2</sub> Ph	DCM	Rt and reflux	24 h, then 24 h reflux	No reaction, SM remained
3	(CH <sub>2</sub> ) <sub>2</sub> Ph	CH <sub>3</sub> CN	Reflux	72 h	No reaction, SM remained

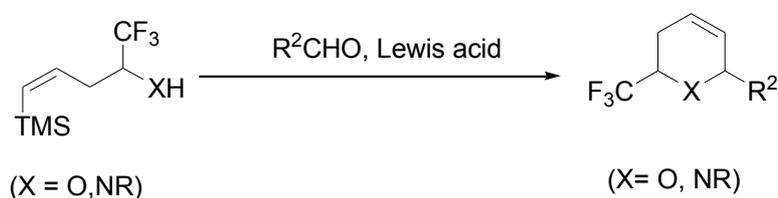
When the standard conditions of indium trichloride and DCM at room temperature were applied to the (*E*)-isomer **157** and hydrocinnamaldehyde (Table 25, entry 1-2), no progress was observed. When a more forcing reflux temperature was adopted, still only starting material remained (Table 25, entry 1-2). Even when the higher boiling acetonitrile was used at reflux, no positive results were obtained (Table 25, entry 3). It would seem that again the issues surrounding the C1 methyl group of the tosylamine substrate are responsible for the failure of these cyclisation reactions. Even the additional stabilisation that was proposed to be present adjacent to the carbocation intermediate has not aided the progress of the reaction. The failure of the C1 methyl substituted tosylamines has been unfortunate as it limits the use of the aza-Prins reaction in other fields such as

pharmaceuticals. However, heterocycles with fewer substituents are accessible using an aza-Prins reaction mediated by either iron(III) halides or indium trichloride. The use of indium trichloride has identified alternative regioselective routes for this reaction, meaning that pyrrolidines as well as piperidines are accessible.

**CHAPTER THREE: Formation of 6-Trifluoromethyl-3,4-dihydropyrans and 6-Trifluoromethyl-3,4-tetrahydropyridines**

### . II literature Review for Formation of Trifluoromethyl Containing Heterocycles.

With a previous member of the Dobbs group having optimised silyl-Prins methodology in order to obtain simple heterocycles, now desired was the incorporation of a trifluoromethyl substituent, to possibly enhance the biological interest in these studies. The substrates that were required for the silyl-Prins and aza-silyl-Prins reactions were silylated homoallylic alcohols and silylated *N*-protected homoallylic amines respectively. It has been shown that it is possible to form 2,6-disubstituted heterocycles by incorporation of a substituent at C1 in the amine or its alcohol precursor. It occurred to the Dobbs group that it may be possible to introduce a trifluoromethyl group in the C6 position of the heterocycle with the silyl-Prins and aza-silyl-Prins reactions by introducing this group adjacent to the hydroxyl or secondary amine function (Scheme 49).



**Scheme 49.** Proposed scheme for silyl-Prins cyclisations with 2-trifluoromethyl substituted substrates.

Mechanistically, both cyclisations involve attack by the oxygen or nitrogen of each substrate on a Lewis acid-activated aldehyde. If a highly electron withdrawing group is introduced on the adjacent carbon, then the nucleophilicity of the heteroatom will presumably be reduced, thus affecting the kinetics of the reaction. These electronic effects may in turn also have an effect on synthesis of the precursor molecules. The following review cites examples of success in forming trifluoromethyl containing heterocycles as well as the appropriate substrates.

### . 9 Literature Examples of Formation of Fluorinated

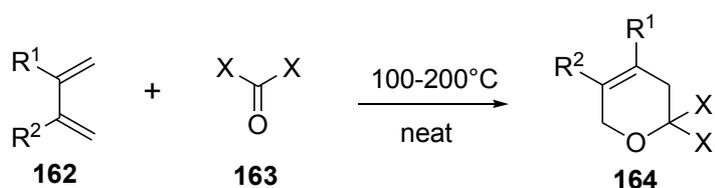
#### Oxacycles

The following review describes the synthesis of 6-trifluoromethyl-3,4-dihydropyrans and their precursors previously reported in the literature.

An early article by Linn describes the use of acyclic fluoroketones in the hetero Diels-Alder reaction. At the time, the use of carbonyl compounds in the Diels-Alder reaction was limited, although examples did include the reaction of formaldehyde with 2-methyl-1,3-pentadiene at 185 °C. The same aldehyde did not however produce a Diels-Alder adduct on reaction with butadiene, although there were examples of extremely labile hexafluorocyclobutanone reacting at 0 °C. Linn describes the successful addition of

acyclic fluoro-ketones **163** such as hexafluoroacetone, decafluoro-3-pentanone and 1,3-dichlorotetrafluoroacetone to dienes **162**, such as butadiene, isoprene and 2,3-dimethylbutadiene. These reactions were performed at 100-200 °C without any solvent and produced dihydropyran products in good yields (Table 26). Although the Diels-Alder adducts **164** from these reactions contain additional fluorinated substituents to those dihydropyrans targeted, it does show that these types of compounds may be synthesised and isolated.

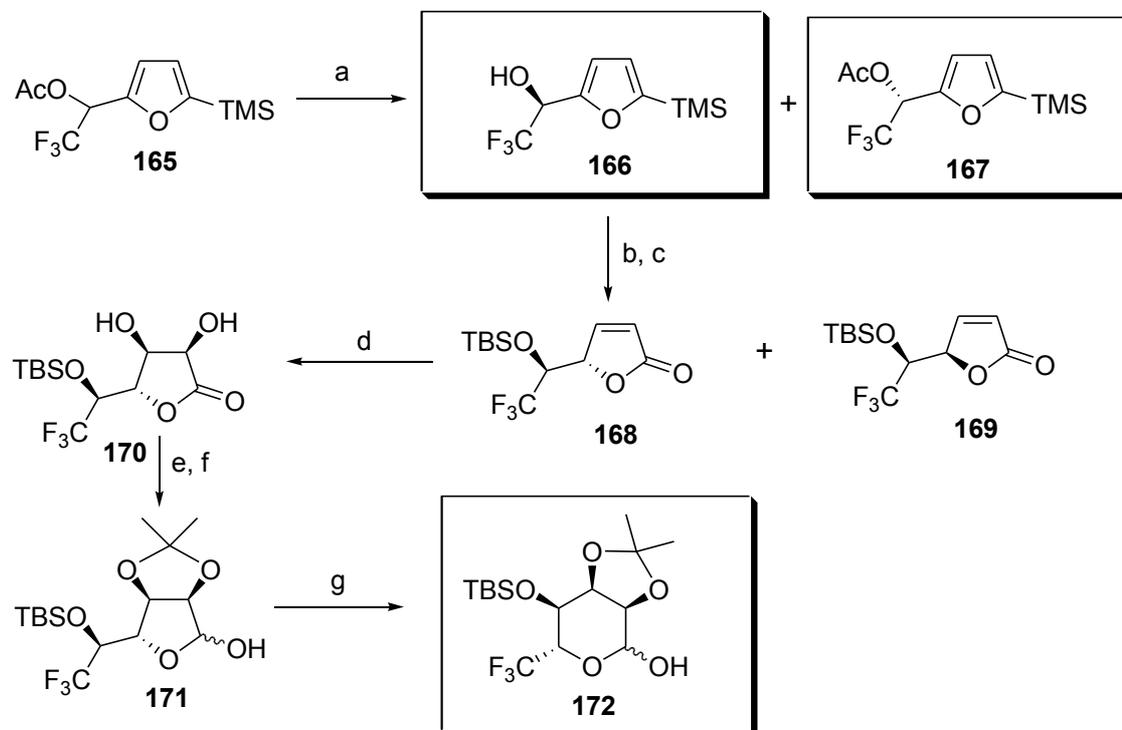
**Table 26. Formation of fluorinated oxa-cycles using the Diels-Alder reaction.**



Entry	R <sup>1</sup>	R <sup>2</sup>	X	%Yield
1	Me	Me	CF <sub>3</sub>	92
2	Me	Me	CF <sub>2</sub> Cl	76
3	Me	Me	C <sub>2</sub> F <sub>5</sub>	95
4	H	H	CF <sub>2</sub> Cl	88
5	Me	H	CF <sub>3</sub>	83

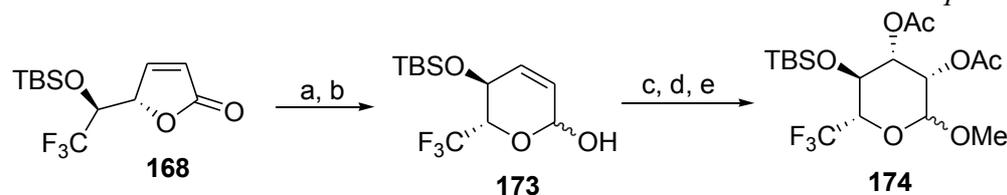
The next example by Yamazaki and co-workers includes the formation of a 6-trifluoromethyl-3,4-dihydropyran and also the corresponding 3,4-dihydroxy analogue which might also be accessed by our methodology. They emphasise the importance of the introduction of fluorine for enhanced biological activity, namely in “sugar-type” molecules. At that time, the production of trifluoromethyl sugar analogues was rare and production of mono- or di-fluorinated sugars was more common. For example, the reagent DAST has been utilised to transform carbonyl groups into difluoromethylene or difluoromethyl groups. The preparation of 6-deoxy-6,6,6-trifluoro-D-mannose and D-allose from the same key intermediate, *anti*-trifluoromethyl-2-butenolide has been described **168**. This was obtained from a furan analogue **165**, by deacetylation to give the alcohol **166**, which could be separated from the acetylated enantiomer **167**. This was then simply silyl-protected and then oxidised by a modified Kuwajima-Urabe procedure to give the desired trifluorinated 2-butenolide as a 1:1 mixture of diastereomers. The unwanted *syn* product **169** could be epimerised to the desired *anti* product **168** after treatment with LDA followed by quenching the reaction mixture with acetic acid. This butenolide **168** could be oxidised with potassium permanganate in the presence of a crown ether to yield the di-hydroxylated species **170** which was produced face-selectively

due to the steric hindrance of the 1-*t*-butyldimethylsiloxy-2,2,2-trifluoroethyl group. The diol **170** was protected as its acetonide and after DiBAL reduction a lactol was produced **171**. Base-promoted rearrangement/isomerisation conditions utilised the tautomeric forms of the cyclic hemi-acetal eventually to afford the tetrahydropyran **172** (Scheme 50).



**Scheme 50. Reagents and conditions:** (a) lipase PS, 50% (98% ee); (b) TBSCl, imidazole, 93%; (c) MMPP, AcOH, 89%; (d) KMnO<sub>4</sub>, 18-crown-6, 42%; (e) Me<sub>2</sub>C(OMe)<sub>2</sub>, H<sup>+</sup>; (f) DiBAL; (g) KO<sup>*t*</sup>-Bu, 35%.

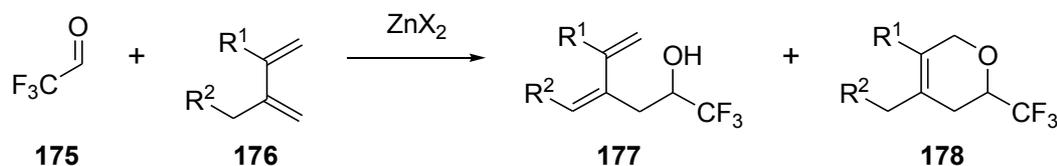
The preparation of 6-deoxy-6,6,6-trifluoro-D-mannose required di-hydroxylation from the opposite face of the olefin and so the order of the synthetic sequence was altered. The same butenolide **168** as previously employed was subjected firstly to DiBAL reduction and then potassium *t*-butoxide effected the isomerisation pathway which yielded a 2-hydroxy-5-siloxy-6-trifluoromethyl-3,4-dihydropyran **173**. The dihydropyran was then converted into methyl glycoside and then di-hydroxylated with potassium permanganate on the less hindered  $\alpha$ -face to give a diol. This diol was then simply protected as the diacetate **174** (Scheme 51).



**Scheme 51. Reagents and conditions:** (a) *DiBAL*; (b) *KOtBu*, 63%; (c) *MeOH*,  $H^+$ ; (d) *KMnO<sub>4</sub>*, 18-crown-6, 55%; (e) *Ac<sub>2</sub>O*, pyridine.

Yoneda describes another example involving the Diels-Alder reaction to access 6-trifluoromethyl-3,4-dihydropyrans. In this case however, the Lewis acid-catalysed conditions also promoted the “ene” reaction. In this report the use of zinc(II) triflate and zinc(II) chloride was successful for the reaction between trifluoroacetaldehyde **175** and conjugated dienes **176** for producing both ene **177** and Diels-Alder products **178**. It seems that the relatively low acidity of the zinc Lewis acids allows unwanted side reactions to be avoided, such as self-polymerisation of both starting materials. Optimal conditions for ene or Diels-Alder reactions were gained by use of DCM or nitromethane as solvent, mostly at room temperature. To favour the formation of 6-trifluoromethyl-3,4-dihydropyrans **178** from the Diels-Alder reaction, it seemed that zinc(II) chloride must be adopted and this was predominantly observed in the reaction between trifluoroacetaldehyde and 2,3-dimethylbuta-1,3-diene or 5,6-dimethyleneundecane. Zinc(II) triflate was insoluble in DCM which meant that it could be isolated by conventional filtration and also be re-used without the deterioration of catalytic activity (Table 27). This example has perhaps highlighted that weakly acidic Lewis acids can be employed in the production of 6-trifluoromethyl-3,4-dihydropyrans without the occurrence of unwanted side-reactions.

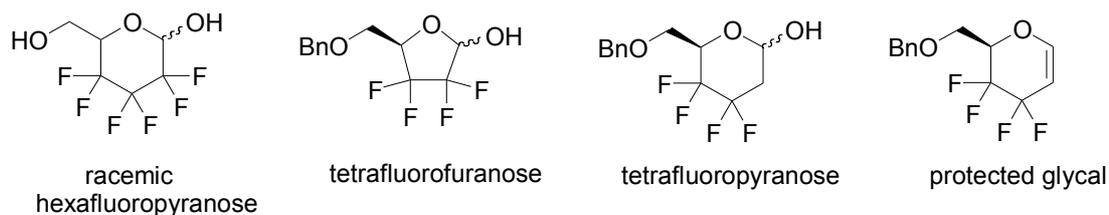
**Table 27. Zinc mediated Diels-Alder reaction for formation of fluorinated oxa-cycles.**



Entry	R <sup>1</sup>	R <sup>2</sup>	X	Solvent	Temp. (°C)	%Yield of 177	%Yield of 178
1	Me	H	OTf	DCM	25	25	31
2	Me	H	OTf	DCM	50	29	31
3	Me	H	Cl	MeNO <sub>2</sub>	50	12	52
4	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	OTf	DCM	25	7	48
5	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	Cl	MeNO <sub>2</sub>	25	0	54

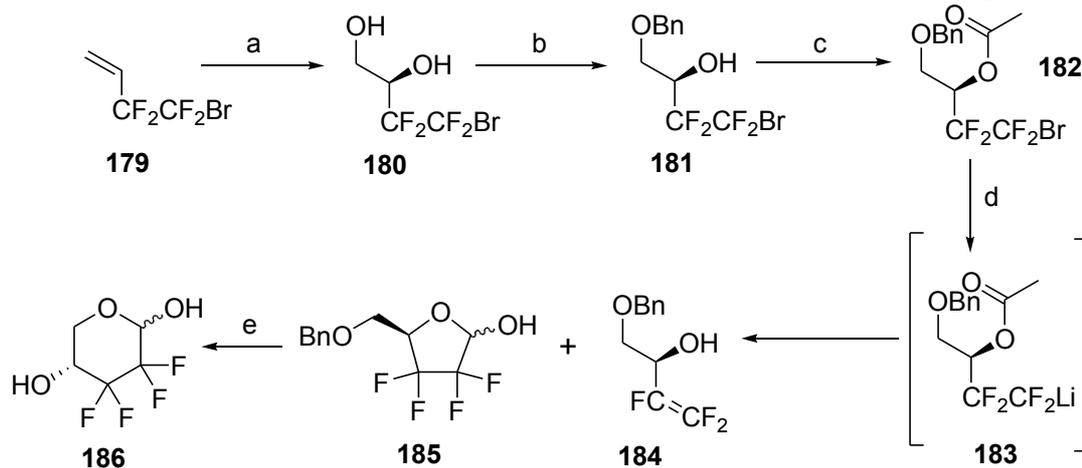
The next literature example shows compounds of biological importance that contain internal perfluoroalkane diyl fragments (IPF) rather than the more common terminal perfluorinated moieties. This study focussed on incorporating IPF's into carbohydrate or

glycoside molecules, which are comparable to the pyran systems that the silyl-Prins reaction affords (Figure 16). This work by Linclau follows on from work by DiMargo, focussing on enhancing polar hydrophobicity for molecular recognition by replacing polar hydrophilic groups such as hydroxyl groups with polar hydrophobic groups like fluorine and difluoromethylene moieties. Effects of these replacements include the 10-fold increase in diffusion across red blood cell membranes with racemic hexafluoropyranose compared to 3-deoxy-3-fluoroglucose.



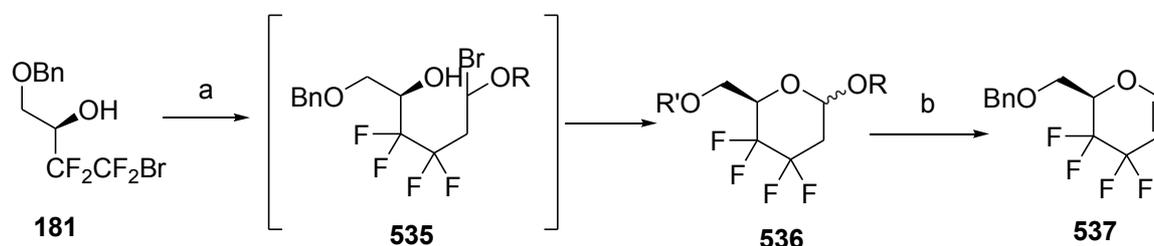
**Figure 16. Examples of carbohydrates and glycosides containing IPFs.**

The precursor synthesis began with the Sharpless asymmetric dihydroxylation of allyl bis(difluoromethylene) bromide **179** to the dihydroxyl substrate **180** in 89% yield and in 78% ee. Selective benzyl protection with benzyl bromide was performed to give **181** in 96% yield and the secondary hydroxyl was coupled to formic acid with DCC and DMAP in 95% yield. The resulting fluorinated formic ester **182** underwent cyclisation to the furanose **185** *via* a lithium fluoromethylene species **183** in 78% yield with only trace amounts of a  $\beta$ -fluoride eliminated product **184**. A 2,4-dihydroxy-3,4-tetrafluoropyran **186** was also accessible *via* hydrogenolysis of the benzyl group (Scheme 52).



**Scheme 52.** Synthesis of IPF containing furanose. *Reagents and conditions:* (a)  $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$  (2 mol%), (DHQ)<sub>2</sub>PYR (2 mol%),  $\text{K}_3[\text{Fe}(\text{CN})_6]$ ,  $\text{K}_2\text{CO}_3$ , *t*-BuOH,  $\text{H}_2\text{O}$ , 4 °C, 9 days; (b)  $\text{Bu}_2\text{SnO}$ , toluene, reflux, 24 h, then BnBr,  $\text{Bu}_4\text{NI}$ , reflux, 16 h; (c) DCC, DMAP, HCOOH, DCM, rt, 16 h; (d) MeLi (1 equiv.), THF, -78 °C, 3 h; (e)  $\text{Pd}(\text{OH})_2/\text{C}$ ,  $\text{H}_2$ , rt, 16h.

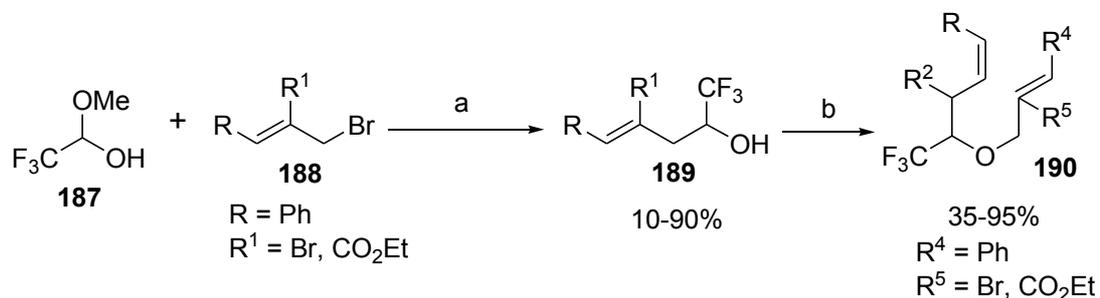
Other IPF molecules were available by generating an intermediate  $\alpha$ -bromoether **535** from the monobenzylated hydroxyl bromide **181**. The tetrafluoropyranose formed from cyclisation, and then hydrogenolysis was given in variable yields depending on the deprotection method. Furthermore the pyranose **536** could be converted into the glycal **537** by Grieco elimination, *via* deprotection at the anomeric position (Scheme 53).



**Scheme 53.** Synthesis of IPF containing glycal. *Reagents and conditions:* (a)  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{NaHCO}_3$ , DMSO,  $\text{CH}_2\text{CHOR}$ , rt, 16 h; (b) *o*- $\text{NO}_2\text{C}_6\text{H}_4\text{SeCN}$ ,  $\text{PBU}_3$ , THF, rt, 1 h, then  $\text{H}_2\text{O}_2$  (30% aq.),  $\text{NaHCO}_3$ , rt, 1.5 h.

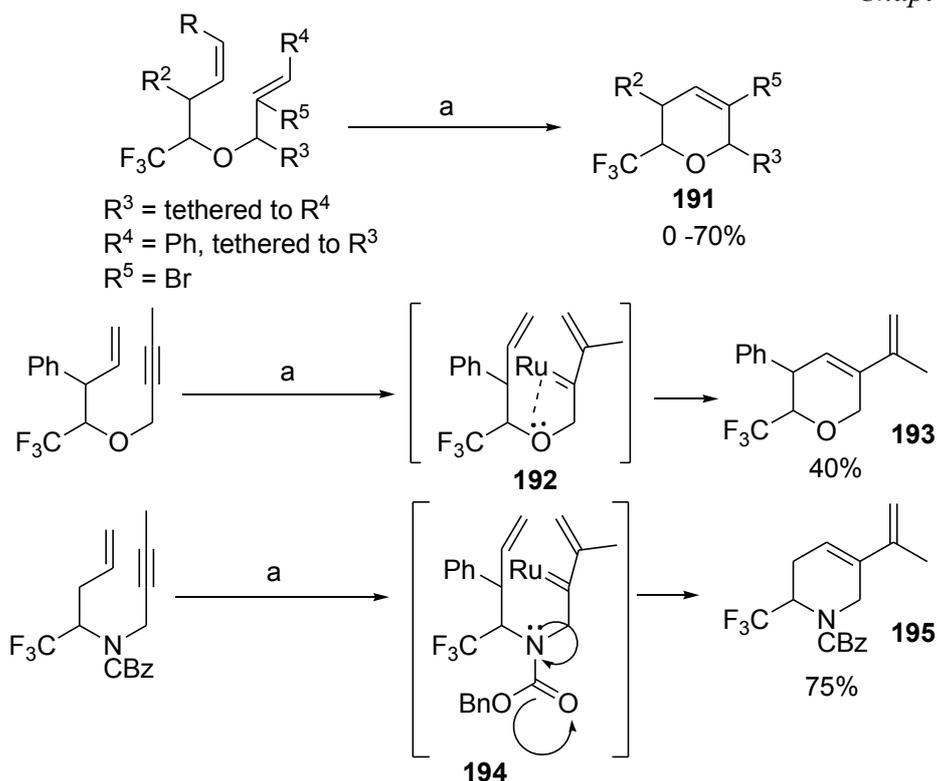
The following report by Billard and Langlois focuses on the use of ring-closing metathesis to furnish 6-trifluoromethyl-3,4-dihydropyrans. The precursor synthesis was designed to incorporate easily used, commercially available starting materials, unlike gaseous trifluoroacetaldehyde, which has been used in other strategies. The starting material in question, a fluoral methyl hemiacetal **187** is essentially equivalent to trifluoroacetaldehyde and was used to access 1-trifluoromethyl homoallylic alcohols **189**. This was done by treatment with allyl bromides **188** in the presence of one equivalent of indium metal in DMF. This methodology produced a range of homoallylic alcohols **189** in

good to moderate yields and afterwards these alcohols were esterified. This was performed by the deprotonation of the alcohol with sodium hydride in DMF followed by the coupling to allylic halides to yield the RCM precursors **190** (Scheme 54).



**Scheme 54.** Precursor synthesis for RCM. *Reagents and conditions* : (a) 1 eq.In, DMF; (b) NaH, DMF, allylic halides.

The optimal conditions for the cyclisation pathway required the Grubbs II catalyst and gave dihydropyran products **191** in a few instances but frequently, a complex mixture of products. The enyne metathesis reaction was also attempted under the same conditions to achieve the synthesis of a conjugated diene **193** in only moderate yields. However under the same conditions, good yields were obtained for the corresponding nitrogen series to afford a 6-trifluoromethyl-3,4-tetrahydropyridine **195**. The improvement in yields was thought to originate from the use of a carbamate function on the nitrogen, which inhibits the nitrogen lone pair from chelating to the ruthenium carbene **194**, as would be the case in the oxygen series **192** (Scheme 55).



Scheme 55. Ring-closing metathesis and enyne metathesis. *Reagents and conditions:* (a) Grubbs II, DCM, 50 °C.

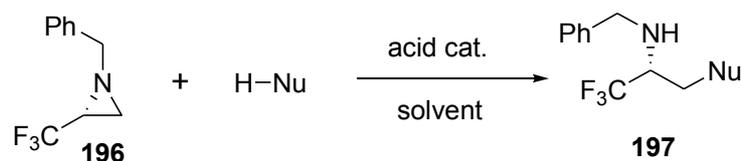
## .10 Literature Review for the Formation of Fluorinated

### Azacycles

The following review shows examples of the synthesis of 6-trifluoro-3,4-tetrahydropyridines or 6-trifluoromethyl piperidines and their precursors reported in the literature. The first example allowed the Dobbs group to make proposals for the synthesis of the trifluoromethyl amine substrate for the aza-silyl-Prins reaction. It is based on the synthesis of  $\alpha$ -trifluoromethyl amines **197** *via* ring opening of optically active *N*-benzyl-2-trifluoromethyl aziridines **196**. The author reports that optically active *N*-benzyl trifluoromethyl aziridine **196** is actually afforded *via* commercially available 1,1,1-trifluoromethyl-2,3-epoxypropane (75% ee) in good yields. The opening of trifluoromethylated aziridines using oxygen, sulfur nucleophiles or halogens has already been reported but opening with nitrogen or carbon nucleophiles was not possible. It is well documented that there is difficulty in opening the epoxide analogue with carbanions, probably owing to the electrostatic repulsion between lone pairs on the fluorines and the negative charge on the nucleophile. Karimova and co-workers reported the opening of the racemic trifluorinated aziridine with Brønsted acids such as thioacetic acid, sulfuric acid and *p*-tosylic acid. Initially studied was acid catalysed ring opening with nucleophiles,

which proceeded regiospecifically to give  $\beta$  cleaved products in good yields. These included using halogenated Brønsted acids as well as water as nucleophiles (in the presence of sulfuric acid for the latter) resulting in  $\alpha$ -trifluoromethyl amines in good yields at room temperature (Table 28).

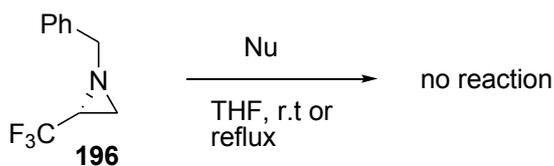
**Table 28.** Acid promoted ring-opening reactions of trifluoromethyl *N*-benzyl aziridine.



Entry	%ee	Temp.	HNu	Acid catalyst	Solvent	%Yield
1	94	rt	HCl	None	H <sub>2</sub> O	94
2	94		HBr			93
3	unknown		H <sub>2</sub> O	CF <sub>3</sub> CO <sub>2</sub> H	THF	64
4	>99			H <sub>2</sub> SO <sub>4</sub>		98
5	83		EtOH		88	
6	unknown	90 °C	PhSH	CF <sub>3</sub> SO <sub>3</sub> H		85
7	unknown		None		40	
8	92	rt	PhSeH	CF <sub>3</sub> SO <sub>3</sub> H	DCM	97
9	unknown	40 °C		None		87
10	unknown	rt		Ph <sub>2</sub> PH		CF <sub>3</sub> SO <sub>3</sub> H

It is worth noting that the  $\beta$ -brominated amines could be possible building blocks for precursors for the aza-silyl-Prins reaction, as substitution of alkyl bromides with trimethylsilyl acetylides is well documented.

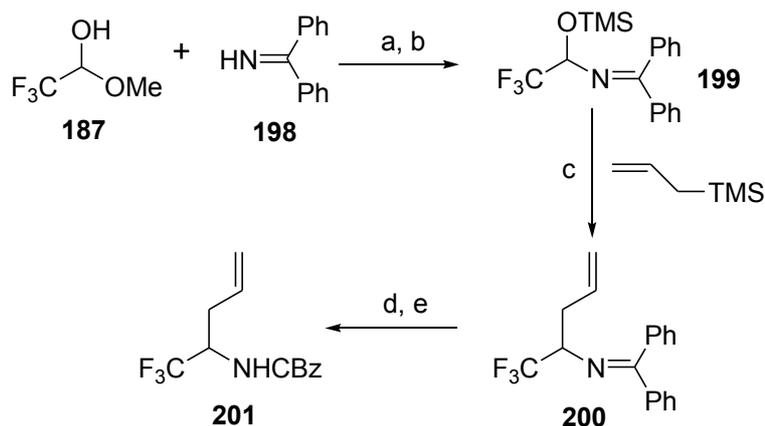
Direct opening of the aziridine **196** under neutral or basic conditions only afforded starting material when using nucleophiles such as benzylamine, sodium cyanide, sodium azide, and diethylamine (Scheme 56).



**Scheme 56.** Un-successful opening of aziridine with nucleophiles.

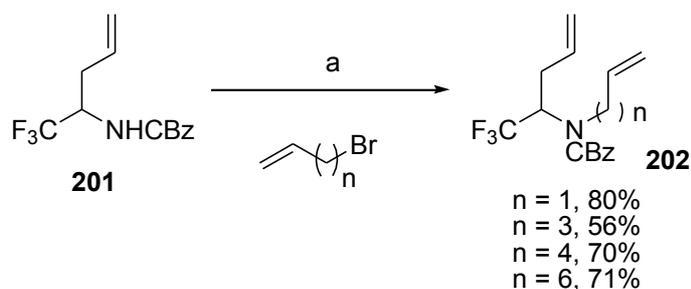
Interestingly, molecular orbital calculations suggested that the aziridine should have higher reactivity than its epoxide counterpart, as there is a higher positive charge on the methylene carbon (from a more polar  $\beta$  carbon-nitrogen bond) and a much lower LUMO than for non-fluorinated aziridines and epoxides. Also investigated, but with no success, was the Lewis acid-promoted ring-opening of the trifluoromethylated aziridine **196** at room temperature or reflux with benzylamine or diethylamine nucleophiles using aluminium chloride, titanium(IV) chloride, boron trifluoride etherate or ytterbium triflate. It is assumed that it is the low co-ordinating ability of the lone pair on the nitrogen atom towards Lewis acids restricted the forward reaction whereas the epoxide equivalent is known to co-ordinate with success to Lewis acids.

Langlois and Billard have published a paper related to their work on the synthesis of 6-trifluoromethyl-3,4-dihydropyrans. In this case, they again used ring-closing metathesis to form 6-trifluoromethyl-3,4-tetrahydropyridines and then used this core to synthesise trifluoropipicoline **204**. They targeted a homoallylamine for their synthesis **201**, beginning with the commercially available fluoral hemiacetal **187**. This involved the coupling of the hemiacetal **187** to an imine **198** and the resulting substituted imine protected as the trimethylsilyl ether **199**. This was then treated with allylsilane under Lewis acid conditions to furnish the allylimine **200**, and finally formation of the free amine under acid conditions, which was protected as the benzyl carbamate **201** in 65% overall yield over 5 steps (Scheme 57).



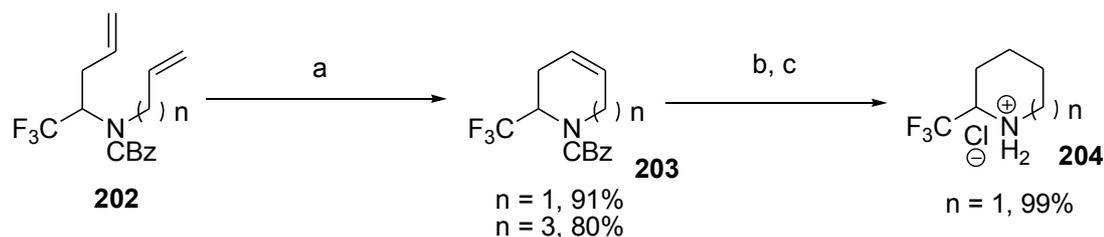
**Scheme 57. Reagents and conditions:** (a) MS 4Å, DCM, 48 h, rt, 90%; (b) ImTMS, THF, 5 h, rt, 99%; (c)  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , DCM, 50 °C, 24 h, 84%; (d) 2.0 M HCl(aq), DCM, 50 °C, 24 h, 99%; (e) CBzCl,  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , 12 h, rt, 88%.

The protected homoallylamine **201** was then alkylated with a number of  $\omega$ -alkenyl bromides in the presence of sodium hydride in DMF (Scheme 58).



**Scheme 58. Alkylation of protected homoallylamine. Reagents and conditions:** (a) NaH, DMF, 0 °C to rt.

These precursors **202** underwent ring-closing metathesis in the presence of Grubbs I catalyst at room temperature in DCM. Simple catalytic hydrogenation was performed on the six-membered heterocycle, 6-trifluoromethyl-3,4-tetrahydropyridine **203**. This was followed up by formation of the hydrochloride salt to give trifluoropipercoline **204** in 47% overall yield from fluoral hemiketal **187** (Scheme 59).



**Scheme 59. RCM and piperidine formation.** *Reagents and conditions:* (a) Grubbs I (1 mol%), DCM, rt, 5 h; (b) Pd/C, H<sub>2</sub>, EtOH, rt, 24 h; (c) HCl.

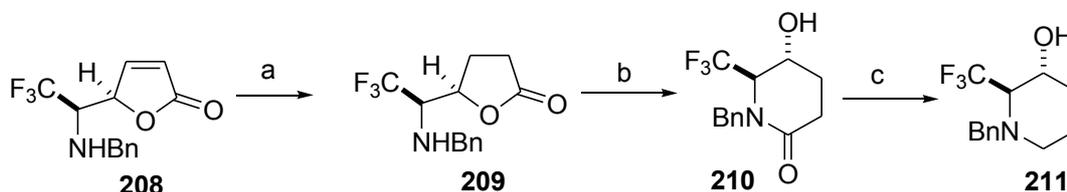
Bonnet-Delpon has reported an approach based on the vinylogous Mannich reaction between trimethylsiloxyfuran **206** and fluorinated aldimines **205**. The lactones **207** formed are a useful handle to synthesise trifluoromethylpiperidines. The key Mannich-type reaction had optimal conditions using either TBS triflate or boron trifluoride etherate in DCM at -78 °C. The reaction proceeded in very good yields and excellent diastereoselectivity for benzyl, allyl or *p*-methoxyphenyl protected aldimines (Table 29).

**Table 29. Mannich reaction of aldimines and trimethylsiloxyfuran.**



Entry	R	LA	De(%)	%Yield
1	Bn	BF <sub>3</sub> .Et <sub>2</sub> O	>98	90
2	Bn	TBSOTf	>98	97
3	Allyl	BF <sub>3</sub> .Et <sub>2</sub> O	>98	92
4	Allyl	TBSOTf	>98	95
5	PMP	BF <sub>3</sub> .Et <sub>2</sub> O	80	87
6	PMP	TBSOTf	36	80

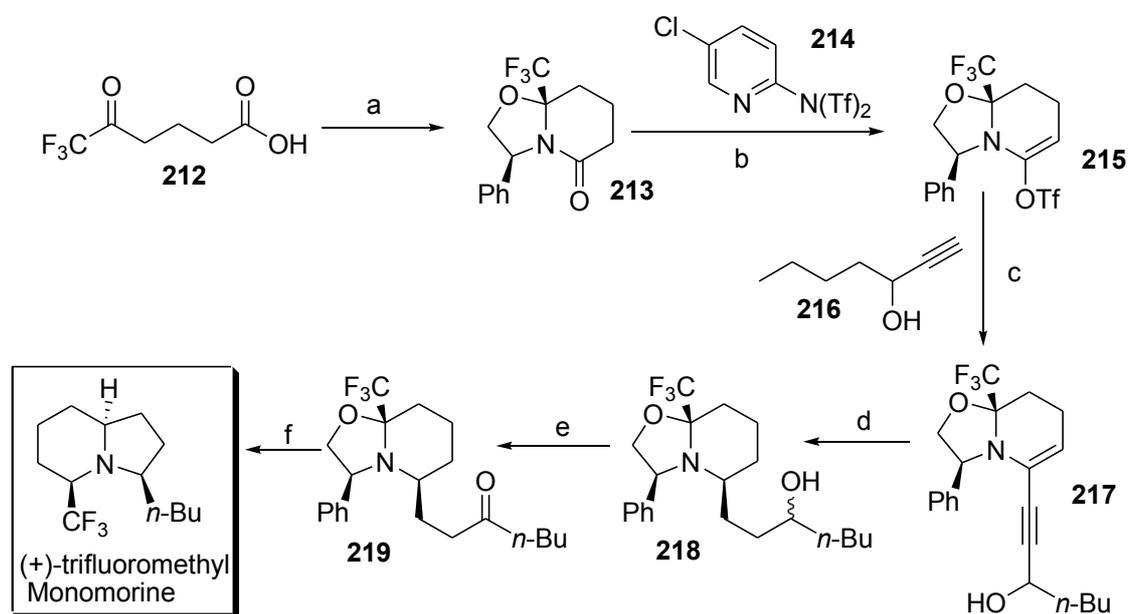
The lactone resulting from the use of the benzyl protected aldimine was utilised to form 3-hydroxy-2-trifluoromethylpiperidine **211** in excellent yields. Catalytic hydrogenation of **208** removed the olefin function giving a butyrolactone **209**; treatment of this with methanol or ethanol in the presence of a catalytic amount of sulfuric acid furnished the  $\delta$ -hydroxylactam **210**, which, after reduction, gave the desired trifluoromethylpiperidine **211** (Scheme 60).



**Scheme 60. Reagents and conditions:** (a) Pd/C, H<sub>2</sub>, THF, 85%; (b) H<sub>2</sub>SO<sub>4</sub>, MeOH or EtOH, 80%; (c) LAH, AlCl<sub>3</sub>, THF, 90%.

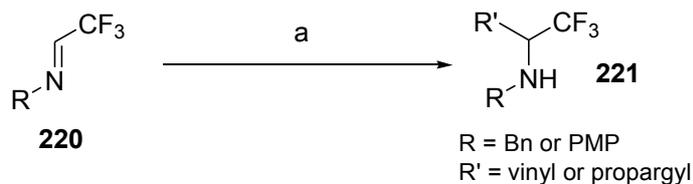
Kim has reported upon the replacement of a methyl group in the natural product monomorine with a trifluoromethyl group, with a view to enhancing biological activity. This indolizidine alkaloid is found as a trail pheromone of the Pharaoh ant, *Monomorium*

*pharaonis* L. The synthesis begins with the condensation of carboxylic acid **212** with (*S*)-(+)-phenylglycinol to form a hexahydrooxazolopyridinone **213**. This bicycle **213** was converted to the enol triflate **215** by treatment with *N*-(5-chloro-2-pyridinyl)triflimide **214**. The enol triflate **215** was then coupled to 1-heptyne-3-ol **216** using a palladium catalysed Sonogoshira coupling to give the desired bicycle **217**. Catalytic hydrogenation over platinum oxide afforded an epimeric mixture of alcohols **218**, which could be separated. However, the mixture could be used for further synthesis by oxidation of the alcohol function with DMP to a ketone **219**, which had an enantiomeric purity of greater than 98% by chiral HPLC. From here the trifluoromethyl monomorine analogue could be obtained by catalytic hydrogenation of the ketone **219** (Scheme 61).



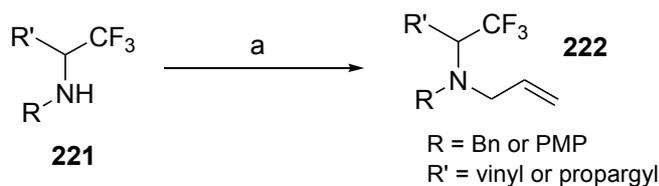
**Scheme 61. Reagents and conditions:** (a) (*S*)-(+)-phenylglycinol; (b) *N*-(5-chloro-2-pyridinyl)triflimide; (c) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, THF, (*i*-Pr)<sub>2</sub>NH, rt, 65%; (d) H<sub>2</sub> (50 psi), Pt<sub>2</sub>O, toluene, 68%; (e) DMP, DCM, 91%; (f) H<sub>2</sub>, Pd(OH)<sub>2</sub>, EtOH, rt, 62%.

Bonnet-Delpin and co-workers have fashioned a simple route to trifluoromethyl piperidines or tetrahydropyridines using either ring closing metathesis or the Pauson-Khand reaction on doubly unsaturated amines. Previous work using a Barbier-type allylation reaction reported the conversion of trifluoromethyl aldimines **220** into homoallylic or homopropargylic amines **221** using activated zinc and trimethylsilyl chloride as promoters (Scheme 62).



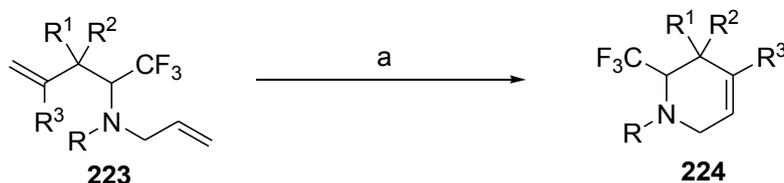
**Scheme 62.** Barbier type allylation reaction of trifluoromethyl imines. *Reagents and conditions:* (a) 1.3 eq. propargyl bromide, 1.1 eq. Zn, DMF, rt or THF, reflux.

Access to the doubly unsaturated amines **222** involved *N*-allylation of the homoallyl or homopropargylic amines **221** (Scheme 63).



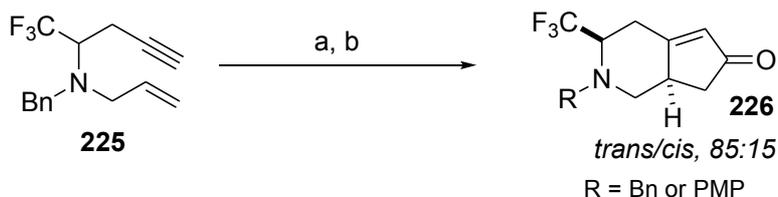
**Scheme 63.** Synthesis of doubly unsaturated amines. *Reagents and conditions:* (a) 3 eq. vinyl or allyl bromide, 5 eq. NaHCO<sub>3</sub>, 0.1 eq. KI, CH<sub>3</sub>CN, reflux.

The doubly allylated amines **223** were then cyclised by ring closing metathesis using Grubbs II catalyst (5-10 mol%) to furnish trifluoromethyl dehydropiperidines **224** in >89% yield (Scheme 64).



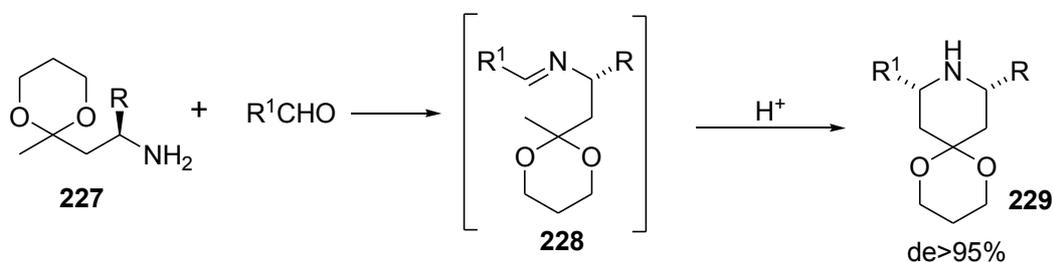
**Scheme 64.** Cyclisation of doubly unsaturated amines by RCM. *Reagents and conditions:* (a) Grubbs II (5-10 mol%), DCM, rt.

The enynes or allyl/propargyl amines **225** were also cyclised using the Pauson-Khand [2+2+1] cycloaddition to **226** with NMO and stoichiometric quantities of dicobalt octacarbonyl (Scheme 65).



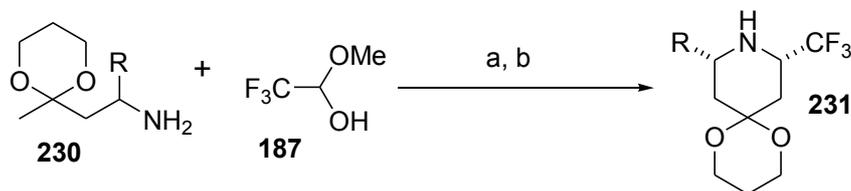
**Scheme 65.** Synthesis of trifluoromethyl containing heterobicyclic compounds by the Pauson-Khand reaction. *Reagents and conditions:* (a) 1.2 eq.  $\text{Co}_2(\text{CO})_8$ , DCM, 0.5 h; (b) 9 eq. NMO, 0 °C to rt, 3 h.

The next method by Bariau shows the formation of  $\alpha$ -trifluoromethyl piperidines but in this instance, with more functionality being introduced. Condensation of an  $\alpha$ -chiral 1,3-aminoketal **227** with various aldehydes formed intermediate imines **228** which, under acid catalysed conditions, underwent cyclisation to form 2,6-disubstituted piperidines **229** with exclusive *cis* stereoselectivity across the heteroatom (Scheme 66).



**Scheme 66.** Mannich type process yielding piperidines.

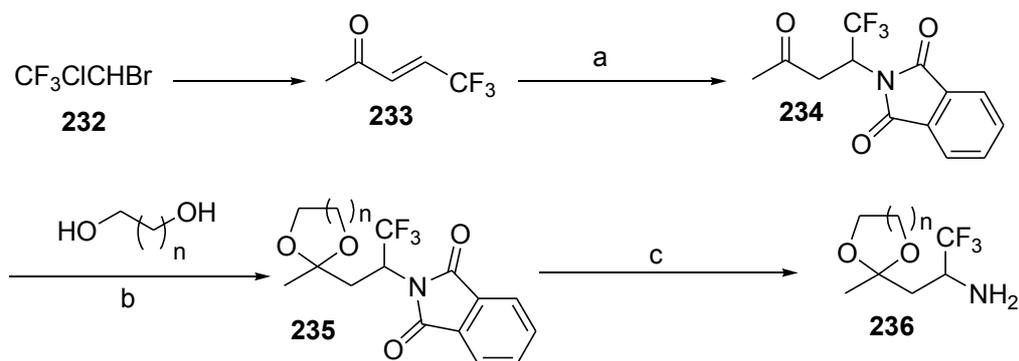
The fluorinated moiety may either be introduced *via* the aldehyde source, route A, or *via* a preformed fluorinated amine, route B. The first route generated trifluoroacetaldehyde *in situ* from the condensation of the methylhemiacetal derivative **187** using catalytic amounts of *p*-toluenesulfonic acid. This was coupled to the amine **230** in the same pot and also cyclised using the same acid to form the piperidine **231** in reasonable yields (35–76%) and with high diastereoselectivity (Scheme 67).



**Scheme 67.** Trifluoromethyl piperidines *via* route A. *Reagents and conditions:* (a) *p*-TsOH,  $\text{MgSO}_4$ , DCM, reflux; (b) *p*-TsOH, toluene, 70 °C.

Route B, although requiring a longer synthesis, utilizes a number of different aldehydes. First the *N*-hetero Michael acceptor 5,5,5-trifluoro-3-penten-2-one **233** was prepared from commercially available halotane<sup>®</sup> **232** and this was coupled to phthalimide in the presence of triton B<sup>®</sup> to give a phthalimido derivative **234**. Subsequent ketal protection of the

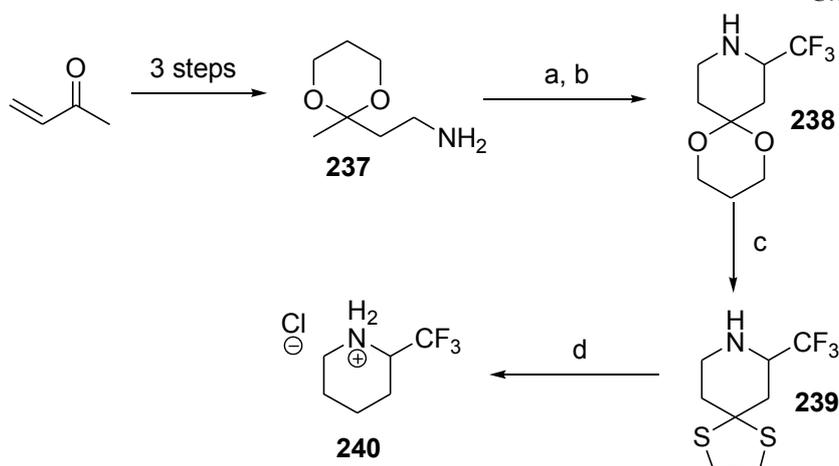
ketone moiety gave **235** and then hydrazinolysis with hydrazine afforded the amines **236** in >75% overall yield from the  $\alpha,\beta$ -unsaturated ketone **233** (Scheme 68).



**Scheme 68.** Precursor synthesis for route B. *Reagents and conditions:* (a) phthalimide, Triton B, EtOAc, reflux; (b) *p*-TsOH, toluene, reflux; (c)  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ , MeOH, reflux.

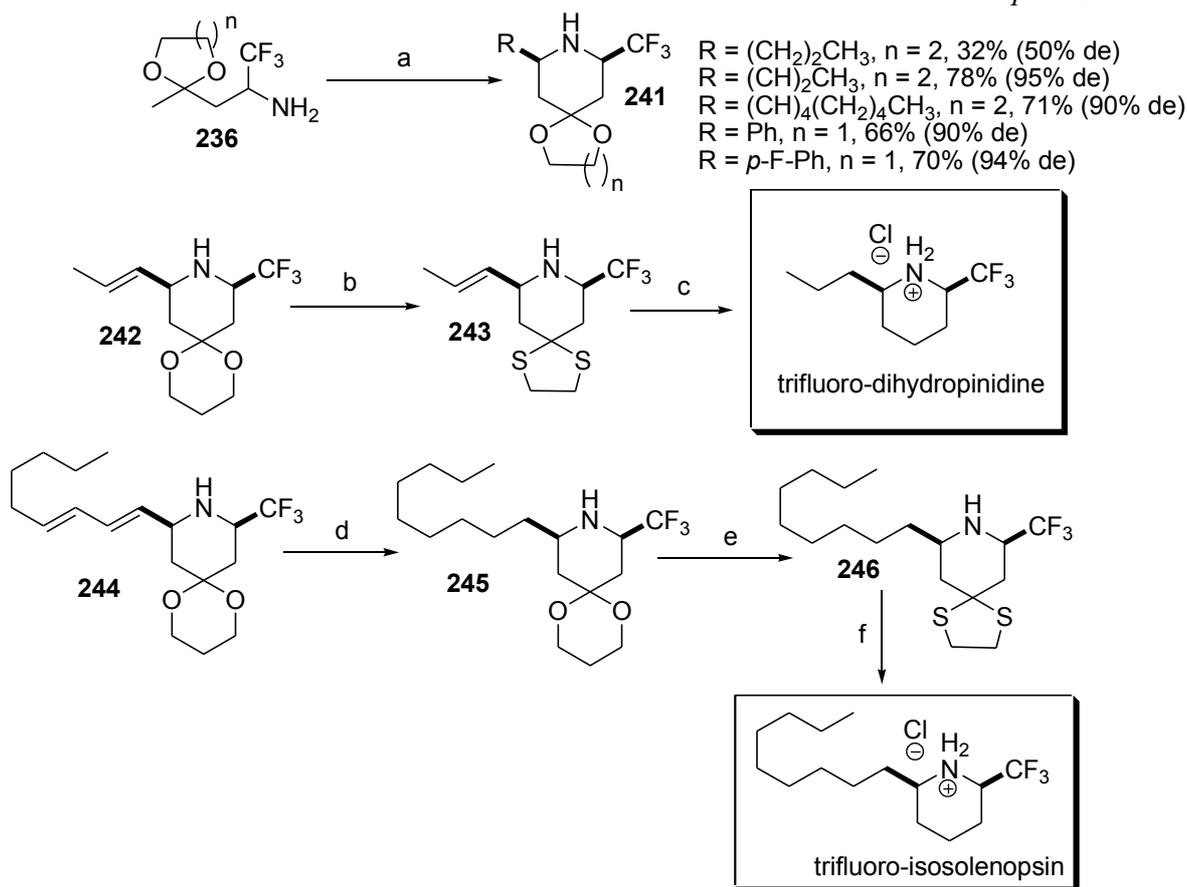
The cyclisations were then performed on a range of aromatic, or alkyl aldehydes giving yields between 70-80% and with exclusive *cis* stereoselectivity across the heteroatom.

Canet has extended his work utilising the Mannich reaction of 1,3-aminoketals to form natural product analogues containing trifluoromethyl groups. In fact, their first target was pipercoline, the same compound targeted by Billard and Langlois, where the C2 methyl group of the piperidine is substituted for a trifluoromethyl group. Using route A, the aminoketal **237** was treated with trifluoroacetaldehyde under acidic cyclisation conditions to afford the desired (trifluoromethyl)piperidine **238**. This piperidine was then treated with an excess of ethanedithiol in the presence of boron trifluoride etherate to yield the dithioketal derivative **239**. Finally, hydrogenolysis of the thioketal function and treatment with acid afforded the pipercoline analogue **240** as its hydrochloride salt (Scheme 69).



**Scheme 69.** *Reagents and conditions:* (a)  $\text{CF}_3\text{CH}(\text{OH})\text{OMe}$ , *p*-TsOH,  $\text{MgSO}_4$ , DCM, reflux; (b) *p*-TsOH, toluene,  $80\text{ }^\circ\text{C}$ , 71%; (c) ethanedithiol,  $\text{BF}_3\cdot\text{OEt}_2$ , DCM, r.t., 88%; (d) Raney Ni, EtOH, reflux, then HCl, 90%.

Next, Canet utilised route B to synthesise trifluoromethyl analogues of some naturally occurring 2,6-disubstituted piperidines. The advantages of route B over route A are that alterations to the second ring substituent are easily obtained, as it originates from an aldehyde. As with the previous example, the cyclisation precursor ( $\alpha$ -trifluoromethyl aminoketal) **236** was synthesised beginning with a 5,5,5-trifluoropent-3-en-2-one **233**. Two different ketals were submitted to the acid-catalysed cyclisation pathway in the presence of different aldehydes to afford a series of *cis*-2-substituted-6-(trifluoromethyl)piperidines **241** in moderate to good yields (32-94%) and with exclusive *cis* diastereoselectivity in most cases. Following highly similar methods to the synthesis of 2-(trifluoromethyl)pipecoline, the trifluoromethyl analogues of dihydropinidine and isosolenopsin were isolated as their hydrochloride salts. This involved, in the case of dihydropinidine, the formation of the dithioketal **243** from **242**, followed by global reduction over Raney Nickel and acid treatment. In the case of isosolenopsin, the unsaturated side chain of the ketalpiperidine precursor **244** was firstly reduced to **245** and then again dithioketal formation to **246** followed by hydrogenolysis and acid treatment afforded the desired analogue (Scheme 70).



Scheme 70. *Reagents and conditions:* (a) (i) RCHO, *p*-TsOH, MgSO<sub>4</sub>, DCM, reflux; (ii) *p*-TsOH, toluene, 70-110 °C; (b) ethanedithiol, BF<sub>3</sub>·Et<sub>2</sub>O, DCM, rt, 77%; (c) Raney Ni, EtOH, reflux, then HCl, 90%; (d) HCO<sub>2</sub>NH<sub>4</sub>, Pd(OH)<sub>2</sub>/C, MeOH, 60 °C, 92%; (e) ethanedithiol, BF<sub>3</sub>·Et<sub>2</sub>O, DCM, rt, 60%; (f) Raney Ni, EtOH, reflux, then HCl, 92%.

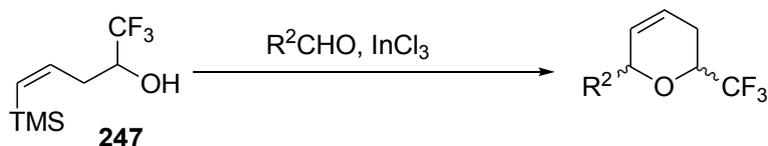
## . II Results and Discussion: Studies into the Formation of Fluorinated Heterocycles

As previously discussed, it was proposed to synthesise dihydropyrans and tetrahydropyridines that contain a trifluoromethyl group (CF<sub>3</sub>) in the C6 position, using the indium trichloride-mediated silyl-Prins and aza-silyl-Prins reactions. The reasoning behind this was to firstly synthesise heterocycles with interesting biological properties and secondly, to investigate the effects the strong electron withdrawing trifluoromethyl group may have on precursor synthesis and the kinetics of the cyclisation reactions.

### . 11 Synthesis of 6-Trifluoromethyl-3,4-dihydropyrans

Using the silyl-Prins reaction, the synthesis of trifluoromethyl-substituted dihydropyrans was attempted. These heterocycles should be a useful handle towards the total synthesis of fluorinated analogues of dihydropyran containing natural products. The α-trifluoromethyl group in the precursor **247** will be transferred to the C6 position in the

dihydropyran product, whereas the aldehyde source will functionalise the C2 position (Scheme 71).

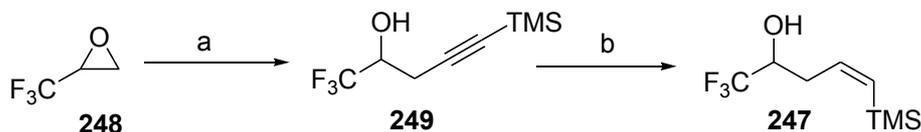


Scheme 71. Proposed scheme for synthesis of 6-trifluoromethyl-3,4-dihydropyrans.

### . aPrecursor Synthesis I- Formation of 1-CF<sub>3</sub>-

#### Homoallylic Alcohol

The desired substrate for this silyl-Prins reactions was (*Z*)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247**. This was synthesised in 2 steps from commercially available 3,3,3-trifluoromethylpropylene oxide **248** (Scheme 72).



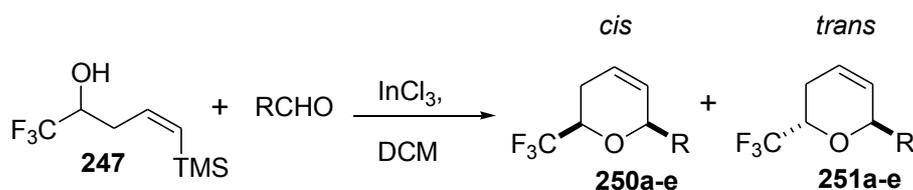
Scheme 72. *Reagents and conditions:* (a) *n*-BuLi, TMS acetylene, Et<sub>2</sub>AlCl, hexane, -30 °C, 82%; (b) DiBAL, Et<sub>2</sub>O, reflux, 24 h, 61%.

The silylated homopropargylic alcohol was prepared by the nucleophilic ring opening of the commercially available epoxide **248** using a metallated trimethylsilyl acetylide species, to afford the alcohol **249** in 82% yield, using a modified literature procedure. Next the *cis* reduction of the alkynylsilane **249** by the action of DiBAL afforded the desired silylated homoallylic alcohol **247** in 61% yield.

### . bSilyl-Prins Reactions of 1-CF<sub>3</sub>-

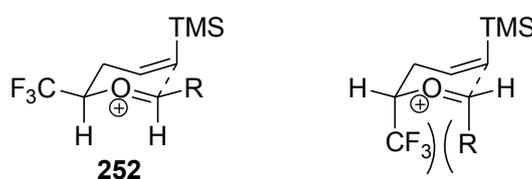
#### Homoallylic Alcohol

With the required trifluoromethyl-substituted alcohol **247** in hand, the silyl-Prins reaction was attempted with a range of commercially available aldehydes, initially using standard conditions previously described: dichloromethane at room temperature, with a 1:1:1 ratio of alcohol, aldehyde and indium trichloride. For the majority of aldehydes, there was no reaction at room temperature; on elevation of the temperature to reflux temperature, the formation of 6-trifluoromethyldihydropyran products **250** and **251** was observed for most aldehydes screened (Table 30).

Table 30. The silyl-Prins reactions of  $\alpha$ -trifluoromethyl homoallyl alcohol.

Entry	R	Temp	Time (h)	Total %Yield	<i>Cis:trans</i>
1	<i>c</i> -Hex	Reflux	43	32 (a)	100:0
2	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Reflux	66	55 (b)	100:0
3	PhCH <sub>2</sub>	Reflux	44	42 (c)	100:0
4	Ph	Reflux	42	25 (d)	60:40
5	CO <sub>2</sub> Et	rt	24	Traces (e)	N/A

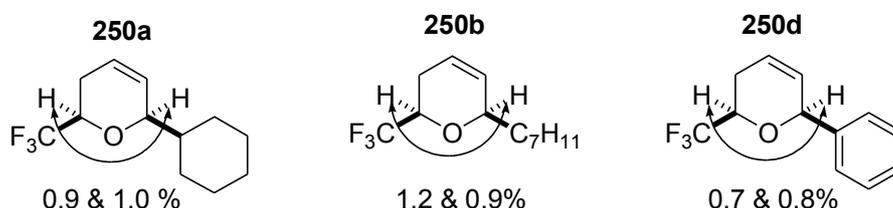
Success was found in four of the five aldehydes screened (Table 30, entries 1-4) but these required longer reaction times than previously observed in the silyl-Prins reaction (42-66 h, *c.f.* 5-12 h). The best yields were achieved on use of octanal and phenylacetaldehyde (Table 30, entries 2-3). Unfortunately, the dihydropyran formed from phenylacetaldehyde (Table 30, entry 3) was highly unstable and decomposed readily during purification by flash column chromatography and so a true yield could not be recorded. Therefore, only the <sup>1</sup>H NMR spectra could be obtained rapidly enough and analysed accurately; however no mass spectra could be obtained. On use of cyclohexanecarboxaldehyde (Table 30, entry 1) the yield of dihydropyran product was disappointing. When using benzaldehyde (Table 30, entry 4), a lower yield was observed and this is comparable with previous examples. However, unlike previous examples, here a 3:2 mixture of *cis* and *trans* dihydropyran products was formed. This is the only example where this occurred; for all other aldehydes only the *cis* stereochemistry across the heteroatom was observed, in keeping with previous examples. It was assumed that the preference for these *cis*-2,6-dihydropyrans is to adopt a di-equatorial conformation **252** which keeps ring substituents facing away from one another (Figure 17).

Figure 17. Possible conformations of *cis*-2,6-disubstituted-3,4-dihydropyrans.

On use of ethyl glyoxylate, the starting material was consumed after 24 hours at room temperature. The temperature and time are in keeping with previous use of ethyl

glyoxylate in Prins-type reactions, showing its high reactivity. Unfortunately, only trace amounts of product were observed on analysis of the GCMS data for the crude reaction material. This follows previous examples of the silyl-Prins reaction where a complicated mixture of unidentifiable products was observed.

The relative stereochemistry of the *cis*-2,6-disubstituted dihydropyrans **250** was assigned by NOESY experiments. For the dihydropyran **250b** derived from octanal there was a small 1.2% enhancement of the C2 hydrogen on irradiation of the C6 hydrogen. Similar nOe effects were observed for the dihydropyrans **250d** and **250a** derived from benzaldehyde and cyclohexanecarboxaldehyde (Figure 18). The decomposition of the dihydropyran **250c** derived from phenylacetaldehyde meant that a NOESY experiment could not be completed.



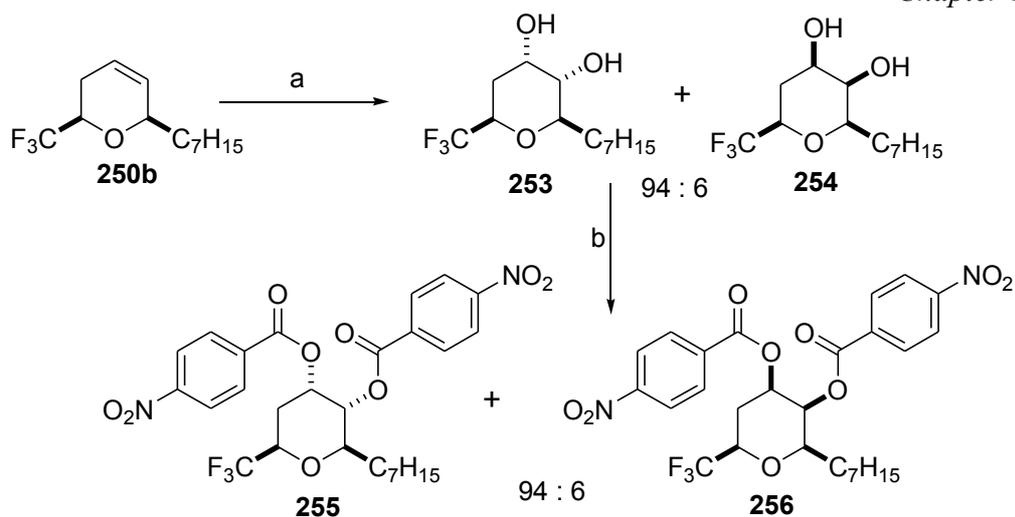
**Figure 18.** The nOe effects in 6-trifluoromethyldihydropyrans.

Overall the yields are obviously quite disappointing and this is most probably attributable to the strong electron-withdrawing effects of the trifluoromethyl group. It was assumed that this decreases the nucleophilicity of the alcohol precursor towards the activated aldehyde, thereby affecting yields and reaction times.

### . cFurther Functionalisation of

#### Dihydropyran olefin

A major advantage of the silyl-Prins reactions is the formation of an olefin, which is useful for further functionalisation. It was decided to dihydroxylate the 6-trifluoromethyldihydropyran **250b** derived from the use of octanal and then further elaborate the diol **253** and **254** (Scheme 73).



**Scheme 73. Reagents and conditions:** (a) OsO<sub>4</sub> (1.0 M in H<sub>2</sub>O), NMO, THF, H<sub>2</sub>O, rt, 72 h, 83%; (b) *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COCl, DMAP, pyridine, DCM, rt, 24 h, 69%.

The exclusive *cis*-2,6-disubstituted-3,4-dihydropyran **250b** was reacted with a catalytic quantity of osmium tetroxide in the presence of the co-oxidant NMO, a method taken from the thesis of a previous group member. Dihydroxylation occurred predominantly from the least hindered (bottom) face to give a 94:6 mixture of diols **253** and **254** determined by GCMS analysis, in 83% yield. The diols **253** and **254** could not be fully purified or characterised and so were further elaborated to the di-*p*-nitrobenzoate esters **255** and **256**. This conversion was performed using 4-nitrobenzoyl chloride in the presence of pyridine and catalytic quantities of 4-dimethylaminopyridine. This gave the *p*-nitrobenzoate esters in 69% yield and in the same ratio of diastereomers.

The relative stereochemistry of these compounds was also proven by NOESY experiments and this further supported the observation that the silyl-Prins reaction for the  $\alpha$ -trifluoromethyl homoallyl alcohol **247** produced exclusively *cis*-2,6-dihydropyrans **250**. On analysis of the major diastereomer **255**, a 3.6% enhancement of C2 and C6 hydrogens on irradiation of each demonstrated the *cis* relationship. A smaller 1.6% enhancement of the C2 hydrogen on irradiation of the C3 hydrogen highlights a *trans* relationship between these two positions and showed that the di-hydroxylation has occurred from the opposite face. The occurrence of the *syn* addition is suggested by the large 3.6% and 3.2% enhancement of C3 and C4 hydrogens on irradiation of each. Conversely, on observation of the minor diastereomer **256**, there was a large 3.2% enhancement of the C2 hydrogen on irradiation of the C3 hydrogen and also a 3.6% enhancement of the C2 hydrogen on irradiation of the C4 hydrogen. This demonstrates a *cis* relationship between the C2, C3, and C4 positions and that the *syn* hydroxylation and

has occurred from the more hindered face (Figure 19). Although this material was crystalline, unfortunately an X-ray crystal structure could not be obtained and so this assignment could not be confirmed.

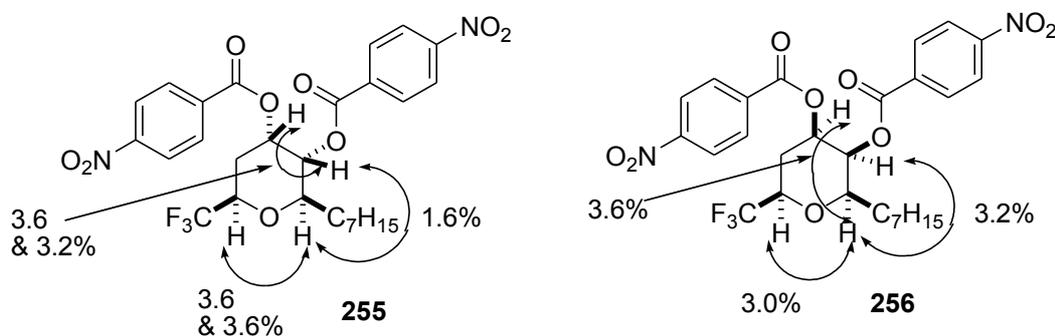
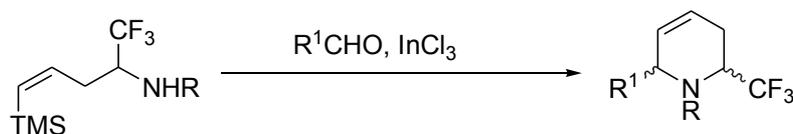


Figure 19. The nOe effects in *p*-nitrobenzoate esters.

## 12 Synthesis of 6-Trifluoromethyl-3,4-tetrahydropyridines

Having found success in synthesising 6-trifluoromethyl-3,4-dihydropyrans, attention turned to the synthesis of their tetrahydropyridine analogues using the aza-silyl-Prins reaction (Scheme 74). Both 2-substituted-3,4-tetrahydropyridines and *trans*-2,6-disubstituted-3,4-tetrahydropyridines were produced in good yields and short reaction times from coupling commercially available aldehydes to silicon-substituted homoallylic secondary amines under indium trichloride mediated conditions. The fluorinated precursors screened in the silyl-Prins reaction had a detrimental effect on reaction times and product yields and so it was predicted that similar effects would be observed in the aza-Silyl-Prins reaction.



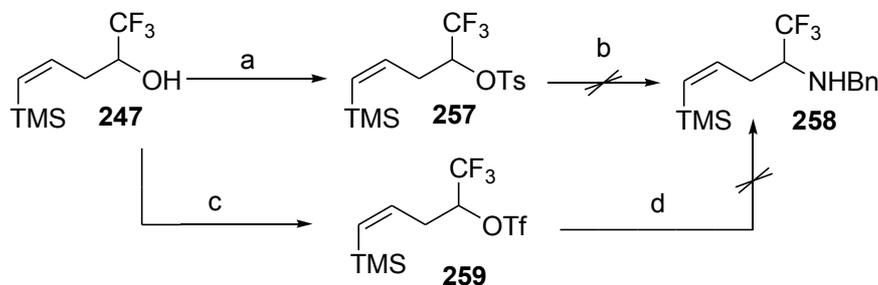
Scheme 74. Proposed scheme for synthesis of 6-trifluoromethyl-3,4-tetrahydropyridines.

## aPrecursor Synthesis II- Formation of 1-CF<sub>3</sub>-

### Homoallylic Amine

The precursor required for the aza-silyl-Prins reaction was (*Z*)-*N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **258**. As before, the  $\alpha$ -trifluoromethyl group would functionalise the C6 position in the tetrahydropyridine product and the aldehyde precursor would provide the substituent at C2. It was decided to synthesise the *N*-benzyl substituted

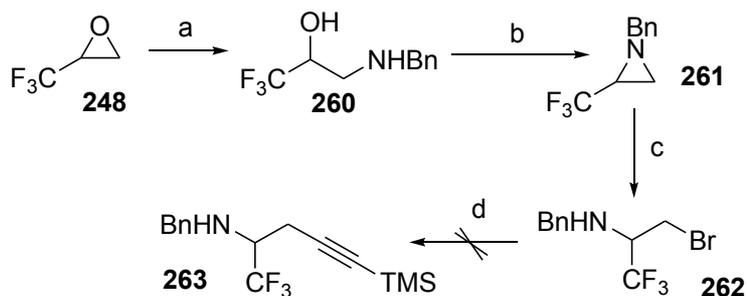
precursor as this gave the best yields in previous examples. The amine synthesis was not straightforward; it was first proposed that the amine could be obtained in 2 steps from the previously synthesised (*Z*)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247**. This route was similar to previous precursor syntheses for the aza-silyl-Prins reactions (Scheme 75).



**Scheme 75.** *Reagents and conditions:* (a) TsCl, Et<sub>3</sub>N, DMAP, DCM, 0 °C, 20 h, 50%; (b) BnNH<sub>2</sub>, EtOH, reflux or NaI, *i*-Pr<sub>2</sub>EtN, BnNH<sub>2</sub>, DMF, reflux; (c) Tf<sub>2</sub>O, pyridine, DCM, rt, 4 h, 66%; (d) BnNH<sub>2</sub>, EtOH, reflux or BnNH<sub>2</sub>, Et<sub>3</sub>N, CHCl<sub>3</sub>, reflux.

The homoallylic alcohol **247** was transformed into the corresponding tosylate **257** in 50% yield by the action of tosyl chloride in the presence of triethylamine and a catalytic quantity of 4-dimethylaminopyridine. This was then subjected to previously successful conditions to allow substitution by benzylamine in ethanol. However, no reaction was observed and so more forcing conditions were attempted with Hunig's base in DMF at reflux temperature and with a catalytic quantity of sodium iodide. Again no success was found and so it was decided to employ a better leaving group on the alcohol by transforming it into the triflate **259**. This was achieved by the reaction of triflic anhydride in the presence of pyridine to give the desired triflate **259** in 66% yield. This was subjected to the same conditions for amine formation as the tosylate, but again with no success. It was assumed that the strong electron withdrawing character of the  $\alpha$ -trifluoromethyl group was inhibiting the S<sub>N</sub>2 reaction of either the tosylate or triflate by benzylamine.

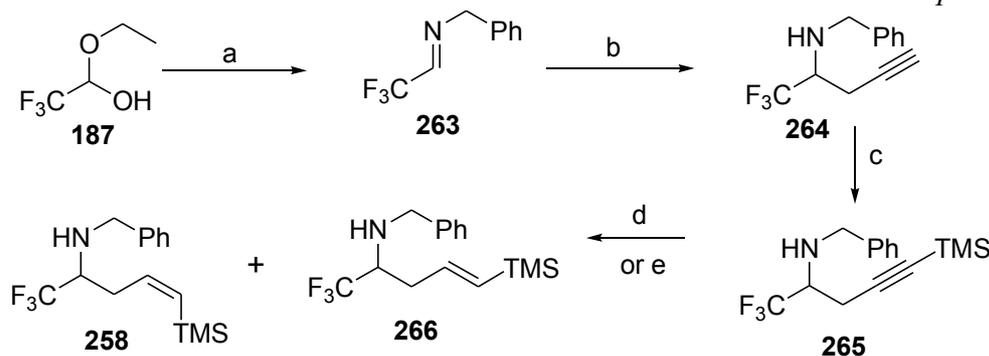
Success for formation of the corresponding alcohol precursor **247** was found when commercially available 3,3,3-trifluoromethylpropylene oxide **248** was opened with a metallated acetylide species. Therefore it was proposed that the corresponding aziridine could be manipulated in a similar manner. This pathway meant that no substitution of either a tosylate or triflate was required. This route also had literature precedent, as described in the introduction to this chapter (Scheme 76).



**Scheme 76.** Reagents and conditions: (a)  $\text{BnNH}_2$ ,  $\text{CH}_3\text{CN}$ , rt, 48 h, 82%; (b)  $(\text{Ph})_3\text{PCl}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_3\text{CN}$ , reflux, 24 h, 68%; (c)  $\text{HBr(aq)}$ , rt, 16 h, 41%; (d)  $n\text{-BuLi}$ , TMS acetylene, HMPA, THF,  $-78^\circ\text{C}$ .

Formation of the aziridine **261** was completed in 2 steps from the commercially available epoxide **248**. First, the epoxide **248** was opened by treatment with benzylamine to afford the amino-alcohol **260** in 82% yield. The alcohol was activated by treatment with dichloro(triphenyl)phosphorane in the presence of triethylamine to promote ring closure and form the aziridine **261** in 68% yield. Direct ring-opening of aziridines with carbanions has been proven to be unsuccessful due to the electronic repulsion from the trifluoromethyl group. Therefore, it was decided to ring open the aziridine with bromide under Brønsted acid conditions, using aqueous hydrogen bromide, to give the bromoamine **262** in 41% yield. It was assumed that the bromide function could be more readily substituted by carbanions such as trimethylsilyl acetylide. However, even when the nucleophilicity of the carbanion was enhanced by the presence of HMPA, there was no substitution and only starting material **262** recovered, so the route was abandoned.

The next route involved the Barbier-type allylation of a trifluoromethyl imine **263** with propargyl bromide, followed by subsequent silylation and reduction. This methodology also had literature precedent as reviewed in the introduction and afforded the desired homoallylic amine **258** in 4 steps from a commercially available hemiacetal **187** (Scheme 77).



**Scheme 77. Reagents and conditions:** (a)  $\text{BnNH}_2$ , toluene,  $140\text{ }^\circ\text{C}$ , 2 h, 64%; (b) propargyl bromide, Zn, TMSCl, DMF, rt, 2 h, 59%; (c)  $n\text{-BuLi}$ , TMSCl, THF,  $-78\text{ }^\circ\text{C}$ , 65%; (d) DiBAL,  $\text{Et}_2\text{O}$ , reflux, 24 h, 45% (*Z*:*E*; 50:50); (e)  $\text{Ti}(\text{O}i\text{-Pr})_4$ ,  $i\text{-PrMgCl}$ ,  $\text{Et}_2\text{O}$ ,  $-60\text{ }^\circ\text{C}$ , 5 h, 51% (*Z*:*E*; 100:0).

First, the commercially available hemiacetal **187** was condensed with benzylamine using a Dean and Stark apparatus to afford the imine **263** in 64% yield. Then, using the allylation conditions described in the introduction, propargyl bromide was coupled to the imine in the presence of zinc and TMSCl as promoters. The propargylic amine **264** that was furnished in 59% yield was silylated with TMSCl, using *n*-butyllithium to deprotonate the alkyne. This produced the alkynylsilane **265** in 65% yield, which was then subjected to DiBAL reduction conditions, as previously employed. However this produced a 1:1 inseparable mixture of olefinic isomers **258** and **266**. This was unexpected when considering the exclusive production of (*Z*)-homoallylic alcohols previously (Scheme 72). It was subsequently found that the (*Z*)-isomer **258** could be generated exclusively, in 51% yield, when the alkynylsilane was subjected to a hydrotitanation procedure involving the use of titanium(IV) isopropoxide and *iso*-propylmagnesium chloride. This reaction only found moderate success on a small scale and so the product could not be used for further chemistry.

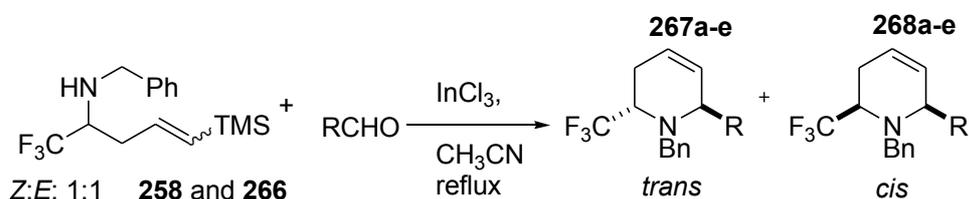
### . bAza-silyl-Prins Reactions of 1-CF<sub>3</sub>-

#### Homoallylic Amine

Having successfully synthesised the required homoallylic amine, the aza-silyl-Prins reaction was attempted with a range of aldehydes. Since the amine precursor was only available as an inseparable 1:1 mixture of geometric isomers **258** and **266**, it was decided to proceed with this mixture in the hope that it would allow us to quantify the reactivity of both isomers. It could also support past observations that the (*Z*)-isomer is required to maximise the orbital overlap present in the  $\beta$ -effect of silicon for the intermediate carbocation. The conditions required for the aza-silyl-Prins cyclisation reaction were use

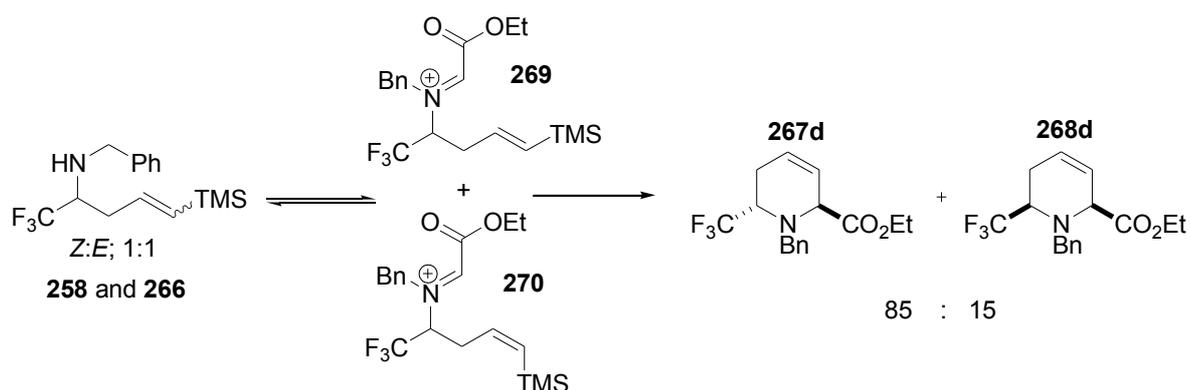
of acetonitrile at reflux temperature as well as a 1:1:1 ratio of amine (**258** and **266**), aldehyde and indium trichloride (Table 31).

**Table 31.** The aza-silyl-Prins reactions of  $\alpha$ -trifluoromethyl homoallyl amines.



Entry	R	Time (h)	Total %Yield	Trans:cis	Comment
1	<i>c</i> -Hex	48	25 (a)	100:0	<i>E</i> -alkene remained
2	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	48	43 (b)	100:0	<i>E</i> -alkene remained
3	PhCH <sub>2</sub>	48	55 (c)	85:15	<i>E</i> -alkene remained
4	CO <sub>2</sub> Et	17	69 (d)	85:15	Both alkenes consumed
5	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	48	Traces (e)	N/A	<i>Z</i> -alkene consumed, <i>E</i> -remained

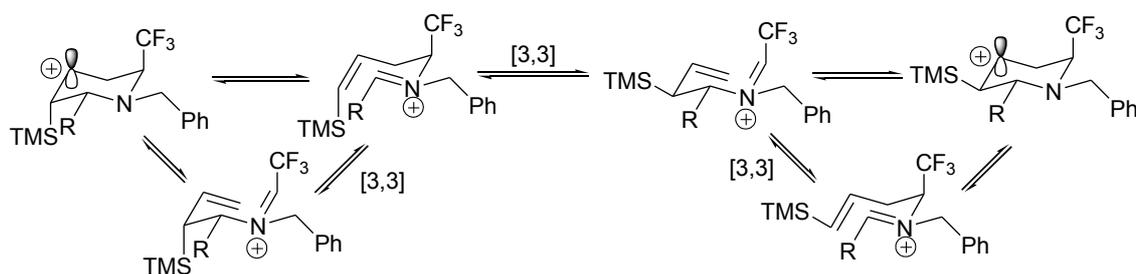
The aza-silyl-Prins reaction for the trifluoromethyl homoallyl amine precursors was successful for 4 out of 5 aldehydes used (Table 31, entries 1-4). The use of aliphatic aldehydes (Table 31, entries 1-3), and also ethyl glyoxylate (Table 31, entry 4) produced positive results. The greatest yield obtained was for ethyl glyoxylate, where both geometric isomers were consumed in the reaction and it was assumed this was due to the reactivity of the intermediate iminium ion in either form, **269** and **270** (Scheme 78). As with previous examples, the reactivity of ethyl glyoxylate contributes to the shorter reaction time.



**Scheme 78.** Formation of either form of iminium ion intermediates lead to heterocyclic product.

In the other aldehydes, only the (*Z*)-alkene **258** was consumed and the (*E*)-alkene **266** remained in approximately the same amount as in the starting material on analysis of GCMS and <sup>1</sup>H NMR data. From this, it can be assumed that the (*Z*)-alkene **258** is the

more reactive isomer, probably because it maximises orbital overlap in the  $\beta$ -effect. However, the (*E*)-alkene **266** is capable of cyclisation due to its consumption in the example involving ethyl glyoxylate. It was assumed that even in the other examples, the (*E*)-alkene **266** must be consumed to a certain extent because on use of phenylacetaldehyde, a yield of over 50% was observed. It was also believed that some of the (*Z*)-alkene **258** was converted to the (*E*)-isomer **266** via the aza-Cope [3,3] sigmatropic rearrangement (Scheme 79). The evidence for this is from previous examples of the aza-silyl-Prins reaction where the (*E*)-isomer **16** was isolated by column chromatography (Scheme 6).



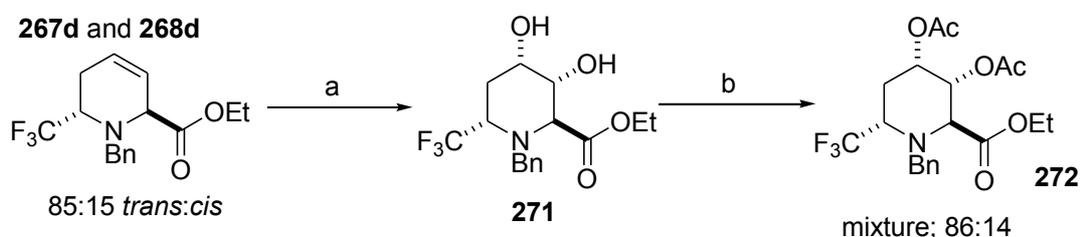
**Scheme 79.** The role of the aza-Cope rearrangement in the formation of reaction intermediates.

As with the previous examples, the reaction times for the fluorinated precursors were longer than before. It was assumed that this is due to the electronic effect the trifluoromethyl group has on the nucleophilicity of the amine precursor. The yields for phenylacetaldehyde and octanal are reasonably good based on the fact that the starting material was a geometric mixture (**258** and **266**). Unfortunately, the tetrahydropyridines **267c** and **268c** derived from phenylacetaldehyde were relatively unstable and decomposed over time, comparable with the example from the silyl-Prins reaction. This meant that full characterisation could not be obtained for this compound as decomposition gave inaccurate analysis. As with the silyl-Prins examples, the use of cyclohexanecarboxaldehyde (Table 31, entry 1) gave lower yields. The diastereoselectivity of the reaction was still reasonably good when considering that two examples exclusively produced *trans*-2,6-disubstituted-3,4-tetrahydropyridines **267** and the other two gave a high percentage of the *trans*-diastereomer. It was not possible to separate the mixtures of diastereomers by chromatography. It is assumed that the presence of the large *N*-substituent favours the formation of the *trans*-isomer, a phenomenon known as  $A^{1,3}$  strain. For the time being, the relative stereochemistry could only be supported by the absence of any nOe effect between the C2 and C3 hydrogens. The aromatic example (Table 31, entry 5) was the only aldehyde that failed to produce any significant product. In this case, the (*Z*)-isomer **258** was consumed in the reaction but

only trace quantities of product were observed on analysis of the crude material. The majority of the product mass was attributed to unidentifiable species.

### . cFurther Functionalisation of Tetrahydropyridine Olefin

As before, the formation of an olefin allowed further functionalisation of the 2,6-disubstituted-3,4-tetrahydropyridine. The use of ethyl glyoxylate in the aza-silyl-Prins reaction has the potential for the formation of pipercolate derivatives. These pipercolate esters are ideal precursors for the total synthesis of pipercolic acid analogues. Pipercolic acid is a nonproteinogenic amino acid, which is a precursor to a number of bioactive compounds such as synthetic peptides and local anesthetics. Therefore it was decided to functionalise the 6-trifluoromethyl pipercolate species **267d** and **268d** by dihydroxylation, followed by ester formation (Scheme 80).



**Scheme 80.** Reagents and conditions: (a) OsO<sub>4</sub> (1.0 M in H<sub>2</sub>O), NMO, THF, H<sub>2</sub>O, rt, 48 h, 83%; (b) Ac<sub>2</sub>O, DMAP, DCM, rt, 20 h, 50%.

The 85:15 mixture of *trans/cis*-2,6-disubstituted-3,4-tetrahydropyridine **267d** and **268d** was subjected to a dihydroxylation reaction using osmium tetroxide in the presence of NMO to give the diol **271** in 83% crude yield. The crude diol (included a major **271** and minor diastereomer, although the minor diastereomer could not be characterised) could not be purified or fully characterised in this form so was further functionalised. The diol was transformed into the di-acetate **272** in 50% yield by the action of acetic anhydride in the presence of 4-dimethylaminopyridine, using a method from the thesis of a previous group member. The di-acetate was an inseparable 86:14 mixture of diastereomers, but only the major diastereomer **272** could be characterised. It was assumed that the minor diastereomer was a di-acetate of the *cis*-2,6-disubstituted-3,4-tetrahydropyridine **268d**, although this could not be confirmed by <sup>1</sup>H NMR and NOESY experiments. NOESY experiments were used and supported the relative stereochemistry of the major di-acetate **272**. This study also allowed us to confirm the *trans*-diastereoselectivity of the aza-silyl-Prins reaction for the fluorinated precursors. A 1.4 and 1.9% enhancement for C3 and C4 hydrogens on irradiation of each confirmed the *syn* dihydroxylation. The absence of any

significant nOe effect between the C2 hydrogen and the C3 or C4 hydrogens suggests that the dihydroxylation had occurred from the opposite face to the C2 substituent. Lastly, the 1.4% enhancement of the C6 hydrogen on irradiation of the C4 hydrogen suggests the *trans* stereochemistry across the heteroatom (Figure 20). Although the di-acetate **272** was crystalline, unfortunately the X-ray crystal structure could not be obtained and so the relative stereochemistry could not be confirmed.

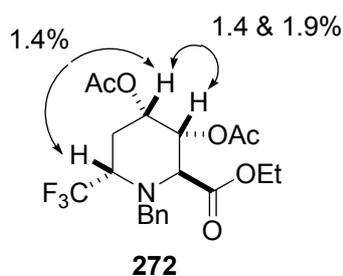
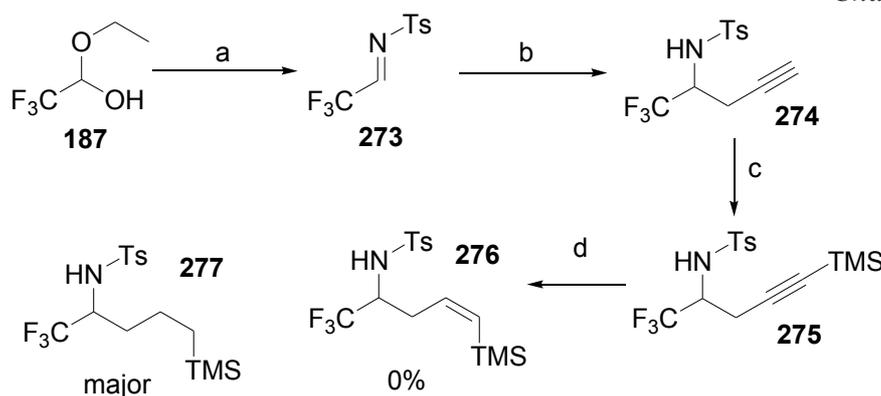


Figure 20. The nOe effects in 3,4-diacetylated-pipecolate.

### . dPrecursor Synthesis III – Formation of 1-CF<sub>3</sub>-Homoallylic

#### Tosylamine

Based on the success found in the aza-Prins reaction of an *N*-tosyl amine, it was decided to incorporate this group into the  $\alpha$ -trifluoromethyl homoallylic amine, for screening in the aza-silyl-Prins reaction. Our studies into the aza-Prins reaction showed that the presence of the *N*-tosyl group enhanced the reactivity of the reaction intermediates. If this was utilised for the fluorinated precursor, perhaps greater yields of product and shorter reaction times could be obtained for the aza-silyl-Prins reaction. It was proposed to obtain the target precursor in 4 steps from the gaseous trifluoroacetaldehyde, generated *in situ* from commercially available 2-ethoxy-1,1,1-trifluoropropane **187** and then to use the same successful methodology that gave the  $\alpha$ -trifluoromethyl-*N*-benzyl amine precursor using the Barbier-type allylation reaction (Scheme 81).



**Scheme 81. Reagents and conditions:** (a) (i) 98%  $\text{H}_2\text{SO}_4$  (aq), 80 °C, (ii)  $p\text{-TsNH}_2$ , pyridine, THF, rt, 48 h, (iii)  $\text{SOCl}_2$ ,  $\text{C}_6\text{H}_6$ , reflux, 5 h; (b) propargyl bromide, Zn,  $\text{TMSCl}$ , DMF, rt, 2 h, 22% for 2 steps; (c)  $n\text{-BuLi}$ ,  $\text{TMSCl}$ , THF, -78 °C, 45%; (d)  $\text{DiBAL}$ ,  $\text{Et}_2\text{O}$ , reflux, 18 h.

The commercial hemiacetal **187** was converted to trifluoroacetaldehyde by addition to sulfuric acid at 80 °C. The condensed gas was immediately transferred as an excess to a sealed vessel containing 4-methylbenzenesulfonamide and pyridine. After subsequent treatment with thionyl chloride, the  $N$ -tosyl imine **273** was afforded and used immediately as it is reported to be highly unstable. The Barbier-type allylation procedure using propargyl bromide with zinc and  $\text{TMSCl}$  as promoters afforded the propargylic  $N$ -tosyl amine **274** in 22% overall yield for 3 steps. The low yield for these 3 steps could be based on the gaseous medium used and also the stability of the intermediate imine **273**. The alkyne **274** was then silylated using  $\text{TMSCl}$ , with  $n$ -butyllithium as base to afford the alkynylsilane **275** in 45% yield. Unfortunately, when the *cis* reduction with  $\text{DiBAL}$  was performed, only the related alkane **277**, produced by over-reduction, was observed on analysis by GCMS and  $^1\text{H}$  NMR. The other organic matter isolated after acidic work-up was insoluble in all tested organic solvents, including DMSO and methanol. Owing to this failure, this approach was abandoned.

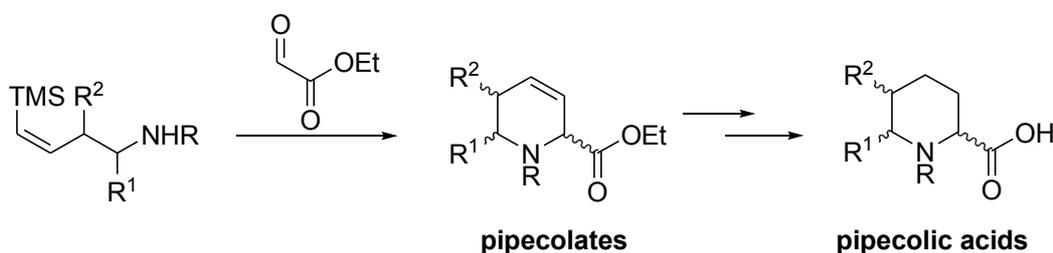
The use of the aza-silyl-Prins reaction has allowed access to heterocycles that are of biological interest as they contain a trifluoromethyl group. This group has had major effects on the reactivity of substrates and reaction intermediates. The use of a geometric mixture of homoallyl amines has allowed us to suggest that (*Z*)-isomers are more reactive than the (*E*)-isomer based on our observations. Future studies could include targeting the trifluoromethyl-substituted homoallyl- $N$ -tosyl amine **276** to improve reaction times and product yields; it is possible that an alternative route to this molecule could be the hydrotitration of the propargylic  $N$ -tosyl amine **275**.

**CHAPTER FOUR: Towards the Synthesis of  
Pipelicolic Acid Analogues and Pipecolates**

### . II Literature Review for Synthesis of Pipecolic Acid and Analogues

It has been previously shown that the aza-silyl-Prins reaction may be utilized to synthesize the racemic form of small natural products. For example, solenopsin A was obtained by using a simple long chain aliphatic aldehyde as the substrate for the aza-silyl-Prins reaction and then, after hydrogenation of the product tetrahydropyridine species, the piperidine-containing natural product was produced (Scheme 2).

It has been proposed that pipecolic acid analogues or the ester-containing pipecolates could be prepared using ethyl glyoxylate as substrate in the aza-silyl-Prins reaction. To obtain the carboxylic acid function of the pipecolic acids, subsequent hydrolysis of the ester function is required, followed by the reduction step or *vice versa*s (Scheme 82).



**Scheme 82. Proposal for access to pipecolates and pipecolic acid analogues.**

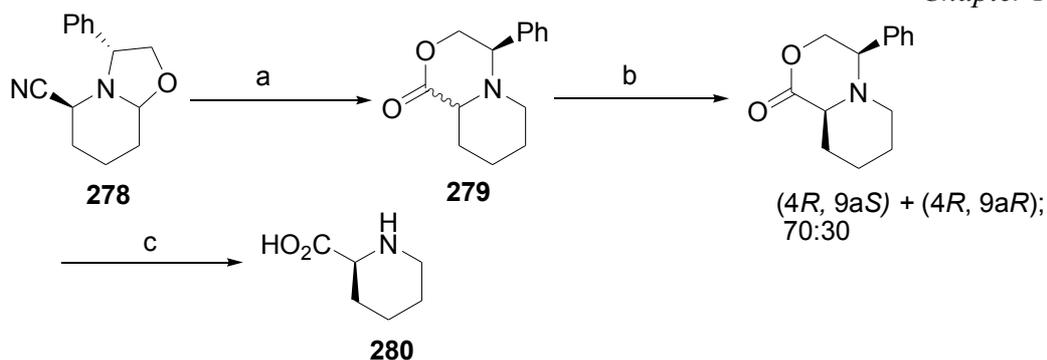
It is also proposed that di-substituted or even tri-substituted analogues could be produced by simply varying the substituent on the  $\alpha$  and  $\beta$  positions of the homoallylic amine precursor or even by functionalising the olefin on the tetrahydropyridine ring. The total synthesis of pipecolic acid itself has been completed on numerous occasions; therefore only analogues would be targeted. However to make observations on the efficiency of our route, comparisons were made with the syntheses of pipecolic acid in the literature.

### . 13 Formation of 2-Substituted Pipecolic

#### Acids

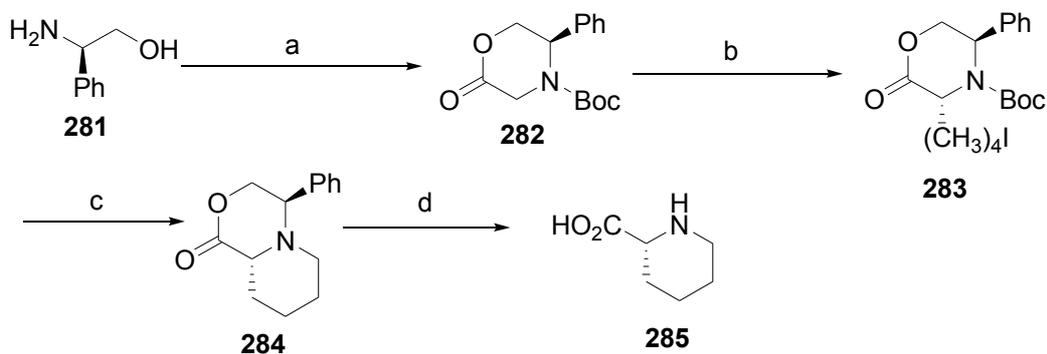
Examples of the synthesis of pipecolic acid reported are *via* enzyme-catalysed reactions, asymmetric hydrogenation, or by ring closing metathesis.

One example by Hou involved treating (*R*)-2-cyano-6-phenyloxazolopiperidine **278** with acid, followed by reduction to form a unknown mixture of diastereomers of 4-phenylhexahydropyrido[2,1-c][1,4]-oxazin-1-ones **279**. These were then converted into (*S*)-pipecolic acid **280** after epimerisation and hydrogenation (Scheme 83). With replacement of the proton source with an alkyl halide in the epimerisation step, 2-substituted piperidines could also be formed.



**Scheme 83.** Hou's route to (*S*)-pipecolic acid. *Reagents and conditions:* (a) (i) HCl, EtOH, (ii) Zn(BH<sub>4</sub>)<sub>2</sub>; (b) (i) LDA, (ii) H<sup>+</sup>; (c) H<sub>2</sub>, Pd/C.

Biological studies have shown that the (*R*)-form of pipecolic acid **285** has a higher affinity towards muscarinic receptors in humans than the (*S*)-form **280**. To synthesise the more active form, Hou began by forming a chiral glycine enolate **282** synthon from commercially available (*R*)-2-phenylglycinol **281**. Monoalkylation of the enolate **282** with diiodobutane gave **283**, followed by deprotection of the nitrogen substituent and then cyclisation under basic conditions, to provide the oxazinone **284**. This was submitted to catalytic hydrogenation to afford the (*R*)-form **285** in good yield (Scheme 84).



**Scheme 84.** (*R*)-pipecolic acid accessed *via* chiral glycine enolate synthon. *Reagents and conditions:* (a) (i) BrCH<sub>2</sub>CO<sub>2</sub>, (ii) Boc<sub>2</sub>O, (iii) PTSA, 34% for 3 steps; (b) NaN(SiMe<sub>3</sub>)<sub>2</sub>, I(CH<sub>2</sub>)<sub>4</sub>I, HMPA, THF, -78 °C, 65%; (c) (i) TFA, (ii) EtNi-Pr<sub>2</sub>, 83 °C, 65% for 2 steps; (d) H<sub>2</sub>, Pd(OH)<sub>2</sub>, 99%.

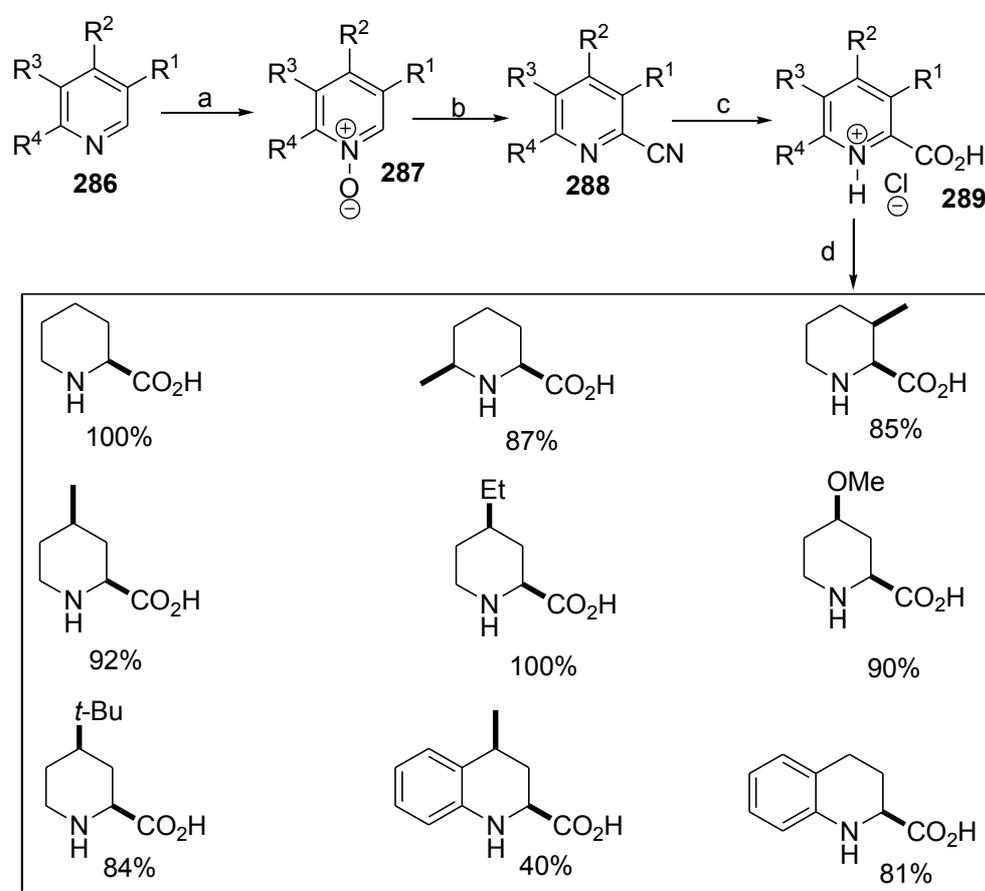
So, from this example, it has been shown that both forms of pipecolic acid can be obtained relatively easily. However racemic pipecolic acid could be obtained in a smaller number of steps using the aza-silyl-Prins reaction and more importantly, produce analogues of variable functionality by utilizing the olefin on the tetrahydropyridine ring and by introducing substituents in the C6 position. If the aza-silyl-Prins reaction could be utilised to form tetrahydropyridines enantioselectively, then perhaps both enantiomers of pipecolic acid could be synthesised with relative ease.

## . 14 Formation of 2,6-Disubstituted Pipercolic Acids and Other

## Analogues

Next the synthesis of 6-substituted pipercolic acids will be reviewed, which could possibly be accessed *via* the aza-silyl-Prins reaction.

The first example by Shuman does not contain a cyclisation step but features the selective 2-cyanation of pyridines and quinolines (**286**) *via* the related *N*-oxide **287**, utilising a modified Reissert-Henze reaction. The resulting nitriles **288** were simply hydrolysed to the corresponding 2-carboxylic acids **289** and hydrogenation of the pyridine ring over platinum oxide afforded various substituted pipercolic acids in good yields (Scheme 85).

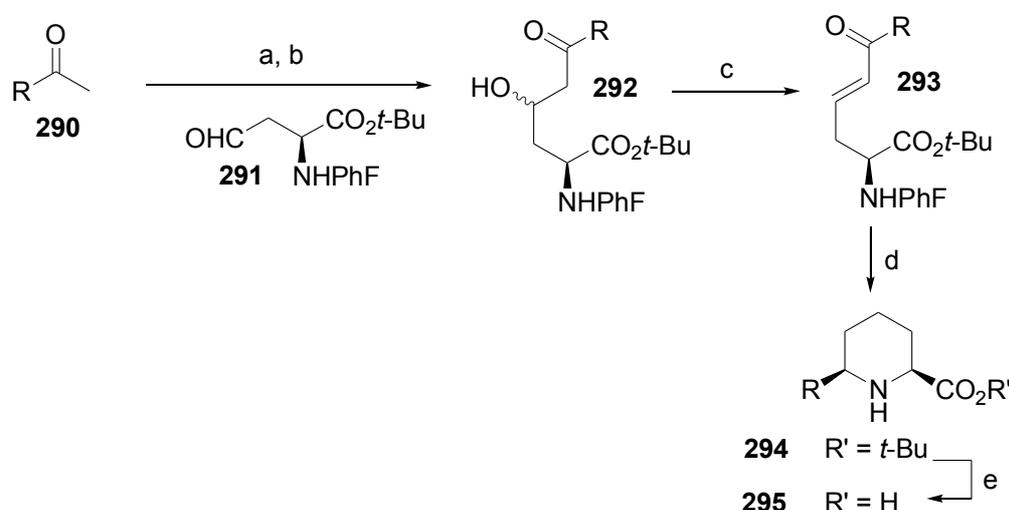


Scheme 85. Reagents and conditions: (a)  $\text{H}_2\text{O}_2$ ,  $\text{HOAc}$ ; (b)  $\text{TMSCN}$ ,  $\text{DCM}$ ,  $(\text{Me})_2\text{NCOCl}$ ; (c)  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ; (d)  $\text{H}_2$ ,  $\text{PtO}_2$ , 60 psi.

Lubell also focuses on the synthesis of 6-substituted pipercolic acid analogues but in high enantiopurity. The route employs an aldol condensation/reductive amination sequence to transform *N*-(PhF)aspartate  $\beta$ -aldehyde into alkylpipercolic acids. This route also offers the opportunity to introduce alkyl substituents into 4 of the 5 ring carbons by using  $\beta$ -alkyl-branched aspartates and alkyl-substituted enolates. In the first step, the aldol

condensation between the *N*-(PhF)aspartate  $\beta$ -aldehyde **291** and the lithium enolates of a variety of methyl alkyl ketones **290** gives the  $\epsilon$ -oxo  $\gamma$ -hydroxy  $\alpha$ -*N*-(PhF)amino esters **292** in 61-93% yields. After mesylate formation and *in situ* elimination to give **293**, these were subjected to catalytic hydrogenation, which effected reduction of the double bond, the cleavage of the PhF group, iminium ion formation and reduction to afford *t*-butyl 6-alkylpipercolates **294** in 86-91% yield. These were isolated quantitatively as hydrochloride salts **295** on treatment with HCl in DCM. Unfortunately the same hydrogenation of the enone directed towards a 6-arylpipercolate only gave a maximum 20% yield (Table 32).

**Table 32. Formation of 6-substituted pipercolic acids. Reagents and conditions:** (a) *n*BuLi, (*i*Pr)<sub>2</sub>NH, THF, -78 °C; (b) THF, -78 °C; (c) MsCl, Et<sub>3</sub>N, DCM, 0 °C; (d) H<sub>2</sub>, Pd/C, MeOH; (e) HCl, DCM.



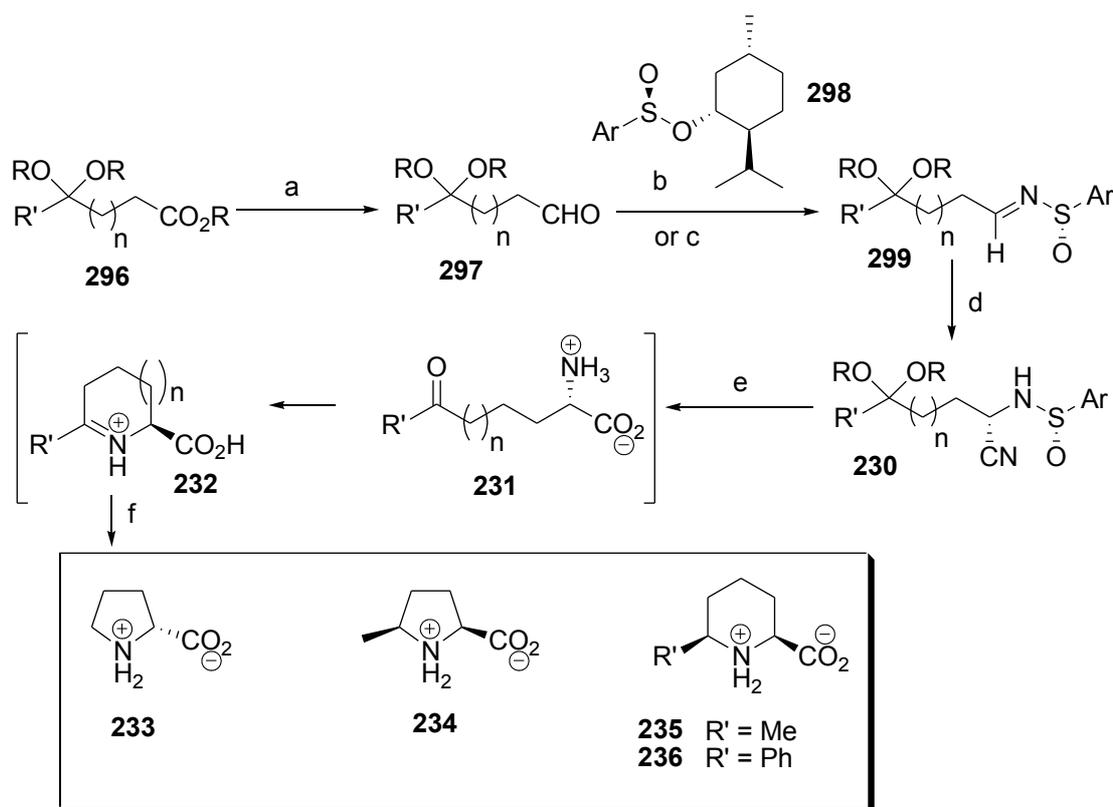
Entry	Ketone	R	%Yield of 292	% Yield of 293	%Yield of 294	%Yield of 295
1	Pinacolone	<i>t</i> -Bu	84	64	86	98
2	3-Methyl-2-butanone	<i>i</i> -Pr	77	87	91	100
3	2-Pentanone	<i>n</i> -Pr	72	91	86	97
4	Acetone	Me	68	86	90	98
5	Acetophenone	Ph	93	92	20	96
6	2-Acetylpyridine	2-Pyridyl	61	80	0	-

The enantiomeric purity of the 6-methylpipercolate **294d** was determined by conversion into the *N*-benzylpipercolate and then coupling to a chiral amine, giving a diastereomeric excess of >99%.

Davis has reported the asymmetric synthesis of proline and pipercolic acid derivatives *via* masked oxo sulfinimines. The general approach involved the synthesis of a masked oxo sulfinimine from a masked oxo aldehyde. The masked oxo aldehydes **297** were easily accessed by the *Di*BAL reduction of the corresponding esters **296**. Then the sulfinimines

**299** could be accessed by a one-pot procedure involving the treatment of these aldehydes **297** with (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate **298** with LiHMDS at -78 °C. From here, a sulfinimine-mediated asymmetric Strecker synthesis was used to generate an  $\alpha$ -aminonitrile **230** with the desired stereochemistry, followed by hydrolysis and reduction to give the cyclic amino acids. The asymmetric Strecker synthesis involves addition of isopropanol to diethylaluminium cyanide followed by the sulfinimine **299** to afford amino nitriles **230** in good yields and diastereoselectivity. To complete the synthesis, the aminonitriles were treated with 6M HCl at reflux. This achieved essentially five operations in one-pot: first hydrolysis to remove the *N*-sulfinyl auxiliary with concomitant conversion of the nitrile to the acid; then the oxo group was unmasked to give the intermediate oxo  $\alpha$ -amino acid **231** which then cyclised to an iminium ion **232**, isolated as an imine salt. The salt was then catalytically hydrogenated to afford proline **233** and pipercolic analogues **234**, **235** and **236** in good to excellent yields and high enantiomeric excess (Table 33). The geometry of the disubstituted species was exclusively *cis* across the heteroatom and the authors believe this had arisen from the hydrogenation of the least hindered face (Scheme 86).

**Scheme 86. Reagents and conditions:** (a) DiBAL, -78 °C; (b) LiHMDS, -78 °C; (c) Ti(OEt)<sub>4</sub>, DCM; (d) Et<sub>2</sub>AlCN, *i*-PrOH; (e) 6 M HCl, reflux; (f) H<sub>2</sub>, Pd, MeOH.

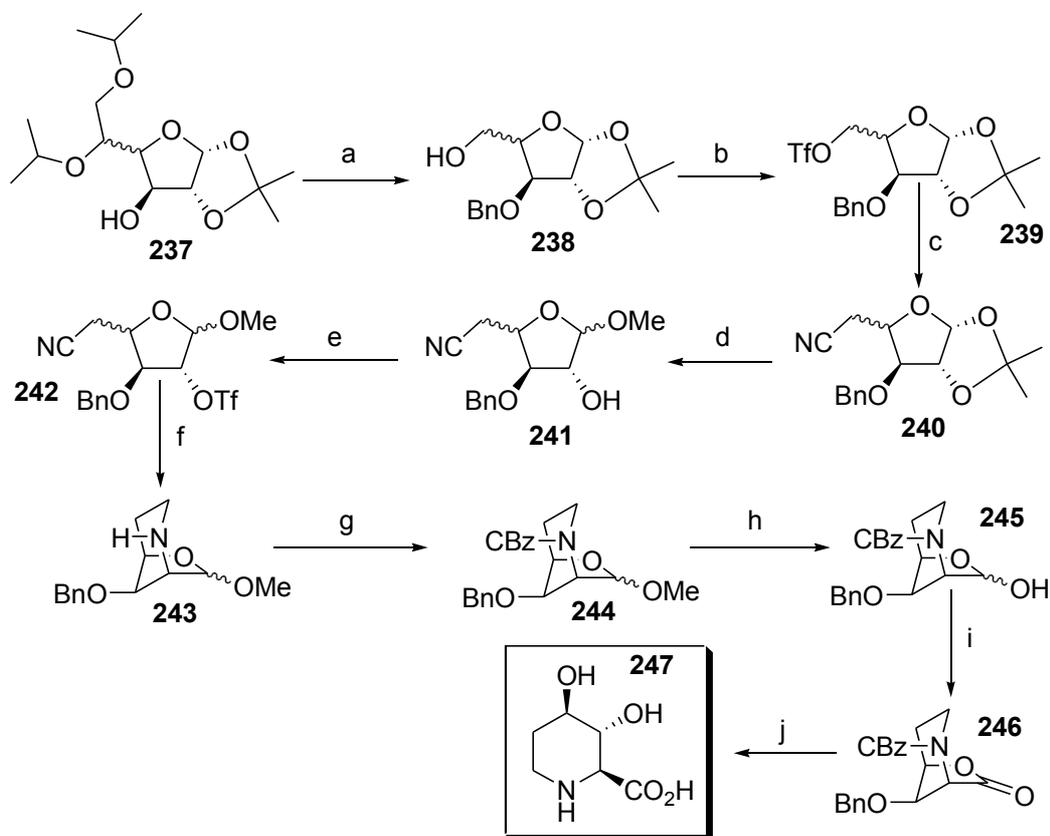


**Table 33. Formation of proline and pipercolic acid derivatives by Davis.**

Entry	R	R'	n	%Yield of 299	%Yield of 230	%Yield of 233-236	% ee
1	Me	H	1	74	58	77	98
2	allyl	Me	1	92	54	80	95
3	allyl	Me	2	98	61	85	97
4	allyl	Ph	2	65	80	48	95

Finally, Fleet has targeted the cyclic amino acid for screening as a potential inhibitor of HIV replication. The precursor for this synthesis was a protected xylose **238** which itself was generated in 3 steps from diacetone glucose. The free hydroxyl group of the xylose was converted to triflate **239** in the presence of trifluoromethanesulfonic anhydride. This was subsequently transformed into a nitrile **240** by substitution with potassium cyanide. Further treatment with methanolic hydrogen chloride gave the methyl furanosides **241** as a 3:4 mixture of  $\alpha$ : $\beta$  anomers. This mixture was converted into the corresponding triflates **242**, which after treatment with borane-dimethyl sulfide and work-up with potassium carbonate, gave the bicyclic piperidines **243**. These were protected as the benzyl carbamates **244**, the methoxy functions were hydrolysed with TFA to afford a mixture of

lactols **245**. These lactols were oxidised with bromine to give the carbamate-protected lactones **246**. From here the (2*S*,3*R*,4*R*)-3,4-dihydroxy pipercolic acid **247** was obtained in 34% overall yield from the protected xylose **238** by the hydrogenolytic removal of both protecting groups as well as cleavage of the ester linkage (Scheme 87).



**Scheme 87. Reagents and conditions:** (a) 3 steps; (b)  $\text{Ti}_2\text{O}$ , pyridine, 94%; (c) KCN, DMF, 96%; (d) HCl/MeOH, 95%; (e)  $\text{Ti}_2\text{O}$ , pyridine, 95%; (f) borane. $\text{Me}_2\text{S}$ ,  $\text{K}_2\text{CO}_3$ , 96%; (g) CBzCl,  $\text{NaHCO}_3$ , THF,  $\text{H}_2\text{O}$ ; (h)  $\text{NaBH}_4$ , EtOH(aq), 97%; (i)  $\text{Br}_2$ , Barium carbonate, dioxane(aq), 84%; (j)  $\text{H}_2$ , Pd/C, 89%.

## . II Results and Discussion: Studies into the Formation of Pipercolic Acid Analogues and Pipercolates

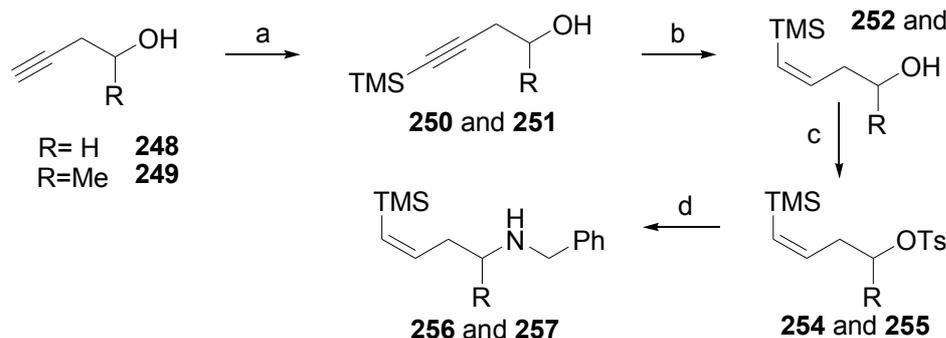
Work in our group had already achieved the synthesis of the racemic forms of solenopsin A and *epi*-dihydropinidine using the aza-silyl-Prins reaction.

It was envisaged that a similar synthetic sequence could afford the racemic form of an analogue of pipercolic acid. Also, utilising the olefin functionality of the tetrahydropyridine core would allow the simple synthesis of the related pipercolate analogues.

The *N*-benzyl (*Z*)-4-trimethylsilyl-1-ylamine starting materials for the aza-silyl-Prins reaction have previously been prepared from the commercially available starting

### Amines

materials, 3-butyne-1-ol and 4-pentyne-2-d (Scheme 88).



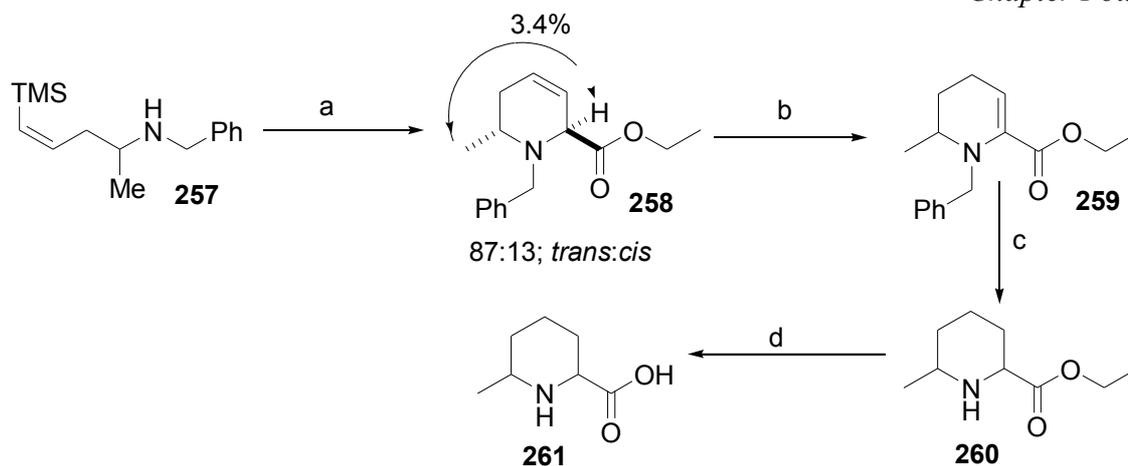
**Scheme 88. Reagents and conditions:** (a) *n*-BuLi, THF, -78 °C, 2 h, followed by TMSCl, -78 °C to rt, 1 h, 1.0 M HCl, rt, 45 min, R=H, 61%; R=Me, 79%; (b) 1.0 M DiBAL in hexane, Et<sub>2</sub>O, 0 °C, 0 °C to rt and then reflux overnight, R=H, 65%, R=Me, 66%; (c) Et<sub>3</sub>N, TsCl, 4-DMAP, 0 °C, 4 h, R=H, 87%, R=Me, 57%; (d) EtOH, benzylamine, 80 °C, 5 h, R=H, 78%, R=Me, 100%.

Firstly the silylated homopropargylic alcohols were easily prepared in 61% (R=H, **250**) and 79% (R=Me, **251**) yields using literature methods, using two equivalents of *n*-butyllithium, in THF at -78 °C, followed by addition of two equivalents of trimethylsilyl chloride and then quenching with hydrochloric acid. The alkyne function was then *cis* reduced with DiBAL in diethyl ether at reflux to afford the homoallylic alcohols in 65% (R=H, **252**) and 66% (R=Me, **253**) yields respectively. Displacement of the alcohol function was effected by tosylation and then subsequent amination. Tosylated alcohols were obtained in 87% (R=H, **254**) and 57% (R=Me, **255**) yields and the required *N*-benzyl *Z*-4-trimethylsilyl-1-ylamines in 78% (R=H, **256**) and 100% (R=Me, **257**) yields by the action of benzylamine.

## . 16Synthesis of 6-Methyl

### Pipecolic Acid

Initially, the aim of this study was the total synthesis of simple analogues of (±)-pipecolic acid, and so the 6-methyl substituted derivative, (±)-6-methylpiperidine-2-carboxylic acid was targeted. In theory this could be obtained by the use of ethyl glyoxylate in the azasilyl-Prins reaction, hydrolysis of the ester function and reduction to the piperidine. The proposed three-step synthesis began with coupling in equimolar quantities, the silylated homoallylic amine to ethyl glyoxylate, activated by indium trichloride in acetonitrile (Scheme 89).



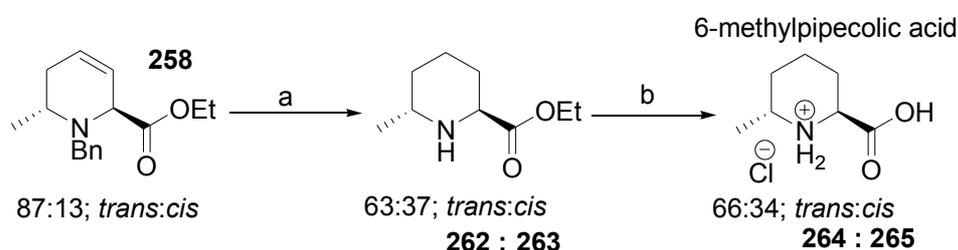
**Scheme 89. Reagents and conditions:** (a)  $\text{InCl}_3$ , ethyl glyoxylate,  $\text{CH}_3\text{CN}$ , rt, 48 h, 74%; (b) 1M LiOH, MeOH, 0 °C, overnight, 58%; (c)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$  (20%), EtOH, r.t, 5 h, quantitative; (d) 1M LiOH, MeOH, 0 °C, overnight.

The tetrahydropyridine **258** was obtained in 74% yield, and nOe studies confirmed mostly *trans* selectivity across the nitrogen with a large 3.4% enhancement of the C2 proton on irradiation of the 6-Me protons, and no enhancement of the C2 proton on irradiation of the C6 proton. Reflux temperatures were investigated for the aza-silyl-Prins reaction but were found to be detrimental to the product yields (c.f.8% for reflux). Next, instead of following the exact pathway that had been used in the ( $\pm$ )-solenopsin A and ( $\pm$ )-*Epi*-dihydropinidine synthesis, it was proposed to hydrolyse the ester function before hydrogenation as reported by Gotor and co-workers in their attempts to make enantiopure (*S*)-pipercolic acid. The action of a 1M aqueous solution of lithium hydroxide, with methanol at 0 °C overnight showed complete consumption of starting material by TLC. After GCMS and  $^1\text{H}$  NMR analysis it was found that no carboxylic acid had been generated, but in fact the  $\alpha,\beta$ -unsaturated ester derivative **259** of the tetrahydropyridine had been formed in 58% yield. Instead of the hydroxyl anion attacking the ester carbonyl function, it had actually deprotonated the acidic C-2 proton and subsequent quenching with acid allowed the alkene migration. This had the effect of epimerising the C2 centre and therefore destroying the previously established diastereoselectivity. This species is a possible precursor to access enantiopure pipercolic acid analogues, *via* the asymmetric hydrogenation of this 2,3-tetrahydropyridine, inducing chirality in the C2 position, a method utilised by Comins. However, it was decided to continue with the synthesis of racemic pipercolic acid analogues.

It was now proposed to firstly remove the *N*-substituent and olefin from the tetrahydropyridine **259** by hydrogenation and then hydrolyse the ester function. Now, using hydrogen gas over catalytic quantities of palladium hydroxide on carbon in ethanol,

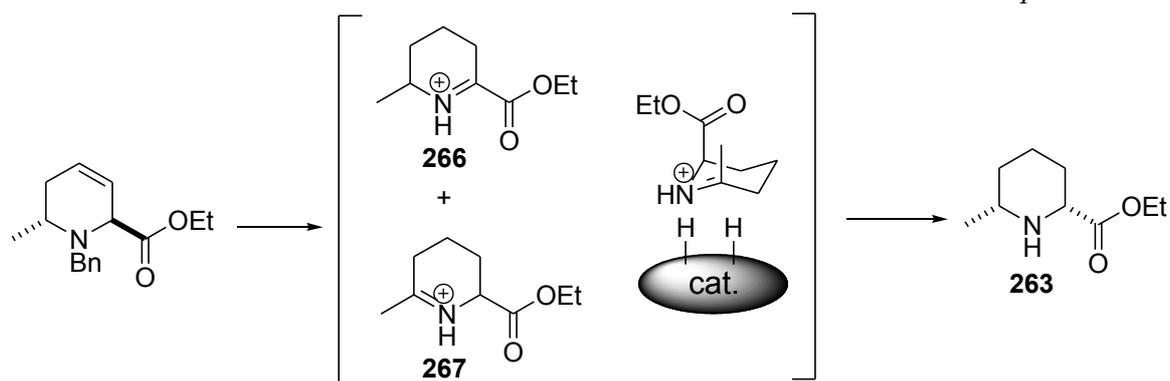
afforded the piperidine 2-ethyl ester **260** in quantitative yield. With no further purification, the crude extract was hydrolysed, as previously described, to afford the 6-methyl derivative of pipercolic acid **261** (Scheme 38). This positive assumption is only based upon HRMS analysis with the presence of the  $[M+H]^+$  ion at 144.1026, with other data being inconclusive (Scheme 89). Some literature precedent for the formation of this pipercolic acid analogue shows that it is normally characterised as a hydrochloride salt, so the synthesis was modified.

This proposal began with the pre-formed 87:13 mixture of *trans* and *cis* 2,6-disubstituted-3,4-tetrahydropyridines **258** derived from the aza-silyl-Prins reaction involving ethyl glyoxylate. It was proposed to use catalytic hydrogenation to remove the *N*-substituent and the olefin, followed by the acid hydrolysis of the C2 ester substituent (Scheme 90).



**Scheme 90. Reagents and conditions:** (a)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$  (20%), EtOH, rt, 5 h, 87%; (b) 6.0M HCl(aq), reflux, 2 h, 83%.

Simultaneous removal of the *N*-substituent and olefin was completed by the action of hydrogen over palladium hydroxide on carbon to give the piperidine-2-carboxylate in 87% yield. Unfortunately, the hydrogenation step gave a 63:37 crude mixture of *trans* **262** and *cis* piperidines **263** (*c.f.*-started with 87:13). It was assumed that when catalytic debenylation took place, there was partial formation of an intermediate iminium ion which racemised either the C2 (**266**) or C6 (**267**) centre. When the iminium ion was reduced, the hydrogenation took place from the least hindered face (Scheme 91). Therefore the *cis*-2,6-disubstituted-3,4-tetrahydropyridine **263** was favoured, which was reported by Davis (Scheme 86). The synthesis was completed by acid hydrolysis of the ester substituent on treatment of hydrochloric acid. This afforded the racemic hydrochloride salt of 6-methylpipercolic acid as a 66:34 mixture of *trans* **264** and *cis* **265** diastereomers (*c.f.*-started with 63:37). Overall this 6-methylpipercolic acid was obtained in 16% overall yield and in 7 steps, beginning with the commercially available 4-pentyn-2-ol.



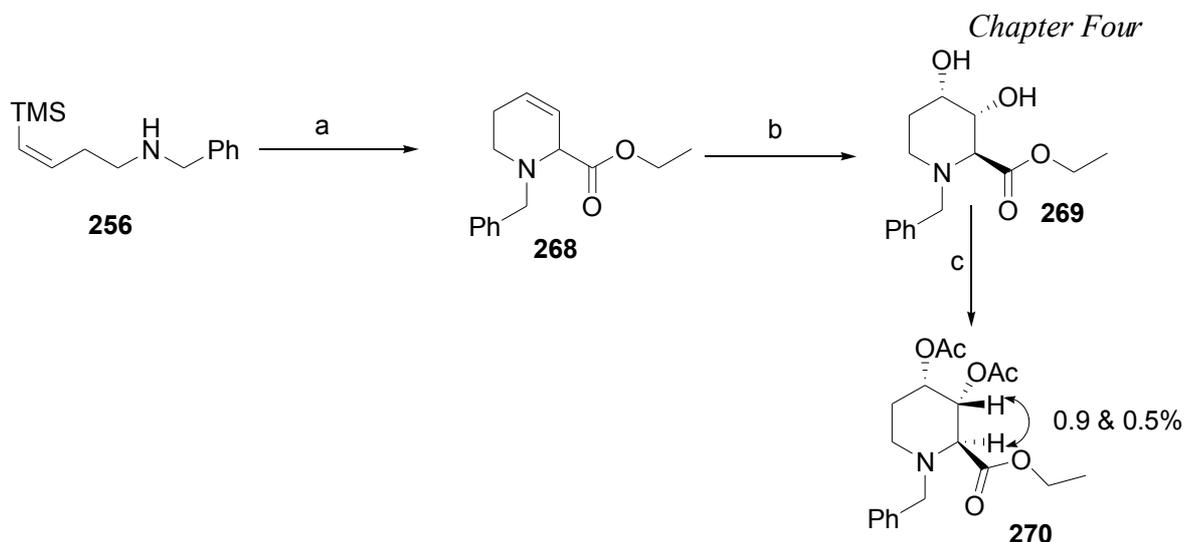
**Scheme 91. De-benzylation and iminium ion formation leads to *cis* product.**

Overall, the formation of a pipercolic acid analogue using the aza-silyl-Prins reaction has been successful and proves the usefulness of this cyclisation reaction in the total synthesis of small natural products. Unfortunately, although the diastereoselectivity of the cyclisation reaction was good, the de-benzylation process affords a mixture of diastereomers.

### . 17Synthesis of 3,4-Dihydroxy

#### Pipercolates

To demonstrate the usefulness of the olefin functionality, the formation of a 3,4-substituted pipercolate derivative was desired. In this instance, the aza-silyl-Prins reaction could be utilised to couple ethyl glyoxylate to the unsubstituted silylated-homoallylic amine. This amine was derived from 3-butyn-1-ol **248** as previously discussed and would form a simple 2-substituted-3,4-tetrahydropyridine **268** (Scheme 92). Then the olefin function could be functionalised for example, by di-hydroxylation as previously employed (Scheme 73 and 80) to form 3,4-dihydroxypipercolate **269**.



**Scheme 92. Reagents and conditions:** (a)  $\text{InCl}_3$ , ethyl glyoxylate,  $\text{CH}_3\text{CN}$ , reflux, 15 h, 70%; (b)  $\text{OsO}_4$  (1.0 M in  $\text{H}_2\text{O}$ ), NMO, THF,  $\text{H}_2\text{O}$ , rt, 72 h, 36%; (c)  $\text{Ac}_2\text{O}$ , DMAP, DCM, rt, 24 h, 69%.

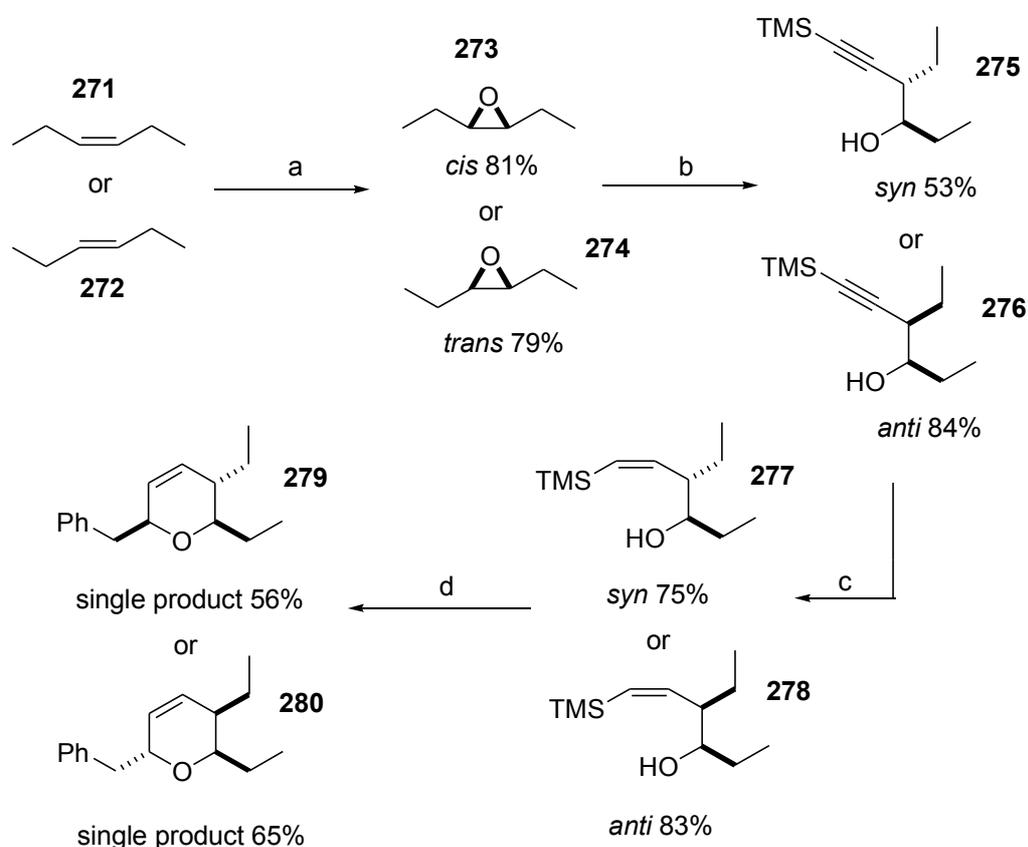
The aza-silyl-Prins reaction of the homoallylic amine **256** and ethyl glyoxylate proceeded smoothly in acetonitrile at reflux temperature to give the 2-substituted-3,4-tetrahydropyridine **268** in 70% yield. This is in contrast to the  $\alpha$ -methyl homoallylic amine **257**, which produced better yields at room temperature. The di-hydroxylation of the tetrahydropyridine was then performed by treatment with osmium tetroxide and NMO, which formed the diol **269** in a disappointing 36% crude yield. This diol could not be purified or characterised fully in this form so it was functionalised further. This was accomplished by transformation to the di-acetate **270** by treatment with acetic anhydride in the presence of 4-dimethylaminopyridine, as previously employed (Scheme 80). The di-acetate **270** was formed in 69% yield from the crude starting material and the occurrence of the di-hydroxylation on the least hindered face was proven by NOESY experiments on this species. Small 0.9% and 0.5% enhancements of C2 and C3 hydrogens on irradiation of either confirmed this. Unfortunately the occurrence of the *syn* di-hydroxylation could not be confirmed as the C3 and C4 hydrogens occur too close to one another in the  $^1\text{H}$  NMR spectrum, but it is assumed based on previous examples (Scheme 73 and 80).

Again the usefulness of the olefin function from tetrahydropyridines has been proven by forming piperolate molecules with high functional diversity. For future work, other substituents could be introduced into the 6-position of the piperidine core of piperolic acids and piperolates. Also worthy of future study would be an attempt to form enantiopure analogues of piperolate molecules using enantiopure substrates or other asymmetric methods that will be discussed at a later stage in this thesis.

**CHAPTER FIVE: Formation of 1,2,5,6-  
Tetrasubstituted-3,4-tetrahydropyridines**

### . Literature Review on the Formation of Multi-substituted Tetrahydropyridines

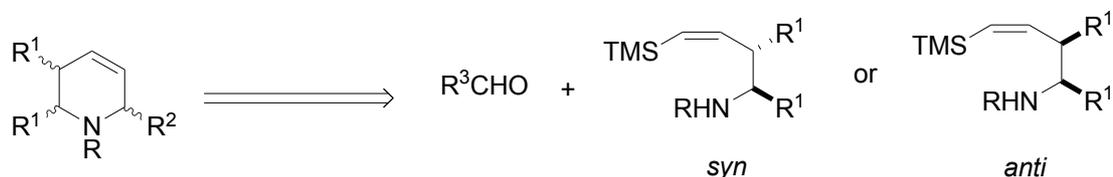
Past work by the group has utilized the silyl-Prins reaction to synthesise 2,5,6-trisubstituted dihydropyrans **279** and **280** from  $\alpha,\beta$ -disubstituted silicon-containing homoallylic alcohols. These cyclisations were completely diastereoselective when beginning with either the *syn* or *anti* alcohols, which themselves were obtained *via* a short synthetic pathway beginning from commercially available symmetrical alkenes. Either the (*Z*) **271** or (*E*)-alkene **272** was transformed to the corresponding epoxide **273** and **274**, each of which was opened with a trimethylsilyl aluminium acetylene species to yield the propargylic alcohols **275** and **276**. These were reduced as with previous examples, to give the desired cyclisation substrates **277** and **278** (Scheme 93).



**Scheme 93.** Synthesis of 2,5,6-trisubstituted dihydropyrans *via* silyl-Prins reaction. *Reagents and conditions:* (a) 77% *m*-CPBA, H<sub>2</sub>O, NaHCO<sub>3</sub>, DCM, 0 °C; (b) (i) *n*-BuLi, toluene, TMS acetylene, -30 °C, 30 min, (ii) Et<sub>2</sub>AlCl, -30 °C, 30 min; (c) (i) DiBAL, Et<sub>2</sub>O, 0 °C, (ii) reflux, 24 h, (iii) H<sub>2</sub>SO<sub>4</sub>(aq), 0 °C; (d) PhCH<sub>2</sub>CHO, InCl<sub>3</sub>, DCM, 16 h, rt.

The proposal was to produce *syn* and *anti*  $\alpha,\beta$ -disubstituted silylated homoallylic amines to test in the aza-silyl-Prins reaction, hopefully to furnish tetrasubstituted tetrahydropyridines in synthetically useful yields (Scheme 94). This would allow us to see if the stereochemical issues follow the same pattern as previously observed when

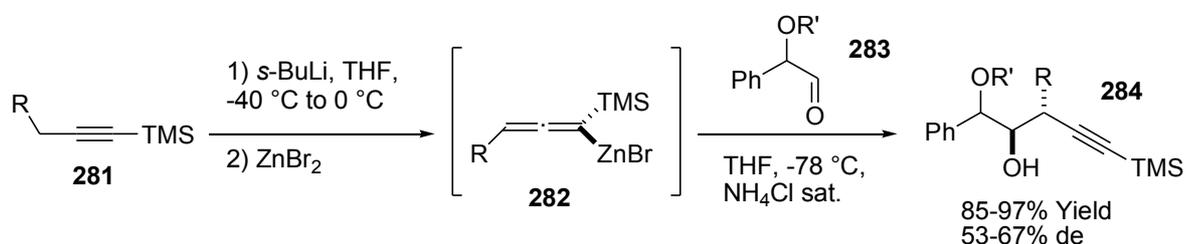
comparing the silyl-Prins and aza-silyl-Prins reactions. Also worthy of note is the fact that the precursor synthesis towards both stereoisomers of the allylic amine could be more challenging and so literature examples for synthesising  $\alpha,\beta$ -disubstituted homoallylic amines will be reviewed, in addition to examples of the synthesis of tetrasubstituted tetrahydropyridines.



**Scheme 94.** Proposal for the formation of N,2,5,6-tetrasubstituted-3,4-tetrahydropyridines.

Firstly the diastereoselective production of  $\alpha,\beta$ -disubstituted homopropargylic amines will be discussed.

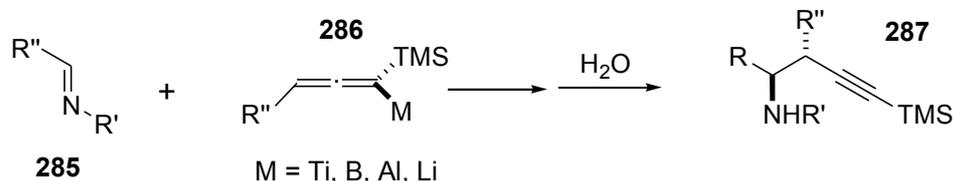
The first example by Normant involves a novel coupling reaction between an allenyl zinc reagent and  $\alpha$ -alkoxy (or siloxy) imines. Before this article, there was little known about the double diastereoselection during addition of chiral allenyl zinc reagents to chiral electrophiles such as aldehydes and imines. Addition of allenylzinc reagents to simple aldehydes has been studied extensively and Zweifel obtained an excellent *anti:syn* ratio (>96:4), dependant on the allenyl moiety substituent groups. The proposal was to investigate whether carbozincation using allenylzinc bromides (derived from the corresponding lithium derivatives) would show the same reactivity as other allenylzinc reagents. Normant obtained his allenyl zinc species **282** via propargylic deprotonation of **281** using *s*-BuLi in THF at  $-40\text{ }^{\circ}\text{C}$ ; and this was followed by transmetalation of the lithium species using zinc(II) bromide. On coupling these species to  $\alpha$ -oxygenated aldehydes **283**, the corresponding trimethylsilyl propargylic alcohols **284** were obtained with low diastereoselectivity for a range of  $\alpha$ -siloxy aldehydes (Scheme 95).



**Scheme 95.** Synthesis of  $\alpha$ -alkoxy (or siloxy) di-substituted alcohols.

It was assumed that the nucleophilicity of the allenylzinc bromides towards aldehydes was too great and so responsible for the low diastereoselection, therefore it was proposed to use a less electrophilic imine. The use of imines was highly appropriate as their

electrophilicity may be fine tuned by varying nitrogen substituents. Interestingly, Yamamoto exclusively obtained *anti* product **287** (Scheme 96) on addition of allenyl metals (Ti, B, Al, Li), derived from 1-(trimethylsilyl)-but-1-yne **286**, to aliphatic imines **285**.

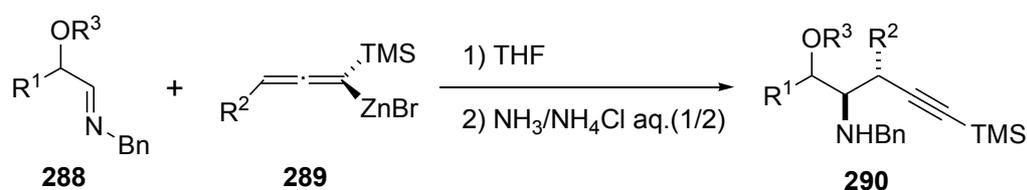


**Scheme 96.** Yamamoto found exclusive *anti* selectivity with imine addition.

This example would be particularly relevant for obtaining precursors for the aza-silyl-Prins reactions, as it would allow us to have possibly identical alkyl substituents in both the  $\alpha$  and  $\beta$  positions as previously used for the examples of the silyl-Prins reaction.

Normant initially screened benzyl imines of mandelic aldehyde, which were protected as silyl derivatives or as MOM ethers. At  $-70\text{ }^{\circ}\text{C}$ , exclusive diastereoselectivity was observed for the addition of the zinc reagents derived from 1-(trimethylsilyl)hex-1-yne with imines containing an  $\alpha$ -hydroxy group bearing either a TIPS, TBS or benzyl group. Exclusive stereochemistry was also obtained at  $-35\text{ }^{\circ}\text{C}$  on adding the TBS imine to the same zinc reagent although the yields were slightly lower (Table 33).

**Table 33.** Imine screening for allenyl zinc additions.



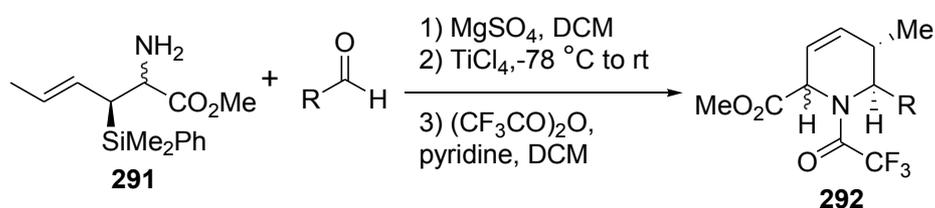
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Temp.( $^{\circ}\text{C}$ )	%Yield	d.e (%)
1	Ph	Pr	TBDPS	-70	90	93
2	Ph	Pr	TIPS	-70	70	>99
3	Ph	Pr	TBS	-70	85	>99
4	Ph	Pr	TBS	-35	75	96
5	Ph	Pr	TBS	0	78	68
6	Me	Pr	Bn	-70	80	>99
7	Ph	Me	TBS	-70	68	>99

So it would seem feasible to be able to use Normant's methodology to produce the  $\alpha,\beta$ -disubstituted homopropargylic amines which could later be used as substrates for the aza-silyl-Prins reaction. Yamamoto does however report upon using simple aliphatic imines with other allenyl metal reagents. If either methodology could be incorporated into the

synthesis of the desired substrate, then there would still be the problem of forming the *syn* product, as these methods report exclusive *anti* selectivity.

The next example by Panek is a route to highly enantioenriched tetrahydropyridines from chiral organosilanes **291** and the methodology was applied to the synthesis of the quinolizidine alkaloid (-)-217A. This study is important as there is little precedent in the literature for synthesis of tetrahydropyridines with high enantiopurity. They suggest that formation of 2,6-tetrahydropyridines with use of allyl and vinylsilanes as the  $\pi$ -nucleophile is limited due to the competitive aza-Cope rearrangement which often compromises reaction diastereoselectivity. Panek reports a highly stereoselective approach to both 2,6-*cis* and *N*,2,6-*trans*-3-*trans*-tetrasubstituted tetrahydropyridines *via* intramolecular imine crotylation. This approach utilised the silicon-bearing centre as the dominant stereocontrol element leading to highly selective annulation. Initial screening used ytterbium triflate to activate the imines generated *in situ* and catalyse an intramolecular crotylation to provide tetrahydropyridines in one pot. The reaction proceeded under mild conditions but unfortunately, the diastereoselectivity was low. It seemed that the vinylglycine type moiety embedded in the annulation product was prone to epimerisation. Eventually titanium(IV) chloride was identified as the most general and effective Lewis acid in promoting annulation and provided an efficient route to the tetrahydropyridines. These were then protected as the trifluoroacetamides **292**, which could be isolated as single stereoisomers in up to 90% yield. It was shown that the reactions involving imines isolated from aromatic aldehydes were more efficient than aliphatic examples with both *cis* and *trans*-2,6-disubstituted tetrahydropyridines being prepared with higher diastereoselectivities. It was also demonstrated that annulation could proceed with complete transfer of chirality from the chiral silane **291** to the product (Table 34).

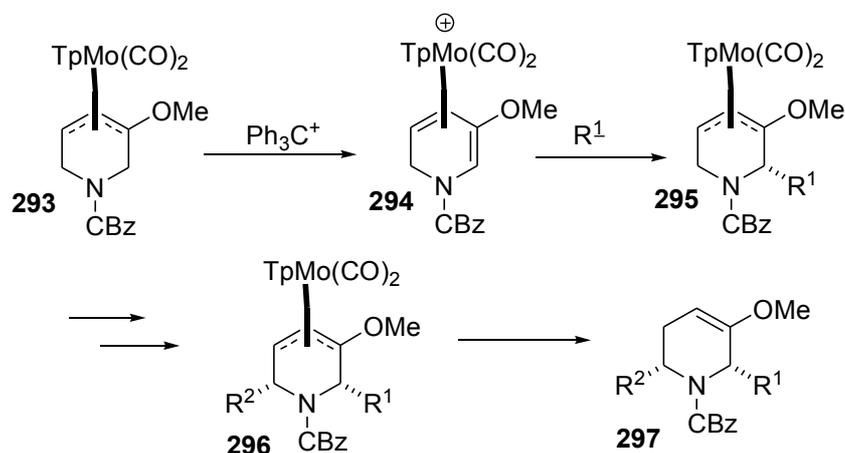
Table 34. Aldehyde screening for asymmetric synthesis of 1,2,5,6-tetrahydropyridines.



Entry	R	Chiral silane	%Yield	dr C2 to C6; <i>cis:trans</i>
1	<i>i</i> -Pr	2,3- <i>anti</i>	73	1:13
2	<i>m</i> -NO <sub>2</sub> Ph	2,3- <i>anti</i>	90	<1:30
3	2-furyl	2,3- <i>anti</i>	89	1:12
4	( <i>trans</i> )PhCHCH	2,3- <i>anti</i>	64	1:9

5	C <sub>6</sub> H <sub>12</sub>	2,3- <i>syn</i>	78	10:1
6	4-BrPh	2,3- <i>syn</i>	82	>30:1
7	2-furyl	2,3- <i>syn</i>	75	8:1

The reaction products could also be converted into isomeric 1,4,5,6-tetrahydropyridines on treatment with DBU in THF, with both *cis* and *trans* isomers converted in >90% yield. The next example by Liebeskind is very different since it does not involve a cyclisation process. It is the enantiocontrolled synthesis of *N*,2,3,6-tetrasubstituted tetrahydropyridines using ( $\eta^3$ -dihydropyridinyl) molybdenum complexes as chiral scaffolds. Complexes with molybdenum centres such as TpMo(CO)<sub>2</sub>(pyranyl) and TpMo(CO)<sub>2</sub>(dihydropyridinyl) are excellent chiral scaffolds for enantioselective synthesis of highly functionalized heterocycles. They have reported the synthesis of *N*,2,3,6-tetrasubstituted tetrahydropyridines using regiocontrolled abstraction of hydride from (3-methoxy- $\eta^3$ -dihydropyridinyl)TpMo(CO)<sub>2</sub> complexes **293**. Abstraction of the hydride with Ph<sub>3</sub>CPF<sub>6</sub> gave the  $\eta^4$ -diene cation **294** and this reacted with several nucleophiles to provide the C2 substituent in **295**. After a second hydride abstraction and subsequent nucleophilic addition, the (2,6-disubstituted-3-methoxy-dihydropyridinyl)molybdenum complex **296** was obtained. Decomplexation gave the *N*,2,3,6-tetrasubstituted tetrahydropyridines **297**, with poor regioselectivity for the first hydride abstraction except when the 3-substituent is a methoxy or phenoxy (Scheme 97).



Scheme 97. General procedure for asymmetric synthesis of *N*,2,3,6-tetrahydropyridines by Liebeskind.

These few literature examples have shown us that multi-substituted tetrahydropyridines are obtainable, however controlling the relative stereochemistry is often challenging.

Using  $\alpha,\beta$ -disubstituted homopropargylic amines in the aza-silyl-Prins reactions would give us a novel route to these highly functionalised heterocycles and hopefully in high diastereoselectivity.

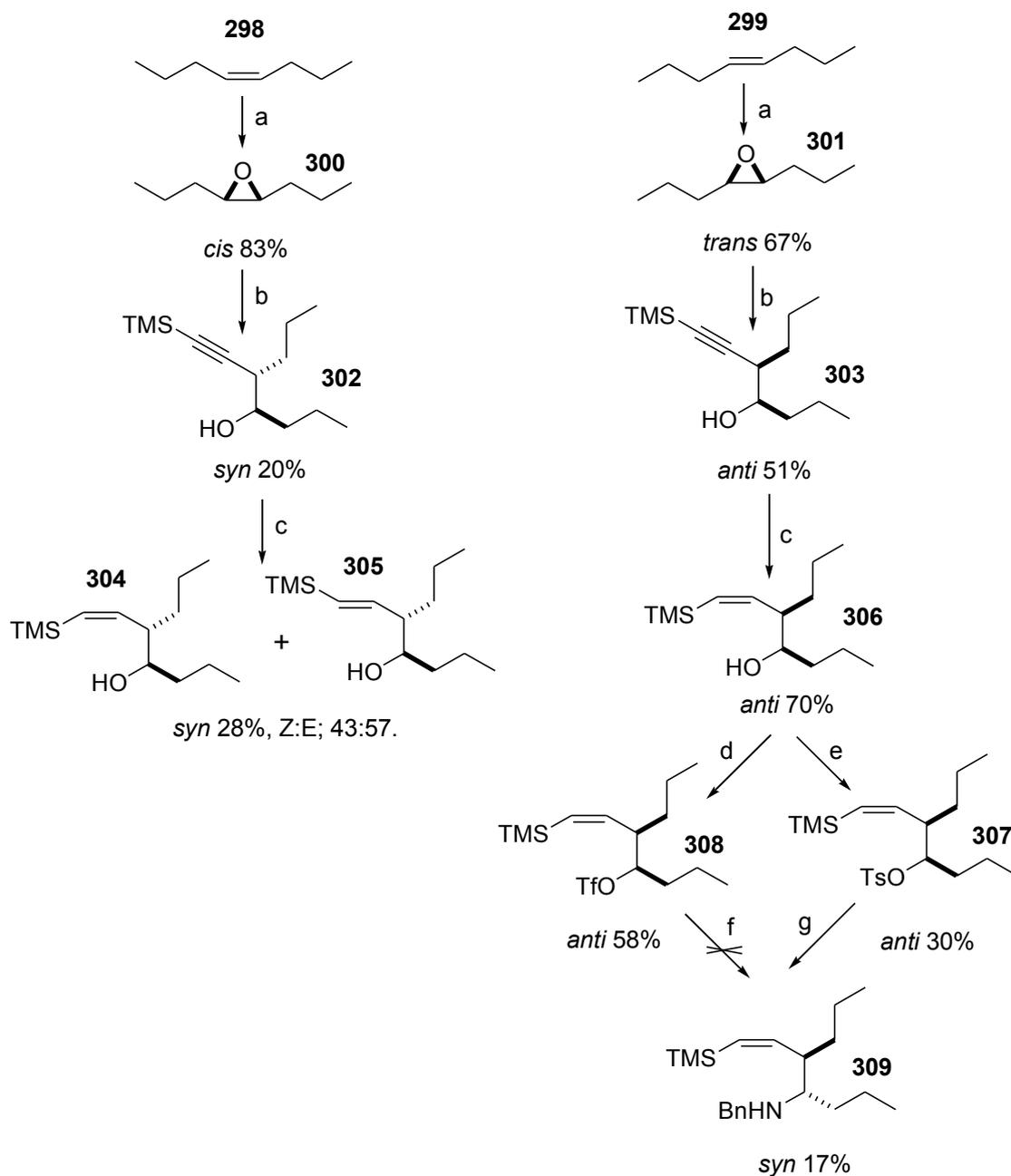
### . II Results and Discussion: Studies into Synthesis of *N,2,5,6*-Tetrasubstituted-3,4-tetrahydropyridines

As previously discussed, the formation of tetrasubstituted-3,4-tetrahydropyridines *via* the aza-silyl-Prins reaction was to be attempted. This follows the success found in utilising the silyl-Prins reaction to form 2,5,6-trisubstituted-3,4-dihydropyrans using  $\alpha,\beta$ -disubstituted silylated homoallylic alcohols. Therefore, coupling  $\alpha,\beta$ -disubstituted silylated homoallylic amines to aldehydes under indium trichloride mediated conditions was attempted. Although the first priority was to find conditions to form these multiply-substituted tetrahydropyridines, attempts were also made to vary the substitution pattern of the  $\alpha,\beta$ -disubstituted precursors from *syn* to *anti*. It was interesting to study the stereoselectivity of the aza-silyl-Prins reaction in comparison with the oxygen series and also to investigate the effect that the additional *N*-substituent plays in controlling the selectivity.

#### . 18 Precursor Synthesis I: Formation of $\alpha,\beta$ -Disubstituted

##### Amines

The  $\alpha,\beta$ -disubstituted amines were required for screening in the aza-silyl-Prins reaction and our first proposal was to use the same methodology with which our group previously accessed the alcohol precursors. Then the tosylation and amination methodology to access the required amines could be utilised. The previous synthesis began with (*Z*)-hex-3-ene **271** and (*E*)-hex-3-ene **272**. Unfortunately these starting materials could no longer be obtained commercially so the synthesis began with the octene analogues. This meant that our proposed targets were *syn* **309** or *anti* (4,5,*Z*)-*N*-benzyl-5-(2-(trimethylsilyl)vinyl)octan-4-amine. It was decided to maintain the use of the *N*-benzyl substituent as it had brought positive results in all other studies. Based on the studies into the aza-silyl-Prins reaction with fluorinated precursors, it was attempted to obtain strictly the (*Z*)-geometric isomers as it was felt that these would be the most reactive substrates. Using this methodology, it was possible to obtain the *syn*- $\alpha,\beta$ -dialkyl diastereomer **309** in 5 steps from the commercially available alkene **299**. However attempts to obtain the *anti*- $\alpha,\beta$ -dialkyl diastereomer were unsuccessful (Scheme 98).



**Scheme 98. Reagents and conditions:** (a) 77% *m*-CPBA, H<sub>2</sub>O, NaHCO<sub>3</sub>, DCM, 0 °C, *cis*-83% & *trans*-67%; (b) *n*-BuLi, TMS acetylene, Et<sub>2</sub>AlCl, hexane, -30 °C, *syn*-20% & *anti*-51%; (c) DiBAL, Et<sub>2</sub>O, reflux, 48 h, *syn*-28% (Z:E; 43:57) & *anti*-70%; (d) Tf<sub>2</sub>O, pyridine, DCM, 0 °C, 4 h, *anti*-58%; (e) TsCl, Et<sub>3</sub>N, DMAP, DCM 0 °C, 48 h, *anti*-30%; (f) BnNH<sub>2</sub>, EtOH, reflux or BnNH<sub>2</sub>, Et<sub>3</sub>N, DCM, 0 °C; (g) BnNH<sub>2</sub>, EtOH, reflux, 20 h, *syn*-17%.

Following previous methodology for the first two steps, firstly the epoxidation of the commercially available alkenes, (*Z*)-oct-3-ene **298** and (*E*)-oct-3-ene **299** was completed. This was performed by the treatment of the alkenes with *m*-CPBA in the presence of

sodium hydrogen carbonate to give the *cis*-epoxide **300** and *trans*-epoxide **301** in 83% and 67% yields respectively. Again using previous methods, the epoxides were opened with an aluminium TMS acetylide species to give the *syn*- **302** and *anti*- $\alpha,\beta$ -dialkyl alkynylsilanes **303** in 20% and 51% yields respectively. These reactions were completed by the treatment with TMS acetylene in the presence of *n*-butyllithium and diethylaluminium chloride. It is clear that the stereochemistry of the epoxide precursors had a large influence on the yield of product. Next the alkynylsilanes **302** and **303** were reduced by the treatment with DiBAL, which afforded exclusively the (*Z*)-alkene **306** for the *anti* starting material **303** in 70% yield. However reduction of the *syn*- $\alpha,\beta$ -dialkyl alkynylsilane **302** produced approximately a inseparable 1:1 mixture of (*Z*) **304** and (*E*) **305** geometric isomers in 28% total yield. The low yield and the poor reduction stereoselectivity highlight the steric effects present due to the  $\alpha$  and  $\beta$  substituents. The *anti* **306** and also the inseparable *syn* mixture of silylated homoallylic alcohols **304** and **305** were then submitted to tosylation procedures using tosyl chloride. Product formation was only observed in the case of the *anti* starting material. Even in this example, a disappointing purified yield of 30% for the tosylated alcohol **307** was obtained, with mostly starting material remaining in the crude mixture after 48 hours. The amination of the *anti*- $\alpha,\beta$ -dialkyl tosylated alcohol **307** was completed by the action of benzylamine in refluxing ethanol to afford the *syn*- $\alpha,\beta$ -dialkyl homoallylic *N*-benzyl amine **309** in 17% yield. Complete inversion of configuration was assumed to have occurred by the S<sub>N</sub>2 nucleophilic substitution of the *anti*- $\alpha,\beta$ -dialkyl tosylated alcohol **307** by benzylamine. It was not possible to accurately confirm the relative stereochemistry of all substrates by NOESY experiments for the <sup>1</sup>H NMR spectra. However the large enhancements between olefinic hydrogens for both *syn* **304** and *anti*- $\alpha,\beta$ -dialkyl **306** homoallylic alcohols and the *syn*- $\alpha,\beta$ -dialkyl homoallylic amine **239** example confirm the presence of the (*Z*)-isomer (Figure 21). Attempts to maximise the yield for the formation of the *syn*- $\alpha,\beta$ -dialkyl homoallylic amine **309** were performed first by employing a better leaving group by the formation of the *anti*- $\alpha,\beta$ -dialkyl triflate **308** in 58% yield. This was completed by the treatment of the *anti*- $\alpha,\beta$ -dialkyl homoallylic alcohol **306** with triflic anhydride in the presence of pyridine. Although this yield is an improvement in comparison to formation of the tosylate, the amination of this compound with benzylamine was unsuccessful. Attempts to also obtain the *syn*- $\alpha,\beta$ -dialkyl triflate from the inseparable mixture of **304** and **305** were unsuccessful using the same methodology.

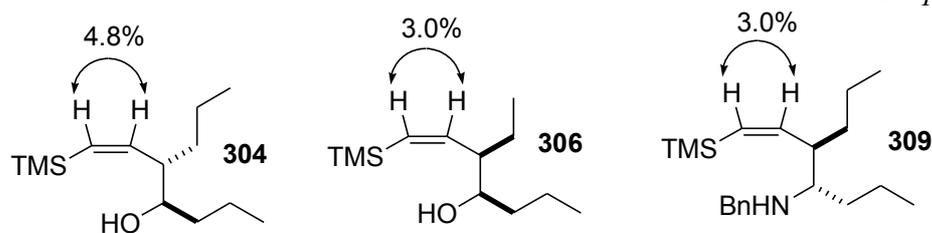
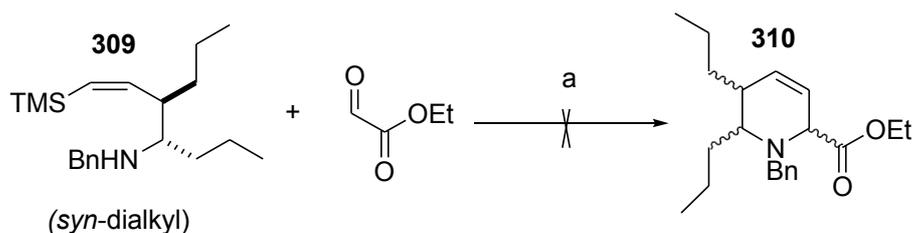


Figure 21. The nOe effects in  $\alpha,\beta$ -disubstituted homoallylic precursors.

The *syn*- $\alpha,\beta$ -dialkyl homoallylic *N*-benzyl amine **309** was now available for screening in the indium trichloride-mediated aza-silyl-Prins reaction. At this stage, only sufficient amine for one trial reaction was available and so it was decided to screen ethyl glyoxylate in 1:1:1 equivalents of amine, aldehyde and Lewis acid in acetonitrile. This was due to the high reactivity of ethyl glyoxylate in previous examples, suggesting this would give the greatest probability of a positive result (Scheme 99). Also, if the *N*,2,5,6-tetrasubstituted-3,4-tetrahydropyridine **310** was formed, then this could be utilised in the total synthesis of other pipercolic acid analogues (cf-chapter 4).



Scheme 99. Reagents and conditions: (a) (i)  $\text{InCl}_3, \text{CH}_3\text{CN}$ , rt, 4 h, (ii) reflux, 48 h.

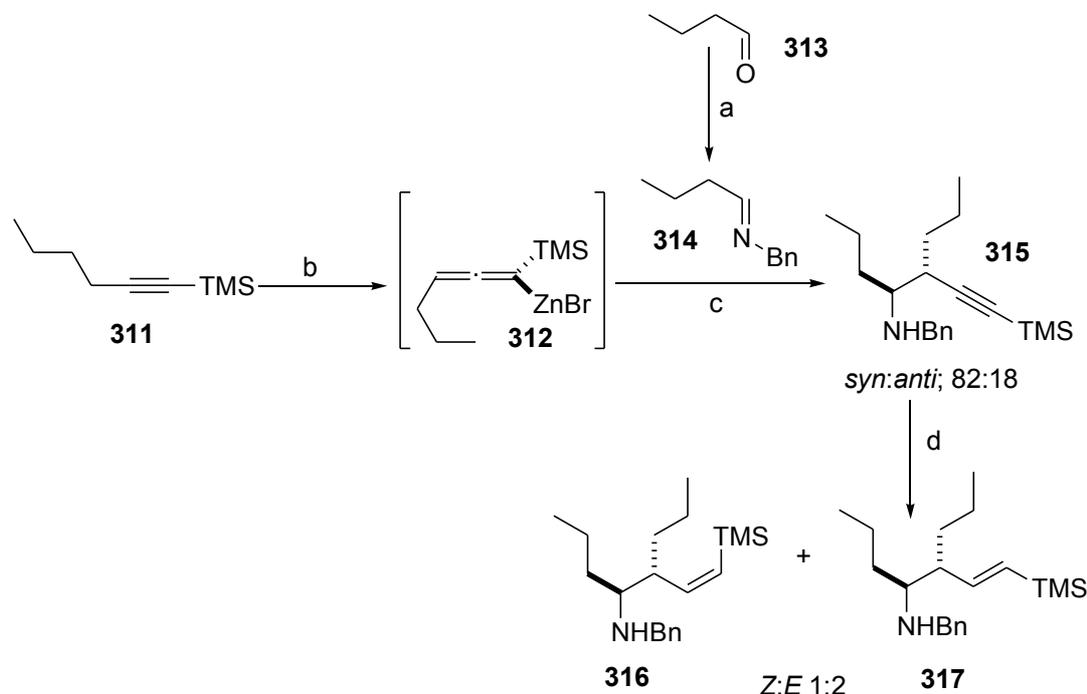
Initially the reaction was begun at room temperature, but no progress was observed after 4 hours. Therefore, the conditions were changed to reflux temperature for 48 hours but still no progress or trace of product was observed on analysis by GCMS or  $^1\text{H}$  NMR.

### . 19 Precursor Synthesis II- Zinc Bromide Mediated $\alpha,\beta$ -Dialkyl

#### Amine Formation

In order to screen other aldehydes or vary reaction conditions, more starting material was required and so a new precursor synthesis was proposed. Even if utilising the aza-silyl-Prins reaction to form *N*,2,5,6-tetrasubstituted-3,4-tetrahydropyridines was unsuccessful, then at least there would have been a contribution towards new methodology for the synthesis of multi-substituted silylated-homoallylic amines. The new proposal was to use a coupling reaction between an allenyl zinc reagent and an imine to synthesise  $\alpha,\beta$ -dialkyl silylated-homopropargylic amines, as reported in the literature (Scheme 100). As previously discussed, these reactions were exclusively diastereoselective under certain

conditions. However, the imines that were utilised in the literature examples were  $\alpha$ -alkoxy (or siloxy) imines, whereas the intention was to couple simple alkylated imines. This could alter the diastereoselectivity of the coupling reaction. If successful, simple *cis* reduction would hopefully give the required homoallylic amine.

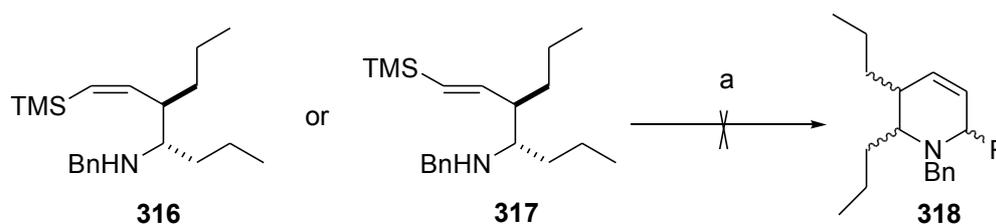


**Scheme 100.** Reagents and conditions: (a) BnNH<sub>2</sub>, MgSO<sub>4</sub>, DCM, rt, 20 h, 19%; (b) (i) *s*-BuLi, THF, 0 °C, 1h, (ii) ZnBr<sub>2</sub>, -20 °C; (c) THF, -70 °C, 1h, 65% over 2 steps; (d) DiBAL, Et<sub>2</sub>O, reflux, 48 h, 30% overall (*Z:E*; 1:2).

The condensation of butyraldehyde **313** with benzylamine in the presence of magnesium sulfate afforded the desired imine **314** in a disappointing 19% yield. The reported coupling reaction was initiated by the addition of *s*-butyllithium to commercially available 1-trimethylsilyl-1-hexyne **311**. After treatment with anhydrous zinc bromide, the intermediate allenyl zinc compound **312** was formed, which was used immediately in the next step. When the pre-formed imine **314** was added at -70 °C, it generated the desired *N*-benzyl silylated-alkynyl amine **315** in an inseparable 82:18 mixture of *syn* and *anti*-dialkylated amines. This inseparable mixture was then submitted to standard *cis* reduction by DiBAL to afford a 1:2 separable mixture of (*Z*) **316** and **317** (*E*)-geometric isomers in 30% overall yield. These (*Z*) **316** and **317** (*E*) alkenes were also separable from the minor *anti*-dialkyl diastereomers. This mixture of geometric isomers was comparable with the poor stereoselectivity observed for formation of the  $\alpha$ -trifluoromethyl homoallylic amine precursors from the related alkynylsilanes (Scheme 77). It seems that the Lewis acid-Lewis base compatibility required for selectivity in the *cis* reduction is poor on the use of

amines rather than alcohols. The spectral analysis of the (*Z*)-alkene **316** was identical to that found for the *syn*-dialkylated homoallylic amine **309** derived from the amination of the related tosylated alcohol **307**.

With the desired *syn* precursor obtained, the (*Z*)-homoallylic amine **316** was again screened in the aza-silyl-Prins reaction. It was also decided to introduce the pre-separated (*E*)-alkene **317** to indium trichloride mediated Prins conditions. If success was found with either geometric isomer, then again, conclusions could be drawn upon the requirement for the (*Z*)-geometry to maximise the stability of important intermediates. Unfortunately when using ethyl glyoxylate or phenylacetaldehyde, there was no positive progress for either geometric isomer at room temperature or reflux temperatures. When all substrates were submitted for up to 120 hours at reflux, only starting material remained and any trace quantities of product were not identifiable (Scheme 101). It was assumed that the negative results for the formation of tetrasubstituted tetrahydropyridine product **318** were based upon the presence of an *N*-substituent in comparison with the oxygen series.



**Scheme 101.** *Reagents and conditions:* (a) (i)  $\text{InCl}_3$ ,  $\text{CH}_3\text{CN}$ ,  $\text{RCHO}$  ( $\text{R}=\text{CO}_2\text{Et}$  or  $\text{PhCH}_2$ ), rt, 8 h, (ii) reflux, 120 h.

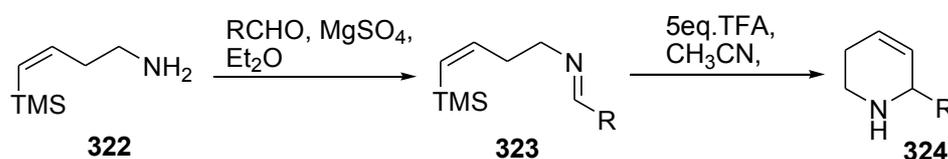
Even though synthesising tetrasubstituted tetrahydropyridines *via* the aza-silyl-Prins reaction was unsuccessful, new methodology for precursor formation has been introduced and perhaps could be adapted for other studies. For future work, it would be beneficial to complete thorough screening of all variables involved in the cyclisation reaction, such as the Lewis acid, solvent, aldehyde or *N*-substituent adopted. Perhaps then if success is found for the formation of multi-substituted nitrogen heterocycles, then the methodology could be adapted towards the formation of natural product analogues, such as pipercolic acid.

**CHAPTER SIX: Towards the Synthesis of  
Enantiopure 2-Substituted-3,4-  
tetrahydropyridines**



tetrahydropyridines **324** via a protic acid promoted cyclisation of imine precursors. Several imines **323** were prepared by the condensation of an amine **322** with various commercially available aldehydes. These imines **323** were then treated with an excess of trifluoroacetic acid to promote the cyclisation in moderate yields (26-55%). Surprisingly, five equivalents of protic acid gave greater yields than one equivalent, in spite of the greater opportunity for protodesilylation. Similar conditions were unsuccessful in promoting the cyclisation in cases where the imine was derived from aldehydes with  $\alpha$ -hydrogens, where it was assumed that self-condensation between the imine and the enamine tautomer occurred (Table 35).

**Table 35. Protic acid mediated imine-vinylsilane cyclisations.**

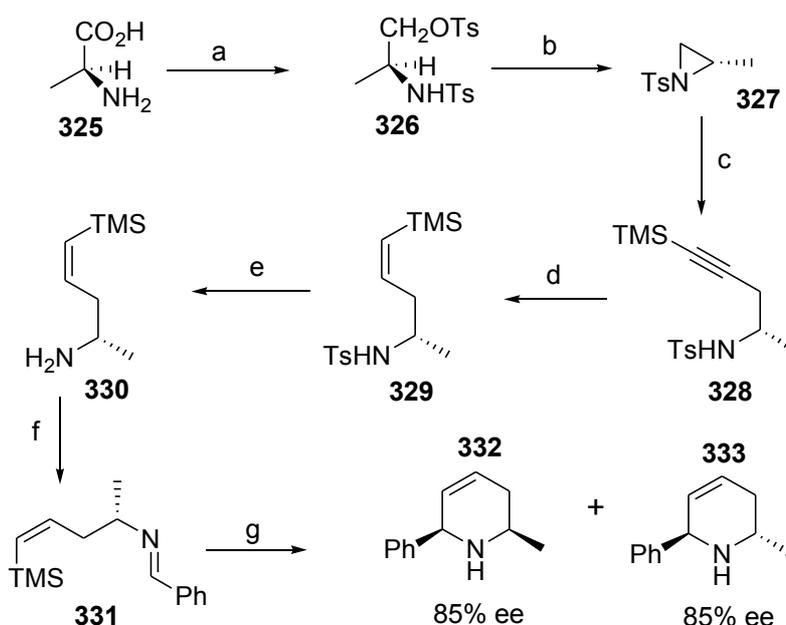


Entry	R	Temp. (°C)	Time (h)	%Yield
1	3-bromophenyl	55	48	55
2	3-pyridinyl	60	40	33
3	C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> Ph	120	24	66
4	C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> Ph	60	40	26
5	(CH <sub>2</sub> ) <sub>2</sub> Ph	-	-	0

Next Overman reported the formation of 2,6-disubstituted tetrahydropyridines via the same imine-vinylsilane cyclisations. The imine precursor **331** required for the study was taken from the condensation of benzaldehyde and an  $\alpha$ -substituted chiral vinyl-silyl amine **330**. This amine was derived in 7 steps from commercially available L-alanine **325**. Firstly, the amino acid **325** was converted into an *N*-tosylaziridine **327** by known procedures, and it was then opened in the least hindered position by (trimethylsilyl)alkynyllithium. The resulting alkynylsilane **328** was *cis* reduced to the (*Z*)-alkene **329** using dicyclohexylborane, followed by protonolysis. The stereochemically pure sulfonamide **329** was deprotected by the action of sodium naphthalide in 1,2-dimethoxyethane to give the required amine **330** in >96% ee. After the condensation of the amine **330** with benzaldehyde, the resulting imine **331** was introduced to the previously employed conditions of TFA in acetonitrile at 60 °C. The results of this cyclisation were the production of a 1:1 mixture of separable *cis*- **332** and *trans*-2,6-tetrahydropyridines **333** in 85% yield (Scheme 104). This is surprising as you would

presume that a di-equatorial conformation or *cis* geometry would be highly favoured to reduce steric strain between ring substituents.

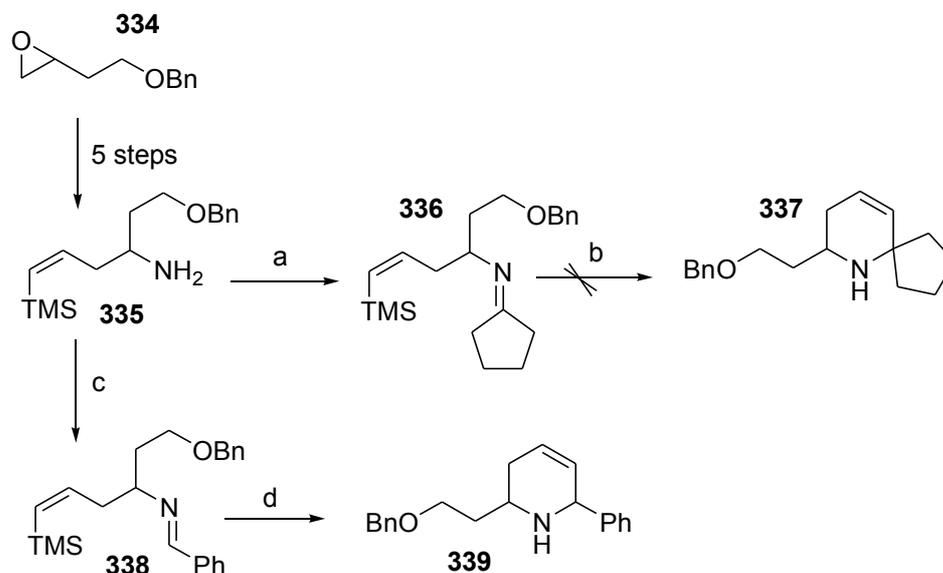
The enantiopurity of the 2,6-tetrahydropyridine products **332** and **333** were investigated by Overman in a later article. On use of chiral HPLC analysis, the previously separated diastereomers each had an enantiopurity of 85%. This shows partial racemisation of a iminium-ion intermediate *via* the intermediate aza-Cope rearrangement.



**Scheme 104.** *Reagents and conditions:* (a) (i) LAH, (ii) TsCl, pyridine, 58% for 2 steps; (b) KOH, MeOH, 72%. (c) Lithium TMS acetylide, TMEDA, 92%. (d) (i) (*c*-Hex)<sub>2</sub>BH, (ii) Acetic acid, NaOH, H<sub>2</sub>O<sub>2</sub>, 83% for 2 steps; (e) Na, naphthalene, 1,2-dimethoxyethane, 68%; (f) PhCHO, MgSO<sub>4</sub>/Na<sub>2</sub>SO<sub>4</sub>, DCM, 62%; (g) 3 eq.TFA, CH<sub>3</sub>CN, 60 °C, 85%.

The next example by Tanner again shows high similarities with our work on the aza-silyl-Prins reaction, with various examples of iminium-ion vinyl-silane cyclisations. Based on the previous example by Overman, which is cited in this article, they attempted a ketimine cyclisation. This was performed firstly by the formation of an  $\alpha$ -substituted primary amine **335** which was derived in five steps from the commercially available epoxide **334**. After condensation with cyclopentanone, the resulting imine **336** did not undergo cyclisation to **337** on treatment with TFA in acetonitrile at reflux. However under the same cyclisation conditions, the imine **338**, derived from the same primary amine **335** and benzaldehyde, did yield success. The resulting 2,6-disubstituted tetrahydropyridine **339** interestingly produced a 1:1 diastereomeric mixture, comparable with Overman's studies. Further attempts to cyclise the ketimine **336** to the corresponding spirocycle were

unsuccessful on treatment with Lewis acids, TMS triflate, boron trifluoride etherate, titanium(IV) chloride or titanium(IV) isopropoxide (Scheme 105).



**Scheme 105.** Reagents and conditions: (a) cyclopentanone, 4 Å mol sieves, Et<sub>2</sub>O, 92%; (b) no reaction; (c) PhCHO, 4 Å mol sieves, Et<sub>2</sub>O; (d) TFA, CH<sub>3</sub>CN, 80 °C, 37% (2 steps).

There are no examples in the literature that involve Lewis acids in imine-vinylsilane cyclisations, only protic acids. Therefore our initial screening towards the synthesis of enantiopure 2-substituted-3,4-tetrahydropyridines would involve testing Lewis acids for racemic examples.

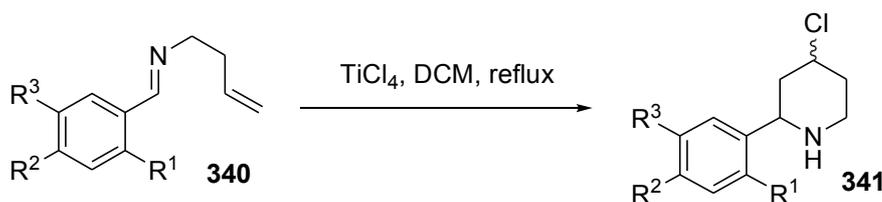
## . 21 Activation of Imines with Lewis

### Acids

Previously discussed, is the proposal of synthesising 2-substituted tetrahydropyridines *via* a Lewis acid-mediated cyclisation of imine-vinylsilanes. In the literature, this has been reported under protic acid conditions. This section will examine examples where Lewis acids have been used to activate imines, so that a list of azaphilic Lewis acids may be identified for screening.

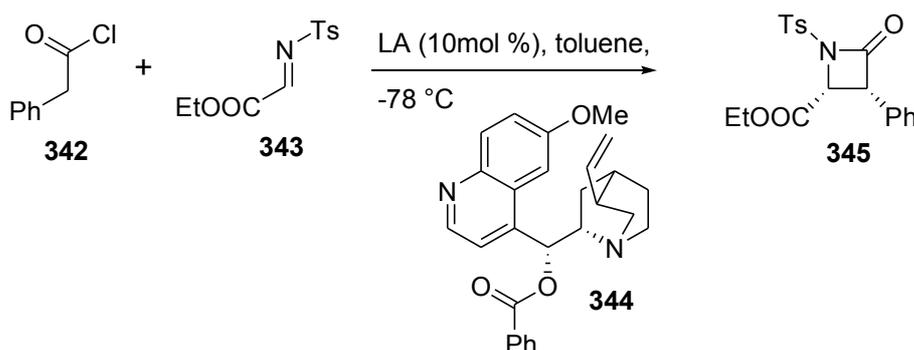
Aube examined Lewis acid-mediated imine-olefin cyclisations in order to produce 2-aryl-4-chloropiperidines (Table 7). The use of titanium(IV) chloride to activate the imine **340**, produced piperidine products **341** in reasonably low yields of 18-52% (Scheme 106). It is uncertain whether it was the low reactivity of the imine precursor **340** (containing an unactivated olefin nucleophile) or the stability of the intermediate carbocation which contributes to the low yields. It could also be due to the use of the titanium Lewis acid,

since this is very moisture-sensitive. However, the Lewis acid is, at least to some extent, compatible with the imine precursor.



**Scheme 106.** The titanium mediated imine-olefin cyclisations.

Lectka has reported the extensive screening of Lewis acids for the synthesis of  $\beta$ -lactams *via* the activation of imines. Initial screening was performed with a variety of Lewis acids for the coupling of phenylacetyl chloride **342** with an imino ester **343**. Most success was found using metal triflates of Sc(III), Al(III), Zn(II) and In(III). More specifically, the metal triflates of Zn(II) and In(III) resulted in the greatest yields of **345** of 85% and 95% respectively (Scheme 107).



**Scheme 107.** Lewis acid mediated coupling of imino ester to phenylacetyl chloride.

The Lewis acids reviewed here are some of the very few examples of imine activation discussed in the literature.

## . 22Utilisation of Chiral Lewis

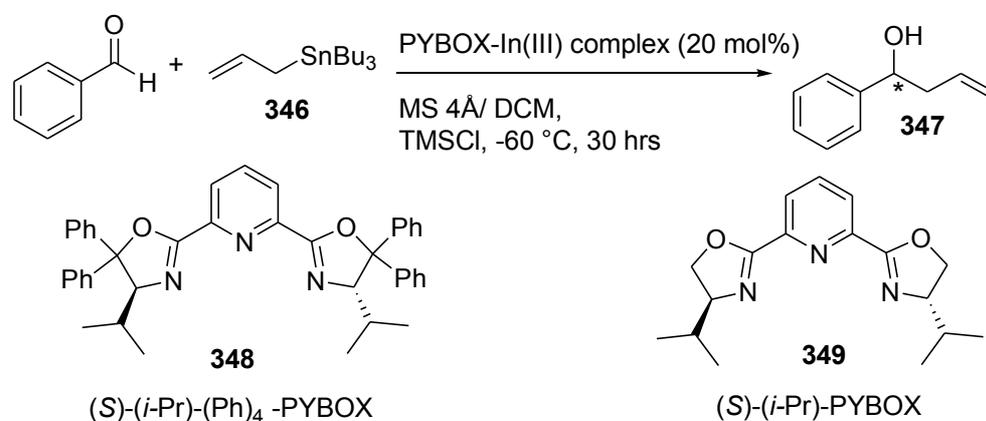
### Acids

In order for the aza-silyl-Prins reaction to be a short novel route to natural product cores, then there is a desire to control the absolute stereochemistry of the tetrahydropyridine product. The Dobbs group has already described the diastereoselectivity of the aza-silyl-Prins reaction as being exclusively *trans* across the nitrogen atom but the products are still racemic. Attempts to make the reaction asymmetric have proved unsuccessful to date with the use of chiral auxiliaries on the *N*-substituted moiety giving poor to moderate enantiomeric excesses. Other possibilities for enhancing the enantioselectivity of the

reaction include using chiral Lewis acids or chiral ligand-Lewis acid complexes and so the use of these species will be reviewed.

Loh and co-workers have reported the synthesis of enantiomerically enriched homoallylic alcohols **347**. This area is of great requirement as these alcohols are versatile intermediates for synthesis. Work has already been undertaken using chiral Lewis acid catalysed additions of allyl moieties to carbonyl function. These include ligands attached to metals such as Zn, Ti and Rh. Loh first reported the use of chiral In(III)-PYBOX complexes to catalyse the addition of allyltributylstannanes **346** to aldehydes. Initial studies involved complexation using a catalytic amount of indium triflate and also PYBOX ligands. These were stirred together at room temperature for 2 hours in the presence of molecular sieves. Then addition of excess allylstannane **346** and TMSCl as well as an aldehyde derivative gave homoallylic alcohols **347** in varying yields and % ee. First the reaction was studied at room temperature using the solvents DCM, toluene, ethyl cyanide, and also a 1:1 mixture of DCM/toluene, with DCM proving the superior solvent, giving 59% ee. Various temperatures were used and -60 °C proved to be the most effective giving 80% yield and 85% ee (Table 36).

**Table 36.** Ligand screening for enantioselective alcohol synthesis.

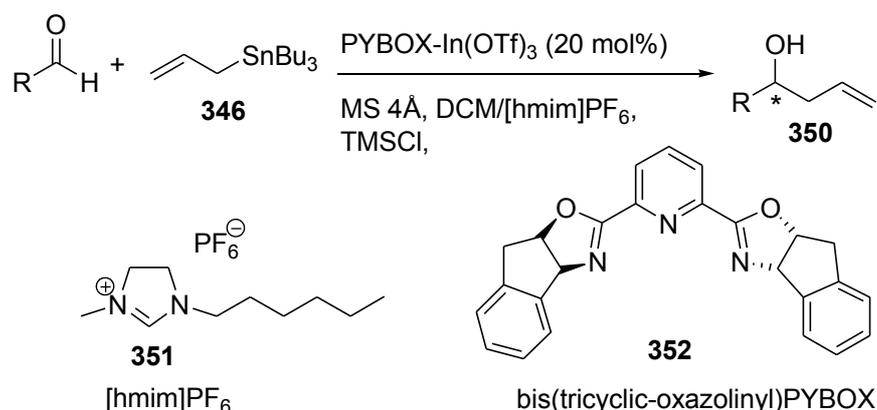


Entry	Chiral ligand	Indium salt	%Yield	%ee
1	(S)-(i-Pr)PYBOX	In(OTf) <sub>3</sub>	80	85
2	(S)-(i-Pr)PYBOX	In(OTf) <sub>3</sub>	81	22 (TMSCl absent)
3	(S)-(i-Pr)PYBOX	InBr <sub>3</sub>	12	31
4	(S)-(i-Pr)PYBOX	InCl <sub>3</sub>	84	40
5	(S)-(i-Pr)(Ph) <sub>4</sub> PYBOX	In(OTf) <sub>3</sub>	81	92

Other In(III) salts were screened and proved unsuccessful. Different PYBOX and also BOX ligands were screened in the presence of indium triflate, with the (S)-(i-Pr)-PYBOX **349** complex yielding 80% and 85% ee. With the same ligand **349**, InCl<sub>3</sub> produced an

increase in yield to 85% but with a reduction in enantioselectivity to 40%. The best results were obtained for the tetraphenyl substituted (*S*)-(*i*-Pr)-PYBOX ligand **348**, giving 81% yield and 92% ee. Observations from these results were that tridentate PYBOX ligands gave the best yields and ee and that these results were further dependent on the In(III) salt, with the order of improvement being Br<Cl<OTf (Table x). Also TMSCl was found to be the superior promoter over other silyl chlorides such as TESCl, TBSCl, and TIPSCl. With the most beneficiary conditions in hand, aldehydes were screened and after 30 hours at -60 °C, the best results were obtained from aromatic aldehydes, notably 2-naphthylaldehyde giving 86% yield and 94% ee.

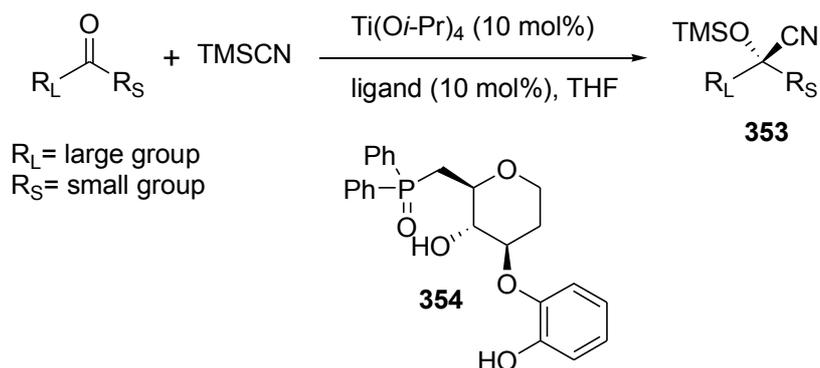
Loh's work progresses, to allow the recyclability of the chiral Lewis acid complex in order to make the reaction truly catalytic. The use of ionic liquids allows immobilisation of chiral catalysts and allows re-use with comparable enantioselectivity and yields, up to 4 times in this case. The optimal conditions for the same addition of allyltributylstannanes **346** to aldehydes used a mixture of [hmim]PF<sub>6</sub> **351** and DCM to give the best yield of 88% and also 94% ee for homoallylic alcohol product **350**. This was with the use of a bis(tricyclic-oxazoliny) pyridine ligand **352** and indium(III) triflate (Scheme 108).

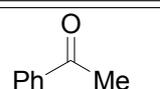
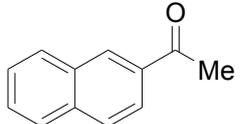
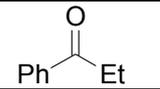
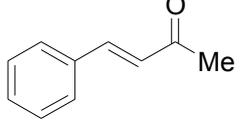
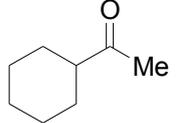
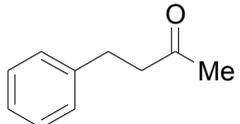


**Scheme 108. Enantioselective alcohol formation with ionic liquid.**

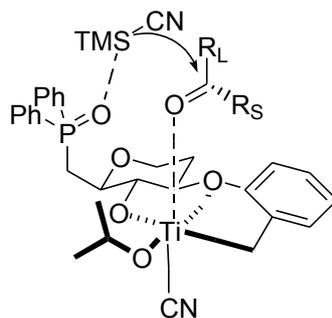
Shibasaki has further evolved the use of chiral ligand–Lewis acid complexation by using a ligand system where both Lewis acid, Lewis base and other substrates are all held in close proximity. Here, addition of ketones to TMSCN can allow the formation of chiral quaternary  $\alpha$ -hydroxy carbonyl derivatives **353** with a novel titanium promoter being utilised for the transformation. The screening of the multi-functional ligand **354** with several Lewis acids to promote addition of TMSCN to acetophenone led to the optimal conditions of using titanium(IV) isopropoxide, at < -20 °C with THF to give for example, high yields of 85% and 92% ee (Table 37).

Table 37. Ketone screening in asymmetric cyanosilation.



Entry	Ketone	Temp. (°C)	Time (h)	%Yield	%ee
1		-30	36	85	92
2		-40	80	82	95
4		-20	64	89	91
5		-50	88	72	91
6		-50	36	86	90
7		-50	36	92	85

The mechanism for the use of this ligand and promoter system is as thus. The titanium Lewis acid transforms to include a monocyano and monoisopropoxide function *via* ligand exchange and is then bound in a tridentate fashion to the ligand. This complex then activates the ketone substrate, which is also held above the plane of the pyran ring. A phosphine oxide of the ligand is bound to the silane function of the cyanide, which allows it to be held in close proximity to the ketone (Figure 22).

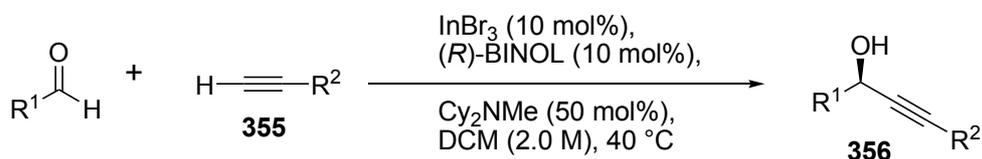


**Figure 22. Mechanistic model of enantioselective cyanosilation.**

It seems feasible that this system could be applied to the aza-silyl-Prins reaction since the silylated homoallylic amine could be held in close proximity to the aldehyde Lewis base *via* the co-ordinating phosphine oxide-silane system.

Another literature example of interest is the asymmetric alkynylation of aldehydes catalysed by a In(III)-BINOL complex. This study is important due to the versatility of the corresponding propargylic alcohol products **356** and is highly relevant to our work as it utilises In(III) salts, which are present in our cyclisation reactions. These systems are fashioned on the bifunctional character of In(III) salts which act as hard Lewis acids and activators of alkynyl groups **355**. Initial studies showed the use of BINOL, which gives high enantioselectivity for the addition of phenylacetylene to cyclohexanecarboxaldehyde. These reactions required 10 mol% of indium bromide, 10 mol% of (*R*)-BINOL, and 50 mol% of (*i*-Pr)<sub>2</sub>NEt in DCM at 40 °C and afforded the product in 96% ee and 46% yield after 7 hours. This was further improved by altering the promoter to Cy<sub>2</sub>NMe to give the yield as 84% and 98% ee (Table 38).

**Table 38. Aldehyde screening for asymmetric alkynylation using (*R*)-BINOL.**



Entry	Aldehyde	R <sup>2</sup>	Time (h)	%Yield	%ee
1		Ph	9	95	98
2		(CH <sub>2</sub> ) <sub>2</sub> Ph	36	77	>99
3		(CH <sub>2</sub> ) <sub>2</sub> Ph	48	46	98

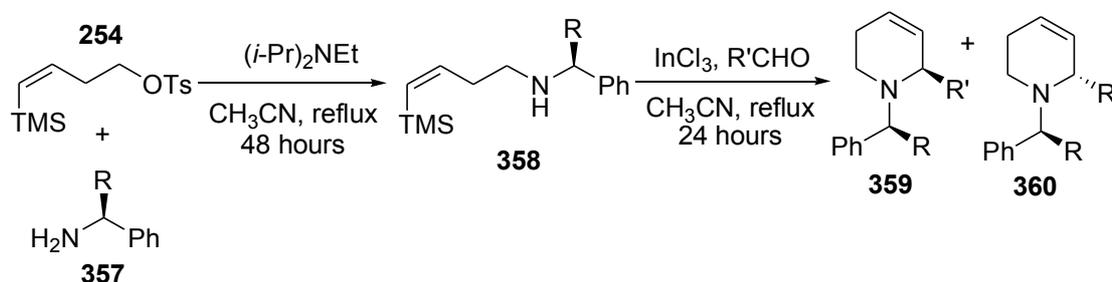
4		Ph	24	85	98
5		Ph	24	70	98
6		(CH <sub>2</sub> ) <sub>2</sub> Ph	24	61	99
7		Ph	20	84	98

This review shows that chiral-Lewis acids can be utilised in many organic transformations to form desired products with high enantioselectivity. Some of the ligands reviewed are either commercially available or synthesised easily. The Lewis acids discussed are also readily available and some have been shown to be compatible with our cyclisation reactions in previous screening studies.

#### . IV Results and Discussion: Studies Towards Asymmetric Imine-vinylsilane Reaction

Previous work in group had already examined an asymmetric version of the aza-silyl-Prins reaction using chiral auxiliaries on the nitrogen atom. A range of enantiopure primary amines **357** were coupled to the tosyl activated alcohol **254** to produce enantiomerically pure silylated homoallylic amines **358**. Coupling of these amines to a range of aldehydes in the aza-silyl-Prins reaction using indium trichloride produced *N*-substituted 2-substituted tetrahydropyridines **359** and **360** in moderate yields and poor diastereomeric excesses (Table 39). The only combination that gave moderate success was the use of ethyl glyoxylate with a chiral ether auxiliary to give tetrahydropyridines in 62% yields and 76% diastereomeric excess.

Table 39. Utilisation of chiral auxiliaries in the aza-silyl-Prins reaction.

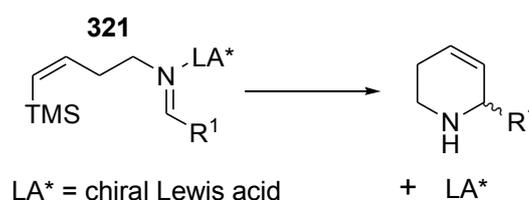


Entry	R	%Yield of <b>358</b>	R'	%Yield of <b>359 and 360</b>	%De
1	Me	65	<i>n</i> -Pn	36	26
2			Bn	53	12
3			Ph	45	31

4	Et	66	Ph	23	18
5	OMe	80	CO <sub>2</sub> Et	62	76

As an alternative to a chiral auxillary, it was proposed to develop an asymmetric aza-silyl-Prins reaction using a chiral Lewis acid, formed from the complexation of a Lewis acid and a chiral ligand. However, as previously discussed, this proposal was not be utilised with any success since the aza-silyl-Prins reaction proceeds *via* an achiral iminium ion intermediate. The chiral Lewis acid would be present initially when either the aldehyde or secondary amine is activated. When the iminium ion is formed however, the Lewis acid-Lewis base interaction would be dissociated.

Therefore the proposal was to examine the cyclisation of imine-vinylsilanes. This involved the cyclisation of imines derived from the condensation of silylated-homoallylic primary amines and simple aldehydes to form 2-substituted-3,4-tetrahydropyridines. However it was proposed to form 2-substituted tetrahydropyridines in high enantiopurity using chiral Lewis acids. It was hoped that the chiral Lewis acid would remain complexed to the imine-vinylsilane **321** at the point of cyclisation (Scheme 109). If this were the case, then perhaps asymmetry could be induced at the C2 position in the tetrahydropyridine product. To date, only protic acids such as TFA have been used to promote these types of cyclisation. Therefore, before screening chiral Lewis acids, standard Lewis acids would have to be screened in a racemic example of imine-vinylsilane cyclisations.

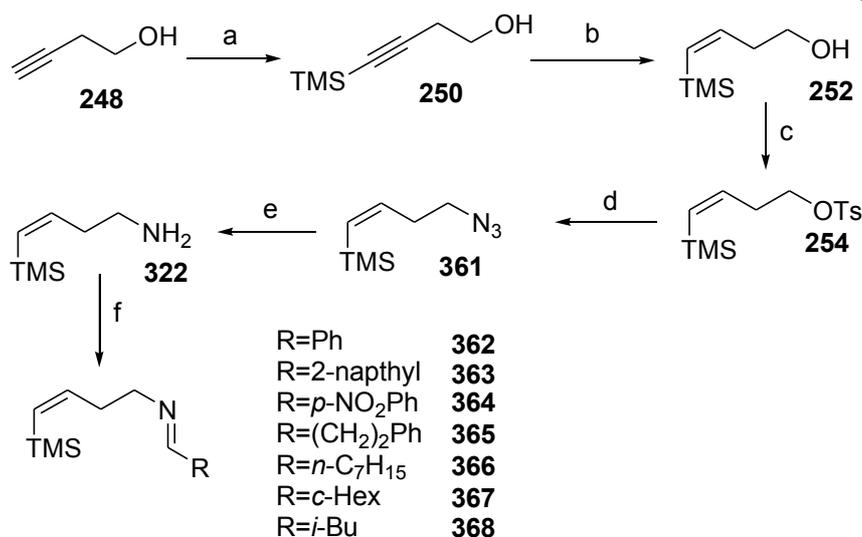


**Scheme 109.** Proposal for the use of chiral Lewis acids in imine-vinylsilane cyclisations.

## . 23 Lewis Acid Mediated Imine-vinylsilane Cyclisations for Racemic Products

### . a Precursor Synthesis: Synthesis of Imine-vinylsilanes

First, it was necessary to develop a route to the pre-requisite silylated homoallylic primary amine. This could then be condensed with aldehydes to afford the required imines. The silylated primary amine **322** was obtained in 5 steps from commercially available 3-butyn-1-ol **248** (Scheme 110). This synthetic pathway had already been completed in the Dobbs group.



**Scheme 110. Reagents and conditions:** (a) *n*-BuLi, TMSCl, THF, -78 °C, 61%; (b) DiBAL, Et<sub>2</sub>O, reflux, 24 h, 65%; (c) TsCl, Et<sub>3</sub>N, DMAP, DCM, 0 °C, 5 h, 87%; (d) NaN<sub>3</sub>, DMF, 60 °C, 4 h, 82%; (e) LAH, THF, 0 °C, 67%; (f) RCHO, MgSO<sub>4</sub>, DCM, rt, 20 h, R=Ph, quant.; R=2-naphthyl, quant.; R=*p*-NO<sub>2</sub>Ph, quant.; R=(CH<sub>2</sub>)<sub>2</sub>Ph, 96%; R=*n*-C<sub>7</sub>H<sub>15</sub>, 87%; R=*c*-Hex, quant.; R=*i*-Bu, quant.;

The 5-step synthesis begins with the silylation of 3-butyn-1-ol **248** by the action of *n*-butyllithium followed by TMSCl, to give the alkynylsilane **250** in 65% yield. This was then submitted to *cis* reduction by treatment with DiBAL to give the homoallylic alcohol **252** in 65% yield. After reaction with tosyl chloride in the presence of triethylamine and 4-dimethylaminopyridine, the tosylated alcohol **254** was afforded in 87% yield. The corresponding azide **361** was prepared in 82% yield *via* nucleophilic substitution of the tosylated alcohol **254** by sodium azide. This was then simply reduced to the desired primary amine **322** in 67% yield by LAH and in 19% overall yield for 5 steps from **248**. The primary amine **322** could then be condensed with a range of commercially available aldehydes to give imines **362** to **368**, mostly in quantitative yields. These imines could then be used in the following step without further purification and were identified by the analysis of the <sup>1</sup>H NMR of the crude extract.

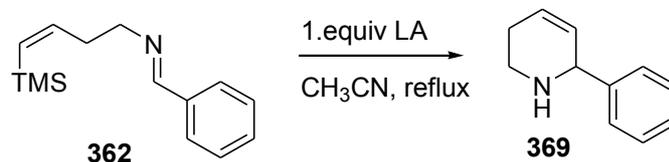
## . b Cyclisations Reactions for

### Racemic Products

With the desired imines in hand, different Lewis acids were screened with 1 equivalent of Lewis acid in acetonitrile as solvent firstly with the imine **362** derived from benzaldehyde (Table 40). The solvent acetonitrile was chosen based on the success found with TFA by Overman. Lewis acids were chosen based on literature precedent for the activation of imines as previously discussed and also for their compatibility with chiral ligands that have previously been successfully employed to induce asymmetry. Other Lewis acids

were chosen based on their availability commercially or their reported affinity for nitrogen. No progress was observed at room temperature, so the temperature was raised to reflux; this is comparable with the higher temperatures required on use of TFA.

**Table 40. Lewis acid screening in imine-vinylsilane cyclisations**



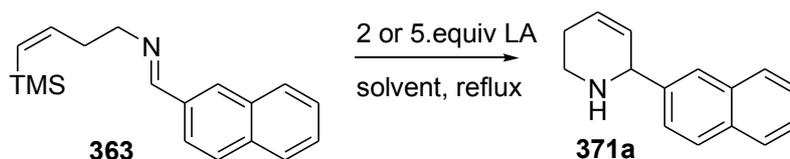
Entry	Lewis acid	Time(h)	% Completion*	% Yield
1	TiCl <sub>4</sub>	72	100%	Trace
2	AlCl <sub>3</sub>	72	0%	0%
3	Cu(OTf) <sub>2</sub>	72	2%	Trace
4	Yb(OTf) <sub>3</sub>	240	81%	35%
5	InCl <sub>3</sub>	240	100%	15%
6	In(OTf) <sub>3</sub>	240	100%	32%
7	Sc(OTf) <sub>3</sub>	240	100%	50%
8	La(OTf) <sub>3</sub>	240	100%	25%

\* = based on consumption of starting material

The yields of product **369** were calculated from the LCMS and <sup>1</sup>H NMR analysis of the crude material after aqueous work-up. In general, these reactions were difficult to monitor, as the use of TLC or analysis by LCMS could not be utilised effectively. Therefore small extractions were made at regular intervals and <sup>1</sup>H NMR analysis performed on the crude material. In the reaction mediated by titanium(IV) chloride, the starting material was consumed fairly rapidly in comparison with others, but only trace quantities of 2-substituted-3,4-tetrahydropyridine **369** were observed. The use of aluminium(III) chloride and copper(II) triflate failed to promote this reaction adequately. When the triflate salts of Yb(III), In(III), Sc(III) and La(III), together with indium trichloride were used to promote this reaction, the starting material was consumed after 240 hours at reflux temperature. While the reaction times for these Lewis acids were very long, it may be that the imine **362**, derived from benzaldehyde, is of low reactivity. This is comparable with other studies involving iminium ion-vinylsilane cyclisations, where the phenyl group is adjacent to the iminium ion. The greatest yields were obtained on use of scandium(III) triflate, with the triflate salts of Yb(III) and In(III) also giving respectable yields.

Therefore it was decided to take the triflate salts of Sc(III), In(III) and also indium trichloride and screen different solvents while using an excess of the Lewis acid. Both triflate salts gave reasonably good yields and all three had literature precedent for the coordination to chiral ligands in asymmetric synthesis. In this instance the imine starting material was altered to that derived from 2-naphthylaldehyde **363** (Table 41). The greater absorption of this chromophore made analysis based on UV detection such as that used in TLC and LCMS more efficient. This chromophore also made UV detection more feasible in chiral HPLC analysis and purification by preparative HPLC. It was hoped that an excess of Lewis acid would shorten the reaction times and make this methodology more synthetically viable. Although using an excess of reagents is a disadvantage to cost, the use of scandium(III) triflate, which can be recycled from an aqueous work-up, overcomes this. It was also hoped that the screening of higher boiling solvents and hence higher reaction temperature might also allow shorter reaction times.

**Table 41. Solvent screening in imine-vinylsilane cyclisations.**



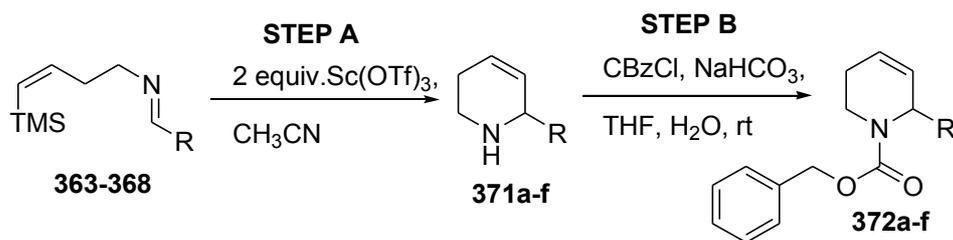
Entry	Lewis acid	Equiv.	Solvent	Time (h)	%Yield
1	InCl <sub>3</sub>	2	CH <sub>3</sub> CN	72	37
2			Toluene	48	47
3			DMF	24	0
4		5	CH <sub>3</sub> CN	72	26
5			Toluene	48	38
6			DMF	24	0
7	In(OTf) <sub>3</sub>	2	CH <sub>3</sub> CN	72	17
8			Toluene	48	0
9			DMF	24	0
10		5	CH <sub>3</sub> CN	72	12
11			toluene	48	0
12			CH <sub>3</sub> CN	72	58
13	Sc(OTf) <sub>3</sub>	2	Toluene	48	0
14			CH <sub>3</sub> CN	72	27
15		5	Toluene	48	0

The yields of product **371a** were calculated as isolated yields after purification by preparative HPLC. Again monitoring these reactions was difficult and to monitor the consumption of starting material, <sup>1</sup>H NMR analysis of crude extracts was required. The use of acetonitrile, toluene or DMF allowed the reactions to be complete in 72, 48, or 24 hours respectively. In general, the use of toluene or DMF at reflux temperature was

detrimental to the isolated yields of products. It was assumed that in these cases the imine starting material **363** was decomposing at the high boiling temperatures. This assumption is supported by observations during distillation under reduced pressure of the imine starting material. During attempts to purify the imines, the neat crude extract went from light yellow to a very dark brown in colour. However, in one instance, using toluene as solvent with indium trichloride in 2 or 5 equivalents, the yield of product was greater than on use of acetonitrile. It was discovered that this was based on the solubility of the Lewis acid in the solvent media. When other Lewis acids were used with toluene, the mixture remained a suspension, even after warming to reflux temperature, perhaps allowing decomposition over cyclisation. Overall scandium(III) triflate (2 eq.) proved to be the Lewis acid of choice, with acetonitrile as solvent, as this produced the greatest product yields. The use of 2 equivalents of Lewis acid also seemed more viable than the use of 1 equivalent as the reaction times were much shorter than in our initial screening (Table 40).

With these optimised reaction conditions, different imine substrates **363-368** were screened in the scandium(III) triflate mediated imine-vinylsilane cyclisations. This included imines derived from aliphatic (cyclic and non-cyclic) and aromatic aldehydes. This is particularly relevant as the TFA mediated imine-vinylsilane cyclisations completed by Overman were attempted on imines that contained no  $\alpha$ -hydrogens because those imines containing  $\alpha$ -hydrogens underwent self-condensation *via* an enamine intermediate. The purification of the 2-substituted-3,4-tetrahydropyridine products **371** by flash column chromatography was made difficult by the lack of chromophores for visualisation by UV or other TLC visualisation techniques. Therefore most examples were further functionalised using methods used previously by the group, to the *N*-benzyl carbamate tetrahydropyridines **372** and these were purified and fully characterised. The yields for the free amine tetrahydropyridines **371** were calculated by analysis of GCMS or LCMS and  $^1\text{H}$  NMR data for the crude organic material. The yields for the *N*-benzyl carbamate derivatives **372** were calculated as isolated yields after the purification by flash column chromatography. For completeness, some examples of the cyclisation reaction were performed at room temperature. The products from the cyclisation reactions completed at room temperature were not further elaborated to the *N*-benzyl carbamate tetrahydropyridines **372** (Table 42).

Table 42. Imine screening in imine-vinylsilane cyclisations and further functionalisation.



Entry	R	Temp.	Time (h)	% Yield (Step A)	% Yield (Step B)
1	2-naphthyl	Reflux	72	58 (a)	43
2	<i>p</i> -NO <sub>2</sub> Ph	Rt	120	13 (b)	N/A
3		Reflux	17	86 (b)	62
4	(CH <sub>2</sub> ) <sub>2</sub> Ph	Rt	120	36 (c)	N/A
5		Reflux	17	57 (c)	55
6	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	Rt	120	42 (d)	N/A
7		Reflux	17	83 (d)	50
8	<i>c</i> -Hex	Rt	120	66 (e)	N/A
9		Reflux	17	88 (e)	44
10	<i>i</i> -Bu	Reflux	17	0 (f)	N/A

In general, all reactions attempted at room temperature had long reaction times and poor to moderate product yields (Table 42, entries 2,4,6,8). Significant improvements were found when the reaction was attempted at reflux temperature with most reactions being completed overnight and the yields being moderate to good (Table 42, entries 1,3,5,7,9,10). In general, the functionalisation of the free amines **371** to the *N*-benzyl carbamates **372** was completed in disappointing yields but this step was mainly required for analytical purposes. Interestingly, good yields of products were obtained from the use of imines with  $\alpha$ -hydrogens, proving that the use of a Lewis acid is more advantageous than using protic acids. The use of the imine derived from the condensation of isobutyraldehyde **368** (Table 42, entry 10) showed that the starting material was consumed overnight but unfortunately, no cyclised product could be identified on analysis by GCMS or <sup>1</sup>H NMR.

#### . 24Imine-vinylsilane Reactions: Formation of Enantiopure

##### Products

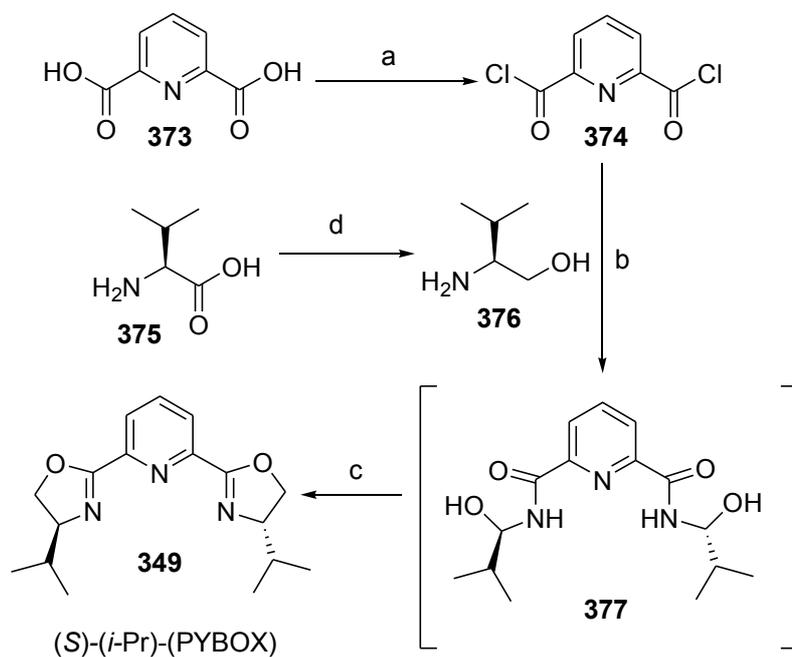
After optimising the conditions required for the racemic synthesis of 2-substituted-3,4-tetrahydropyridines, attention was focussed on turning this into an asymmetric synthesis. As previously discussed, it was proposed to investigate the use of chiral Lewis acids, specifically chiral ligands, co-ordinated to a promoter Lewis acid. Before any screening

could begin, it was necessary to synthesise PYBOX ligands, which were either expensive or not commercially available. These ligands were chosen for their compatibility, based on literature precedent, with the Lewis acids that found success in the racemic series.

### . aChiral

#### ligand Synthesis

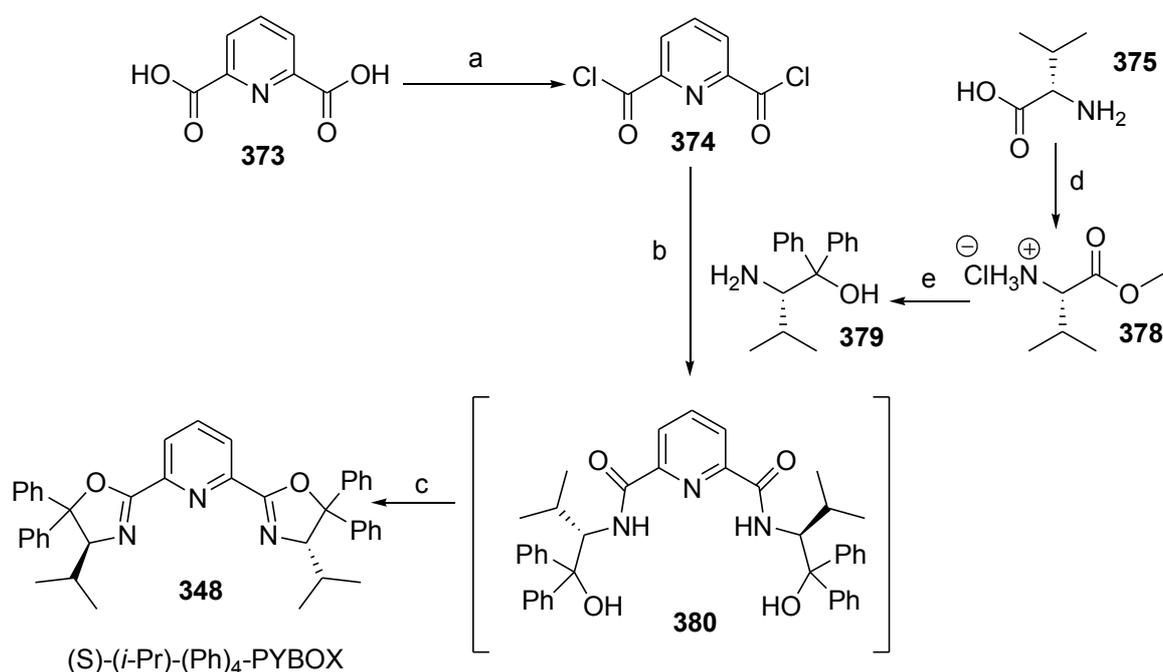
The first ligand to be synthesised was the 2,6-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine ligand [(*S*)-(*i*-Pr)-PYBOX] **349** which is available in three steps from the commercially available pyridine-2,6-dicarboxylic acid **373**. Initially the dicarboxylic acid was converted into the diacid chloride **374** in quantitative yield by the action of thionyl chloride. This acid chloride was then coupled to the amino alcohol (*S*)-valinol **376**, which was the source of chirality. The amino alcohol **376** was easily obtained in 77% yield directly from the amino acid (*S*)-valine **375** by reduction using lithium aluminium hydride in THF (Scheme 111). The chiral ligand **349** was afforded after further treatment with thionyl chloride and sodium hydroxide stepwise and all data were in agreement with literature values.



Scheme 111. *Reagents and conditions:* (a) SOCl<sub>2</sub>, 85 °C, 15 h, quantitative; (b) (*S*)-Valinol, Et<sub>3</sub>N, CHCl<sub>2</sub>, 0 °C, 1 h, r.t., 24 h; (c) (i) SOCl<sub>2</sub>, 85 °C, 2 h, (ii) NaOH, H<sub>2</sub>O, MeOH, 72 h, 22%; (d) LAH, THF, 0 °C, 70 °C, 15 h, 77%.

The second ligand required for synthesis was the tetra-phenyl substituted derivative of the (*S*)-(*i*-Pr)-PYBOX ligand, [(*S*)-(*i*-Pr)-(Ph)<sub>4</sub>-PYBOX] **348**. This was obtained, again in 3 steps, from the pyridine-2,6-dicarboxylic acid **373**. After generation of the acid chloride

**374** as previously described, the preformed amino alcohol **379** was coupled under base-catalysed conditions to generate the di-amide intermediate **380** in 38% yield. The amino alcohol **379** was again formed from (*S*)-valine **375** but in 2 steps. Initially the methyl ester hydrochloride salt **378** was formed in 69% yield by the treatment of the amino acid **375** with thionyl chloride and methanol. Addition of 2 equivalents of the preformed Grignard reagent to the ester function furnished the diphenyl substituted amino alcohol **379** in 76% yield. When the di-amide intermediate **380** was treated with calcium hydride and methanesulfonic acid, the desired chiral ligand **348** was obtained in 75% yield (Scheme 112).



Scheme 112. *Reagents and conditions:* (a) SOCl<sub>2</sub>, 85 °C, 15 h, quantitative; (b) (*S*)-(Ph)<sub>2</sub>-Valinol, Et<sub>3</sub>N, DCM, rt, 20 h, 38%; (c) CaH<sub>2</sub>, MeSO<sub>3</sub>H, DCM, reflux, 6 h, 75%; (d) SOCl<sub>2</sub>, MeOH, 85 °C, 20 h, 69%; (e) Mg, PhBr, 65 °C, 24 h, 76%.

### . bImine-vinylsilane Cyclisations: Towards

#### Enantiopure Products

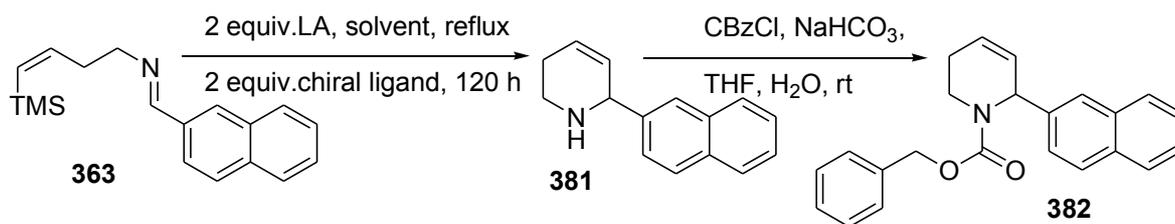
It was now proposed to attempt the asymmetric synthesis of 2-substituted-3,4-tetrahydropyridines *via* chiral Lewis acid-mediated imine-vinylsilane cyclisation. For the initial screening, the ligands (*S*)-(*i*-Pr)-PYBOX **349**, (*S*)-(*i*-Pr)-(Ph)<sub>4</sub>-PYBOX **348**, (*R*)-BINOL and (*S*)-BINOL would be used. These were reported to co-ordinate to scandium(III) triflate or indium trichloride in the literature and also these Lewis acids have produced good yields of products in the racemic examples (Table 41, entries 1-6 and 12-15). These combinations would be utilised in either acetonitrile or toluene as these

solvents have also had success in the racemic examples. Finally, the use of 2 equivalents of Lewis acid would be maintained from the initial studies and therefore an equal quantity of chiral ligand would be used.

The imine derived from 2-naphthylaldehyde **363** was screened initially because purification by flash column chromatography and preparative HPLC of the product 2-substituted-3,4-tetrahydropyridine was more efficient. Unfortunately, the free secondary amine tetrahydropyridine product **381** could not be analysed by chiral HPLC, as these species were not compatible with the chiral column. Therefore the free amine **381** was further functionalised to the *N*-benzyl carbamate **382** by treatment with CBzCl and sodium hydrogen carbonate. The *N*-protected species were more easily purified by preparative HPLC, due to ease of UV detection and they gave good separation on the chiral column. Yields were therefore calculated over two steps (it was assumed that the yields would remain reasonably constant for the second *N*-protection step in all examples; this was because all major contaminants were removed by passing the crude extract of the cyclisation reactions through a short silica plug).

Before the imine **363** was added to the reaction mixtures, flame-dried flasks were charged with the Lewis acid and the chiral ligand. Anhydrous THF was added, the resulting mixture stirred, and the solvent removed under vacuum to azeotropically remove any residual moisture. This process was repeated and then anhydrous DCM was added and the mixture stirred overnight to allow complexation to occur between the Lewis acid and the ligand. The DCM was removed under vacuum and then the cyclisation procedure commenced. Again the use of reflux temperature was required as no progress was monitored at room temperature (Table 43).

Table 43. Chiral ligand screening in imine-vinylsilane cyclisations.



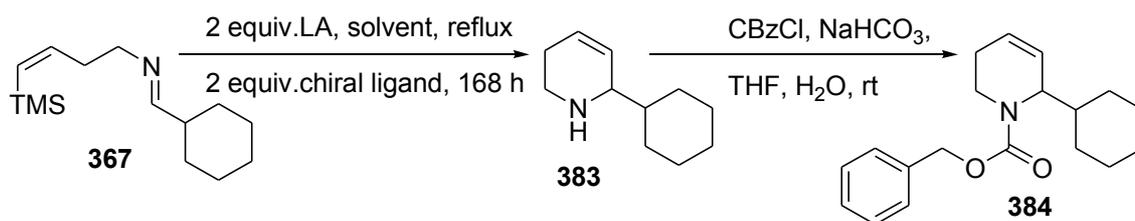
Entry	Lewis acid	Chiral ligand	Solvent	%Yield for 2 steps	%ee
1	InCl <sub>3</sub>	<i>(R)</i> -BINOL	CH <sub>3</sub> CN	0	N/A
2			Toluene	0	N/A
3		<i>(S)</i> -( <i>i</i> -Pr)-PYBOX	CH <sub>3</sub> CN	3	0
4			Toluene	0	N/A
5		<i>(S)</i> -( <i>i</i> -Pr)-(Ph) <sub>4</sub> -PYBOX	CH <sub>3</sub> CN	0	N/A
6			Toluene	0	N/A
7	Sc(OTf) <sub>3</sub>	<i>(S)</i> -BINOL	CH <sub>3</sub> CN	13	0
8			Toluene	5	0
9		<i>(S)</i> -( <i>i</i> -Pr)-PYBOX	CH <sub>3</sub> CN	37	0
10			Toluene	13	0
11		<i>(S)</i> -( <i>i</i> -Pr)-(Ph) <sub>4</sub> -PYBOX	CH <sub>3</sub> CN	10	0
12			Toluene	8	0

As with previous examples, it was difficult to monitor the reactions with LCMS analysis. Even the analysis by <sup>1</sup>H NMR of crude extracts became difficult due to the presence of excess amounts of the chiral ligand. Therefore the time of 5 days at reflux temperature was approximate for each reaction, although trial reactions of shorter and longer reaction times allowed this approximation to be reached. Overall, the use of indium trichloride with all ligands and either solvent gave very poor yields. It is assumed this is based on solubility problems identified for the chiral Lewis acid complex in either solvent. Only one instance of the use of this Lewis acid gave positive results, when it was used in conjunction with the *(S)*-(*i*-Pr)-PYBOX ligand **349** and acetonitrile as solvent. Clearly from these results, scandium(III) triflate is a more efficient promoter of these reactions when considering product yield, since in all examples some of the desired tetrahydropyridine was formed (Table 43, entries 7-12). This was also the case when acetonitrile was replaced with toluene, which is in contrast to previous examples. A possible reason for this could be that the chiral Lewis acid complexes are more soluble in refluxing toluene than the Lewis acid used independently. However, in general, the yields of the reactions in acetonitrile were greater than the corresponding transformations in toluene. The greatest product yields were obtained for the combination of scandium(III)

triflate, the (*S*)-(*i*-Pr)-PYBOX ligand **349** and acetonitrile. Unfortunately, in all cases, the enantiomeric excess was negligible and so each chiral Lewis acid did not promote enantioselectivity in the imine-vinylsilane reactions. Possible reasons for the failure to induce enantioselectivity could be the raised temperatures, on comparison with examples of asymmetric reactions in the literature, which take place mostly at sub-zero temperatures. Other possibilities could be that the chiral ligand had not coordinated to the Lewis acid metal or that there is negligible difference in the energy of the two possible diastereomeric transition states between the substrate and the chiral Lewis acid.

Therefore, it was attempted to lower the temperature of our imine-vinylsilane reactions, perhaps to induce some enantioselectivity in the reaction. To lower the temperature, the use of imines that furnished higher product yields was required. In our imine screening, it was shown that more reactive imines did react at room temperature, albeit with long reaction times and low product yields. However the use of the imine derived from cyclohexanecarboxaldehyde **367** did produce adequate product yields and so this reaction was the next to be investigated. In this instance, (*S*)-(*i*-Pr)-PYBOX **349**, (*S*)-(*i*-Pr)-(Ph)<sub>4</sub>-PYBOX **348** and (*R*)-BINOL chiral ligands were used. Again reactions were attempted using scandium(III) triflate and indium trichloride but only using acetonitrile as solvent. Once again it was required to functionalise further the free amine tetrahydropyridine product **383** to the *N*-benzyl carbamate **384** (Table 44). As before, this made purification by flash column chromatography more efficient and allowed analysis by chiral HPLC.

Table 44. Chiral ligand screening in imine-vinylsilane cyclisations at room temperature.



Entry	Lewis acid	Chiral ligand	% Yield for 2 steps	%ee
1	InCl <sub>3</sub>	( <i>R</i> )-BINOL	0	unknown
2		( <i>S</i> )-( <i>i</i> -Pr)-PYBOX	0	unknown
3		( <i>S</i> )-( <i>i</i> -Pr)-(Ph) <sub>4</sub> -PYBOX	0	unknown
4	Sc(OTf) <sub>3</sub>	( <i>R</i> )-BINOL	11	unknown
5		( <i>S</i> )-( <i>i</i> -Pr)-PYBOX	28	unknown
6		( <i>S</i> )-( <i>i</i> -Pr)-(Ph) <sub>4</sub> -PYBOX	25	unknown

Again these reactions were difficult to monitor but it seems that the reaction times were longer when using chiral Lewis acid complexes on comparison with the racemic examples. Again, the use of indium trichloride proved to be totally unsuccessful. However, on use of scandium(III) triflate with any chiral ligand, generation of the desired tetrahydropyridine was observed. Unfortunately, analysis by chiral HPLC was unsuccessful for the calculation of enantiomeric excess as the resolution for this compound was poor. Other methods for analysing the samples using NMR experiments, such as the use of chiral shift reagents or chiral solvents were also unsuccessful.

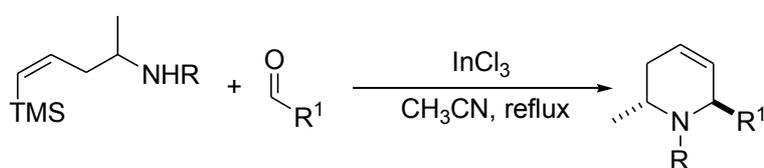
In general, the use of scandium(III) triflate in acetonitrile profited the production of tetrahydropyridines in racemic examples of imine-vinylsilane cyclisations. This combination also allowed the formation of product in conjunction with chiral ligands. At this stage, it is unknown whether the combination could be employed to enantioselectively form tetrahydropyridines, as these compounds are incompatible with standard analytical techniques.

The future work for this study will focus around the protection of the free secondary amine of the tetrahydropyridine product with different substituents in order to find efficient resolution in chiral HPLC.

**CHAPTER SEVEN: Towards the Total Synthesis  
of Cannabisativine**

## . Literature Review for Total Synthesis of Cannabisatvene and Spermidine Alkaloids

The tetrahydropyridine ring system is a common motif found in numerous natural products, drugs and drug candidates. Essential to the structure-activity relationships of natural products containing these motifs is the position of the double bond, the stereochemistry across the heteroatom and also the stereochemistry between other ring substituents. Studies within our group have focussed on utilising the aza-silyl-Prins reaction to generate exclusively *trans*-2,6-disubstituted-3,4-tetrahydropyridines (Scheme 113).



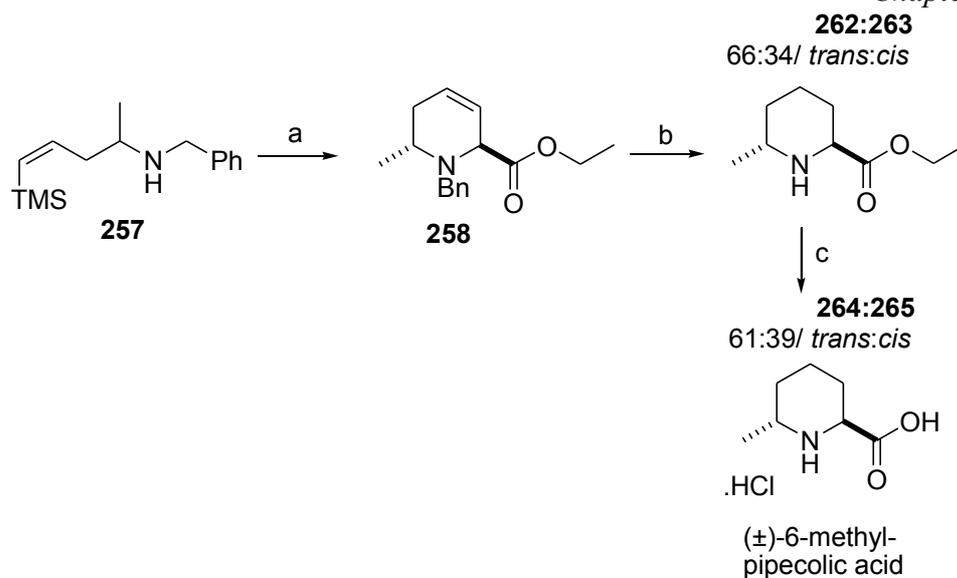
**Scheme 113.** The aza-silyl-Prins reaction produces *trans*-2,6-disubstituted-3,4-tetrahydropyridines exclusively.

With these results in hand, our group successfully completed the total synthesis of racemic solenopsin A, a constituent of fire-ant venom from *Solenopsis* species and racemic *Epi*-dihydropinidine, isolated from pine and spruce species such as *Picea pungens* or *Pinus ponderosa* (Figure 23). These *trans*-2,6-disubstituted piperidine alkaloids were prepared by reduction of the related tetrahydropyridine cores, prepared by the aza-silyl-Prins reaction.



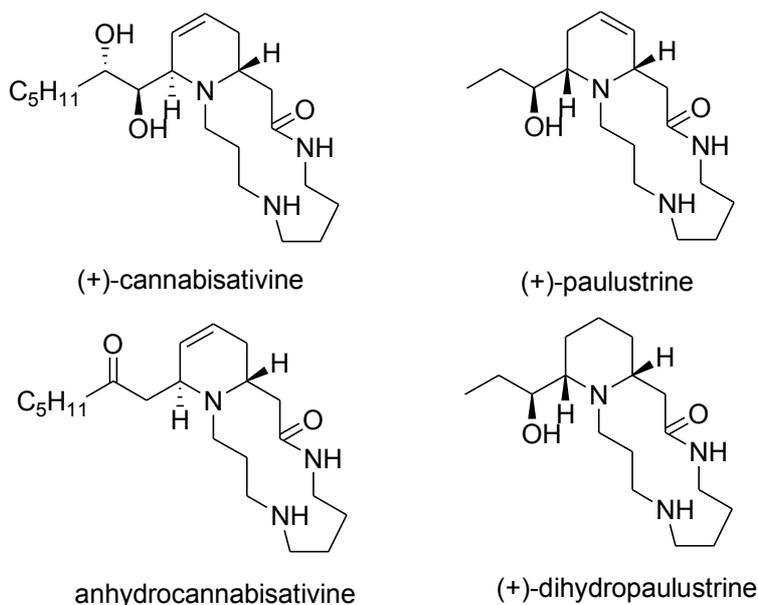
**Figure 23.** Structures of solenopsin A and *epi*-dihydropinidine.

Also, within this thesis, it has been shown how the aza-silyl-Prins reaction can be utilised to form 6-methylpipercolic acid. On coupling an  $\alpha$ -methyl substituted homoallylic amine **257** to ethyl glyoxylate, the desired *trans*-2,6-disubstituted-3,4-tetrahydropyridine **258** was formed. This pipercolate species could then easily be reduced and then acid hydrolysed to afford an analogue of the natural product pipercolic acid **264/265** (Scheme 114).



**Scheme 114.** *Reagents and conditions:* (a) ethyl glyoxylate,  $\text{InCl}_3$ ,  $\text{CH}_3\text{CN}$ , rt, 48 h, 74%; (b)  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$ , EtOH, rt, 5 h, 87%; (c) 6.0 M HCl (aq), reflux, 2 h, 83%.

It was now desired to use the aza-silyl-Prins reaction towards a more complicated target, to prove that it can be utilised to form larger natural products. Our target molecule was cannabistativene, a macrocyclic spermidine alkaloid isolated from the marijuana plant *Cannabis sativa*. It is part of a family of macrocyclic polyamine alkaloids which contain the biogenetic base spermidine. This family includes anhydrocannabistativene, paulustrine and dihydropalustrine. These related species each have the same 13-membered macrocyclic lactam ring which is tethered between the C2 position and the nitrogen of the azacyclic core. Both cannabistativene and anhydrocannabistativene have a *trans*-2,6-disubstituted-4,5-tetrahydropyridine moiety, with only the 6-substituent defining the different structure. However the 2,6-disubstituted tetrahydropyridine containing palustrine and the related 2,6-disubstituted piperidine-containing dihydropalustrine are each *cis* across the nitrogen of the aza-cyclic core (Figure 24). If it were possible to utilise the aza-silyl-Prins reaction to synthesise cannabistativene where the 6-substituent was derived from the coupled aldehyde, then it could be assumed that anhydrocannabistativene would also be obtained from the same aza-silyl-Prins amine precursor.

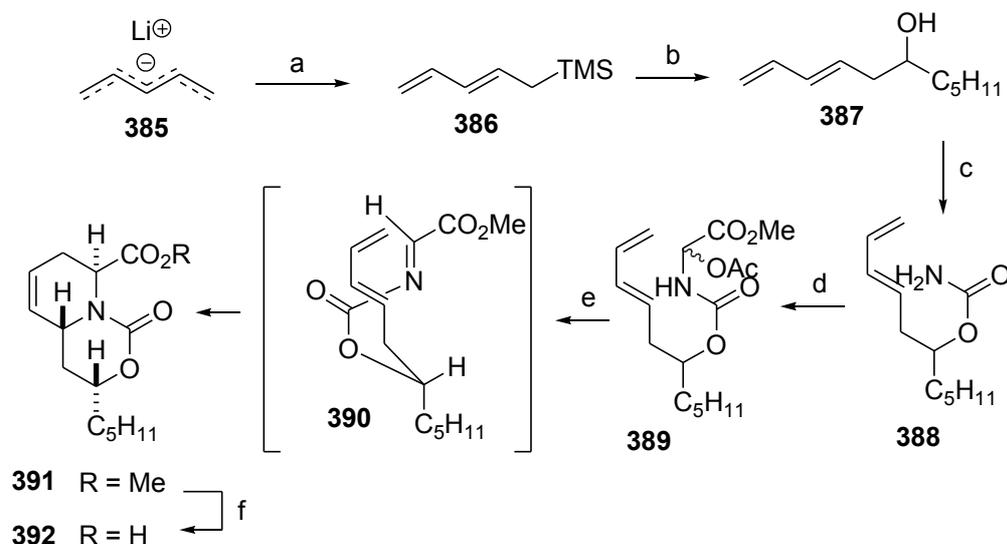


**Figure 24.** The macrocyclic spermidine family.

The following literature review will focus on both racemic and enantioselective syntheses of members of the macrocyclic spermidine alkaloid family. This will hopefully allow a more comprehensive understanding of how to fashion a more efficient route to these molecules, for example, how to prepare the 13-membered macrocyclic lactam ring. Another advantage of this review might be to recognise targets that might constitute a formal synthesis.

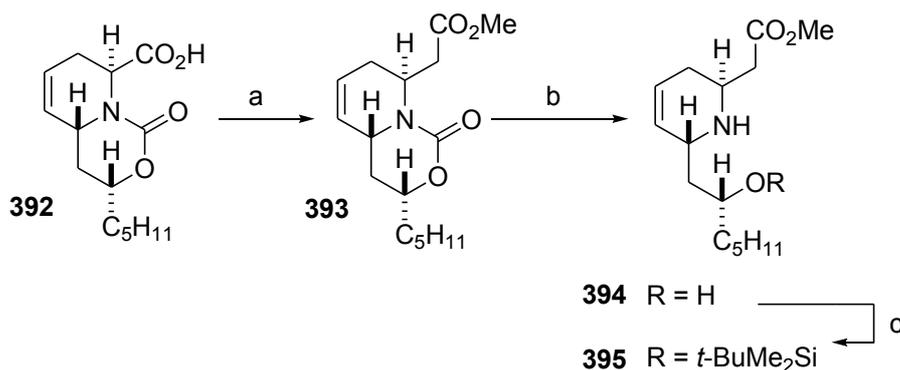
Weinreb has described the racemic synthesis of anhydrocannabisativine, focussing on an intramolecular imino-Diels-Alder cycloaddition to fashion the *trans*-2,6-disubstituted-4,5-tetrahydropyridine core. The required starting material for the imino-Diels-Alder approach was a diene alcohol **387**. This was efficiently prepared from pentadienylsilane **386** by treatment with hexanal and titanium tetrachloride, using a method described by Seyferth and Sakurai. This, in turn, was fashioned from pentadienyllithium **385** by treatment with trimethylsilyl chloride. The alcohol **387** was then converted into the related carbamate **388** using the cyanate method devised by Loev and Kormendy. This then was treated with methyl glyoxylate in acetone at reflux to give an intermediate that was then acetylated to afford an acetate **389**, as a mixture of stereoisomers. This mixture was treated with diisopropylethylamine in toluene at 215 °C in a sealed vessel, to afford a single bicyclic adduct **391**, the relative stereochemistry of which was established by X-ray crystallography. The *trans* configuration of the 2-carboxylate-tetrahydropyridine core could be rationalised by assuming that an intermediate *N*-acylimine was formed which underwent an *in situ* intramolecular Diels-Alder reaction **390** (Scheme 115). The

stereochemistry was assumed to be generated from an (*E*) acyl imine in the transition state, which holds the nitrogen carbonyl *endo* to the diene moiety.



**Scheme 115. Reagents and conditions:** (a) TMSCl; (b)  $\text{TiCl}_4$ , *n*- $\text{C}_5\text{H}_{11}\text{CHO}$ , DCM,  $-45^\circ\text{C}$ , 69%; (c) NaOCN, TFA,  $\text{Et}_2\text{O}$ , rt, 24 h, 95%; (d) methyl glyoxylate, acetone, reflux, 72 h, 82%; (e)  $(i\text{Pr})_2\text{EtN}$ , toluene, sealed vessel,  $215^\circ\text{C}$ , 3 h, 83%; (f) 5% NaOH (aq), MeOH, rt, 2 h, 96%.

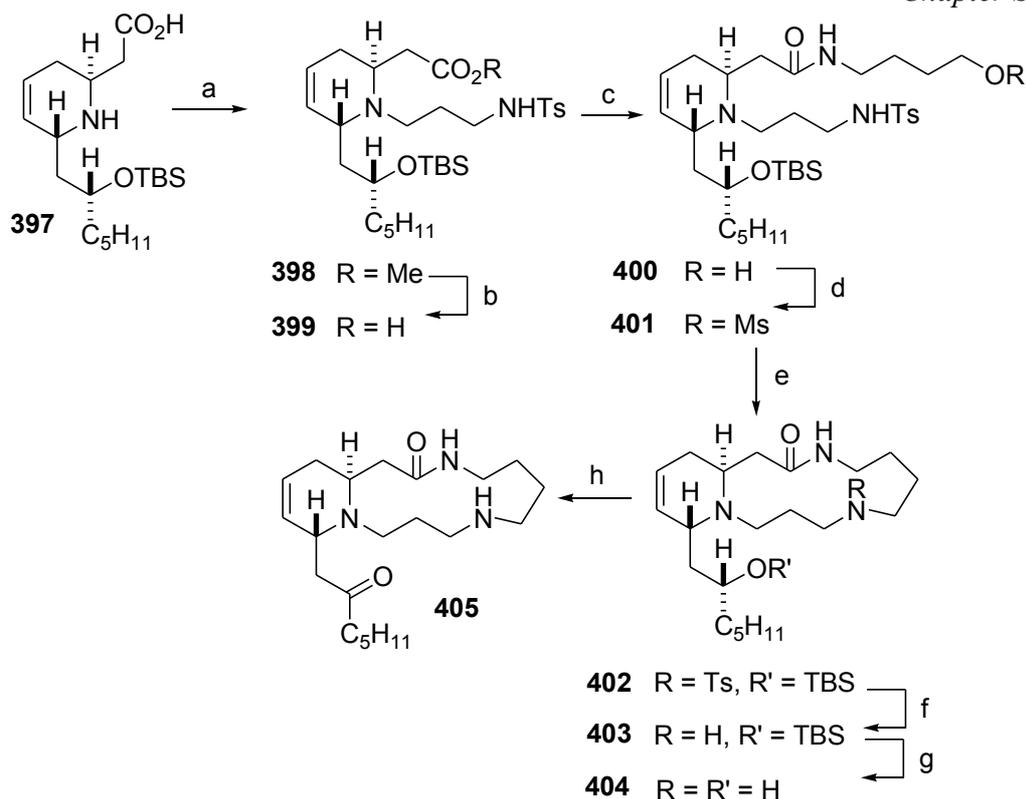
The hydrolysed 2-carboxylate-tetrahydropyridine moiety **392** was then further elaborated by Arndt-Eistert chain elongation of the acid using methanol to generate the methyl ester **393**. The bicyclic **393** was then cleaved by hydrolysis of the carbamate functionality, which was then re-esterified and the alcohol **394** protected as the *t*-butyldimethylsilyl ether **395** (Scheme 116).



**Scheme 116. Reagents and conditions:** (a) (i)  $(\text{COCl})_2$ , toluene, rt, 3 h, (ii)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , 1 h. (iii)  $\text{Ag}_2\text{O}$ , MeOH, rt, 78%; (b) (i)  $\text{Ba}(\text{OH})_2 \cdot (\text{H}_2\text{O})_8$ , glyme, water, reflux, 48 h, (ii)  $\text{SOCl}_2$ , MeOH, reflux, 12 h, 78%; (c) TBSOTf, 2, 6-lutidine, DCM,  $0^\circ\text{C}$ , 4 h, 91%.

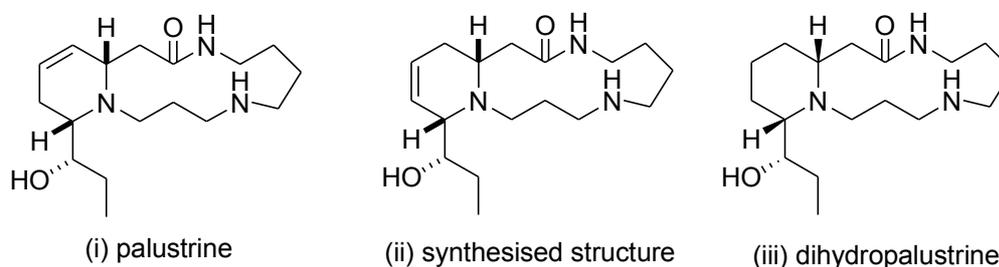
The free *trans*-2,6-disubstituted-4,5-tetrahydropyridine **395** could be a possible target to potentially constitute a formal synthesis of anhydrocannabisativine from this publication. This intermediate could be obtained *via* the aza-silyl-Prins reaction.

To furnish the macrocycle it was first necessary to mono-tosylate 3-aminopropanol, followed by triflate activation of the alcohol terminus. This species was then coupled to the tetrahydropyridine **395** to give an amino ester **398** which could be base hydrolysed to the corresponding acid **399**. This acid **399** was then activated as the 2,4,5-trichlorophenyl ester, which was then coupled to 4-aminobutanol to give the amide alcohol **400**. This alcohol was activated as the mesylate **401** and cyclisation of the macrocycle was effected by treating with a suspension of potassium carbonate in acetonitrile at reflux under dilute conditions. The *N*-tosyl function of **402** was then removed with sodium in liquid ammonia to give the secondary amine **403** and the alcohol was deprotected with boron trifluoride etherate to afford the amino alcohol **404**. Finally, oxidation of the alcohol with Jones' reagent afforded racemic anhydrocannabisativine **405** in 17 steps, starting from the silylpentadiene (Scheme 117).



**Scheme 117. Reagents and conditions:** (a)  $\text{TfO}(\text{CH}_2)_3\text{NHTs}$ , DCM, rt, 4h, 99%; (b) 1.0 M aq. LiOH, MeOH, 0 °C, 15 h, 100%; (c) (i) 2,4,5-trichlorophenol, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate, rt, 45 h, (ii) 4-Aminobutanol, DMF, -20°C, 18 h, 82%; (d) MsCl,  $\text{Et}_3\text{N}$ , DCM, -15 °C to 5 °C, 1 h, 80%; (e)  $\text{K}_2\text{CO}_3$ , MeCN, reflux, 24 h, 58%; (f) Na,  $\text{NH}_3$ , THF, -60 °C, 90%; (g)  $\text{BF}_3 \cdot \text{OEt}_2$ , rt, 1h; (h) Jones' reagent, acetone, rt, 30 mins, 54%.

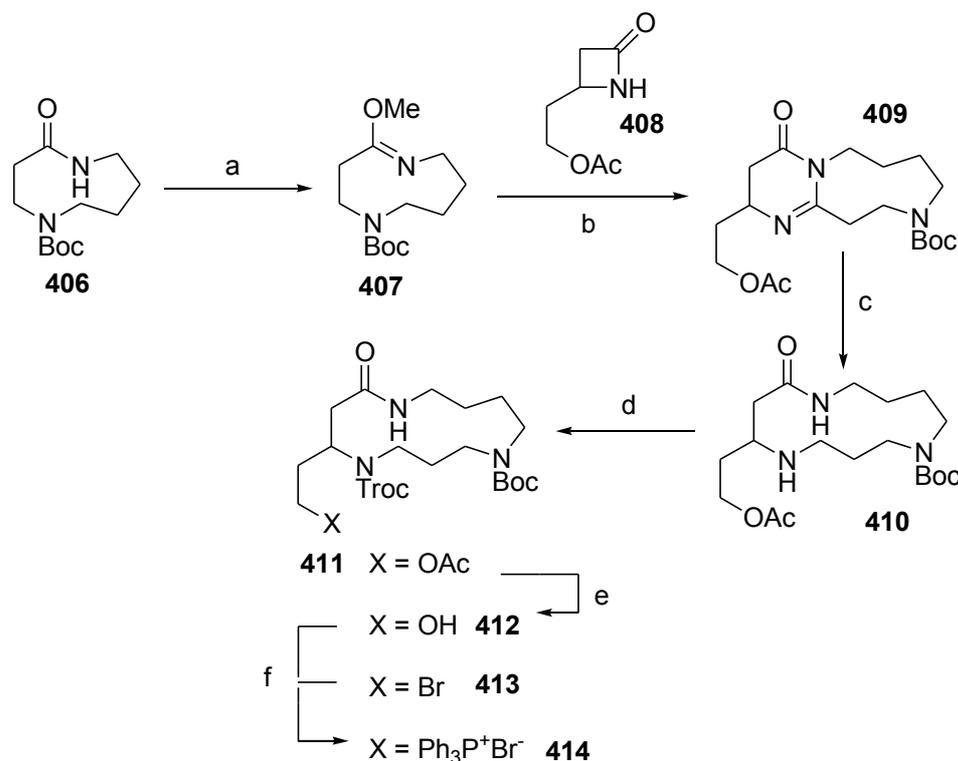
Wasserman synthesised a compound with a palustrine structure (eventually concluded to be the incorrect structure with regard to the position of the tetrahydropyridine olefin), but this was utilised as an intermediate towards the total synthesis of a racemic form of dihydropalustrine (Figure 25).



**Figure 25. Structures of (i) naturally occurring palustrine, (ii) Watsume's compound with a palustrine structure, (iii) dihydropalustrine.**

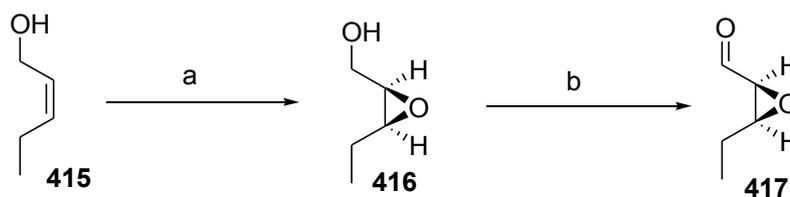
Wasserman's synthesis began with a nine-membered lactam **406**, which was also used previously towards the synthesis of alkaloids chaenorhine and verbascenine. This lactam

**406** was then converted into a methyl imino ether **407** using trimethyloxonium tetrafluoroborate. The species **407** was then coupled to a  $\beta$ -lactam **408** at 145 °C in mesitylene to give **409**. This coupled product **409** was reduced using sodium cyanoborohydride in acetic acid to form the 13-membered lactam **410**. The newly generated amino group was then protected as the trichloroethoxycarbamate and the terminal acetate **411** was converted into the alcohol **412** using sodium methoxide. The alcohol was then converted into the bromide **413** using triphenylphosphite dibromide and then treated with triphenylphosphine to furnish the phosphonium salt **414** (Scheme 118).



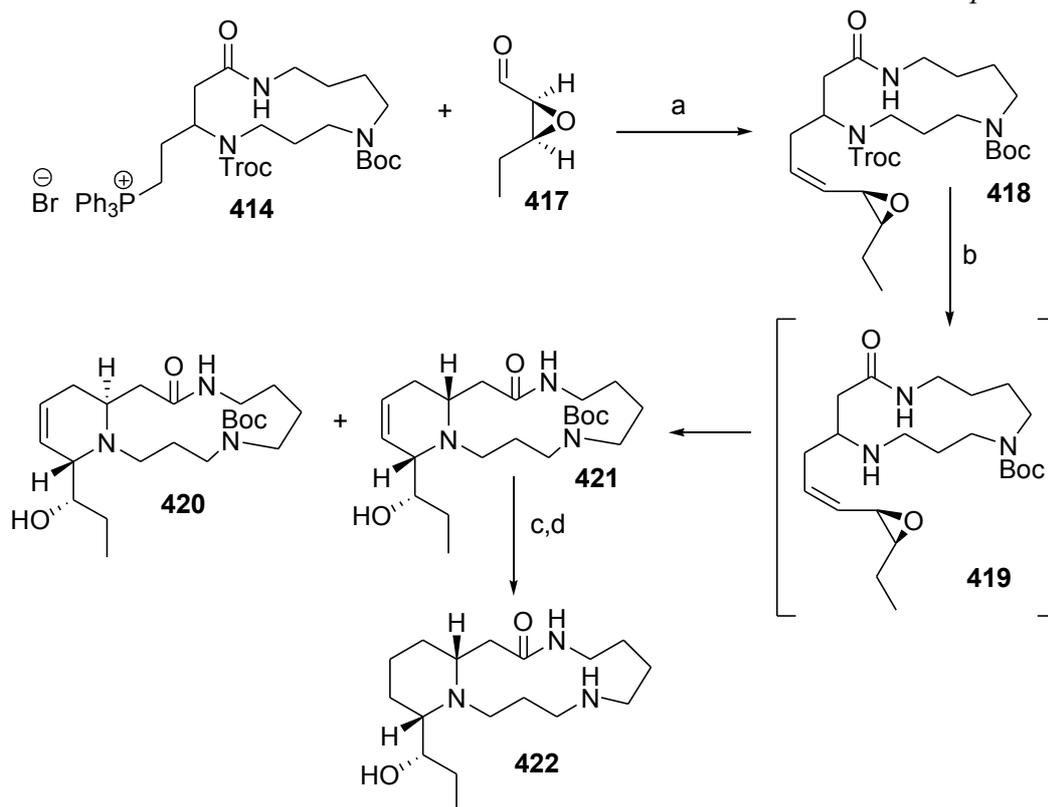
**Scheme 118.** Reagents and conditions: (a) Me<sub>3</sub>O<sup>+</sup>BF<sub>4</sub><sup>-</sup>, 97%; (b) mesitylene, 145°C, 65%; (c) NaBH<sub>3</sub>CN, AcOH, 90%; (d) ClCOOCH<sub>2</sub>CCl<sub>3</sub>, DMAP, 90%; (e) NaOMe, 95%; (f) (i) triphenylphosphite dibromide; (ii) PPh<sub>3</sub>, heating, 50% for 2 steps.

The other precursor required was an epoxy aldehyde **417**, which was prepared from an allylic alcohol **415** via a Sharpless epoxidation procedure, followed by oxidation with PDC (Scheme 119).



**Scheme 119.** Synthesis of aldehyde Wittig precursor. *Reagents and conditions:* (a) *t*-BuOOH, VO(acac)<sub>2</sub>; (b) PDC.

The Wittig reaction using NaH as the base gave **418** *via* an unstabilised ylid which afforded the desired *cis* double bond. Removal of the trichloroethoxycarbonyl group allowed formation of a separable mixture of two diastereomeric tetrahydropyridines, **420** and **421** (47:53) *via* ring opening of the epoxide **419** by the secondary amine. After removal of the Boc group from the *cis* diastereomer **421**, the product with a palustrine structure was obtained. Analysis of this product on comparison with a sample of naturally occurring palustrine showed that the tetrahydropyridine olefin was in the incorrect position. The palustrine type product was then converted to racemic dihydropalustrine **422** by hydrogenation over a poisoned palladium catalyst (Scheme 120).



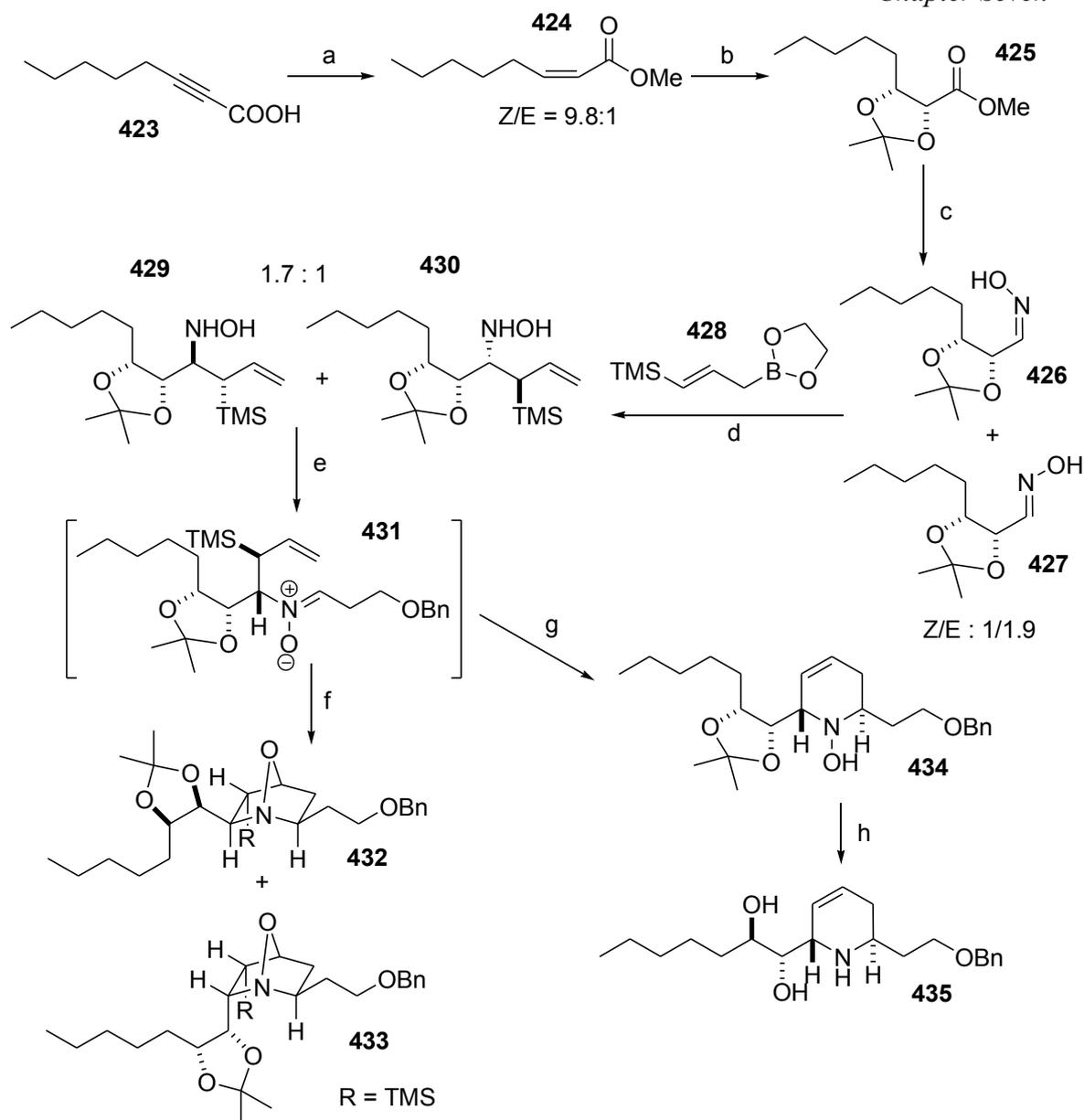
**Scheme 120.** Completion of synthesis of racemic dihydropalustrine. *Reagents and conditions:* (a) NaH, THF/DMSO; (b) Zn, THF/H<sub>2</sub>O, pH 5.5; (c) HCl/DCM; (d) H<sub>2</sub>, Pd/C, BaSO<sub>4</sub>.

Even though no targets could be identified in this publication that would constitute a formal synthesis, it encouraged consideration of fashioning the 13-membered macrocyclic lactam before synthesising the tetrahydropyridine core *via* the aza-silyl-Prins reaction.

Wuts has described a synthetic pathway to 2,6-disubstituted tetrahydropyridines that possess the cannabistatine skeleton, using an intramolecular allylsilane-nitrone cycloaddition. The design of the synthesis relies on an allylboronate to establish the relative stereochemistry at three chiral centres. Asymmetric induction in the addition of the allylboronate to an oxime is likely to produce two possible diastereomers. The resulting hydroxylamines can then be converted to the nitron which is then cyclised to the desired tetrahydropyridine.

The oxime was obtained in six steps from 2-octynoic acid **423**. First the acid **423** was esterified with diazomethane, followed by hydrogenation over Lindlar's catalyst to give a mixture of *cis* and *trans* unsaturated esters **424** in a 9.8:1 ratio. The desired *cis* isomer was isolated by flash chromatography and next treated with osmium tetroxide and the resulting diol protected as the acetonide **425**. This was then reduced with DiBAL and further treated with hydroxylamine hydrochloride in pyridine to afford an (*E/Z*) mixture (1.9:1) of oximes **426** and **427**. The mixture of oximes was then treated with

[(trimethylsilyl)allyl]boronate **428** to give two isomers **429** and **430** with a ratio of 1.7:1 after purification. The relative stereochemistry of these isomers was determined by conversion into bicyclic isooxazolidines **432** and **433** by a thermal [3+2] cycloaddition and analysing the  $^1\text{H}$  NMR spectra of the resulting products. The thermally promoted nitron cyclisation favoured the *cis*-2,6-isooxazolidine **433**. Treating the mixture of isomers **429** and **430** with 3-(benzyloxy)propanal furnished the nitron **431**. Treatment of the intermediate nitron **431** with TMS triflate gave exclusively, a *trans*-2,6-disubstituted *N*-hydroxytetrahydropyridine **434**. The hydroxylamine was then reduced with aqueous zinc and acetic acid followed by hydrolysis of the acetonide to furnish the diol **435** (Scheme 121).

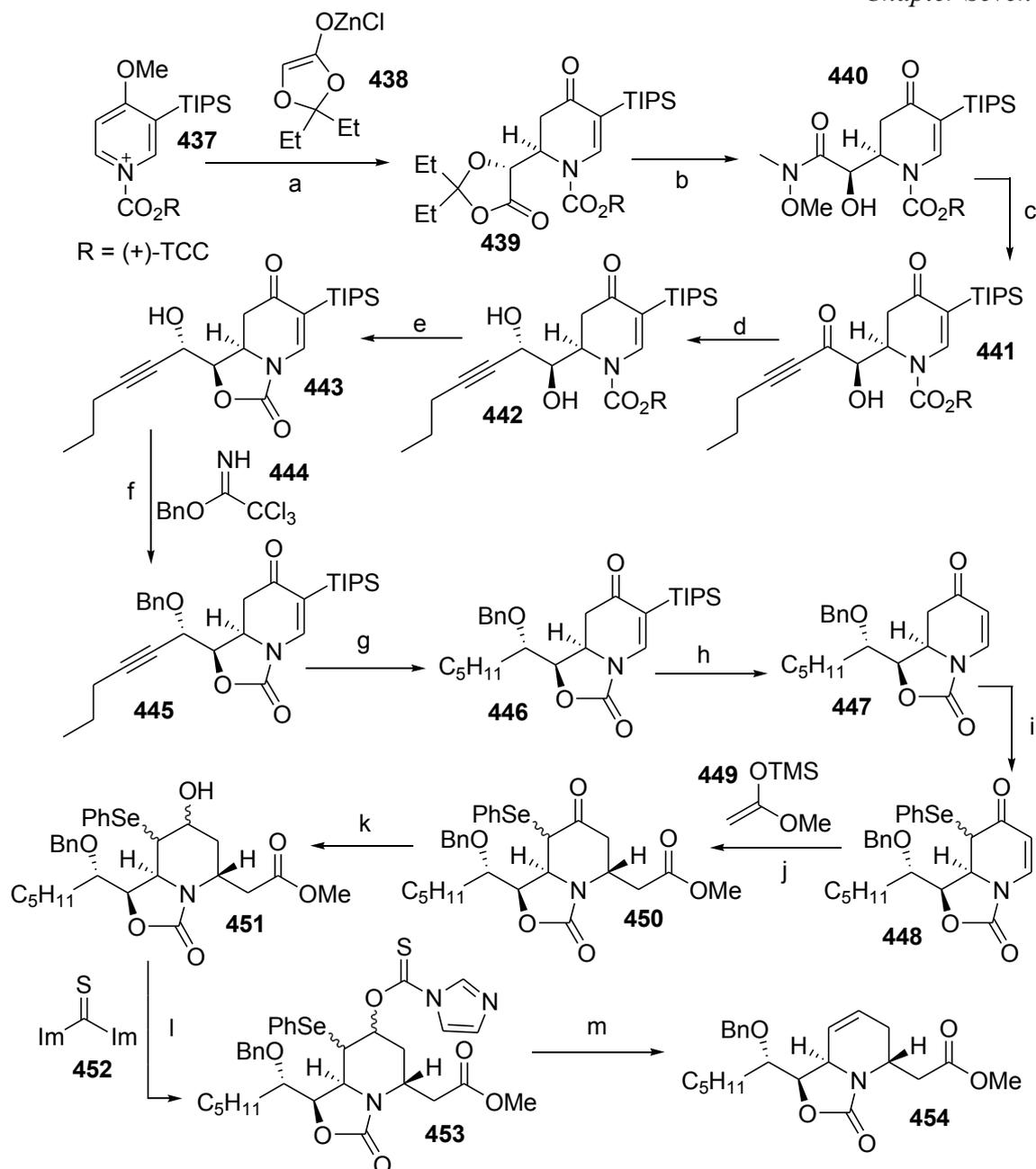


**Scheme 121. Reagents and conditions:** (a) (i)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , 95%, (ii) Lindlar catalyst, quinoline, 91%; (b) (i)  $\text{OsO}_4$ , NMO, 85%, (ii)  $(\text{CH}_3)_2\text{C}(\text{OMe})_2/\text{H}^+$ , 97%; (c) (i) DiBAL,  $-78\text{ }^\circ\text{C}$ , 78%, (ii)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ /pyridine, 97%; (d)  $\text{CCl}_4$ , heat, 55%; (e) 2 eq.  $\text{BnOCH}_2\text{CH}_2\text{CHO}$ , toluene,  $-20\text{ }^\circ\text{C}$ ; (f) toluene, reflux, 2 h, 100%; (g) TMSOTf,  $-40\text{ }^\circ\text{C}$ , 18 h, 79%; (h) (i) Zn,  $\text{HOAc}/\text{H}_2\text{O}$ , (ii) TFA,  $\text{THF}/\text{H}_2\text{O}$ , 73%.

Potentially the tetrahydropyridine **435** could also be accessed using the aza-silyl-Prins reaction and then the product further elaborated to synthesise racemic cannabisativine or another member of the macrocyclic spermidine family.

Comins has described the asymmetric total synthesis of (+)-cannabisativine in 19 steps and in 7% overall yield. The synthesis began with the addition of a zinc enolate **438**, prepared from 2,2-diethyl-1,3-dioxolan-4-one, to a chiral 1-acylpyridinium salt **437**. This

furnished the dihydropyridone **439** as the major diastereomer in a high yield with the *anti* conformation confirmed by the X-ray structure. The dihydropyridone **439** was then transformed into a Weinreb amide **440** by treatment with *N,O*-dimethylhydroxylamine hydrochloride. The amide **440** was then treated with pentynyllithium to give the alkynyl ketone **441**. This was then transformed under Luche conditions to a diol **442** with high diastereoselectivity. The authors used Cram's rule to explain why the reduction occurred from the least sterically demanding side of the intermediate. When the diol **442** was treated with sodium hydride, the chiral auxiliary was released on formation of the 5-membered chiral oxazolidinone **443**. After protection of the free hydroxyl group as the benzyl ether **445**, the alkyne was catalytically reduced over Pt/C to give the desired side-chain **446**. The dihydropyridone was then activated by removal of the TIPS group *via* protodesilylation with TFA to give **447**. The C2 dihydropyridone **447** proton was removed with LiHMDS and treated with phenylselenenyl chloride to afford an inseparable mixture (3.5:1) of diastereomeric selenides **448**. Treatment of this mixture with *o*-silyl ketal acetal **449** under Lewis acidic conditions, gave the Mukaiyama-Michael product, which under acidic work-up afforded the ketones **450** as an inseparable diastereomeric mixture. These ketones **450** were reduced to alcohols **451**, again under Luche conditions. The mixture was converted into thiocarbamates **453** on treatment with 1,1'-thiocarbonyldiimidazole **452** followed by reduction with tributyltin hydride to give a single *trans*-2,6-disubstituted tetrahydropyridine diastereomer **454** (Scheme 122).

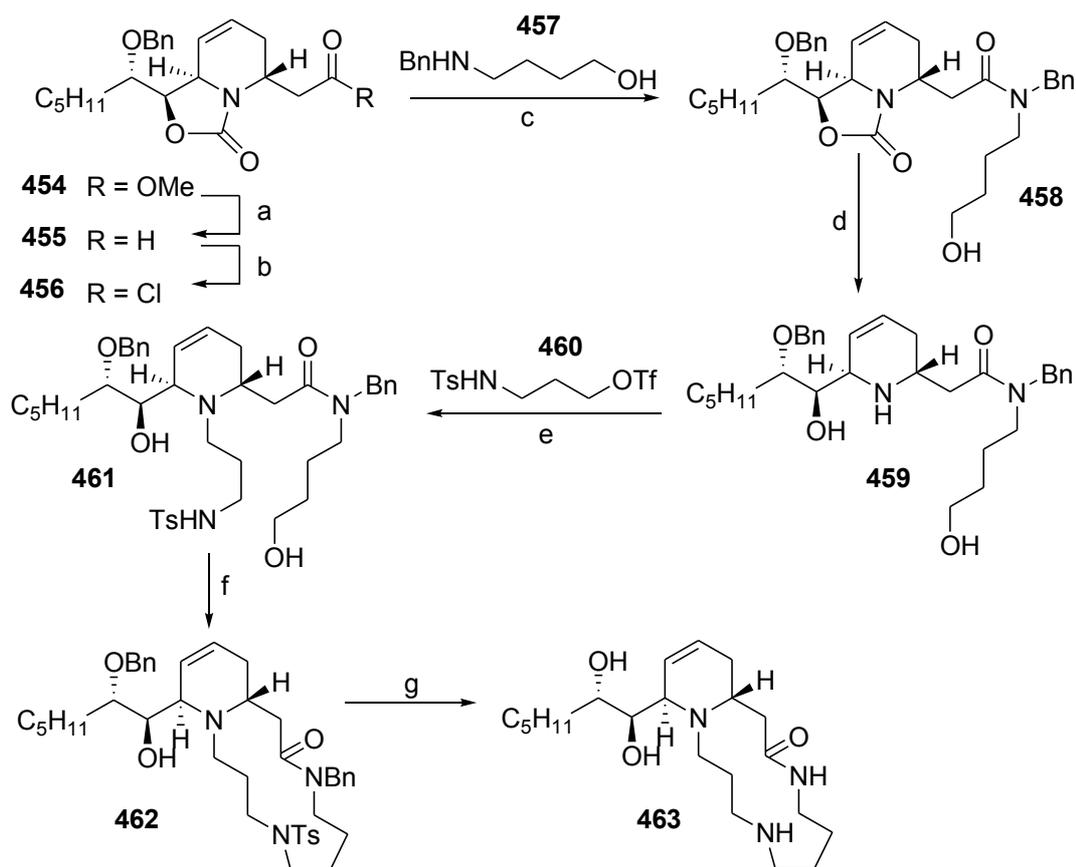


**Scheme 122. Reagents and conditions:** (a) *n*-BuLi, (*i*-Pr)<sub>2</sub>NH, THF, -78 °C, 85%; (b) MeONHMe.HCl, AlMe<sub>3</sub>, DCM, rt, 1.5 h, 97%; (c) 0.5 M 1-pentynyllithium, THF, -78 °C, 96%; (d) CeCl<sub>3</sub>·(H<sub>2</sub>O)<sub>7</sub>, NaBH<sub>4</sub>, MeOH, -50 °C, 96%; (e) NaH, THF, rt, 3h, 88%; (f) TfOH, Et<sub>2</sub>O, rt, 5 h, 86%; (g) H<sub>2</sub>, 5% Pt/C, Li<sub>2</sub>CO<sub>3</sub>, EtOAc, rt, 12 h, 97%; (h) TFA/CHCl<sub>3</sub> (1:1), reflux, 12 h, 77%; (i) LiHMDS, PhSeCl, -78 °C, 73%; (j) BF<sub>3</sub>·OEt<sub>2</sub>, DCM, 100%; (k) CeCl<sub>3</sub>·(H<sub>2</sub>O)<sub>7</sub>, NaBH<sub>4</sub>, MeOH, rt, 85%; (l) DMAP, toluene, reflux, 3 h, 91%; (m) Bu<sub>3</sub>SnH, AIBN, toluene, reflux, 95%.

This tetrahydropyridine product **454** could be targeted towards an asymmetric formal synthesis of (+)-cannabisativine using the aza-silyl-Prins reaction.

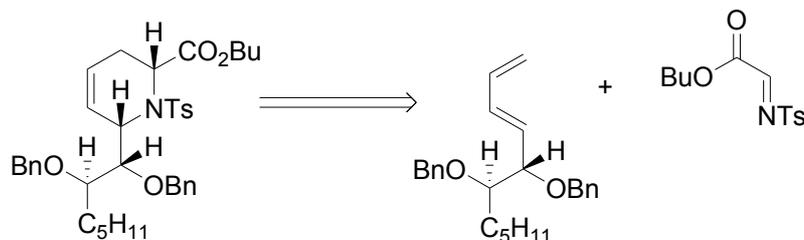
The synthesis was completed by converting the *trans*-2,6-disubstituted tetrahydropyridine **454** into the carboxylic acid **455** by base hydrolysis. From here, after acid chloride

formation **456**, this was coupled to an *N*-benzyl protected amino alcohol **457** to afford the amide **458**. The oxazolidinone function was then cleaved under basic conditions to afford the aminodiol **459** and the core tetrahydropyridine *N*-alkylated on treatment with an *N*-tosylamino triflate **460** to afford the tertiary amine **461**. Conversion of the terminal alcohol into the mesylate, followed by treatment with potassium carbonate, furnished the desired macrocyclic lactam **462**. After global deprotection using sodium in liquid ammonia, the synthesis of the natural product **463** was complete (Scheme 123).



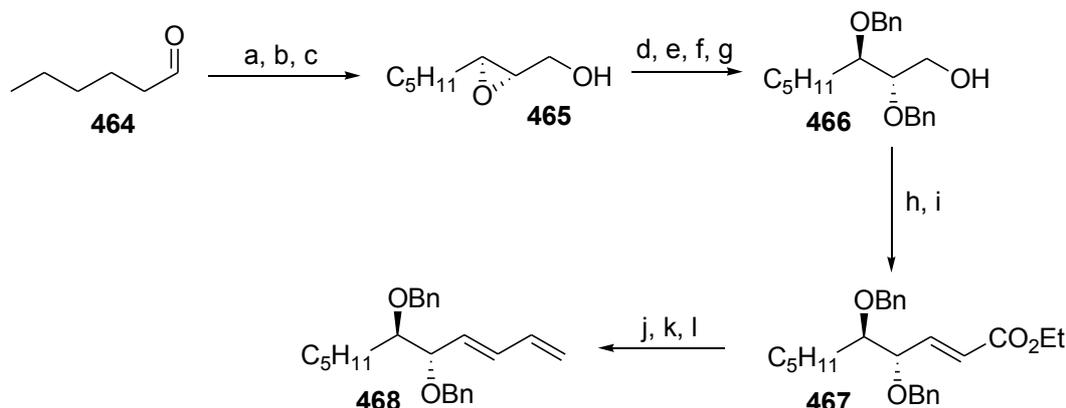
**Scheme 123. Reagents and conditions:** (a) KOH, H<sub>2</sub>O, MeOH, rt, 2 h, 100%; (b) (COCl)<sub>2</sub>, DMF, DCM, rt, 1 h; (c) 10% aq. NaOH, DCM, rt, 1.5 h, 82%; (d) 50% KOH (aq), MeOH, reflux, 18 h, 88%; (e) (*i*-Pr)<sub>2</sub>EtN, DCM, rt, 3 h, 84%; (f) (i) MsCl, Et<sub>3</sub>N, DCM, -20 °C, 95%, (ii) K<sub>2</sub>CO<sub>3</sub>, MeCN, reflux, 24 h, 70%; (g) Na, NH<sub>3</sub>, THF, reflux, 76%.

Hamada has described the total synthesis of the unnatural product, (-)-cannabisativine. The retrosynthetic strategy towards this compound was to utilise a hetero Diels-Alder reaction between an optically active diene and an *N*-tosylimine (Scheme 124).



**Scheme 124.** Retrosynthetic strategy utilising a hetero Diels-Alder reaction.

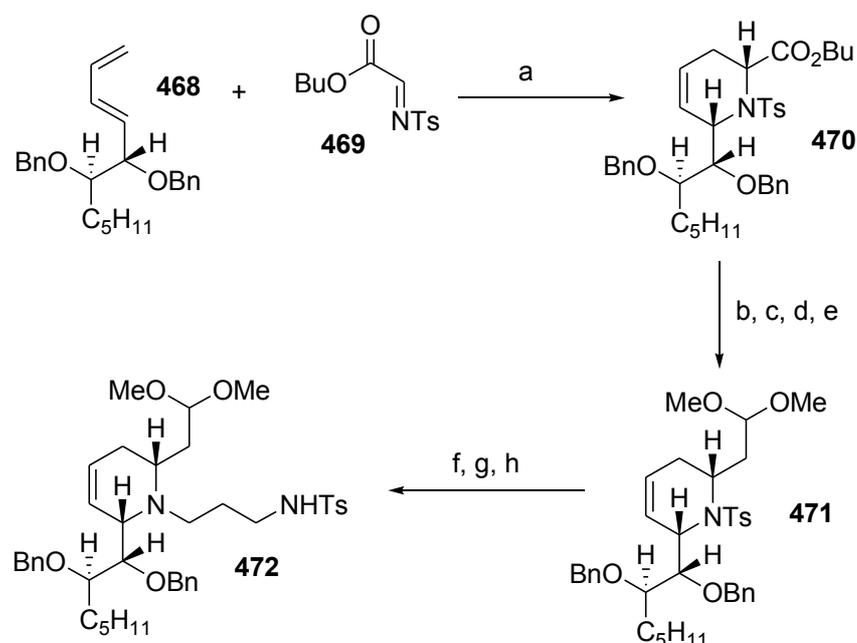
The chiral diene **468** was accessed in several steps starting from a chiral epoxide **465**, formed by Sharpless asymmetric epoxidation of *trans*-2-octenol **464** using (+)-diethyl tartrate. This epoxide **465** was opened also using a Sharpless method involving a titanium(IV) alkoxide species, directly followed by tritylation, benzylation and acid hydrolysis. The alcohol product **466** was then oxidised under Swern conditions, followed by Wittig olefination with a stable phosphorane to give the (*E*)-alkene **467**. The ester function was then reduced with *Di*BAL to the desired allyl alcohol, which underwent Swern oxidation. The resulting aldehyde underwent Wittig olefination to yield the required optically active diene **468** in 12 steps and 21% overall yield, starting from *n*-hexanal **464** (Scheme 125).



**Scheme 125.** *Reagents and conditions:* (a)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ , NaH,  $\text{Et}_2\text{O}$ , 88%; (b) *Di*BAL, DCM, 78%; (c)  $\text{Ti}(\text{O}i\text{-Pr})_4$ , *t*BuOOH, (+)-DET, DCM, 68%; (d)  $\text{Ti}(\text{OBn})_4$ , BnOH, 82%; (e) TrCl, DMAP,  $\text{NEt}_3$ ; (f) NaH, BnCl, THF-DMSO(1:2); (g) 4M HCl-THF, 3 steps, 96%; (h)  $(\text{COCl})_2$ , DMSO,  $\text{NEt}_3/\text{DCM}$ ; (i)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ , NaH,  $\text{Et}_2\text{O}$ , 2 steps, 96%; (j) *Di*BAL, DCM, 90%. (k) PDC, DMF; (l)  $\text{Ph}_3\text{PCH}_2$ , THF, 2 steps, 75%.

This diene **468** was used in the hetero Diels-Alder reaction with an *N*-tosylimine **469** to furnish the *N*-tosyl-2,6-disubstituted tetrahydropyridine **470** with *cis* geometry across the heteroatom. The carboxylate side chain of this species was then reduced with LAH to the aldehyde, followed by a Wittig reaction with methoxymethylene phosphorane to give an enol ether that was elaborated further by acetalisation to give **471**. The tosyl function of the tetrahydropyridine core was then deprotected by sodium-naphthalenide reduction, and

the resulting free amine was acrylated with *N*-tosyl alanyl chloride, followed by a reduction with LAH to furnish the tertiary amine **472**. The acetal function was later converted into an aldehyde by acetal exchange and on treatment with potassium carbonate in methanol, the C6 centre was epimerised to the desired *trans* diastereomer (Scheme 126). From here the construction of the macrocyclic lactam followed a similar pattern to previous literature examples.



**Scheme 126. Reagents and conditions:** (a) neat, 40 °C, 6 days, 81%; (b) LAH, Et<sub>2</sub>O, 92%; (c) (COCl)<sub>2</sub>, DMSO, NEt<sub>3</sub>, DCM, -60 °C; (d) MeOCHP<sup>+</sup>Ph<sub>3</sub>, THF, 2 steps, 72%; (e) CSA, MeOH, 93%; (f) Na, C<sub>10</sub>H<sub>8</sub>, THF, 86%; (g) TsNH(CH<sub>2</sub>)<sub>2</sub>COCl, K<sub>2</sub>CO<sub>3</sub>, C<sub>6</sub>H<sub>6</sub>, toluene, H<sub>2</sub>O, 94%; (h) LAH, THF, reflux, 94%.

## . II Results and Discussion: Studies Towards the Total Synthesis of Cannabisativine

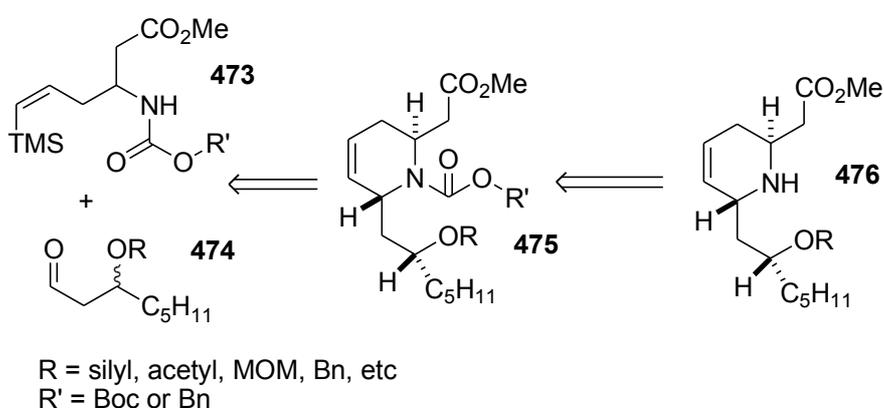
Attempts at utilising the aza-silyl-Prins reaction in the total synthesis of cannabisativine are now discussed. In previous examples, the aza-silyl-Prins reaction produced *trans*-2,6-disubstituted-3,4-tetrahydropyridines exclusively and our natural product target contains an azacyclic core with this configuration. The spermidine alkaloid cannabisativine occurs naturally as the (+)-enantiomer but initially the synthesis of a racemic mixture was studied. If successful, the route could hopefully be adapted towards the asymmetric synthesis of the natural product. An attractive option would be to exploit previous studies into the asymmetric imine-vinylsilane cyclisations or the use of chiral auxiliaries in the aza-silyl-Prins reaction. While the diastereoselectivity of the aza-silyl-Prins reaction is attractive, it was considered that the use of complex starting materials in the aza-silyl-Prins reaction may negatively affect this selectivity. If this were the case, then this

methodology could be adapted to synthesise other members of the spermidine family such as anhydrocannabisativine, paulustrine and dihydropalustrine.

### . 25 Retrosynthetic Analysis of Literature Examples, Towards the Formal Synthesis of Spermidine Alkaloids

In order to identify an appropriate synthetic target for a formal synthesis of a member of the spermidine family, intermediates from selected literature examples were analysed retrosynthetically. Although cannabisativine was our priority target, problems that may arise during the synthesis may allow us to direct our efforts towards other spermidine alkaloids.

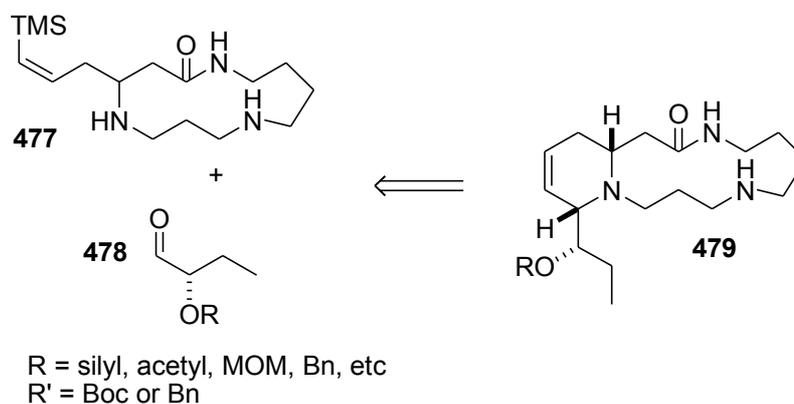
The first example to be analysed was from the total synthesis of anhydrocannabisativine by Weinreb. The intermediate free amine *trans*-2,6-disubstituted-4,5-tetrahydropyridine **476** is the desired target and this could also be adapted with a different aldehyde **474** towards the synthesis of cannabisativine. The homoallylic amine precursor **473** that would be required for the aza-silyl-Prins reaction needs a  $\alpha$ -methylene-carboxylate functionality as well as an easily removed protecting group on the nitrogen, such as a carbamate function (Scheme 127).



Scheme 127. Retrosynthetic analysis of possible formal synthesis, *via* Weinreb's intermediate.

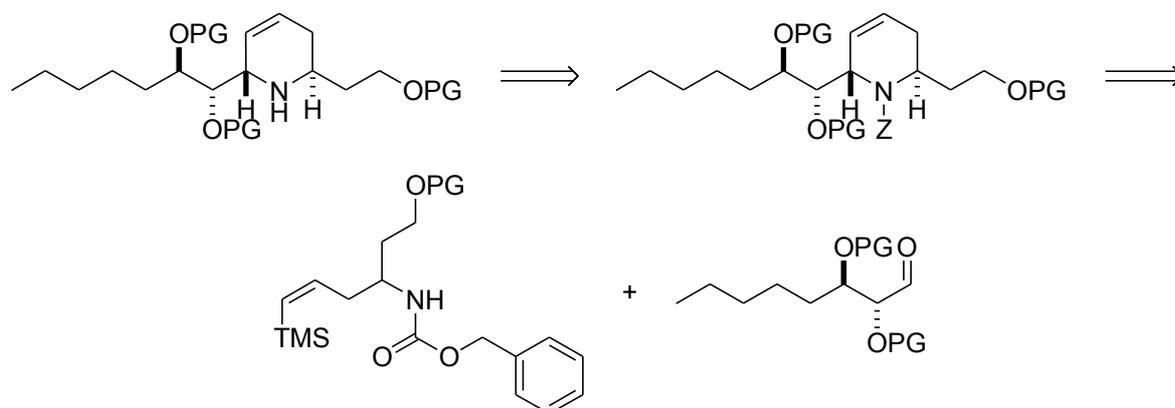
The next publication analysed is based on the synthesis of a compound with a palustrine structure (eventually concluded to be the incorrect structure with regards to the position of the olefin) by Wasserman. This article does not contain an intermediate that would be ideal for a formal synthesis. However, it allowed us to ponder the possibility of fashioning the 13-membered macrocyclic lactam before the synthesis of the tetrahydropyridine core **479** *via* the aza-silyl-Prins reaction. The aldehyde precursor to the cyclisation would be a simple protected- $\alpha$ -hydroxy aliphatic aldehyde **478**. However, the homoallylic amine precursor **477** required, would have the 13-membered lactam tethered between the

nitrogen and the  $\alpha$ -position. This could alter the stereochemical outcome of the cyclisation, as perhaps the  $A^{1,3}$  strain between ring substituents would be altered with the tethered macrocycle. With all other nitrogen-bearing substituents used in the aza-silyl-Prins reaction such as benzyl, phenyl and alkyl, the tetrahydropyridine product was exclusively *trans* across the heteroatom (Scheme 128).



**Scheme 128. Retrosynthetic analysis of possible palustrine analogue.**

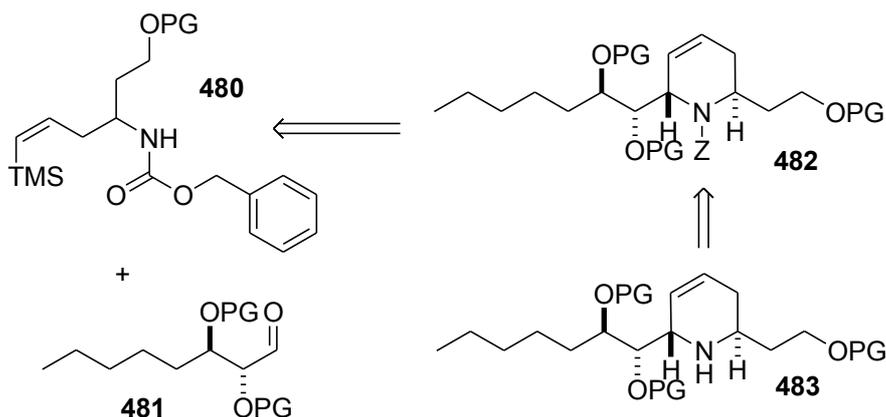
The next example from the literature is based on the formation of the tetrahydropyridine skeleton of cannabistatine by Wuts. Even though this does not allow a formal synthesis, access to this tetrahydropyridine using the aza-silyl-Prins reaction with further elaboration might allow the synthesis of racemic cannabistatine or another member of the macrocyclic spermidine family. The condensation between a di-protected  $\alpha,\beta$ -dihydroxy aliphatic aldehyde and a homoallylic amine would be required. The amine would require a protected- $\alpha$ -ethanol substituent and perhaps a carbamate function on the nitrogen, which could be easily removed without reducing the double bond (Scheme 129).



**Scheme 129. Retrosynthetic analysis of possible target molecule for cannabistatine synthesis.**

If the studies towards the synthesis of the racemic form of cannabistatine were successful, then work could progress towards an asymmetric synthesis. Comins

completed the synthesis of naturally occurring (+)-cannabisativine and again a tetrahydropyridine intermediate **482** could be targeted using the aza-silyl-Prins reaction. The precursors required for the cyclisation would be one enantiomer of a di-protected  $\alpha$ ,  $\beta$ -dihydroxy aliphatic aldehyde **481**, accessed perhaps from Sharpless asymmetric dihydroxylation. Also, required would be a homoallylic amine **480** with an  $\alpha$ -methylene carboxylate function and also a nitrogen-bearing carbamate function. Such an intermediate might be utilised as a single enantiomer (Scheme 130).



**Scheme 130. Retrosynthetic analysis of possible asymmetric formal synthesis target.**

This section has not only allowed us to target intermediate compounds for a formal synthesis of spermidine alkaloids but also to design new targets based on the different methodologies utilised.

## . 26ROUTE 1

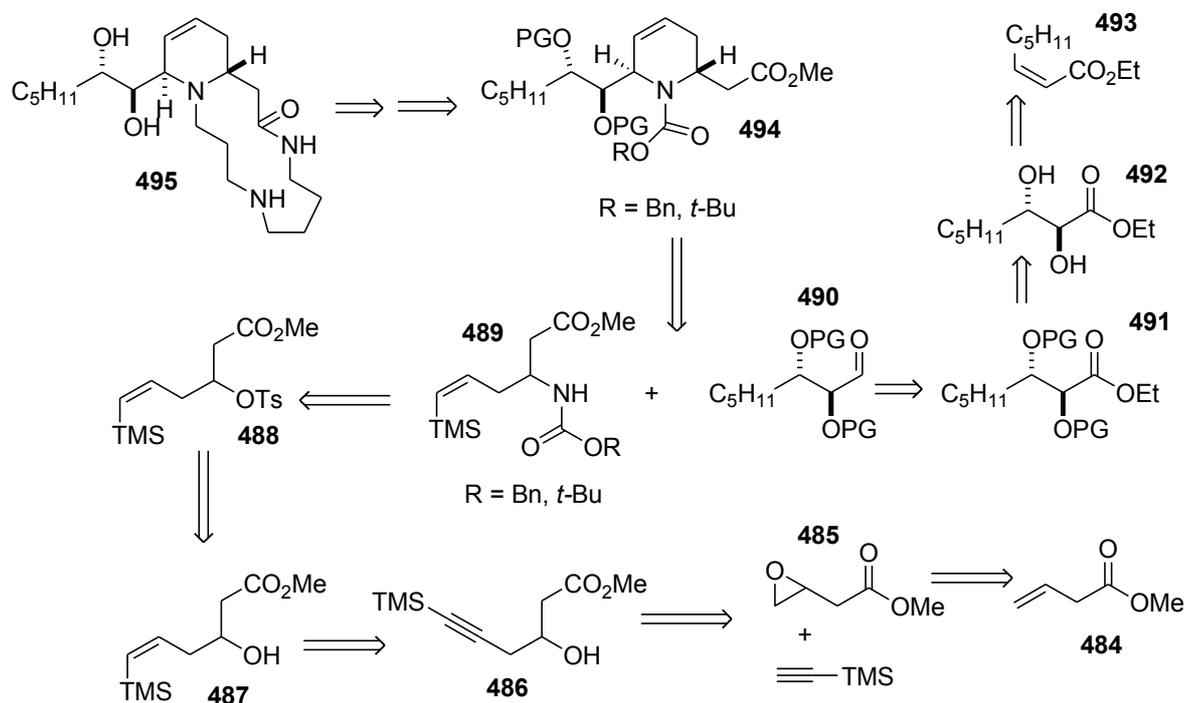
### . aRetrosynthetic Analysis of

#### Cannabisativine I

In the majority of total syntheses of cannabisativine and also other members of the macrocyclic spermidine family, the 13-membered macrocyclic lactam, tethered between the tetrahydropyridine nitrogen and the adjacent C6 position, is constructed after the azacyclic core has been prepared. Many macrocyclic lactam ring closures are fashioned by nucleophilic attack by a primary or secondary amine on an activated ester function. Similarly, this can also be effected by the coupling of carboxylic acids and amines to give the amide function by treatment with coupling reagents such as DCC. At this stage, macrocycle formation would not be a concern as very similar methodology has been used each time in the literature examples. However, such an approach requires the presence of the ester function or similar tethered to the C6 position of the azacyclic core. Also

required is an *N*-substituent that can easily be removed without affecting other functionality on the ring such as an *N*-Boc or *N*-CBz substituent; if an *N*-benzyl substituent were to be employed, as in previous examples, then removal by catalytic hydrogenation would also reduce the 3,4-olefin function.

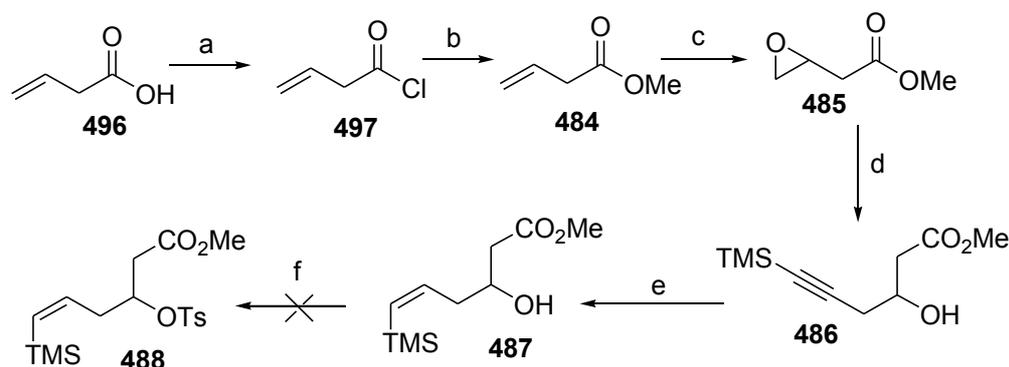
Disconnection of the *trans*-2,6-disubstituted-3,4-tetrahydropyridine core **494** gives the aza-silyl-Prins precursors, a homoallylic secondary amine **489** and an  $\alpha,\beta$ -disubstituted aldehyde **490**. The amine precursor **489** requires an  $\alpha$ -methylene-carboxylate moiety to functionalise the C6 position of the 3,4-tetrahydropyridine core. It also contains the *N*-carbamate function, which has provided success in previous aza-silyl-Prins examples. The aldehyde component **490** functionalises the C2 position of the 3,4-tetrahydropyridine and the 2,3-dihydroxy function contained within this is required to be protected throughout the synthesis of the 13-membered macrocycle, as in previous literature examples. The protected 2,3-dihydroxyaldehyde **490** may be obtained from the corresponding ester **491**. The desired 2,3-dihydroxy diastereomer **492** is taken from the *syn* di-hydroxylation of the (*Z*)-alkene **493**. The silylated-homoallylic secondary amine precursor could be obtained by using methods already discussed in this thesis (Scheme 131).



Scheme 131. Retrosynthetic analysis of racemic cannabistavine.

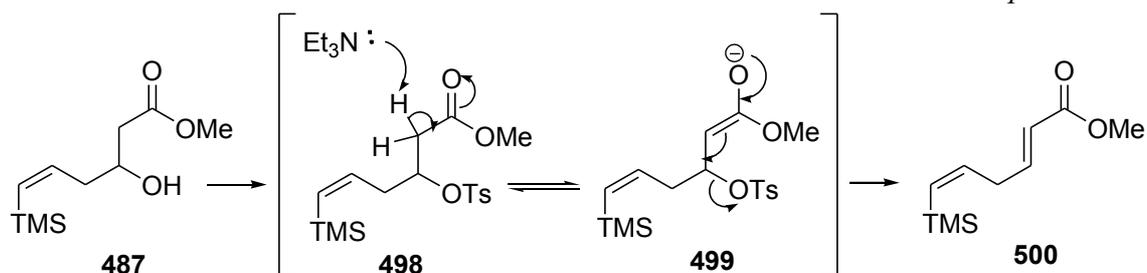
The amine required for the aza-silyl-Prins reaction *via* this route was (*Z*)-methyl 3-(**Amine Precursor** (carbamate)-6-(trimethylsilyl)hex-5-enoate **489**. It was proposed that either the *N*-Boc or *N*-CBz analogue could be obtained in 7 steps from the commercially available but-3-

enoic acid **496** (Scheme 132). This pathway would proceed *via* the amination of a tosylated alcohol **488**, comparable with our previous methodology.



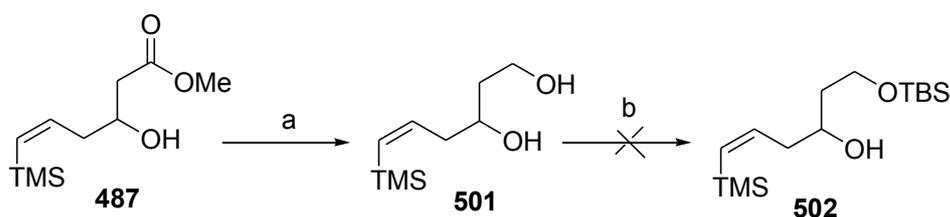
**Scheme 132.** *Reagents and conditions:* (a)  $\text{SOCl}_2$ ,  $40\text{ }^\circ\text{C}$ , 3 h; (b) MeOH, rt, 1 h, 43% for 2 steps; (c) 77% *m*-CPBA in  $\text{H}_2\text{O}$ , DCM,  $0\text{ }^\circ\text{C}$ , 24 h, 88%; (d) *n*-BuLi, TMS acetylene,  $\text{Et}_2\text{AlCl}$ , toluene,  $-30\text{ }^\circ\text{C}$ , 52%; (e)  $\text{Ti}(\text{O}i\text{-Pr})_4$ , *i*-PrMgCl,  $\text{Et}_2\text{O}$ ,  $-60\text{ }^\circ\text{C}$ , 3 h, 41%; (f) TsCl,  $\text{Et}_3\text{N}$ , DMAP, DCM,  $0\text{ }^\circ\text{C}$  or TsCl, pyridine, DMAP,  $0\text{ }^\circ\text{C}$ ;

The action of thionyl chloride on the commercially available carboxylic acid **496** afforded the acid chloride **497**, which was treated with methanol immediately to give the methyl ester **484** in 43% over 2 steps. The olefin function of this  $\beta,\gamma$ -unsaturated methyl ester **484** was then oxidised to the epoxide **485** in 88% yield by the action of *m*-CPBA. The epoxide **485** was then opened using the TMS-acetylide-diethyl aluminium species to give the alkynylsilane **486** in 52% yield. This propargylic species was then reduced to the *cis* olefin **487** using the hydrotitanation procedure to give the homoallylic alcohol **487** in 41% yield. The exclusive generation of the (*Z*)-alkenylsilane was confirmed using NOESY experiments, with a 1.9 and 1.5% reciprocal enhancement of the olefinic hydrogen on irradiation of each. Unfortunately, all attempted methods for tosyl activation **488** of the alcohol were unsuccessful. A variety of conditions were surveyed, such as the use of DMAP with either triethylamine or pyridine, where all starting material was consumed but only the  $\alpha,\beta$ -unsaturated methyl ester **500** was identified as the major product. After initial tosylation, it is assumed that one of the acidic  $\alpha$ -hydrogens is removed **498** and subsequent elimination from the enolate **499** leads to the double bond **500** (Scheme 133).



Scheme 133. Formation of  $\alpha,\beta$ -unsaturated methylester.

Owing to the acidity of the  $\alpha$ -hydrogens adjacent to the methyl ester, it was decided to reduce the ester to the primary alcohol **501** and then protect this function selectively. It was proposed to protect this alcohol as the TBS ether **502** (Scheme 134).



Scheme 134. Reagents and conditions: (a) LAH, THF, 0 °C to rt, 2 h, 81%; (b) TBSCl, imidazole, DMF, rt.

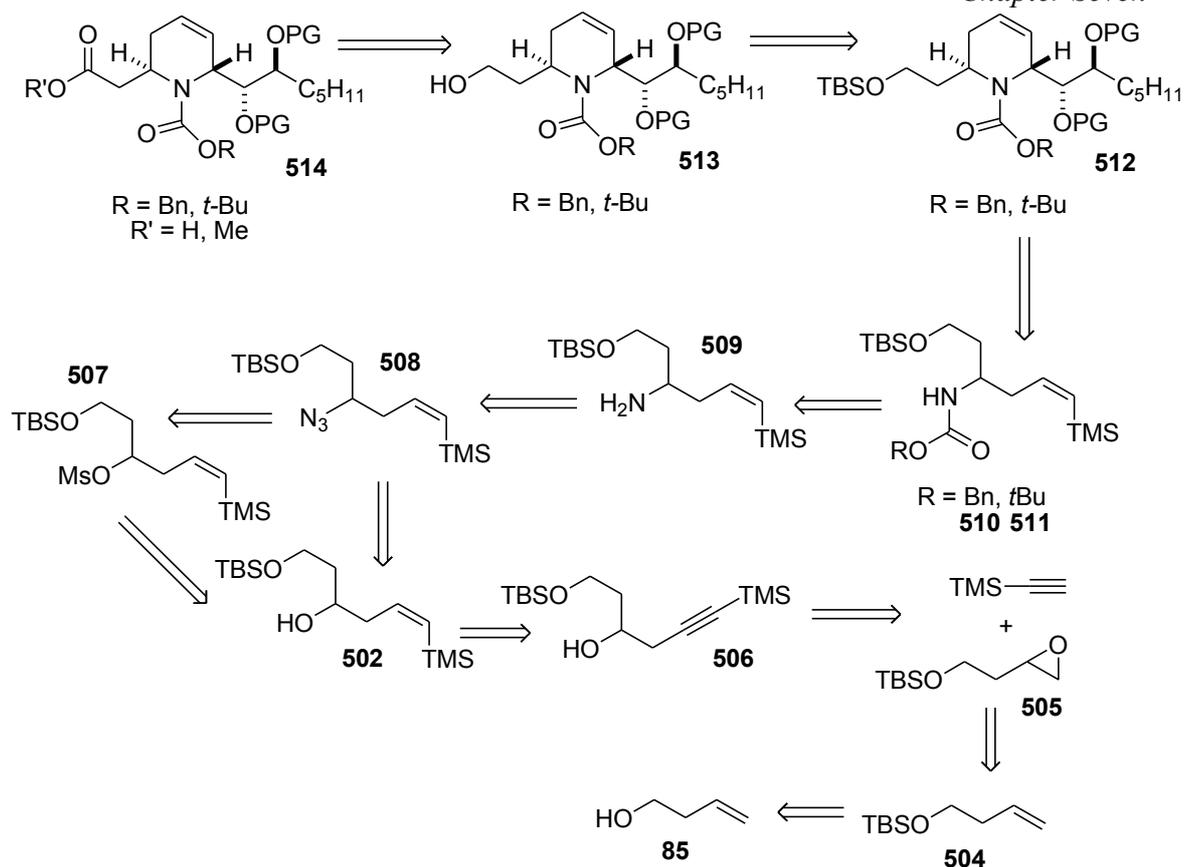
The methyl ester **487** was therefore reduced with 2 equivalents of LAH to the primary alcohol to give the 1,3-diol **501** in 81% yield. The protection of the primary alcohol as the TBS ether **502** was unsuccessful using standard conditions with the starting material being consumed but with no recognisable products being isolated.

## . 27ROUTE 2

### . aRetrosynthetic Analysis of

#### Cannabisativine II

While the idea of maintaining a TBS-protected alcohol through the synthesis remained attractive, a new approach to the protected alcohol-containing amine was clearly required. The new route involved starting with a homoallylic alcohol **85** and introducing the amine *via* an azide **508** (Scheme 135).

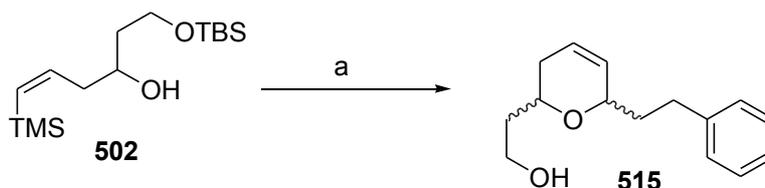


Scheme 135. Retrosynthetic analysis of new amine precursor synthesis.

### . b Amine Precursor

#### Synthesis II

Before the amine precursor synthesis began, it was deemed essential to also trial the (*Z*)-homoallylic alcohol **502** in an indium trichloride-mediated silyl-Prins reaction. This would allow us to study how the siloxy  $\alpha$ -substituent would respond in the presence of a Lewis acid. Also, in our previous studies, only simple  $\alpha$ -substituents had been utilised to form *cis*-2,6-disubstituted-3,4-dihydropyrans. This trial could also give us precedent for the formation of natural products containing *cis*-2,6-disubstituted-3,4-dihydropyrans. Using standard silyl-Prins reaction conditions of indium trichloride in DCM with a 1:1:1 ratio of Lewis acid, aldehyde and alcohol **502** precursor and using hydrocinnamaldehyde, the 2,6-disubstituted-3,4-dihydropyran product **515** was obtained in 79% yield (Scheme 136).

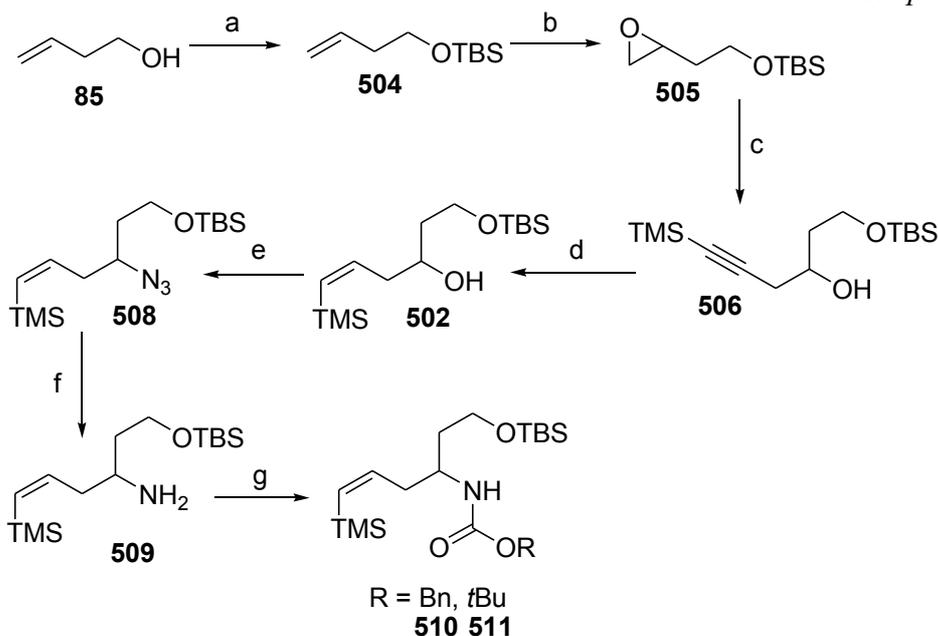


**Scheme 136.** *Reagents and conditions:* (a)  $\text{InCl}_3$ ,  $\text{Ph}(\text{CH}_2)_2\text{CHO}$ , DCM, rt, 20 h, 79%.

However, the TBS ether had also been cleaved to the free hydroxyl function. It was assumed that this has occurred in the presence of indium trichloride. There are examples in the literature where other Lewis acids such as boron trifluoride etherate have cleaved silyl ethers. It was clear from GCMS and  $^1\text{H}$  NMR that one diastereomer was formed exclusively. On the basis of previous work, it was assumed that this is the *cis*-2,6-disubstituted-3,4-dihydropyran but unfortunately this could not be proved using NOESY experiments as too many of the signals in the  $^1\text{H}$  NMR overlapped.

It was assumed from this that the silyl ether function would probably be cleaved to the alcohol when the amine precursor was screened in an indium trichloride mediated azasilyl-Prins reaction. This is fortunate however since it was proposed to cleave this immediately after the formation of the azacyclic core anyway in the total synthesis of racemic cannabisativine.

The amine precursor that was desired was (*Z*)-1-(*t*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ylcarbamate and it was proposed that either the *N*-Boc **511** or *N*-CBz **510** derivative could be obtained in 7 or 8 steps from commercially available 3-buten-1-ol **503** (Scheme 137).



**Scheme 137. Reagents and conditions:** (a) TBSCl, imidazole, DCM, rt, 2 h, 90%; (b) 77% *m*-CPBA in H<sub>2</sub>O, DCM, rt, 72 h, 88%; (c) *n*-BuLi, TMS acetylene, BF<sub>3</sub>·Et<sub>2</sub>O, THF, -78 °C, 92%. (d) Ti(*Oi*-Pr)<sub>4</sub>, *i*-PrMgCl, Et<sub>2</sub>O, -60 °C, 4 h, 60%; (e) DPPA, DIAD, PPh<sub>3</sub>, THF, rt, 1 h, 91%; (f) PPh<sub>3</sub>, THF, H<sub>2</sub>O, 60 °C, 20 h, quantitative; (g) R=Bn, CBzCl, NaHCO<sub>3</sub>, THF, H<sub>2</sub>O, rt, 72 h, 64%; R=*t*-Bu, Boc<sub>2</sub>O, Et<sub>3</sub>N, DCM, rt, 1 h, 72%;

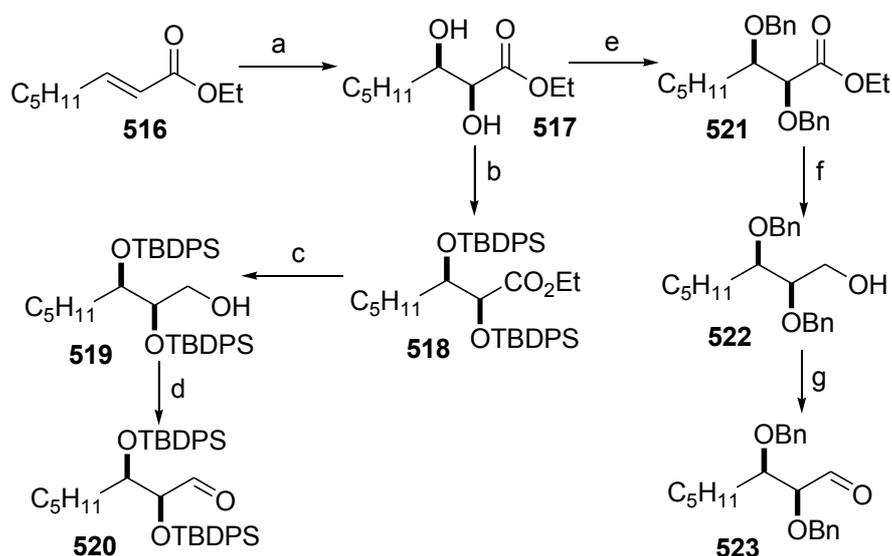
The commercially available 3-buten-1-ol **85** was first converted into the TBS ether **504** in 90% yield using TBSCl in the presence of imidazole. Epoxidation with *m*-CPBA gave the protected epoxy alcohol **505** in 88% yield. Ring-opening with lithium TMS acetylide and boron trifluoride etherate gave the alkynylsilane **506** in 92% yield. The triple bond was *cis*-reduced using the previously employed hydrotitanation procedure to give the (*Z*)-homoallylic alcohol **502** in 60% yield. An azide **508** could be directly obtained in 91% yield by a Mitsunobu reaction involving the allylic alcohol **502**, triphenylphosphine, DIAD and diphenylphosphoryl azide. This was then reduced by the use of triphenylphosphine and water to afford the primary amine **509** in quantitative yield.

The desired aza-silyl-Prins precursors could now be obtained by *N*-protection of the primary amine **509**. The benzyl carbamate derivative **510** was obtained in 64% yield by treatment of the primary amine with CBzCl and sodium hydrogen carbonate, using a method previously employed by the group. The *t*-butyl carbamate **511** was derived in 72% yield by treatment of the amine **509** with di-*t*-butyl dicarbonate and triethylamine. Unfortunately, the benzyl carbamate precursor **510** decomposed readily and could not be forwarded for screening in the aza-silyl-Prins reaction. The HRMS data could not be obtained for this compound and decomposition occurred even when frozen as a solution in benzene.

## . cAldehyd

## e Formation

Now required was the synthesis of the protected  $\alpha,\beta$ -dihydroxyaldehyde **490** for coupling to the Boc-amine **511** in the aza-silyl-Prins reaction. If our proposal was correct, then the diastereomer required would be obtained from the *syn* di-hydroxylation of (*Z*)-ethyl oct-2-enoate **493** by an oxidant such as osmium tetroxide. However, since only the (*E*)-geometric isomer **516** is available commercially, this was utilised initially in order to firstly optimise the conditions of the aza-silyl-Prins reaction for these substrates (Scheme 138). If the 2,6-disubstituted-3,4-tetrahydropyridine were formed, then the use of the correct diastereomer **490** of the protected  $\alpha,\beta$ -dihydroxy aldehyde substrate could be explored.



**Scheme 138. Reagents and conditions:** (a) 0.1M OsO<sub>4</sub> (aq), NMO, THF, H<sub>2</sub>O, rt, 72 h, quantitative; (b) TBDPSCl, imidazole, DMF, rt, 20 h, 81%; (c) DiBAL, toluene, -78 °C, 2 h, 88%; (d) PCC, 4Å MS, DCM, rt, 3 h, 64%; (e) BnBr, NaH, TBAB, 16-crown-6, THF, rt, 1 h, 36%; (f) DiBAL, toluene, -78 °C, 2 h, 64%; (g) PCC, 4Å MS, DCM, rt, 4 h, 39%;

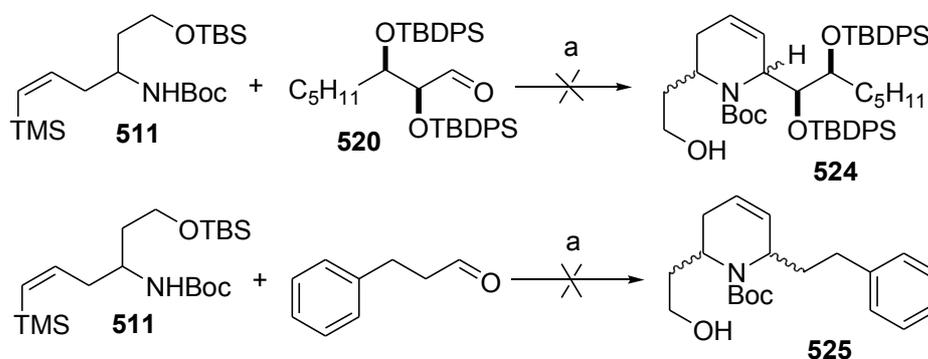
The commercially available unsaturated ethyl ester **516** was first converted into the *syn*-2,3-diol **517** in quantitative yield *via syn*-dihydroxylation by the action of osmium tetroxide in the presence of NMO as previously employed. This diol **517** was protected as the di-silyl ether **518** in 81% yield by the treatment with TBDPSCl and imidazole. It could also be protected as the di-benzyl compound **521** in 36% yield by the treatment with benzyl bromide in the presence of TBAB and 16-crown-6. The protected diols were then submitted to hydride reduction by DiBAL to give the primary alcohols in 88% and 64% yields for the di-silyl ether **519** and di-benzylate **522** respectively. Initially the aim

was to partially reduce to the desired aldehydes, but both substrates underwent full reduction even at low temperatures. The primary alcohol **522**, derived from the di-benzylated diol, was a partial mixture with the desired aldehyde **523** and so was only characterised fully after the subsequent oxidation step. This oxidation step required the use of PCC and gave the desired aldehydes in 64% and 39% yields for the di-silyl ether **520** and di-benzyl **523** compounds respectively.

### . dAza-silyl-

#### Prins Screening

With both amine and aldehyde precursors available, it was now possible to begin screening for the aza-silyl-Prins reaction. Initially, the coupling of the *N*-Boc homoallylic amine **511** to either the di-silyl ether aldehyde **520** or hydrocinnamaldehyde was attempted. It was expected that the TBS silyl ether would be cleaved to the primary alcohol in the presence of the Lewis acid, based on the previous results with the silyl-Prins reaction. However, the di-TBDPS ether was expected to remain intact because harsher conditions are required to cleave this. The reaction was attempted using the standard conditions for the cyclisation reaction of 1:1:1 ratio of aldehyde: amine: Lewis acid, in acetonitrile at reflux temperature (Scheme 139).



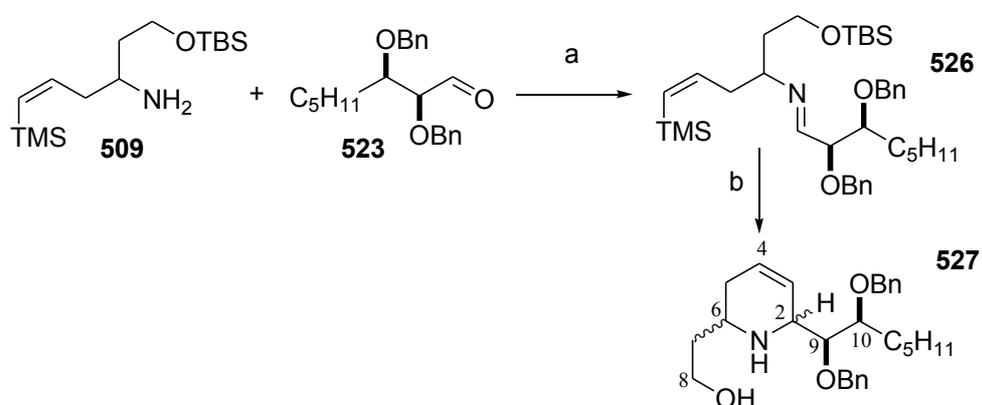
Scheme 139. Reagents and conditions: (a)  $\text{InCl}_3$ ,  $\text{CH}_3\text{CN}$ , reflux, 20 h.

After 20 hours at reflux, TLC and GCMS analysis showed full consumption of starting material. Unfortunately, it seemed that the amine precursor **511** had decomposed on heating, comparable with the decomposition witnessed for the *N*-CBz amine precursor **510**. Only unreacted aldehyde was recovered in both cases.

Fortunately, there was a second proposal to form the core 2,6-disubstituted-3,4-tetrahydroquinoline of racemic cannabistatine. It was proposed to utilise the

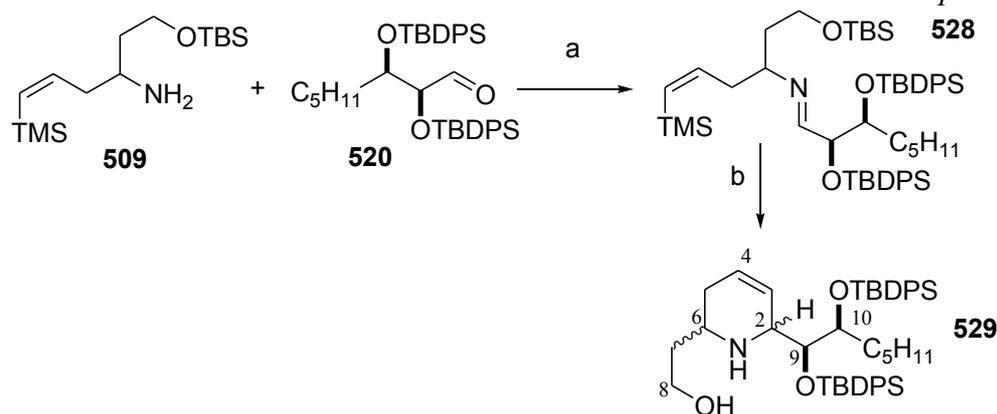
**Cyclisation** scandium(III) triflate-mediated imine-vinylsilane cyclisations introduced in chapter 6. All

of the required precursors for this pathway are already available. This includes the homoallylic primary amine **509**, derived from reduction of the corresponding azide **508**, and also both diol-protected aldehydes. Previously, the primary amine and aldehyde precursors were condensed in the presence of a dehydrating agent and then the imine was exposed to the scandium(III) triflate-mediated conditions. However, all previous examples have contributed towards the synthesis of monosubstituted-3,4-tetrahydropyridines. In this case, the amine precursor **509** has an  $\alpha$ -TBS ether functionality, which would give a 2,6-disubstituted-3,4-tetrahydropyridine (Scheme 140). There was no precedent in our studies to date for the diastereoselectivity of this imine-vinylsilane cyclisation.



**Scheme 140.** Reagents and conditions: (a) MgSO<sub>4</sub>, DCM, reflux, 4 h, 94%; (b) Sc(OTf)<sub>3</sub>, CH<sub>3</sub>CN, reflux, 20 h, 55%;

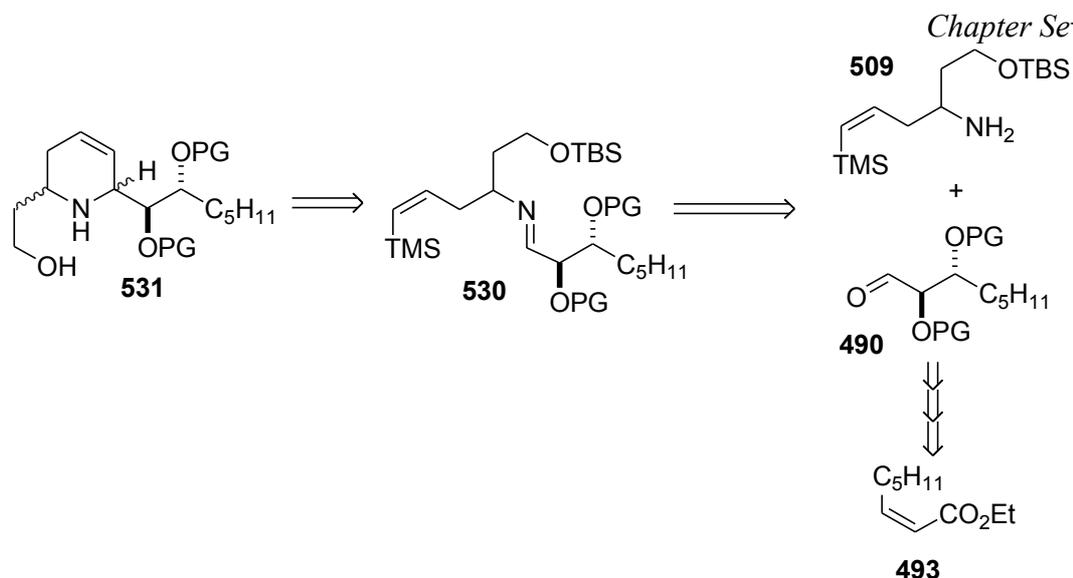
Following previous methodology, condensation of the primary amine **509** with the aldehyde **523** in the presence of magnesium sulphate, at reflux, gave the desired imine **526** in 94% crude yield, which was used immediately in the next step. The imine **526** was treated with 2 equivalents of scandium(III) triflate in acetonitrile at reflux temperature for 20 hours. This afforded an inseparable mixture of 2,6-disubstituted-3,4-tetrahydropyridines **527** in 55% yield as a 1.24:1 mixture of two diastereomers (Scheme 141). It was believed that these diastereomers, were a mixture of *cis* and *trans*-2,6-disubstituted-3,4-tetrahydropyridines. The evidence supporting this assumption is that there were two signals for the C2 proton separated clearly in the <sup>1</sup>H NMR spectrum. Unfortunately the relative stereochemistry could not be confirmed by NOESY experiments as many signals in the <sup>1</sup>H NMR spectra overlapped.



**Scheme 141.** Reagents and conditions: (a) MgSO<sub>4</sub>, DCM, reflux, 20 h, 82%; (b) Sc(OTf)<sub>3</sub>, CH<sub>3</sub>CN, reflux, 17 h, 38%;

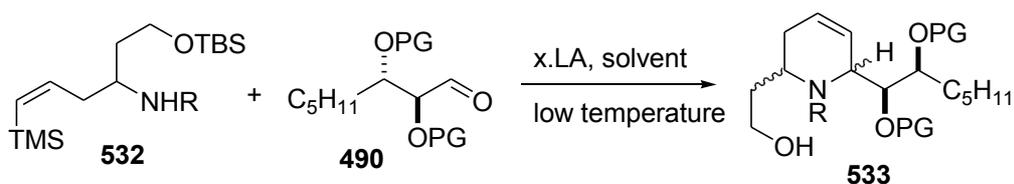
Then the same primary amine **509** was condensed with the di-silyl protected compound **520**, in the presence of magnesium sulphate, to yield the desired imine **528** in 82% yield. This imine was again used immediately in the next step. The cyclisation of this imine **528** required overnight stirring at reflux temperature when treated with scandium(III) triflate and afforded the 2,6-disubstituted-3,4-tetrahydropyridine **529** in 38% yield and as a 1.25:1 mixture of diastereomers. Again these diastereomers were inseparable by flash column chromatography and the relative stereochemistry could not be confirmed by NOESY experiments. Also, there was only a single signal for the C2 proton, perhaps suggesting that the mixture included exclusively, either *cis* or *trans*-2,6-disubstituted-3,4-tetrahydropyridines.

The imine-vinylsilane cyclisation has been utilised to form compounds containing the cannabistatine skeleton. Unfortunately the diastereoselectivity of this reaction for the substrates studied was poor. In order for this methodology to contribute towards a total synthesis of cannabistatine, then this selectivity issue must be resolved. To date, two different types of protecting group chemistry on the aldehyde substrate have been studied and this produced approximately a 1:1 mixture of tetrahydropyridine diastereomers in each case. For the future work, it would seem necessary to use different protecting groups, perhaps less bulky, in order to improve selectivity. Eventually, when this issue has been resolved, then the correct configuration for the  $\alpha,\beta$ -disubstituted aldehyde **490** must be obtained, starting from a (*Z*)-alkene **493** (Scheme 142).



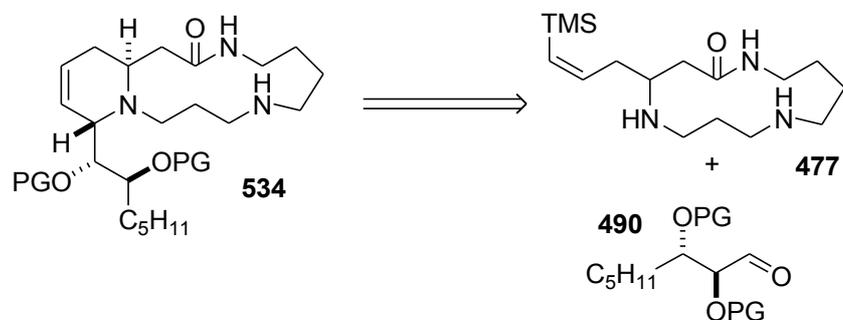
**Scheme 142. Study on protecting group chemistry for imine-vinylsilane cyclisations.**

It would also seem worthwhile to revise the use of the aza-silyl-Prins reaction for this total synthesis. Previously the amine substrates synthesised were highly unstable, and these included the *N*-benzyl carbamoyl **510** and *N*-*t*-butyl carbamoyl **511** amines. The *N*-*t*-butyl carbamoyl amine **511** seemed to be relatively stable at room temperature so perhaps conditions suited to lower temperatures would be beneficial, rather than the reflux temperature attempted in the indium trichloride-mediated aza-silyl-Prins reaction. Other Lewis acids or solvents could also promote the cyclisation of these substrates at lower temperatures. To improve stability issues, perhaps different *N*-substituents could also be utilised. These substituents should be available to be cleaved under conditions that will not effect other protecting group moieties (Scheme 143).



**Scheme 143. Study on *N*-substituent and Lewis acid/solvent/temperature screening.**

Finally, in our initial retrosynthetic analysis, it was proposed that the core tetrahydropyridine should be obtained followed by the lactamisation of the 13-membered macrocycle. However, perhaps it would be possible to synthesise first the macrocycle **477** and then perform an aza-silyl-Prins reaction in order to afford the desired tetrahydropyridine **534** (Scheme 144).



**Scheme 144.** Study on pre-macrocycle formation and subsequent aza-silyl-Prins reaction.

## **CONCLUSION**

### Conclusion

Firstly, the previous optimisation of the silyl-Prins and aza-silyl-Prins reactions to form dihydropyrans and tetrahydropyridines respectively had allowed us to make several new proposals for further studies. This included using this initial methodology as precedent to fashion a new coupling reaction, the aza-Prins reaction. Unfortunately the initial studies failed when screening several different Lewis acids, aldehydes and homoallylic amines and when altering other variables such as temperature, reaction time and solvent. Success in the literature, showed that the reactivity of the amine precursor was of considerable importance and so our studies were adjusted. Using an *N*-tosylamine precursor, success was found in forming 2,3,4-trisubstituted-4-chloropiperidines using indium trichloride as promoter. Reaction times were longer than the examples in the literature using ferric(III) halides, although it was felt that our promoter was easier to use. Using differently substituted homoallylic amines, including the use of internal double bonds, produced regiochemical effects and so allowed the formation of pyrrolidines as well as piperidines. With the optimisation of the silyl-Prins and aza-silyl-Prins reactions using simple substrates, our new studies focussed on using these cyclisation reactions to form oxa- and azacycles with more challenging functionality. This included the introduction of 6-trifluoromethyl groups to these six-membered heterocycles. The precursor synthesis towards the formation of the dihydropyran system was simple and involved use of methodology previously utilised by the group. However, the formation of the desired amine precursor for the nitrogen series was far more challenging, but an efficient pathway was fashioned nonetheless. Success was found for the formation of 6-trifluoromethyl heterocycles, although reaction times were longer and yields lower than for simple precursors. As well as utilising the olefin function of the unsaturated heterocycles, it was also possible to qualitatively conclude that (*Z*)-vinylsilanes are more reactive than their (*E*) counterparts.

Also shown in these studies, was the fact that the aza-silyl-Prins reaction can be adapted to form analogues of natural products such as pipercolic acid in an efficient manner and in good yields. However, further studies are required to see if this reaction can be adapted to form larger, more complex natural products such as cannabistatine and this would be an ideal future project. It was shown however that an imine-vinylsilane reaction mediated by scandium(III) triflate allowed us to afford the core cannabistatine tetrahydropyridine skeleton, although the diastereoselectivity of this reaction was poor. This same reaction was optimised to form simple 2-substituted free amine tetrahydropyridines in racemic form. With future work, this reaction could be adapted to form these azacycles in high enantiopurity using, for example, chiral Lewis acids.

## EXPERIMENTAL

All chemicals were purified by distillation where appropriate. Diethyl ether and tetrahydrofuran were predried over sodium wire and distilled from sodium under nitrogen, with benzophenone ketyl as indicator. Dichloromethane was distilled from calcium hydride and kept under nitrogen. All reactions were carried out under anhydrous conditions and in an atmosphere of nitrogen unless otherwise stated, using flame-dried glassware with all transfers performed using plastic syringes and needles.

All column chromatography was carried out using Fluka Silica Gel 60 (220-440 mesh) (Brockmann 2-3). TLC analysis was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised by ultraviolet light and aqueous potassium permanganate spray ( $\text{KMnO}_4:\text{K}_2\text{CO}_3:\text{water}$  6:1:100, w/w/v). Another purification technique involved the use of Mass-Directed-Auto-Prep (MDAP), a form of preparative HPLC, performed in the laboratories at GlaxoSmithKline, Harlow (confidential).

Melting points were determined using a Gallenkamp melting point apparatus.

Optical rotations were measured on an Optical Activity Ltd. AA-1000 polarimeter, values are quoted in  $10^{-1} \text{ cm}^2 \text{ g}^{-1}$ .

Infrared spectra were recorded in the range  $4000\text{-}600 \text{ cm}^{-1}$  on a Nicolet MAGNA 550 FT-IR spectrometer with internal calibration. Spectra were recorded as thin films between NaCl plates, as KBr disks or as Nujol® pastes.

Proton ( $^1\text{H}$ ) and carbon ( $^{13}\text{C}$ ) NMR spectra were recorded at 300 MHz or at 400 MHz and at 75.5 MHz or 100.6 MHz respectively on JNM-LA300 (300 MHz and 75.5 MHz) and on a Bruker ACF-300 or a Advance DRX 400 spectrometers. Chemical shift values ( $\delta_{\text{H}}$  and  $\delta_{\text{C}}$ ) are reported as values in parts per million (ppm) from the residual protic solvent as the internal standard reference for  $^1\text{H}$  NMR spectra and from the solvent peaks for  $^{13}\text{C}$  NMR.  $^1\text{H}$  NMR spectra are recorded in the form (integration; multiplicity; coupling

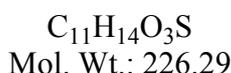
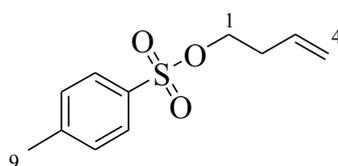
*Experimental*  
constants; assignment). Multiplicities are given as s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet and bs-broad signal. Coupling constants ( $J$  values) are quoted to one decimal place with values in Hz.  $^{13}\text{C}$  NMR spectra are recorded in the form  $\delta_{\text{c}}$  (assignment).

High and low resolution mass spectra were recorded on a Kratos profile instrument or on a VG Analytical ZAB-E instrument (EPSRC Mass Spectrometry Service, Swansea) or on a ThermoQuest Trace GC 2000 series and Agilent 6890 Series GC system, Micromas GCT. Mass spectrometric data were also acquired using LCMS analysis, performed in the laboratories at GlaxoSmithKline, Harlow (confidential).

Full characterisation of a compound within this experimental includes, but is not limited to, data on IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, low-resolution mass spectra and high-resolution mass spectra. Compounds that have been characterised fully in the literature contain two or more from the previous list. On some occasions, it was not possible to obtain all required data; the reasons for this have been alluded to in the main body of this thesis.

**General procedure A: alcohol tosylation on 69.73 mmol scale.** A round-bottomed flask was charged with homoallylic alcohol (69.73 mmol, 1.00 eq.) and dichloromethane (140 mL). The resulting solution was stirred and cooled to 0 °C before adding sequentially 4-dimethylaminopyridine (5.08 g, 41.84 mmol, 0.60 eq.) and *p*-toluenesulfonyl chloride (15.96 g, 83.68 mmol, 1.20 eq.) portionwise and dropwise triethylamine (9.82 mL, 69.73 mmol, 1.00 eq.). The resulting solution was stirred at 0 °C until TLC showed complete consumption of starting material. The resulting suspension was diluted with diethyl ether (150 mL), stirred for a further 30 minutes and the precipitate removed by filtration. The solution was then washed sequentially with 10% aqueous copper sulfate (2 x 75 mL), 10% aqueous sodium hydrogen carbonate (2 x 75 mL) and a saturated aqueous sodium chloride solution (60 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*.

**4-(Toluene-1-sulfonyloxy)-but-3-ene (86).**



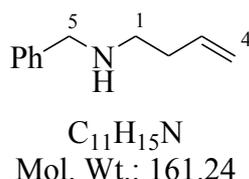
Following the general procedure A, 3-buten-1-ol **85** (3.35 g, 46.40 mmol) gave after 22 hours of stirring, a yellow oil which was purified by flash column chromatography (50% petroleum ether 50% diethyl ether) to give the *title compound* **86** (8.22 g, 36.30 mmol, 78%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.80 (2H, d, *J* 8.3, H-C6), 7.36 (2H, d, *J* 8.3, H-C7), 5.75-5.61 (1H, m, H-C3), 5.13-5.07 (2H, m, H-C4), 4.07 (2H, t, *J* 6.7, H-C1), 2.45 (3H, s, H-C9), 2.44-2.39 (2H, m, H-C2);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 145.2 (C8), 133.5 (C5), 132.8 (C3), 130.3 (C7), 128.3 (C6), 118.7 (C4), 69.8 (C1), 33.6 (C2), 22.1 (C9); *m/z* (CI) 227 (MH<sup>+</sup>, 100), 173 (95), 155 (55). Data in agreement with literature values.

**General procedure B: amination or tosyl displacement by primary amine on 18.00 mmol scale.** A round-bottomed flask equipped with a condenser was charged with primary amine (90 mmol, 5.00 eq.), tosylated alcohol (18 mmol, 1.00 eq.), and ethanol (18ml). The resulting solution was stirred at reflux temperature until TLC showed complete consumption of starting material. The solution was cooled to room temperature,

the ethanol removed *in vacuo* and the excess of primary amine carefully distilled under reduced pressure unless otherwise stated. The resulting residue was partitioned between dichloromethane (60 mL) and 1.0 M aqueous sodium hydroxide solution (40 mL). The organic layer was separated, the aqueous layer extracted with dichloromethane (3 x 10 mL), the combined organic layers dried over magnesium sulphate, filtered and concentrated *in vacuo*.

***N*-Benzyl-*N*-(3-butenyl)amine (87).**



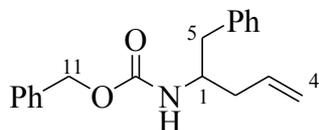
Following the general procedure B, 4-(toluene-4-sulfonyloxy)-but-1-ene **86** (4.07 g, 18.00 mmol), in the presence of benzylamine (9.65 g, 90.00 mmol), was consumed based on analysis by TLC after 20 hours of stirring and heating. The excess of benzylamine was distilled (104 °C, 245 mmHg) and the work-up gave a yellow oil, which was purified by flash column chromatography (75% petroleum ether 24% ethyl acetate 1% triethylamine) to give the *title compound* **87** (2.29 g, 14.00 mmol, 50%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.38-7.24 (5H, m, ArH) 5.88-5.74 (1H, m, H-C3), 5.15-5.03 (2H, m, H-C4), 3.82 (2H, s, H-C5), 2.73 (2H, t,  $J$  6.0, H-C1), 2.31 (2H, dt,  $J$  6.0, 6.0 H-C2), 1.66 (1H, bs, H-NH);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 140.5 (ArC), 136.8 (C3), 128.9 (ArC), 128.5 (ArC), 127.2 (ArC), 116.9 (C4), 54.2 (C5), 48.6 (C1), 34.6 (C2). Data in agreement with literature values.

**General procedure C: iodine catalysed synthesis of homoallylic amines on 15.00 mmol scale.** A round-bottomed flask was charged with aldehyde (15.00 mmol, 1 eq.) and acetonitrile (15 ml). To the resulting solution at room temperature was added sequentially iodine (0.38 g, 1.5 mmol, 0.10 eq.), benzyl carbamate (2.38 g, 15.75 mmol, 1.05 eq.) portionwise, and dropwise allyltrimethylsilane (2.38 mL, 15 mmol, 1.00 eq.). The resulting suspension was stirred at room temperature until TLC showed complete consumption of starting material. To the solution was added sodium thiosulfate (0.90 g), distilled water (10 mL) and the reaction mixture was stirred for a further 20 minutes. The biphasic solution was diluted with diethyl ether (30 mL), the organic layer washed with saturated aqueous sodium chloride (2 x 25 mL) and combined aqueous layers extracted

with diethyl ether (2 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*.

***N*-Benzyloxycarbonyl-(±)-1-benzylbut-3-enylamine (89).**

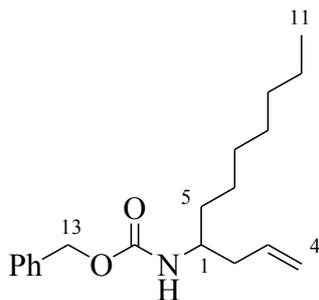


$C_{19}H_{21}NO_2$   
Mol. Wt.: 295.38

Following the general procedure C, phenylacetaldehyde (1.80 g, 15.00 mmol), gave after overnight stirring a yellow oil which was purified by flash column chromatography (90% petroleum ether 10% ethyl acetate) to give the *title compound* **89** (2.00 g, 6.76 mmol, 45%) as a colourless oil.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 7.42-7.18 (10H, m, ArH), 5.88-5.74 (1H, m, H-C3), 5.14-5.07 (2H, m, H-C4), 5.08 (2H, s, H-C11), 4.67-4.64 (1H, m, H-NH), 4.04-3.97 (1H, m, H-C1), 2.89-2.76 (2H, m, H-C2), 2.35-2.28 (1H, m, H-C5), 2.20-2.07 (1H, m, H-C5);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 156.2 (C10), 138.3 (ArC), 137.0 (C3), 134.6 (ArC), 129.8 (ArC), 129.0 (ArC), 128.7 (ArC), 128.5 (ArC), 128.4 (ArC), 126.9 (ArC), 118.7 (C4), 67.4 (C11), 52.1 (C5), 40.8 (C1), 38.6 (C2). Data in agreement with literature values.

***N*-Benzyloxycarbonyl-(±)-1-heptylbut-3-enylamine (90).**



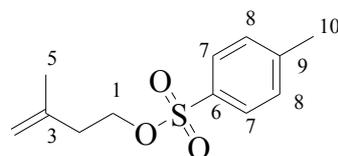
$C_{19}H_{29}NO_2$   
Mol. Wt.: 303.44

Following the general procedure C, octanal (1.80 g, 15.00 mmol) gave, after overnight stirring, a yellow oil which was purified by flash column chromatography (90% petroleum ether 10% ethyl acetate) to give the *title compound* **90** (1.53 g, 5.03 mmol, 34%) as a white solid.

*Experimental*

M.p. 52-53°C (Lit.: 51-52°C);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.38-7.34 (5H, m, ArH), 5.82-5.71 (1H, m, H-C3), 5.10-5.05 (2H, m, H-C4), 5.10 (2H, s, H-C13), 4.57-4.54 (1H, m, H-NH), 3.73-3.71 (1H, m, H-C1), 2.31-2.15 (2H, m, H-C2), 1.32-1.25 (12H, m, H-C5 to C10), 0.89 (3H, t,  $J$  6.0, H-C11);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 156.5 (C12), 137.2 (ArC), 134.8 (C3), 128.9 (ArC), 128.4 (ArC), 118.16 (C4), 66.9 (C13), 51.1 (C5), 39.9 (C1), 35.0 (C2), 32.2 (C6), 29.8 (C7 and C8), 26.3 (C9), 23.1 (C10), 14.5 (C11);  $m/z$  (CI) 304 ( $\text{MH}^+$ , 100), 196 (28), 172 (18). Data in agreement with literature values.

**3-Methylbut-3-enyl 4-methylbenzenesulfonate (97).**

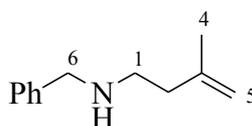


$\text{C}_{12}\text{H}_{16}\text{O}_3\text{S}$   
Mol. Wt.: 240.32

Following the general procedure A, 3-methylbut-3-en-1-ol **96** (6.01 g, 69.73 mmol) was consumed based on analysis by TLC after 48 hours of stirring at 0 °C. The work-up gave the *title compound* **97** (12.63 g, 52.55 mmol, 75%) as a yellow oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.77 (2H, d,  $J$  8.3, H-C7), 7.33 (2H, d,  $J$  8.3, H-C8), 4.77 (1H, s, H-C4), 4.66 (1H, s, H-C4), 4.10 (2H, t,  $J$  6.8, H-C1), 2.43 (3H, s, H-C10), 2.33 (2H, t,  $J$  6.8, H-C2), 1.64 (3H, s, H-C5);  $m/z$  (CI) 241 ( $\text{MH}^+$ , 90), 173 (72), 137 (100). Data in agreement with literature values.

**Benzyl-(3-methyl-but-3-enyl)-amine (98).**



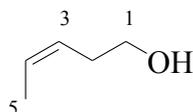
$\text{C}_{12}\text{H}_{17}\text{N}$   
Mol. Wt.: 175.27

Following the general procedure B, 2-methyl-4-(toluene-4-sulfonyloxy)-but-1-ene **97** (2.88 g, 12.00 mmol), in the presence of benzylamine (6.43 g, 60 mmol), was consumed based on analysis by TLC after 18 hours of stirring and heating. The work-up gave a yellow oil, which was purified by flash column chromatography (75% petroleum ether

24% ethyl acetate 1% triethylamine) to give the *title compound 98* (2.55 g, 14.55 mmol, 97%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.37-7.23 (5H, m, ArH), 4.79 (1H, s, H-C5), 4.75 (1H, s, H-C5), 3.81 (2H, s, H-C6), 2.76 (2H, t,  $J$  6.3, H-C1), 2.26 (2H, t,  $J$  6.3, H-C2), 1.72 (3H, s, H-C4);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.9 (C3), 140.5 (ArC), 128.8 (ArC), 128.6 (ArC), 127.4 (ArC), 112.0 (C5), 54.2 (C6), 47.1 (C1), 38.3 (C2), 22.6 (C4);  $m/z$  (CI) 176 ( $\text{MH}^+$ , 100), 120 (93). Data in agreement with literature values.

**(Z)-Pent-3-en-1-ol (112).**



$\text{C}_5\text{H}_{10}\text{O}$   
Mol. Wt.: 86.13

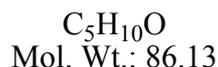
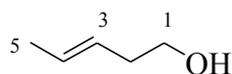
A solution of pent-3-yn-1-ol **111** (5.00 g, 59.44 mmol) in methanol (85 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of Lindlar's catalyst (425 mg) in methanol (10 mL). The hydrogenation was complete in 17 hours. The mixture was filtered through celite, which was washed with diethyl ether (10 mL) and the filtrate was concentrated *in vacuo*. This gave a pale yellow oil, which was purified by distillation at atmospheric pressure (50 °C, 760 mmHg) to give the *title compound 112* (4.02 g, 46.69 mmol, 79%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.66-5.53 (1H, m, H-C3), 5.43-5.31 (1H, m, H-C4), 3.61 (2H, t,  $J$  6.6, H-C1), 2.34-2.26 (2H, m, H-C2), 2.11 (1H, bs, H-OH), 1.64-1.59 (3H, m, H-C5);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 126.9 (C3), 126.0 (C4), 62.0 (C1), 30.3 (C2), 12.8 (C5). Data in agreement with literature values.

**General Procedure D: *trans* reduction of propargylic alcohols with lithium aluminium hydride on 59.44 mmol scale.** A three-necked round-bottomed flask fitted with a reflux condenser, a dropping funnel and a thermometer was charged with lithium aluminium hydride (5.86 g, 153.90 mmol, 2.59 eq.), triglyme (46 mL) and tetrahydrofuran (9 mL). The resulting suspension was cooled to 0 °C and a propargylic alcohol derivative (59.44 mmol, 1.00 eq.) in tetrahydrofuran (10 mL) added dropwise whilst maintaining a temperature below 25 °C. The mixture was then heated to 85 °C and stirred for 72 hours and then cooled to room temperature. To the mixture was added ice (100 g) and a 1.0 M solution of hydrochloric acid (300 mL) with stirring. The resulting

biphasic solution was diluted with diethyl ether (100 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*.

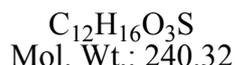
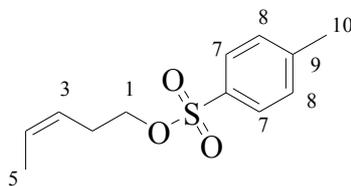
**(E)-Pent-3-en-1-ol (113).**



Following the general procedure D, 3-pentyn-1-ol **111** (5.00 g, 59.44 mmol) gave a pale yellow oil, which was purified by distillation under reduced pressure (100 °C, 114 mmHg) to give the *title compound* **113** (3.33 g, 38.64 mmol, 65%) as a colourless oil.

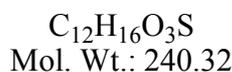
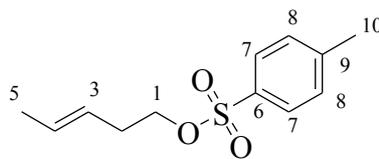
$\delta_H$  (300 MHz;  $CDCl_3$ ) 5.64-5.49 (1H, m, H-C3), 5.46-5.33 (1H, m, H-C4), 3.65-3.57 (2H, m, H-C1), 2.29-2.19 (2H, m, H-C2), 1.89 (1H, bs, H-OH), 1.71-1.65 (3H, m, H-C5). Data in agreement with literature values.

**(Z)-Pent-3-enyl 4-methylbenzenesulfonate (114).**



Following the general procedure A, (Z)-pent-3-en-1-ol **112** (3.99 g, 46.32 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 0 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% petroleum ether, 10% ethyl acetate) to give the *title compound* **114** (9.78 g, 40.71 mmol, 88%) as a colourless oil.

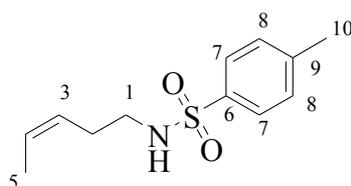
$\delta_H$  (300 MHz;  $CDCl_3$ ) 7.79 (2H, d,  $J$  8.3, H-C7), 7.34 (2H, d,  $J$  8.3, H-C8), 5.62-5.49 (1H, m, H-C3), 5.31-5.19 (1H, m, H-C4), 4.01 (2H, t,  $J$  7.0, H-C1), 2.45 (3H, s, H-C10), 2.44-2.35 (2H, m, H-C2), 1.59-1.54 (3H, m, H-C5);  $m/z$  (CI) 241 ( $MH^+$ , 17), 213 (20), 173 (100). Data in agreement with literature values.

**(E)-Pent-3-enyl 4-methylbenzenesulfonate(115).**

Following the general procedure A, (*E*)-pent-3-en-1-ol **113** (2.10 g, 24.38 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 0 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% petroleum ether, 10% ethyl acetate) to give the *title compound* **115** (3.32 g, 13.82 mmol, 57%) as a colourless oil.

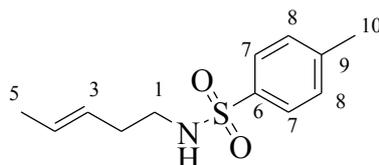
$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.77 (2H, d,  $J$  8.3, H-C7), 7.33 (2H, d,  $J$  8.3, H-C8), 5.55-5.40 (1H, m, H-C3), 5.30-5.17 (1H, m, H-C4), 3.99 (2H, t,  $J$  6.8, H-C1), 2.44 (3H, s, H-C10), 2.34-2.26 (2H, m, H-C2), 1.63-1.57 (3H, m, H-C5);  $m/z$  (CI) 241 ( $\text{MH}^+$ , 15), 213 (20), 173 (100). Data in agreement with literature values.

**General Procedure E: Amination of tosylated alcohol with 4-methylbenzenesulfonamide, catalysed by sodium iodide on a 69.73 mmol scale.** A round-bottomed flask fitted with a reflux condenser was charged with 4-methylbenzenesulfonamide (27.98 g, 160.38 mmol, 2.30 eq.), finely powdered potassium hydroxide (5.06 g, 90.65 mmol, 1.30 eq.) and dimethylsulfoxide (87 mL). The resulting suspension was heated to 50 °C and stirred for 2 hours. The resulting solution was cooled to room temperature and a tosylated alcohol derivative (69.73 mmol, 1.00 eq.) in dimethylsulfoxide (10 mL) added dropwise, followed by sodium iodide (3.15 g, 20.92 mmol, 0.30 eq.) in one portion. The mixture was heated to 50 °C and stirred until TLC showed full consumption of starting material. The mixture was cooled to room temperature, ice-cold water (100 mL) added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with a 15 % aqueous solution of potassium hydroxide (100 mL), water (100 mL) and a saturated aqueous solution of sodium chloride (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*.

**(Z)-4-Methyl-N-(pent-3-enyl)benzenesulfonamide (116).**

Following the general procedure E, (*Z*)-pent-3-enyl 4-methylbenzenesulfonate **114** (1.00 g, 4.16 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 50 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound* **116** (0.93g, 3.89 mmol, 94%) as a colourless oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3282, 2924, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.74 (2H, d,  $J$  8.3, H-C7), 7.31 (2H, d,  $J$  8.3, H-C8), 5.64-5.50 (1H, m, H-C3), 5.25-5.13 (1H, m, H-C4), 4.49-4.39 (1H, m, H-NH), 3.01-2.93 (2H, m, H-C1), 2.43 (3H, s, H-C10), 2.25-2.16 (2H, m, H-C2), 1.59-1.54 (3H, m, H-C5);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.3 (C9), 136.8 (C6), 129.7 (C8), 127.7 (C3), 127.1 (C7), 125.5 (C4), 42.6 (C1), 27.0 (C2), 21.5 (C10), 12.9 (C5);  $m/z$  (CI) 240 ( $\text{MH}^+$ , 100), 184 (65), 172 (26); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  257.1315,  $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$  requires 257.1318.

**(E)-4-Methyl-N-(pent-3-enyl)benzenesulfonamide (117).**

Following the general procedure E, (*E*)-pent-3-enyl 4-methylbenzenesulfonate **115** (1.00 g, 4.16 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 50 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound* **117** (0.97g, 4.04 mmol, 97%) as a colourless oil.

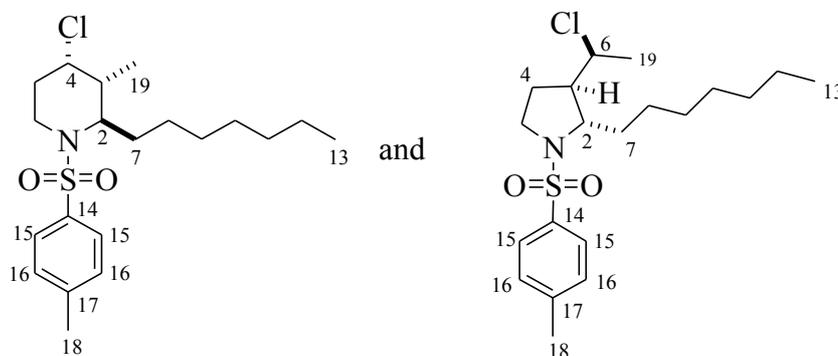
$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3284, 3035, 2918, 1816, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.74 (2H, d,  $J$  8.4, H-C7), 7.31 (2H, d,  $J$  8.4, H-C8), 5.52-5.38 (1H, m, H-C3), 5.25-5.13 (1H, m, H-C4), 4.47-4.37 (1H, m, N-NH), 2.96 (2H, dd,  $J$  12.7, 6.4, H-C1), 2.43 (3H, s, H-C10), 2.15-

2.07 (2H, m, H-C2), 1.64-1.60 (3H, m, H-C5);  $\delta_c$  (75.5 MHz; CDCl<sub>3</sub>) 143.3 (C9), 136.9 (C6), 129.6 (C8), 128.9 (C3), 127.1 (C7), 126.6 (C4), 42.5 (C1), 32.4 (C2), 21.4 (C10), 17.9 (C5);  $m/z$  (CI) 240 (MH<sup>+</sup>, 100), 184 (35), 111 (18); HRMS (ES) Found [M+H]<sup>+</sup> 240.1050, C<sub>12</sub>H<sub>18</sub>NO<sub>2</sub>S requires 240.1053.

**General procedure F: aza Prins reaction on 1.97 mmol scale.**

A round-bottomed flask was charged with indium trichloride (642 mg, 2.96 mmol, 1.50 eq.) and dichloromethane (5 mL). To the resulting suspension was added an aldehyde derivative (2.96 mmol, 1.50 eq.) in dichloromethane (1.5 mL). After stirring the mixture for 15 minutes at room temperature, an amine derivative (1.97 mmol, 1.00 eq.) in dichloromethane (1.5 mL) was added and the resulting mixture stirred until TLC showed complete consumption of starting material. The mixture was diluted with dichloromethane (10 mL) and water (10 mL) and stirred for 30 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*.

**(2*R*\*,3*R*\*,4*S*\*)-4-Chloro-2-heptyl-3-methyl-1-tosylpiperidine (118a), (2*S*\*,3*R*\*)-3-((*S*)-1-Chloroethyl)-2-heptyl-1-tosylpyrrolidine (119a).**



C<sub>20</sub>H<sub>32</sub>ClNO<sub>2</sub>S  
Mol. Wt.: 385.99

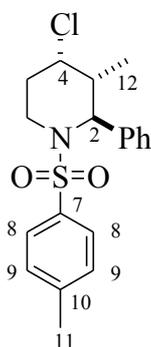
Following the general procedure F, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116** (150 mg, 0.62 mmol), in the presence of octanal (120 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **118a** (84 mg, 0.22 mmol, 35%) as a colourless oil.

### Experimental

$\nu_{\max}$ (neat)/ $\text{cm}^{-1}$  2928, 1729, 1598;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.67 (2H, d,  $J$  8.2, H-C15), 7.27 (2H, d,  $J$  8.2, H-C16), 4.31 (1H, td,  $J$  12.6, 4.6, H-C4), 3.96-3.88 (1H, m, H-C2), 3.78-3.69 (1H, m, H-C6), 2.94 (1H, td,  $J$  13.6, 3.2, H-C6), 2.41 (3H, s, H-C18) 2.16-2.05 (1H, m, H-C3), 2.01-1.84 (1H, m, H-C5), 1.84-1.74 (1H, m, H-C5), 1.66-1.33 (2H, m, H-C7), 1.32-1.11 (10H, m, H-C8 to H-C12), 1.08 (3H, d,  $J$  6.9, H-C19), 0.87 (3H, t,  $J$  6.8, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.1 (C17), 138.1 (C14), 129.5 (C16), 126.9 (C15), 60.1 (C2), 57.4 (C4), 40.6 (C6), 37.3 (C3), 31.7 (C11), 30.0 (C5), 29.4 (C9 and C10), 26.8 (C12), 22.6 (C8), 21.5 (C18), 14.1 (C13), 12.7 (C19);  $m/z$  (CI) 386 ( $\text{MH}^+$ , 100), 350 (60), 286 (42); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  386.1910,  $\text{C}_{20}\text{H}_{33}\text{ClNO}_2\text{S}$  requires 386.1915. Further elution (90% hexane 10% ethyl acetate) provided the other *title compound* **119a** (84 mg, 0.22 mmol, 35%) as a colourless oil.

$\nu_{\max}$ (neat)/ $\text{cm}^{-1}$  2927, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.75 (2H, d,  $J$  8.3, H-C15), 7.32 (2H, d,  $J$  8.3, H-C16), 3.80 (1H, ddd,  $J$  7.6, 4.9, 2.9, H-C2), 3.36 (1H, ddd,  $J$  10.7, 7.3, 5.7, H-C5), 3.25 (1H, td,  $J$  10.7, 7.3, H-C5), 3.09 (1H, qd,  $J$  8.8, 6.5, H-C6), 2.43 (3H, s, H-C18), 2.13-2.01 (1H, m, H-C3), 1.93 (1H, dt,  $J$  14.6, 7.3, H-C4), 1.79-1.66 (1H, m, H-C7), 1.66-1.51 (1H, m, H-C7), 1.48-1.31 (1H, m, H-C4), 1.27 (3H, d,  $J$  6.5, H-C19), 1.33-1.19 (10H, m, H-C8 to H-C12), 0.88 (3H, t,  $J$  6.6, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.4 (C17), 135.0 (C14), 129.6 (C16), 127.5 (C15), 63.7 (C1), 59.2 (C6), 52.5 (C3), 47.3 (C5), 37.0 (C7), 31.8 (C11), 29.4 (C9 and C10), 27.8 (C4), 25.8 (C8), 23.1 (C19), 22.6 (C12), 21.5 (C18), 14.1 (C13);  $m/z$  (CI) 386 ( $\text{MH}^+$ , 100), 350 (25), 286 (27); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{NH}_4]^+$  403.2185,  $\text{C}_{20}\text{H}_{36}\text{ClN}_2\text{O}_2\text{S}$  requires 403.2181.

### (2*S*\*,3*R*\*,4*S*\*)-4-Chloro-3-methyl-2-phenyl-1-tosylpiperidine (**118a**).



$\text{C}_{19}\text{H}_{22}\text{ClNO}_2\text{S}$   
Mol. Wt.: 363.9

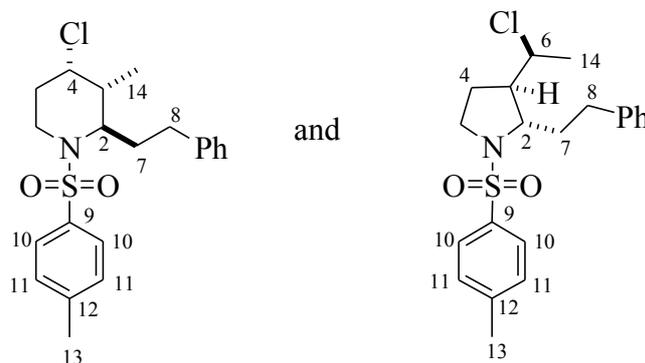
Following the general procedure F, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116** (150 mg, 0.62 mmol) in the presence of benzaldehyde (99 mg, 0.94 mmol), was

*Experimental*

consumed based on analysis by TLC after 144 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound 118a* (34 mg, 0.09 mmol, 15%) as a white solid.

M.p. 112-114 °C;  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3029, 2940, 2344, 1596;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.70 (2H, d,  $J$  7.8, H-C8), 7.45-7.27 (5H, m, Ar-H), 7.21 (2H, d,  $J$  7.8, H-C9), 5.19 (1H, s, H-C2), 4.09 (1H, td,  $J$  11.8, 4.1, H-C4), 3.97-3.80 (1H, m, H-C6), 3.27 (1H, ddd,  $J$  13.9, 11.8, 3.5, H-C6), 2.88-2.72 (1H, m, H-C3), 2.47 (3H, s, H-C11), 2.07-1.91 (1H, m, H-C5) 1.85-1.78 (1H, m, H-C5), 1.16 (3H, d,  $J$  6.9, H-C12);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.8 (C10), 137.8 (C7), 137.7 (ArC), 129.6 (ArC), 128.7 (ArC), 127.2 (ArC), 127.1 (C8), 126.8 (C9), 62.5 (C2), 57.5 (C4), 41.8 (C6), 39.3 (C3), 29.8 (C5), 21.5 (C11), 13.0 (C12);  $m/z$  (CI) 364 ( $\text{MH}^+$ , 64), 328 (30), 210 (55); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  364.1135,  $\text{C}_{19}\text{H}_{23}\text{ClNO}_2\text{S}$  requires 364.1133.

**(2*R*\*,3*R*\*,4*S*\*)-4-Chloro-3-methyl-2-phenethyl-1-tosylpiperidine (118c), (2*S*\*,3*R*\*)-3-((*S*)-1-Chloroethyl)-2-phenethyl-1-tosylpyrrolidine (119c).**



$\text{C}_{21}\text{H}_{26}\text{ClNO}_2\text{S}$   
Mol. Wt.: 391.95

Following the general procedure F, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116** (150 mg, 0.62 mmol) in the presence of 3-phenylpropanal (126 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound 118c* (98 mg, 0.25 mmol, 40%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3063, 2938, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.66 (2H, d,  $J$  8.3, H-C10), 7.34-7.13 (5H, m, Ar-H), 7.08 (2H, d,  $J$  8.3, H-C11), 4.32 (1H, td,  $J$  12.3, 4.6, H-C4), 4.01 (1H, m, H-C2), 3.80 (1H, dd,  $J$  13.3, 4.5, H-C6), 2.99 (1H, td,  $J$  13.3, 3.3, H-C6), 2.66-

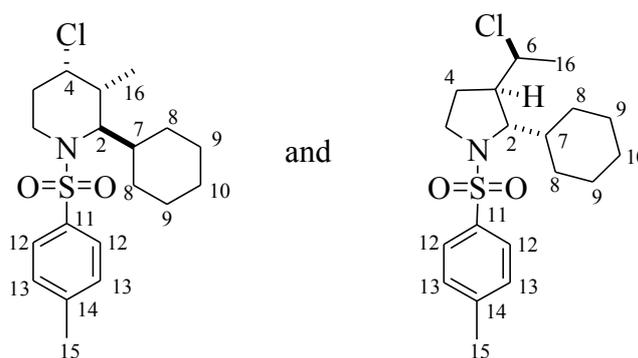
Experimental

2.47 (2H, m, H-C8), 2.42 (3H, s, H-C13), 2.22-2.13 (1H, m, H-C3), 2.02-1.88 (1H, m, H-C5), 1.89-1.77 (1H, m, H-C5), 1.78-1.52 (2H, m, H-C7), 1.07 (3H, d,  $J$  6.9, H-C14);  $\delta_c$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.2 (C12), 140.9 (ArC), 138.0 (C9), 129.7 (C11), 128.5 (ArC), 128.2 (ArC), 126.9 (C10), 126.1 (ArC), 59.6 (C2), 57.2 (C4), 40.7 (C6), 37.4 (C3), 33.1 (C8), 31.8 (C5 or C7), 30.0 (C5 or C7), 21.5 (C13), 12.7 (C14);  $m/z$  (CI) 392 ( $\text{MH}^+$ , 100), 356 (18), 238 (48); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{NH}_4]^+$  409.1716,  $\text{C}_{21}\text{H}_{30}\text{ClN}_2\text{O}_2\text{S}$  requires 409.1711.

Further elution (90% hexane 10% ethyl acetate) provided the other *title compound 119c* (88 mg, 0.22 mmol, 36%) as a white solid.

M.p. 122-123 °C;  $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$  3062, 2955, 1664, 1594;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.81 (2H, d,  $J$  8.3, H-C10), 7.39 (2H, d,  $J$  8.3, H-C11), 7.36-7.24 (5H, m, Ar-H), 3.94 (1H, ddd,  $J$  6.7, 5.8, 3.2, H-C2), 3.55-3.31 (2H, m, H-C5), 3.18 (1H, qd,  $J$  9.1, 6.6, H-C6), 2.82 (2H, t,  $J$  8.3, H-C8), 2.50 (3H, s, H-C13), 2.25-2.17 (1H, m, H-C3), 2.18-2.08 (2H, m, H-C7), 2.19-1.95 (1H, m, H-C4), 1.45 (1H, dt,  $J$  13.0, 6.2, H-C4), 1.34 (3H, d,  $J$  6.6, H-C14);  $\delta_c$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.6 (C12), 141.6 (ArC), 134.8 (C9), 129.6 (C11), 128.4 (ArC), 128.3 (ArC), 127.5 (C10), 125.7 (ArC), 63.4 (C2), 59.2 (C6), 52.9 (C3), 47.6 (C5), 38.6 (C7), 32.1 (C8), 27.9 (C4), 23.1 (C14), 21.5 (C13);  $m/z$  (CI) 392 ( $\text{MH}^+$ , 100), 356 (12), 238 (58); Anal. Calcd. for  $\text{C}_{21}\text{H}_{26}\text{ClNO}_2\text{S}$  requires C, 64.35; H, 6.69; N, 3.57%. Found: C, 64.47; H, 6.58; N, 3.54%.

**(2*R*\*,3*R*\*,4*S*\*)-4-Chloro-2-cyclohexyl-3-methyl-1-tosylpiperidine (118d), (2*S*\*,3*R*\*)-3-((*S*)-1-Chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine (119d).**



$\text{C}_{19}\text{H}_{28}\text{ClNO}_2\text{S}$   
Mol. Wt.: 369.95

Following the general procedure F, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116** (150 mg, 0.62 mmol) in the presence of cyclohexanecarbaldehyde (105 mg, 0.94 mmol), was consumed based on analysis by TLC after 144 hours of stirring at room temperature.

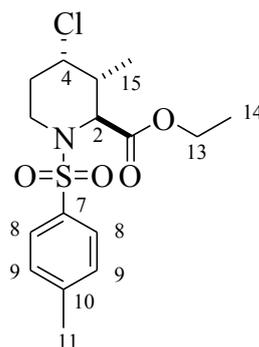
### Experimental

The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound 118d* (60 mg, 0.16 mmol, 26%) as a white solid.

M.p. 89-91 °C;  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3044, 2923, 1597;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.70 (2H, d,  $J$  8.4, H-C12), 7.27 (2H, d,  $J$  8.4, H-C13), 4.34-4.24 (1H, m, H-C4), 3.76-3.64 (2H, m, H-C2 and H-C6), 2.98-2.83 (1H, m, H-C6), 2.42 (3H, s, H-C15), 2.39-2.28 (1H, m, H-C3), 1.85-1.71 (2H, m, H-C5), 1.77-1.53 (5H, m, H-C7 and H-C8), 1.27-0.99 (6H, m, H-C9 and H-C10), 0.95 (3H, d,  $J$  6.9, H-C16);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 142.9 (C14), 138.3 (C11), 129.4 (C13), 127.1 (C12), 65.8 (C2), 57.6 (C4), 41.0 (C6), 36.1 (C3), 34.7 (C7), 31.0 (C8), 30.2 (C8), 29.5 (C5), 26.3 (C10), 26.2 (C9), 26.1 (C9), 21.5 (C15), 13.2 (C16);  $m/z$  (CI) 370 ( $\text{MH}^+$ , 100), 334 (12), 286 (10); Anal. Calcd. for  $\text{C}_{19}\text{H}_{28}\text{ClNO}_2\text{S}$  requires C, 61.68; H, 7.63; N, 3.79%. Found: C, 61.44; H, 7.72; N, 3.76%.

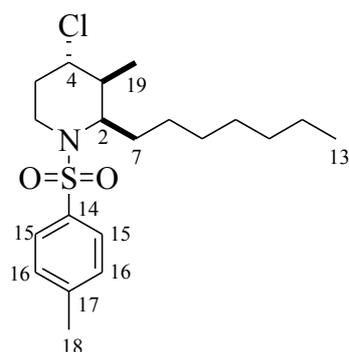
Further elution (90% hexane 10% ethyl acetate) provided the other *title compound 119d* (115 mg, 0.31 mmol, 50%) as a white solid.

M.p. 109-112 °C;  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  2918, 1670, 1597;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.74 (2H, d,  $J$  8.1, H-C12), 7.30 (2H, d,  $J$  8.1, H-C13), 3.69 (1H, dd,  $J$  4.3, 2.5, H-C2), 3.38-3.30 (1H, m, H-C5), 3.28-3.19 (1H, m, H-C5), 3.02 (1H, qd,  $J$  8.8, 6.5, H-C6), 2.41 (3H, s, H-C15), 2.17-2.09 (1H, m, H-C3), 1.98-1.83 (1H, m, H-C4), 1.78-1.58 (5H, m, H-C7 and H-C8), 1.38 (1H, ddd,  $J$  16.8, 8.1, 4.8, H-C4), 1.16 (3H, d,  $J$  6.5, H-C16), 1.22-0.76 (6H, m, H-C9 and H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.4 (C14), 134.8 (C11), 129.5 (C13), 127.6 (C12), 68.1 (C2), 59.5 (C6), 49.6 (C3), 48.0 (C5), 43.3 (C7), 29.8 (C8), 28.5 (C8), 27.9 (C4), 26.4 (C10), 26.3 (C9), 26.2 (C9), 22.7 (C16), 21.5 (C15);  $m/z$  (CI) 370 ( $\text{MH}^+$ , 100), 334 (28), 286 (20); Anal. Calcd. for  $\text{C}_{19}\text{H}_{28}\text{ClNO}_2\text{S}$  requires C, 61.69; H, 7.63; N, 3.79%. Found: C, 61.65; H, 7.84; N, 3.66%; HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  370.1602,  $\text{C}_{19}\text{H}_{29}\text{ClNO}_2\text{S}$  requires 370.1599.

**(2*S*\*,3*R*\*,4*S*\*)-Ethyl-4-chloro-3-methyl-1-tosylpiperidine-2-carboxylate (118e).**

Following the general procedure F, (*Z*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **116** (40 mg, 0.17 mmol), in the presence of a pre-heated 33% solution of ethyl 2-oxoacetate in toluene (76 mg, 0.25 mmol, 1.50 eq.), was consumed based on analysis by TLC after 1 hour of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **118e** (12 mg, 0.03 mmol, 20%) as a pale yellow oil.

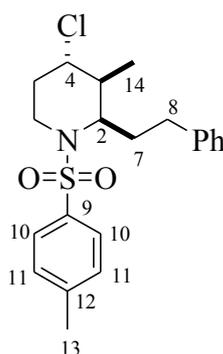
$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  2927, 1736, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.66 (2H, d,  $J$  8.3, H-C8), 7.29 (2H, d,  $J$  8.3, H-C9), 4.54 (1H, d,  $J$  1.2, H-C2), 4.13-4.02 (1H, m, H-C4), 4.04-3.94 (2H, m, H-C13), 3.79-3.70 (1H, m, H-C6), 3.31 (1H, td,  $J$  12.4, 3.4, H-C6), 2.69-2.58 (1H, m, H-C3), 2.42 (3H, s, H-C11), 2.13-1.97 (1H, m, H-C5), 1.94-1.82 (1H, m, H-C5), 1.25 (3H, d,  $J$  6.9, H-C15), 1.16 (3H, t,  $J$  7.1, H-C14);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 169.9 (C12), 143.4 (C10), 136.3 (C7), 129.4 (C9), 127.2 (C8), 61.6 (C13), 61.0 (C2), 57.2 (C4), 42.3 (C6), 37.2 (C3), 29.3 (C5), 21.5 (C11), 13.9 (C14), 11.9 (C15);  $m/z$  (CI) 360 ( $\text{MH}^+$ , 90), 286 (45), 206 (100); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  360.1027,  $\text{C}_{16}\text{H}_{23}\text{ClNO}_4\text{S}$  requires 360.1031.

**(2*R*\*,3*S*\*,4*S*\*)-4-Chloro-2-heptyl-3-methyl-1-tosylpiperidine (124a).**

$C_{20}H_{32}ClNO_2S$   
Mol. Wt.: 385.99

Following the general procedure F, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **117** (150 mg, 0.62 mmol), in the presence of octanal (120 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **124a** (159 mg, 0.41 mmol, 66%) as a white solid.

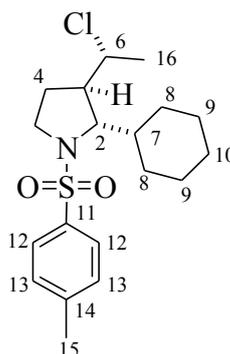
M.p. 56-57 °C;  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2925, 1712, 1461;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.69 (2H, d,  $J$  8.4, H-C15), 7.27 (2H, d,  $J$  8.4, H-C16), 3.98 (1H, td,  $J$  9.7, 4.4, H-C2), 3.84-3.82 (1H, m, H-C4), 3.81-3.75 (1H, m, H-C6), 2.99 (1H, td,  $J$  15.1, 2.7, H-C6), 2.40 (3H, s, H-C18), 2.03-1.93 (1H, m, H-C5), 1.83-1.69 (1H, m, H-C3), 1.67-1.50 (1H, m, H-C5), 1.47-1.34 (2H, m, H-C7), 1.33-1.10 (10H, m, H-C8 to H-C12), 1.01 (3H, d,  $J$  6.9, H-C19), 0.86 (3H, t,  $J$  6.8, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.1 (C17), 138.4 (C14), 129.7 (C16), 126.8 (C15), 60.6 (C4), 58.8 (C2), 42.1 (C3), 39.9 (C6), 35.9 (C5), 31.7 (C11), 29.2 (C9 and C10), 26.2 (C8), 24.4 (C7), 22.6 (C12), 21.4 (C18), 16.4 (C19), 14.0 (C13);  $m/z$  (CI) 386 ( $\text{MH}^+$ , 100), 350 (42), 286 (40); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{NH}_4]^+$  403.2176,  $C_{20}H_{36}ClN_2O_2S$  requires 403.2181.

**(2*R*\*,3*S*\*,4*S*\*)-4-Chloro-3-methyl-2-phenethyl-1-tosylpiperidine (124b).**

$C_{21}H_{26}ClNO_2S$   
Mol. Wt.: 391.95

Following the general procedure F, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **117** (150 mg, 0.62 mmol) in the presence of 3-phenylpropanal (126 mg, 0.94 mmol), was consumed based on analysis by TLC after 17 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **124b** (157 mg, 0.40 mmol, 64%) as a white solid.

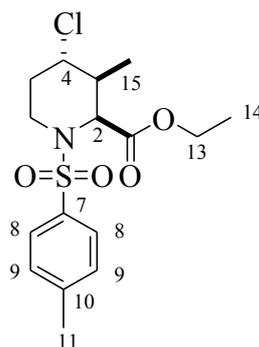
M.p. 105-106 °C;  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3030, 2955, 1596;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.83 (2H, d,  $J$  8.1, H-C10), 7.39 (2H, d,  $J$  8.1, H-C11), 7.36-7.18 (5H, m, Ar-H), 4.26-4.15 (1H, m, H-C2), 3.97 (1H, dd,  $J$  15.0, 4.9, H-C6), 3.85 (1H, td,  $J$  11.6, 4.5, H-C4), 3.25-3.11 (1H, m, H-C6), 2.79-2.66 (1H, m, H-C8), 2.65-2.52 (1H, m, H-C8), 2.51 (3H, s, H-C13), 2.13-2.00 (1H, m, H-C5), 1.95-1.71 (1H, m, H-C3), 1.87-1.63 (2H, m, H-C7), 1.74-1.56 (1H, m, H-C5), 1.09 (3H, d,  $J$  6.8, H-C14);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.4 (C12), 141.6 (ArC), 138.3 (C9), 129.9 (C11), 128.4 (ArC), 128.3 (ArC), 126.9 (C10), 125.9 (ArC), 60.4 (C4), 58.8 (C2), 41.9 (C3), 40.1 (C6), 35.7 (C5), 32.7 (C8), 26.9 (C7), 21.5 (C13), 16.4 (C14);  $m/z$  (CI) 392 ( $\text{MH}^+$ , 40), 238 (20), 202 (74); Anal. Calcd. for  $C_{21}H_{26}ClNO_2S$  requires C, 64.35; H, 7.08; N, 3.57%. Found: C, 64.15; H, 6.70; N, 3.50%; HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  392.1446,  $C_{21}H_{27}ClNO_2S$  requires 392.1444.

**(2*S*\*,3*R*\*)-3-((*S*)-1-Chloroethyl)-2-cyclohexyl-1-tosylpyrrolidine (125c).**

$C_{19}H_{28}ClNO_2S$   
Mol. Wt.: 369.95

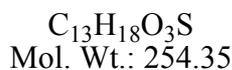
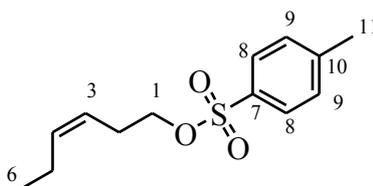
Following the general procedure F, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **117** (150 mg, 0.62 mmol) in the presence of cyclohexanecarbaldehyde (105 mg, 0.94 mmol), was consumed based on analysis by TLC after 240 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **125c** (162 mg, 0.44 mmol, 70%) as a white solid.

M.p. 116-118 °C;  $\nu_{\max}$ (neat)/ $cm^{-1}$  2927, 1669, 1599;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.73 (2H, d, *J* 8.4, H-C12), 7.31 (2H, d, *J* 8.4, H-C13), 3.45-3.41 (1H, m, H-C2), 3.38-3.28 (3H, m, H-C6 and H-C5), 2.43 (3H, s, H-C15), 2.23-2.14 (1H, m, H-C3), 1.91-1.63 (7H, m, H-C4, H-C7 and H-C8), 1.32 (3H, d, *J* 6.6, H-C16), 1.28-0.81 (6H, m, H-C9 and H-C10);  $\delta_c$  (75.5 MHz;  $CDCl_3$ ) 143.5 (C14), 134.9 (C11), 129.5 (C13), 127.7 (C12), 67.2 (C2), 59.4 (C6), 49.1 (C3), 48.1 (C5), 43.3 (C7), 30.1 (C8), 28.0 (C8), 27.3 (C4), 26.5 (C10), 26.3 (C9), 26.2 (C9), 23.9 (C16), 21.5 (C15); *m/z* (CI) 370 ( $MH^+$ , 100), 334 (55), 286 (62); HRMS (ES) Found ( $^{35}Cl$ ) [ $M+NH_4$ ] $^+$  387.1871,  $C_{19}H_{32}ClN_2O_2S$  requires 387.1868.

**(2*S*\*,3*S*\*,4*S*\*)-Ethyl-4-chloro-3-methyl-1-tosylpiperidine-2-carboxylate (124d).**

Following the general procedure F, (*E*)-4-methyl-*N*-(pent-3-enyl)benzenesulfonamide **117** (150 mg, 0.62 mmol), in the presence of a pre-heated 33% solution of ethyl 2-oxoacetate in toluene (287 mg, 0.94 mmol, 1.50 eq.), was consumed based on analysis by TLC after 1 hour of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **124d** (47 mg, 0.13 mmol, 21%) as a pale yellow oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  2980, 1733, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.62 (2H, d,  $J$  8.4, H-C8), 7.27 (2H, d,  $J$  8.4, H-C9), 4.59 (1H, d,  $J$  5.8, H-C2), 4.01 (1H, td,  $J$  11.6, 4.4, H-C4), 3.93-3.81 (1H, m, H-C6), 3.81-3.66 (2H, m, H-C13), 3.49 (1H, td,  $J$  12.8, 2.8, H-C6), 2.41 (3H, s, H-C10), 2.26 (1H, tdd,  $J$  9.5, 5.1, 2.8, H-C5), 2.14-2.01 (1H, m, H-C3), 2.01-1.85 (1H, m, H-C5), 1.14 (3H, t,  $J$  7.2, H-C14), 1.08 (3H, d,  $J$  6.9, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 168.9 (C12), 143.7 (C10), 135.6 (C7), 129.5 (C9), 127.1 (C8), 60.8 (C13), 59.6 (C2), 59.2 (C4), 42.1 (C6), 41.0 (C3), 36.0 (C5), 21.5 (C11), 15.2 (C15), 13.9 (C14);  $m/z$  (CI) 360 ( $\text{MH}^+$ , 100), 286 (65), 206 (87); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  360.1029,  $\text{C}_{16}\text{H}_{23}\text{ClNO}_4\text{S}$  requires 360.1031.

**(*Z*)-Hex-3-enyl 4-methylbenzenesulfonate (127).**

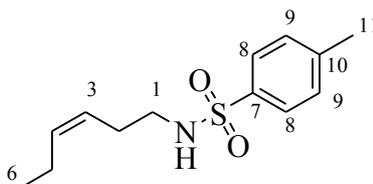
Following the general procedure A, (*Z*)-hex-3-en-1-ol **126** (5.00 g, 49.90 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 0 °C. The work-up gave

*Experimental*

the *title compound 127* (10.67 g, 41.96 mmol, 84%) as a yellow oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.77 (2H, d,  $J$  8.2, H-C8), 7.33 (2H, d,  $J$  8.2, H-C9), 5.52-5.40 (1H, m, H-C3), 5.23-5.12 (1H, m, H-C4), 3.98 (2H, t,  $J$  7.0, H-C1), 2.43 (3H, s, H-C11), 2.42-2.33 (2H, m, H-C2), 2.02-1.90 (2H, m, H-C5), 0.91 (3H, t,  $J$  7.5, H-C6);  $m/z$  (CI) 255 ( $\text{MH}^+$ , 15), 213 (30), 173 (100). Data in agreement with literature values.

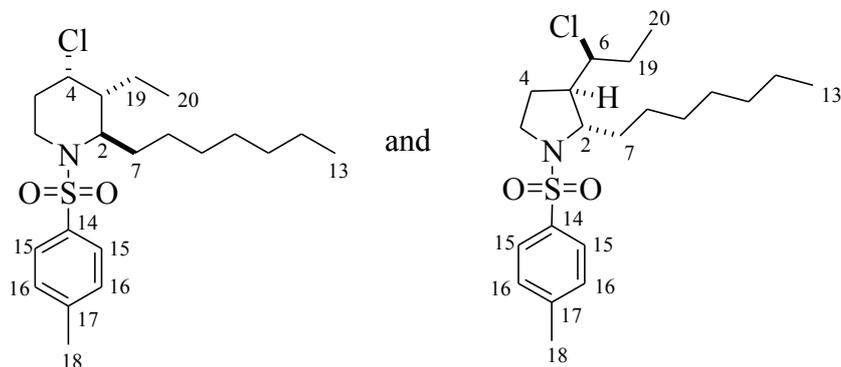
**(Z)-N-(Hex-3-enyl)-4-methylbenzenesulfonamide (128).**



Following the general procedure E, (Z)-hex-3-enyl 4-methylbenzenesulfonate **127** (10.67 g, 41.96 mmol) was consumed based on analysis by TLC after 17 hours of stirring at 50 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound 128* (6.64g, 26.21 mmol, 62%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.74 (2H, d,  $J$  8.3, H-C8), 7.30 (2H, d,  $J$  8.3, H-C9), 5.53-5.42 (1H, m, H-C3), 5.18-5.07 (1H, m, H-C4), 4.55 (1H, t,  $J$  5.4, H-NH), 3.00-2.90 (2H, m, H-C1), 2.42 (3H, s, H-C11), 2.24-2.15 (2H, m, H-C2), 2.02-1.89 (2H, m, H-C5), 0.92 (3H, t,  $J$  7.5, H-C6);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.3 (C10), 136.8 (C7), 135.4 (C3), 129.6 (C9), 127.1 (C8), 123.9 (C4), 42.7 (C1), 27.2 (C2), 21.5 (C5), 20.6 (C11), 14.2 (C6). Data in agreement with literature values.

**(2*R*\*,3*R*\*,4*S*\*)-4-Chloro-3-ethyl-2-heptyl-1-tosylpiperidine (129a), (2*S*\*,3*R*\*)-3-((*S*)-1-Chloropropyl)-2-heptyl-1-tosylpyrrolidine (130a).**



$C_{21}H_{34}ClNO_2S$   
Mol. Wt.: 400.02

Following the general procedure F, (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide **128** (500 mg, 1.97 mmol), in the presence of octanal (379 mg, 2.96 mmol), was consumed based on analysis by TLC after 17 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **129a** (323 mg, 0.81 mmol, 41%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2957, 1729, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.66 (2H, d,  $J$  8.4, H-C15), 7.26 (2H, d,  $J$  8.4, H-C16), 4.37-4.28 (1H, m, H-C4), 4.11-4.03 (1H, m, H-C2), 3.79-3.69 (1H, m, H-C6), 3.01-2.87 (1H, m, H-C6), 2.40 (3H, s, H-C18), 1.91-1.74 (2H, m, H-C5), 1.75-1.63 (1H, m, H-C3), 1.59-1.29 (2H, m, H-C7), 1.32-1.23 (8H, m, H-C8 to H-C11), 1.23-1.16 (4H, m, H-C19 and H-C12), 0.94 (3H, t,  $J$  7.3, H-C20), 0.87 (3H, t,  $J$  6.8, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.0 (C17), 138.1 (C14), 129.5 (C16), 126.8 (C15), 58.1 (C4), 55.8 (C2), 44.7 (C3), 40.6 (C6), 31.7 (C11), 30.9 (C5), 29.1 (C9 and C10), 26.7 (C8), 22.6 (C12), 22.6 (C7), 21.4 (C18), 17.4 (C19), 14.0 (C13), 12.3 (C20);  $m/z$  (CI) 400 ( $\text{MH}^+$ , 100), 364 (78), 300 (42); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  400.2073,  $C_{21}H_{35}ClNO_2S$  requires 400.2072.

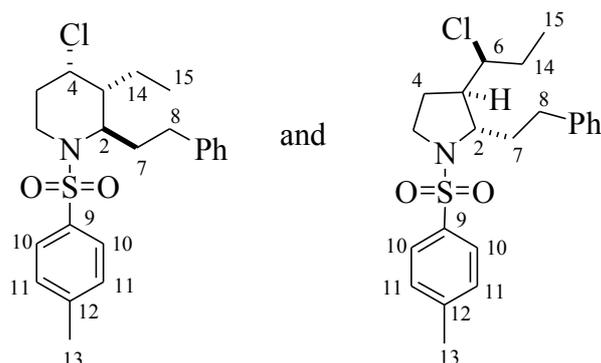
Further elution (90% hexane 10% ethyl acetate) provided the other *title compound* **130a** (339 mg, 0.85 mmol, 43%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2954, 1597,  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.73 (2H, d,  $J$  8.3, H-C15), 7.30 (2H, d,  $J$  8.3, H-C16), 3.83-3.77 (1H, m, H-C2), 3.39-3.20 (2H, m, H-C5), 2.78 (1H, td,  $J$  9.1, 2.8, H-C6), 2.41 (3H, s, H-C18), 2.16-2.05 (1H, m, H-C3), 1.96-1.82 (1H, m, H-C4), 1.73-1.54 (2H, m, H-C7), 1.60-1.39 (2H, m, H-C19), 1.43-1.29 (1H, m, H-C4), 1.31-1.19 (10H, m, H-C8 to H-C12), 0.86 (3H, t,  $J$  6.5, H-C13), 0.83 (3H, t,  $J$  7.2, H-C20);  $\delta$

Experimental

$\delta_c$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.4 (C17), 135.0 (C14), 129.5 (C16), 127.5 (C15), 66.7 (C6), 63.7 (C2), 50.7 (C3), 47.4 (C5), 36.9 (C7), 31.8 (C11), 29.3 (C9 and C10), 28.5 (C19), 27.8 (C4), 25.8 (C8), 22.6 (C12), 21.4 (C18), 14.0 (C20), 10.5 (C13);  $m/z$  (CI) 400 ( $\text{MH}^+$ , 100), 364 (40), 300 (25); Anal. Calcd. for  $\text{C}_{21}\text{H}_{34}\text{ClNO}_2\text{S}$  requires C, 63.05; H, 8.57; N, 3.50%. Found: C, 62.99; H, 8.83; N, 3.50%.

**(2*R*\*,3*R*\*,4*S*\*)-4-Chloro-3-ethyl-2-phenethyl-1-tosylpiperidine (129b), (2*S*\*,3*R*\*)-3-((*S*)-1-Chloropropyl)-2-phenethyl-1-tosylpyrrolidine (130b).**



$\text{C}_{22}\text{H}_{28}\text{ClNO}_2\text{S}$   
Mol. Wt.: 405.98

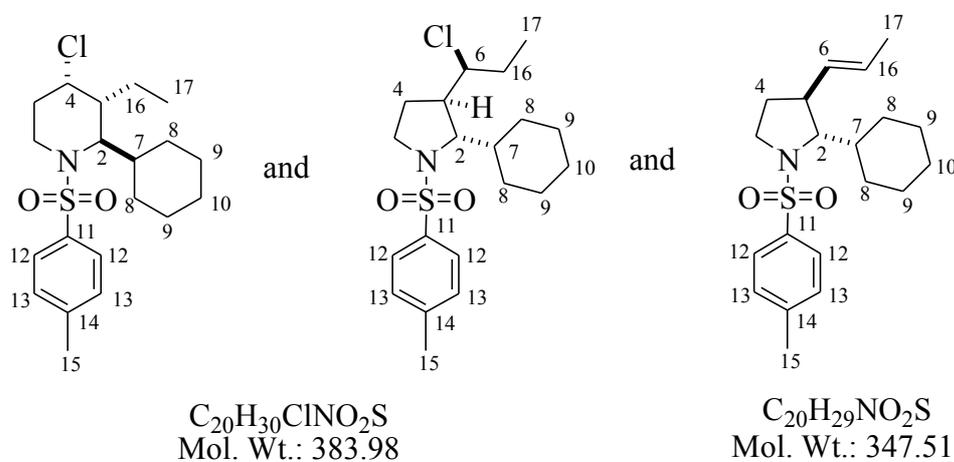
Following the general procedure F, (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide **128** (500 mg, 1.97 mmol), in the presence of 3-phenylpropanal (398 mg, 2.96 mmol), was consumed based on analysis by TLC after 17 hours of stirring at room temperature. The work-up afforded a pale yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **129b** (328 mg, 0.81 mmol, 41%) as a white solid.

M.p. 95-97 °C;  $\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3032, 1941, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.58 (2H, d,  $J$  8.3, H-C10), 7.29-7.11 (5H, m, Ar-H), 7.04 (2H, d,  $J$  8.3, H-C11), 4.35-4.25 (1H, m, H-C4), 4.11-4.04 (1H, m, H-C2), 3.81-3.70 (1H, m, H-C6), 2.99-2.85 (1H, m, H-C6), 2.64-2.39 (2H, m, H-C8), 2.37 (3H, s, H-C13), 1.88-1.73 (2H, m, H-C5), 1.73-1.62 (1H, m, H-C3), 1.73-1.50 (2H, m, H-C7), 1.30-1.11 (1H, m, H-C14), 0.84 (3H, t,  $J$  7.3, H-C15);  $\delta_c$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.2 (C12), 140.6 (ArC), 137.9 (C9), 129.6 (C11), 128.4 (ArC), 128.3 (ArC), 126.8 (C10), 126.1 (ArC), 57.9 (C4), 55.2 (C2), 44.8 (C3), 40.7 (C6), 33.0 (C8), 31.2 (C5 or C7), 30.9 (C7 or C5), 21.4 (C13), 17.4 (C14), 12.2 (C15);  $m/z$  (CI) 406 ( $\text{MH}^+$ , 20), 216 (90), 111 (100); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  406.1606,  $\text{C}_{22}\text{H}_{29}\text{ClNO}_2\text{S}$  requires 406.1602.

Further elution (90% hexane 10% ethyl acetate) provided the other *title compound* **130b** (392 mg, 0.97 mmol, 49%) as a white solid.

M.p. 69-71 °C;  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3088, 2936, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.75 (2H, d,  $J$  8.3, H-C10), 7.35-7.16 (5H, m, Ar-H), 7.23 (2H, d,  $J$  8.3, H-C11), 3.89 (1H, td,  $J$  6.2, 3.1, H-C2), 3.45-3.30 (2H, m, H-C5), 2.84 (1H, td,  $J$  9.1, 2.9, H-C6), 2.80-2.71 (2H, m, H-C8), 2.43 (3H, s, H-C13), 2.24-2.14 (1H, m, H-C3), 2.09-1.84 (2H, m, H-C7), 1.97-1.85 (1H, m, H-C4), 1.59-1.44 (1H, m, H-C14), 1.44-1.29 (2H, m, H-C14 and H-C4), 0.85 (3H, t,  $J$  7.2, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.6 (C12), 141.7 (ArC), 135.0 (C9), 129.6 (C11), 128.4 (ArC), 128.3 (ArC), 127.6 (C10), 125.8 (ArC), 66.7 (C6), 63.6 (C2), 51.2 (C3), 47.7 (C5), 38.6 (C7), 32.2 (C8), 28.6 (C14), 28.0 (C4), 21.5 (C13), 10.6 (C15);  $m/z$  (CI) 406 ( $\text{MH}^+$ , 92), 252 (52), 216 (100); HRMS (ES) Found ( $^{35}\text{Cl}$ )  $[\text{M}+\text{H}]^+$  406.1602,  $\text{C}_{22}\text{H}_{29}\text{ClNO}_2\text{S}$  requires 406.1606.

**(2R\*,3R\*,4S\*)-4-chloro-2-cyclohexyl-3-ethyl-1-tosylpiperidine (129c)**, **(2S\*,3R\*)-3-((S)-1-chloropropyl)-2-cyclohexyl-1-tosylpyrrolidine (130c)**, **(2S\*,3S\*,E)-2-cyclohexyl-3-(prop-1-enyl)-1-tosylpyrrolidine (131c)**.



Following the general procedure F, (*Z*)-*N*-(hex-3-enyl)-4-methylbenzenesulfonamide **128** (500 mg, 1.97 mmol), in the presence of cyclohexanecarbaldehyde (332 mg, 2.96 mmol), was consumed based on analysis by TLC after 72 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* **129c** and **131c** (182 mg, 0.47 mmol, 24%) as a white solid.

Data for **129c**: M.p. 151-153°C (mixture);  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3035, 2928, 1815 (mixture);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.68 (2H, d,  $J$  8.3, H-C12), 7.27 (2H, d,  $J$  8.3, H-C13), 4.37-4.28 (1H, m, H-C4), 3.84 (1H, d,  $J$  10.5, H-C2), 3.76-3.65 (1H, m, H-C6), 2.99-2.85 (1H, m, H-C6),

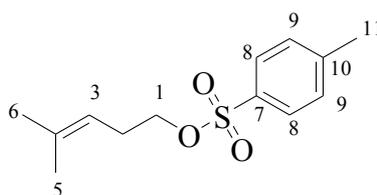
*Experimental*

2.42 (3H, s, H-C15), 1.94-1.84 (1H, m, H-C3), 1.85-1.51 (5H, m, H-C7 and H-C8), 1.75-1.54 (2H, m, H-C5), 1.29-0.88 (6H, m, H-C9 and H-C10), 1.09-0.82 (2H, m, H-C16), 0.97-0.92 (3H, m, H-C17);  $\delta_c$  (75.5 MHz; CDCl<sub>3</sub>) 142.9 (C14), 138.4 (C11), 129.4 (C13), 126.9 (C12), 61.4 (C2), 58.5 (C4), 43.8 (C3), 41.1 (C6), 35.9 (C7), 31.0 (C8), 30.4 (C8), 28.3 (C5), 26.5 (C10), 26.4 (C9), 26.2 (C9), 21.5 (C15), 17.2 (C16), 12.2 (C17);  $m/z$  (CI) 384 (MH<sup>+</sup>, 100), 348 (78), 300 (22); Anal. Calcd. for C<sub>20</sub>H<sub>30</sub>ClNO<sub>2</sub>S requires C, 62.56; H, 7.88; N, 3.65%. Found: C, 62.66; H, 8.01; N, 3.69%.

Data for **131c**:  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 7.73 (2H, d,  $J$  8.2, H-C12), 7.31 (2H, d,  $J$  8.2, H-C13), 5.25-5.11 (1H, m, H-C16), 4.66-4.55 (1H, m, H-C6), 3.40-3.30 (1H, m, H-C5), 3.31-3.25 (1H, m, H-C5), 3.27-3.21 (1H, m, H-C2), 2.62-2.51 (1H, m, H-C3), 2.43 (3H, s, H-C15), 1.84-1.68 (5H, m, H-C7 and H-C8), 1.69-1.56 (2H, m, H-C4), 1.41 (3H, dd,  $J$  6.4, 1.3, H-C17), 1.29-1.03 (6H, m, H-C9 and H-C10);  $\delta_c$  (75.5 MHz; CDCl<sub>3</sub>) 143.2 (C14), 135.1 (C6), 133.0 (C11), 129.5 (C13), 127.7 (C12), 124.7 (C16), 70.7 (C2), 48.5 (C5), 43.4 (C3), 42.0 (C7), 31.7 (C8), 30.2 (C8), 26.6 (C4), 26.4 (C10), 26.3 (C10), 26.1 (C9), 21.5 (C15), 17.7 (C17);  $m/z$  (CI) 348 (MH<sup>+</sup>, 100), 264 (10), 194 (35).

Further elution (90% hexane 10% ethyl acetate) provided the other *title compound* **130c** (470 mg, 1.22 mmol, 62%) as a white solid.

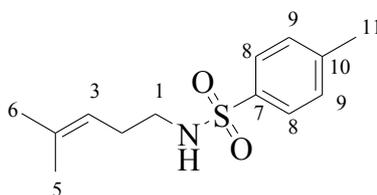
M.p. 102-103 °C;  $\nu_{\max}$ (neat)/cm<sup>-1</sup> 3034, 2927, 1597;  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 7.75 (2H, d,  $J$  8.3, H-C12), 7.31 (2H, d,  $J$  8.3, H-C13), 3.70 (1H, dd,  $J$  4.8, 2.3, H-C2), 3.40-3.20 (2H, m, H-C5), 2.67 (1H, td,  $J$  9.2, 2.6, H-C6), 2.42 (3H, s, H-C15), 2.29-2.19 (1H, m, H-C3), 1.96-1.82 (1H, m, H-C4), 1.83-1.71 (4H, m, H-C8), 1.71-1.60 (1H, m, H-C7), 1.54-1.37 (2H, m, H-C4 and H-C16), 1.37-1.24 (1H, m, H-C16), 1.28-0.96 (6H, m, H-C9 and H-C10), 0.81 (3H, t,  $J$  7.2, H-C17);  $\delta_c$  (75.5 MHz; CDCl<sub>3</sub>) 143.4 (C14), 135.0 (C11), 129.5 (C13), 127.6 (C12), 68.4 (C2), 67.1 (C6), 48.1 (C3), 48.0 (C5), 43.4 (C7), 29.7 (C8), 28.9 (C8), 28.2 (C16), 27.9 (C4), 26.4 (C10), 26.3 (C9), 26.3 (C9), 21.4 (C15), 10.7 (C17);  $m/z$  (CI) 384 (MH<sup>+</sup>, 100), 348 (45), 300 (25); HRMS (ES) Found (<sup>35</sup>Cl) [M+NH<sub>4</sub>]<sup>+</sup> 401.2021, C<sub>20</sub>H<sub>34</sub>ClN<sub>2</sub>O<sub>2</sub>S requires 401.2024.

**4-Methylpent-3-enyl 4-methylbenzenesulfonate (138).**

$C_{13}H_{18}O_3S$   
Mol. Wt.: 254.35

Following the general procedure A, 4-methylpent-3-en-1-ol **137** (250 mg, 2.50 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 0 °C. The work-up gave the *title compound* **138** (630 mg, 2.48 mmol, 99%) as a yellow oil which was used in the next step without any further purification.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 7.78 (2H, d,  $J$  8.3, H-C8), 7.34 (2H, d,  $J$  8.3, H-C9), 4.99-4.91 (1H, m, H-C3), 3.97 (2H, t,  $J$  7.1, H-C1), 2.45 (3H, s, H-C11), 2.37-2.28 (2H, m, H-C2), 1.65 (3H, s, H-C6), 1.55 (3H, s, H-C5);  $m/z$  (CI) 255 ( $MH^+$ , 30), 173 (100), 155 (20). Data in agreement with literature values.

**4-Methyl-N-(4-methylpent-3-enyl)benzenesulfonamide (139).**

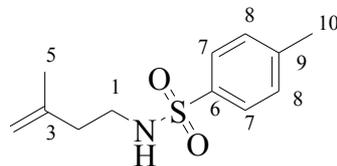
$C_{13}H_{19}NO_2S$   
Mol. Wt.: 253.36

Following the general procedure E, 4-methylpent-3-enyl 4-methylbenzenesulfonate **138** (630 mg, 2.48 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 50 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound* **139** (317 mg, 1.25 mmol, 50%) as a colourless oil.

$\nu_{max}$ (neat)/ $cm^{-1}$  3521, 3281, 2926, 1598;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.74 (2H, d,  $J$  8.3, H-C8), 7.30 (2H, d,  $J$  8.3, H-C9), 4.95-4.87 (1H, m, H-C3), 4.48 (1H, t,  $J$  5.8, H-NH), 2.93 (2H, dd,  $J$  13.1, 6.6, H-C1), 2.42 (3H, s, H-C11), 2.19-2.09 (2H, m, H-C2), 1.66 (3H, s, H-C6), 1.55 (3H, s, H-C5);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 143.3 (C10), 136.8 (C7), 135.6 (C3), 129.6 (C9), 127.1 (C8), 119.6 (C4), 42.9 (C1), 28.1 (C2), 25.7 (C6), 21.5 (C10), 17.8

(C5);  $m/z$  (CI) 254 ( $MH^+$ , 100), 184 (38), 155 (12); HRMS (ES) Found  $[M+H]^+$  254.1207,  $C_{13}H_{20}NO_2S$  requires 254.1209.

#### 4-Methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide (140).

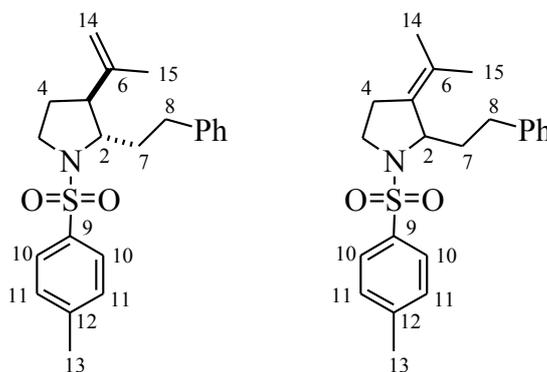


$C_{12}H_{17}NO_2S$   
Mol. Wt.: 239.33

Following the general procedure E, 3-methylbut-3-enyl 4-methylbenzenesulfonate **97** (12.63 g, 52.55 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 50 °C. The work up afforded a yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound* **140** (8.59 g, 35.89 mmol, 68%) as a white solid.

M.p. 38-39 °C;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.70 (2H, d,  $J$  8.4, H-C7), 7.25 (2H, d,  $J$  8.4, H-C8), 4.89-4.78 (1H, m, N-NH), 4.73-4.69 (1H, m, H-C4), 4.59-4.56 (1H, m, H-C4), 2.98 (2H, dd,  $J$  12.9, 6.8, H-C1), 2.36 (3H, s, H-C10), 2.09 (2H, t,  $J$  6.8, H-C2), 1.53 (3H, s, H-C5);  $m/z$  (CI) 240 ( $MH^+$ , 62), 184 (100), 157 (18). Data in agreement with literature values.

#### (2*S*\*,3*S*\*)-2-Phenethyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine (142a), and (±)-2-Phenethyl-3-(propan-2-ylidene)-1-tosylpyrrolidine (141a).



$C_{22}H_{27}NO_2S$   
Mol. Wt.: 369.52

Following the general procedure F, 4-methyl-*N*-(4-methylpent-3-enyl)benzenesulfonamide **139** (100 mg, 0.39 mmol), in the presence of 3-phenylpropanal (80 mg, 0.59 mmol), was consumed based on analysis by TLC after 6 hours of stirring at

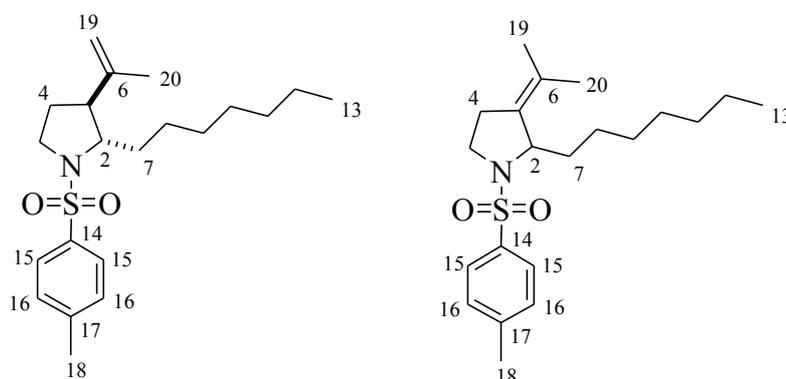
*Experimental*

room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* **141a** and **142a** (108 mg, 0.29 mmol, 75%) as a colourless oil.

Data for **141a**:  $\nu_{\max}$ (neat)/ $\text{cm}^{-1}$  3026, 2925, 1644, 1599 (mixture);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.69-7.61 (2H, m, H-C10), 7.30-7.24 (2H, m, H-C11), 7.27-7.13 (5H, m, Ar-H), 4.46-4.40 (1H, m, H-C2), 3.47-3.32 (2H, m, H-C5), 2.71-2.58 (2H, m, H-C8), 2.40 (3H, s, H-C13), 2.28-2.10 (1H, m, H-C4), 2.09-1.94 (1H, m, H-C4), 1.95-1.81 (2H, m, H-C7), 1.39 (3H, s, H-C15), 1.37 (3H, s, H-C14);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.2 (C12), 142.1 (ArC), 135.2 (C9), 132.2 (C3), 129.3 (C11), 128.4 (ArC), 128.2 (ArC), 127.4 (C10), 125.6 (ArC), 123.8 (C6), 62.0 (C2), 48.7 (C5), 37.2 (C4), 36.4 (C7), 31.7 (C8), 21.4 (C13), 21.0 (C15), 19.9 (C15);  $m/z$  (CI) 370 ( $\text{MH}^+$ , 100), 264 (18), 216 (35); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  (mixture) 370.1837,  $\text{C}_{22}\text{H}_{28}\text{NO}_2\text{S}$  requires 370.1835.

Data for **142a**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.69-7.61 (2H, m, H-C10), 7.30-7.24 (2H, m, H-C11), 7.30-7.24 (5H, m, Ar-H), 4.59-4.56 (1H, m, H-C14), 4.41-4.39 (1H, m, H-C14), 3.51-3.41 (1H, m, H-C2), 3.54-3.38 (2H, m, H-C5), 2.83-2.65 (2H, m, H-C8), 2.66-2.50 (1H, m, H-C3), 2.40 (3H, s, H-C13), 2.28-2.10 (1H, m, H-C4), 2.09-1.94 (1H, m, H-C4), 1.87-1.70 (2H, m, H-C7), 1.51 (3H, s, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.9 (C6), 143.3 (C12), 141.7 (ArC), 134.9 (C9), 129.5 (C11), 128.5 (ArC), 128.2 (ArC), 127.5 (C10), 125.7 (ArC), 111.9 (C14), 62.3 (C2), 51.7 (C3), 46.8 (C5), 31.4 (C8), 29.7 (C7), 28.2 (C4), 21.4 (C13), 20.9 (C15);  $m/z$  (CI) 370 ( $\text{MH}^+$ , 100), 264 (15), 216 (40).

**(2*S*\*,3*S*\*)-2-Heptyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine (142b), and ( $\pm$ )-2-Heptyl-3-(propan-2-ylidene)-1-tosylpyrrolidine (141b).**



$\text{C}_{21}\text{H}_{33}\text{NO}_2\text{S}$   
Mol. Wt.: 363.56

Following the general procedure F, 4-methyl-*N*-(4-methylpent-3-enyl)benzenesulfonamide **139** (100 mg, 0.39 mmol), in the presence of octanal (76 mg,

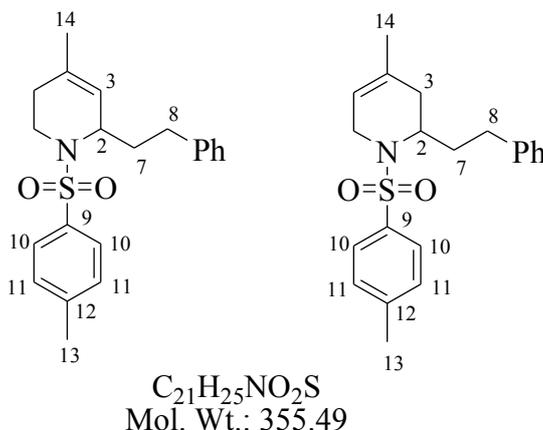
*Experimental*

0.59 mmol), was consumed based on analysis by TLC after 6 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* **141b** and **142b** (85 mg, 0.23 mmol, 60%) as a colourless oil.

Data for **141b**:  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2926, 1735, 1645, 1598 (mixture);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.72 (2H, d,  $J$  8.3, H-C15), 7.29 (2H, d,  $J$  8.3, H-C16), 4.39-4.33 (1H, m, H-C2), 3.52-3.37 (2H, m, H-C5), 2.42 (3H, s, H-C18), 1.86-1.70 (2H, m, H-C4), 1.70-1.57 (2H, m, H-C7), 1.43 (3H, s, H-C20), 1.39 (3H, s, H-C19), 1.37-1.17 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.0 (C17), 135.5 (C14), 132.5 (C3), 129.2 (C16), 127.4 (C15), 123.3 (C6), 62.3 (C2), 46.6 (C5), 34.7 (C4), 31.8 (C11), 29.6 (C7), 29.4 (C9 and C10), 25.4 (C8), 22.6 (C12), 21.5 (C18), 21.0 (C20), 20.2 (C19), 14.1 (C13);  $m/z$  (CI) 364 ( $\text{MH}^+$ , 100), 264 (40), 210 (38); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  (mixture) 381.2569,  $\text{C}_{21}\text{H}_{37}\text{N}_2\text{O}_2\text{S}$  requires 381.2570.

Data for **142b**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.65 (2H, d,  $J$  8.4, H-C15), 7.24 (2H, d,  $J$  8.4, H-C16), 4.56-4.52 (1H, m, H-C19), 4.43-4.37 (1H, m, H-C19), 3.52-3.39 (1H, m, H-C2), 3.40-3.25 (2H, m, H-C5), 2.49 (1H, dd,  $J$  13.2, 6.8, H-C3), 2.40 (3H, s, H-C18), 2.27-2.12 (1H, m, H-C4), 2.08-1.94 (1H, m, H-C4), 1.55 (3H, s, H-C20), 1.54-1.43 (2H, m, H-C7), 1.37-1.17 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 144.2 (C6), 143.2 (C17), 135.4 (C14), 129.5 (C16), 127.5 (C15), 111.4 (C19), 63.2 (C2), 51.2 (C3), 48.5 (C5), 35.8 (C4), 31.8 (C11), 29.7 (C7), 29.3 (C9), 28.2 (C10), 25.1 (C8), 22.6 (C12), 21.5 (C18), 21.0 (C20), 14.1 (C13);  $m/z$  (CI) 364 ( $\text{MH}^+$ , 100), 264 (30), 210 (44).

(±)-4-Methyl-2-phenethyl-1-tosyl-1,2,3,6-tetrahydropyridine (**146a**) and (±)-4-Methyl-2-phenethyl-1-tosyl-1,2,5,6-tetrahydropyridine (**147a**).

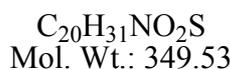
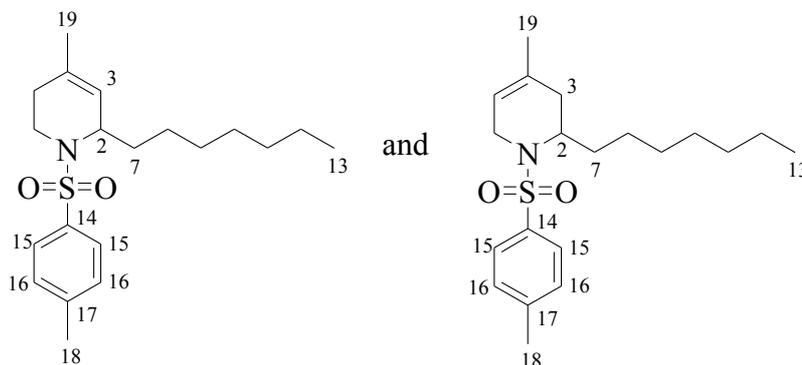


Following the general procedure F, 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide **140** (250 mg, 1.04 mmol), in the presence of 3-phenylpropanal (210 mg, 1.56 mmol), was consumed based on analysis by TLC after 2 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* **146a** and **147a** (331 mg, 0.93 mmol, 90%) as a pale yellow oil.

Data for **146a**:  $\nu_{\max}$ (neat)/ $cm^{-1}$  3026, 2929, 1736, 1598 (mixture);  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.82-7.79 (2H, m, H-C10), 7.44-7.39 (2H, m, H-C11), 7.39-7.23 (5H, m, Ar-H), 5.48-5.42 (1H, m, H-C3), 4.50-4.37 (1H, m, H-C2), 3.98 (1H, dd,  $J$  14.6, 6.1, H-C6), 3.28 (1H, ddd,  $J$  14.6, 11.8, 4.8, H-C6), 3.07 (1H, t,  $J$  7.5, H-C8), 2.95-2.86 (1H, m, H-C8), 2.51 (3H, s, H-C13), 2.00-1.89 (2H, m, H-C7), 1.87-1.72 (2H, m, H-C5), 1.64 (3H, s, H-C14);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 142.9 (C12), 141.9 (ArC), 138.4 (C9), 132.7 (C4), 129.4 (C11), 128.3 (ArC), 128.3 (ArC), 127.0 (C10), 125.7 (ArC), 121.5 (C3), 53.6 (C2), 40.4 (C6), 36.8 (C5), 32.8 (C8), 28.1 (C7), 23.2 (C14), 21.5 (C13);  $m/z$  (CI) (mixture) 356 ( $MH^+$ , 100), 250 (25), 202 (37); HRMS (ES) Found  $[M+H]^+$  (mixture) 356.1682,  $C_{21}H_{26}NO_2S$  requires 356.1679.

Data for **147a**:  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.79-7.75 (2H, m, H-C10), 7.38-7.34 (2H, m, H-C11), 7.39-7.23 (5H, m, Ar-H), 5.40-5.35 (1H, m, H-C5), 4.31-4.23 (1H, m, H-C2), 4.26-4.18 (1H, m, H-C6), 3.77-3.62 (1H, m, H-C6), 2.88-2.70 (2H, m, H-C8), 2.51 (3H, s, H-C13), 2.24-2.12 (1H, m, H-C3), 1.87-1.71 (2H, m, H-C7), 1.77-1.65 (1H, m, H-C3), 1.60 (3H, s, H-C14);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 142.9 (C12), 141.7 (ArC), 137.9 (C9), 131.0 (C4), 129.5 (C11), 128.4 (ArC), 128.3 (ArC), 126.9 (C10), 125.9 (ArC), 116.0 (C5), 50.7 (C2), 45.3 (C6), 38.5 (C3), 32.7 (C8), 27.5 (C7), 23.4 (C14), 21.5 (C13).

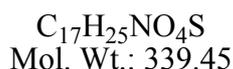
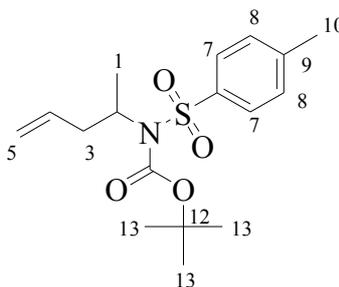
(±)-2-Heptyl-4-methyl-1-tosyl-1,2,3,6-tetrahydropyridine (**146b**) and (±)-2-Heptyl-4-methyl-1-tosyl-1,2,5,6-tetrahydropyridine (**147b**).



Following the general procedure F, 4-methyl-*N*-(3-methylbut-3-enyl)benzenesulfonamide **140** (250 mg, 1.04 mmol), in the presence of octanal (200 mg 1.56 mmol), was consumed based on analysis by TLC after 2 hours of stirring at room temperature. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compounds* **146b** and **147b** (265 mg, 0.76 mmol, 73%) as a pale yellow oil.

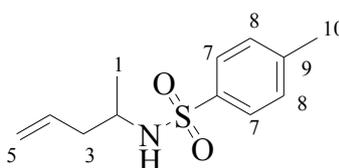
Data for **146b**:  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2927, 1598 (mixture);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.73-7.68 (2H, m, H-C15), 7.27-7.23 (2H, m, H-C16), 5.36-5.30 (1H, m, H-C3), 4.31-4.16 (1H, m, H-C2), 3.82 (1H, dd,  $J$  14.6, 6.2, H-C6), 3.11 (1H, ddd,  $J$  14.6, 11.9, 4.7, H-C6), 2.40 (3H, s, H-C18), 1.77-1.58 (1H, m, H-C5), 1.58-1.44 (1H, m, H-C5), 1.55 (3H, s, H-C19), 1.46-1.34 (2H, m, H-C7), 1.38-1.11 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 142.8 (C17), 138.6 (C14), 132.1 (C4), 129.3 (C16), 127.0 (C15), 121.9 (C3), 53.8 (C2), 38.4 (C6), 32.7 (C5), 31.8 (C11), 31.6 (C7), 29.5 (C9), 29.2 (C10), 26.2 (C8), 23.2 (C19), 22.6 (C12), 21.5 (C18), 14.1 (C13);  $m/z$  (CI) (mixture) 350 ( $\text{MH}^+$ , 100), 250 (12), 196 (40); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  (mixture) 350.2148,  $C_{20}H_{32}NO_2S$  requires 350.2149.

Data for **147b**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.68-7.64 (2H, m, H-C15), 7.23-7.19 (2H, m, H-C16), 5.29-5.22 (1H, m, H-C5), 4.14-4.03 (1H, m, H-C6), 4.09-4.01 (1H, m, H-C2), 3.58-3.46 (1H, m, H-C6), 2.40 (3H, s, H-C18), 2.16-1.98 (1H, m, H-C3), 1.58-1.47 (1H, m, H-C3), 1.49 (3H, s, H-C19), 1.55-1.41 (2H, m, H-C7), 1.38-1.11 (10H, m, H-C8 to H-C12), 0.91-0.84 (3H, m, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 142.8 (C17), 138.0 (C14), 131.1 (C4), 129.4 (C16), 126.9 (C15), 116.0 (C5), 50.9 (C2), 40.3 (C6), 35.2 (C3), 31.8 (C11), 31.2 (C7), 29.3 (C9), 29.2 (C10), 26.4 (C8), 23.5 (C19), 22.7 (C12), 21.5 (C18), 14.1 (C13).

**(±)-*tert*-Butyl pent-4-en-2-yl(tosyl)carbamate (151).**

A round-bottomed flask was charged with (±)-pent-4-en-2-ol **150** (1.00 g, 11.61 mmol, 1.00 eq.) and tetrahydrofuran (160 mL). The resulting solution was stirred at room temperature and triphenylphosphine (9.07 g, 34.83 mmol, 3.00 eq.) added portionwise followed by *tert*-butyl tosylcarbamate (4.72 g, 17.38 mmol, 1.50 eq.) portionwise and diisopropyl azodicarboxylate (5.67 mL, 28.62 mmol, 2.47 eq.) dropwise. The resulting solution was stirred overnight, filtered through a pad of celite and concentrated *in vacuo*. This afforded a pale yellow oil which was purified by flash column chromatography (90% hexane 10% ethyl acetate) to afford the *title compound* **151** (2.72 g, 8.01 mmol, 69%) as a sticky colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.78 (2H, d,  $J$  8.4, H-C7), 7.28 (2H, d,  $J$  8.4, H-C8), 5.74 (1H, tdd,  $J$  17.2, 10.0, 7.2, H-C4), 5.13-5.00 (2H, m, H-C5), 4.69-4.56 (1H, m, H-C2), 2.78-2.66 (1H, m, H-C3), 2.52-2.42 (1H, m, H-C3), 2.43 (3H, s, H-C10), 1.46 (3H, d,  $J$  6.8, H-C1), 1.35 (9H, s, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 150.6 (C11), 143.7 (C9), 137.9 (C4), 135.2 (C6), 129.1 (C8), 127.8 (C7), 117.6 (C5), 83.9 (C12), 54.9 (C2), 39.4 (C3), 27.9 (C13), 21.6 (C10), 19.4 (C1). Data in agreement with literature values.

**(±)-4-Methyl-*N*-(pent-4-en-2-yl)benzenesulfonamide (152).**

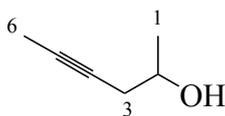
A round-bottomed flask was charged with (±)-*tert*-butyl pent-4-en-2-yl(tosyl)carbamate **151** (2.13 g, 6.27 mmol, 1.00 eq.) and dichloromethane (43 mL). The resulting solution

*Experimental*

was stirred at room temperature and trifluoroacetic acid (3.61 g, 31.66 mmol, 5.00 eq.) added dropwise. The mixture was stirred at room temperature overnight and water (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This afforded a pale yellow oil which was purified by flash column chromatography (80% hexane 20% ethyl acetate) to afford the *title compound* **152** (1.50 g, 6.27 mmol, *quantitative*) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.75 (2H, d,  $J$  8.3, H-C7), 7.29 (2H, d,  $J$  8.3, H-C8), 5.56 (1H, tdd,  $J$  17.4, 10.3, 7.2, H-C4), 5.06-4.95 (2H, m, H-C5), 4.53 (1H, d,  $J$  7.1, H-NH), 3.43-3.29 (1H, m, H-C2), 2.42 (3H, s, H-C10), 2.14-2.08 (2H, m, H-C3), 1.06 (3H, d,  $J$  6.6, H-C1);  $m/z$  (CI) 240 ( $\text{MH}^+$ , 45), 198 (100), 155 (10). Data in agreement with literature values.

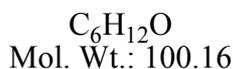
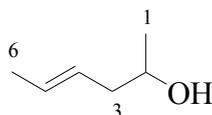
**(±)-Hex-4-yn-2-ol (154).**



$\text{C}_6\text{H}_{10}\text{O}$   
Mol. Wt.: 98.14

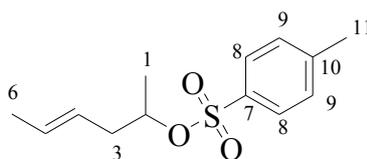
A round-bottomed flask was wrapped in aluminium foil and equipped with a dropping funnel and a thermometer. The flask was charged with (±)-pent-4-yn-2-ol **153** (5.00 g, 59.43 mmol, 1.00 eq.) and tetrahydrofuran (96 mL). The resulting solution was cooled to  $-78\text{ }^\circ\text{C}$  and a 2.5 M solution of *n*-butyllithium in hexane (47 mL, 118.86 mmol, 2.00 eq.) was added dropwise over 30 minutes. The mixture was stirred at  $-78\text{ }^\circ\text{C}$  for a further 90 minutes and iodomethane (18.6 mL, 297.15 mmol, 5.00 eq.) was added dropwise. The mixture was allowed to warm to room temperature for 1 hour and 1.0 M hydrochloric acid (100 mL) was added dropwise over 30 minutes. The mixture was stirred for a further 30 minutes at room temperature, the organic layer separated and the aqueous layer extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a yellow oil, which was purified by distillation under reduced pressure ( $125\text{ }^\circ\text{C}$ , 226 mmHg) to give the *title compound* **154** (3.10 g, 31.59 mmol, 53%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 3.88-3.77 (1H, m, H-C2), 2.37 (1H, bs, H-OH), 2.28-2.18 (2H, m, H-C3), 1.75 (3H, t,  $J$  2.2, H-C6), 1.17 (3H, d,  $J$  6.2, H-C1);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 78.2 (C4), 75.3 (C3), 66.4 (C2), 29.2 (C3), 22.1 (C1), 3.4 (C6). Data in agreement with literature values.

**(±)-(E)-Hex-4-en-2-ol (155).**

Following the general procedure D, (±)-hex-4-en-2-ol **154** (966 mg, 9.84 mmol) gave a pale yellow oil, which was purified by distillation under reduced pressure (120 °C, 213 mmHg) to give the *title compound* **155** (590 mg, 5.89 mmol, 60%) as a colourless oil.

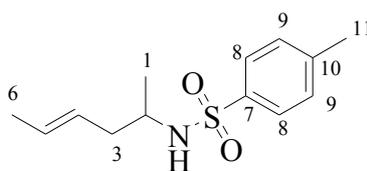
$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.62-5.48 (1H, m, H-C4), 5.47-5.35 (1H, m, H-C5), 3.82-3.70 (1H, m, H-C2), 2.24-2.12 (1H, m, H-C3), 2.12-1.99 (1H, m, H-C3), 1.74 (1H, bs, H-OH), 1.70-1.65 (3H, m, H-C6), 1.17 (3H, d,  $J$  6.2, H-C1). Data in agreement with literature values.

**(±)-(E)-Hex-4-en-2-yl 4-methylbenzenesulfonate (156).**

Following the general procedure A, (±)-(E)-hex-4-en-2-ol **155** (590 mg, 5.90 mmol) was consumed based on analysis by TLC after 40 hours of stirring at 0 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **156** (374 mg, 1.47 mmol, 25%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.78 (2H, d,  $J$  8.2, H-C8), 7.33 (2H, d,  $J$  8.2, H-C9), 5.49-5.35 (1H, m, H-C4), 5.20-5.07 (1H, m, H-C5), 4.61-4.50 (1H, m, H-C2), 2.44 (3H, s, H-C11), 2.32-2.12 (2H, m, H-C3), 1.58-1.53 (3H, m, H-C6), 1.25 (3H, d,  $J$  6.3, H-C1);

$\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 144.3 (C10), 134.4 (C7), 129.6 (C9), 128.3 (C4), 127.7 (C8), 124.7 (C5), 80.1 (C2), 39.6 (C3), 21.6 (C11), 20.4 (C1), 17.9 (C6). Data in agreement with literature values.

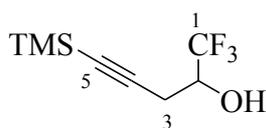
**(±)-(E)-N-(Hex-4-en-2-yl)-4-methylbenzenesulfonamide (157).**

Following the general procedure E, (±)-(E)-hex-4-en-2-yl 4-methylbenzenesulfonate **156** (350 mg, 1.38 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 50 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound* **157** (107 mg, 0.42 mmol, 31%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.66 (2H, d,  $J$  8.3, H-C8), 7.22 (2H, d,  $J$  8.3, H-C9), 5.36-5.23 (1H, m, H-C4), 5.08-4.95 (1H, m, H-C5), 4.66 (1H, d,  $J$  7.2, H-NH), 3.24-3.11 (1H, m, H-C2), 2.33 (3H, s, H-C11), 1.96-1.89 (2H, m, H-C3), 1.50-1.46 (3H, m, H-C6), 0.97 (3H, d,  $J$  6.6, H-C1);  $m/z$  (CI) 254 ( $\text{MH}^+$ , 100), 198 (70), 172 (22). Data in agreement with literature values.

**General procedure G: epoxide opening with diethylaluminium chloride on 23.20 mmol scale.**

A 2.5 M solution of *n*-butyllithium in hexane (21.26 mL, 53.15 mmol, 2.2 eq.,) was added dropwise to a solution of trimethylsilylacetylene (6.65 mL, 46.40 mmol, 2.00 eq.) in hexane (46 ml) at  $-30$  °C and stirred at this temperature for 30 min. After this time, a 1.0 M solution of diethylaluminium chloride in hexane (51.04 mL, 51.04 mmol, 1.00 eq.) was added and the solution was stirred for a further 1 hour, while being allowed to warm to 0 °C. The reaction mixture was then cooled again to  $-30$  °C before adding a solution of the epoxide (1.00 eq.) in hexane (10 mL). The reaction was slowly warmed to room temperature and stirred for 3 hours. The reaction was cooled to 0 °C before adding a 2.0 M solution of dilute sulfuric acid (15 ml) and stirring at room temperature for 30 minutes. The reaction mixture was then further diluted with water (100 ml) and diethyl ether (100 ml), filtered through celite, the layers separated and aqueous layer further extracted with ether (2×100 mL). The combined organic layers were washed with brine (100 ml), water (100 ml), dried over magnesium sulfate and concentrated *in vacuo*.

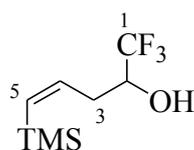
**(±)-1,1,1-Trifluoro-5-(trimethylsilyl)pent-4-yn-2-ol (249).**

C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>OSi  
Mol. Wt.: 210.27

Following the general procedure G, (±)-2-(trifluoromethyl)oxirane **248** (2.00 mL, 23.20 mmol) afforded a colourless oil, which was purified by flash column chromatography (75% hexane, 25% diethyl ether) to give the *title compound* **249** (3.99 g, 19.02 mmol, 82%) as a colourless oil.

$\nu_{\max}$ (neat)/cm<sup>-1</sup> 3435, 2962, 2360, 2183;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 4.06-3.95 (1H, m, H-C2), 2.63 (1H, dd, *J* 17.2, 4.5, H-C3), 2.52 (1H, dd, *J* 17.2, 7.6, H-C3), 0.07 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 99.1 (C5), 89.3 (C4), 68.5 (q, *J* 31.5, C2), 22.4 (q, *J* 2.4, C3), 0.1 (CTMS);  $\delta_{\text{F}}$  (282 MHz, CDCl<sub>3</sub>) -79.88 (d, *J*<sub>H-F</sub> 6.4); *m/z* (CI) 211 (MH<sup>+</sup>, 10), 171 (100), 119 (90); HRMS (ES) Found [M+NH<sub>4</sub>]<sup>+</sup> 228.1023, C<sub>8</sub>H<sub>17</sub>F<sub>3</sub>NOSi requires 228.1026. Data in agreement with literature values.

**General procedure H: *cis* reduction of alkynylsilanes with diisobutylaluminium hydride on 19.27 mmol scale.** A round-bottomed flask equipped with a reflux condenser was charged with a 1.0 M solution of diisobutylaluminum hydride in hexane (57.80 mL, 57.80 mmol, 3.00 eq.) and diethyl ether (86 mL). The resulting solution was stirred and cooled to 0 °C before adding dropwise a solution of alkynylsilane (19.27 mmol, 1.00 eq.) in diethyl ether (9.50 mL). The reaction was then allowed to slowly warm to room temperature and then heated at reflux temperature overnight. After cooling to room temperature and then to 0 °C, a 2.0 M solution of dilute sulfuric acid (78 mL) was added dropwise to the reaction mixture, which was stirred for a further 45 minutes whilst being allowed to warm to room temperature. The mixture was then filtered through a pad of celite, diluted with additional diethyl ether (43 mL), the organic layer separated and the aqueous layer extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with ice cold water (86 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*.

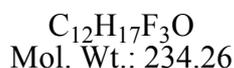
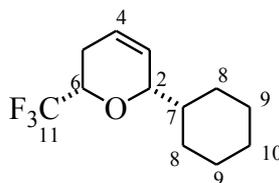
**(±)-(Z)-1,1,1-Trifluoro-5-(trimethylsilyl)pent-4-en-2-ol (247).**

$C_8H_{15}F_3OSi$   
Mol. Wt.: 212.28

Following the general procedure H, (±)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-yn-2-ol **249** (4.87g, 23.2 mmol) afforded a pale yellow oil, which was purified by flash column chromatography (75% hexane, 25% diethyl ether) to give the *title compound* **247** (3.00 g, 14.15 mmol, 61%) as a colourless oil.

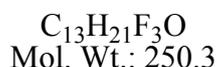
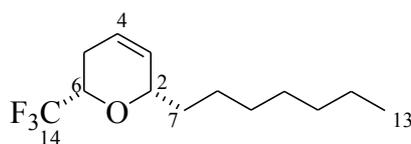
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3428, 2958, 1610 ;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.17 (1H, td,  $J$  14.4, 7.4, H-C4), 5.66 (1H, d,  $J$  14.4, H-C5), 3.95-3.75 (1H, m, H-C2), 2.63-2.51 (1H, m, H-C3), 2.46 (1H, dd,  $J$  15.1, 8.3, H-C3), 2.16 (1H, d,  $J$  5.6, H-OH), 0.15 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75 MHz;  $\text{CDCl}_3$ ) 140.5 (C4), 135.1 (C5), 70.0 (q,  $J$  31.0, C2), 33.4 (q,  $J$  1.6, C3), 0.0 (CTMS);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -80.04 (d,  $J_{\text{H-F}}$  6.6);  $m/z$  (CI) 197 ((M-OH) $\text{H}^+$ , 100), 171 (50), 121 (18); HRMS (CI) Found  $[\text{M}+\text{NH}_4]^+$  230.1184,  $C_8H_{19}F_3NOSi$  requires 230.1183.

**General procedure I: the silyl-Prins reaction on 1.92 mmol scale.** Unless otherwise stated, a round-bottomed flask equipped with a condenser was charged with indium trichloride (406 mg, 1.96 mmol, 1.00 eq.), an aldehyde derivative (1.96 mmol, 1.00 eq.) and dichloromethane (10 mL). The resulting suspension was stirred at room temperature for 15 minutes and a solution of a homoallylic alcohol (1.96 mmol, 1.00 eq.) in dichloromethane (2 mL) was added dropwise. The reaction was then heated to reflux temperature. Once TLC showed full consumption of starting material, the solution was cooled to room temperature, poured into dichloromethane (10 mL), water (10 mL) added and the resulting biphasic solution stirred for a further 30 minutes at room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*.

**(±)-cis-2-Cyclohexyl-6-(trifluoromethyl)-3,6-dihydro-2H-pyran (250a).**

Following the general procedure I, (±)-(Z)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247** (44 mg, 0.21 mmol), in the presence of cyclohexanecarbaldehyde (24 mg, 0.21 mmol), was consumed based on analysis by TLC after 43 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (90% hexane 10% ethyl acetate) to give the *title compound* **250a** (6 mg, 0.03 mmol, 12%) as a pale yellow oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  2928, 1658;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.90-5.78 (1H, m, H-C4), 5.74-5.66 (1H, m, H-C3), 4.09-4.02 (1H, m, H-C6), 4.01-3.89 (1H, m, H-C2), 2.36-2.21 (1H, m, H-C5), 2.12-2.01 (1H, m, H-C5), 1.79-1.61 (4H, m, H-C8), 1.61-1.47 (1H, m, H-C7), 1.31-1.01 (6H, m, H-C9 and H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 128.6 (C3), 122.7 (C4), 79.4 (C2), 71.9 (q,  $J$  30.6, C6), 42.3 (C7), 28.2 (C8), 27.6 (C8), 26.5 (C10), 26.2 (C9), 26.1 (C9), 24.0 (q,  $J$  2.0, C5);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -79.80 (d,  $J_{\text{H-F}}$  6.3);  $m/z$  (CI) 235 ( $\text{MH}^+$ , 100), 233 (80), 151 (86); HRMS(EI) Found  $[\text{M}+\text{H}]^+$  234.1227,  $\text{C}_{12}\text{H}_{18}\text{F}_3\text{O}$  requires 234.1226.

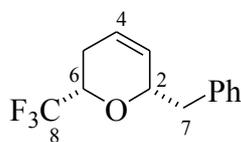
**(±)-cis-2-Heptyl-6-(trifluoromethyl)-3,6-dihydro-2H-pyran (250b).**

Following the general procedure I, (±)-(Z)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247** (407 mg, 1.92 mmol), in the presence of octanal (247 mg, 1.92 mmol), was consumed based on analysis by TLC after 66 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (98% hexane 2% ethyl acetate) to give the *title compound* **250b** (264 mg, 1.06 mmol, 55%) as a colourless oil.

*Experimental*

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2929, 1656;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.85-5.77 (1H, m, H-C4), 5.67 (1H, tdd,  $J$  10.3, 2.5, 1.2, H-C3), 4.26-4.17 (1H, m, H-C2), 4.04-3.91 (1H, m, H-C6), 2.40-2.25 (1H, m, H-C5), 2.15-1.99 (1H, m, H-C5), 1.62-1.52 (2H, m, H-C7), 1.47-1.34 (2H, m, H-C8), 1.33-1.23 (8H, m, H-C9 to H-C12), 0.88 (3H, t,  $J$  6.6, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 130.2 (C3), 122.1 (C4), 75.5 (C2), 72.0 (q,  $J$  31.9, C6), 35.0 (C7), 31.8 (C11), 29.5 (C9), 29.2 (C10), 24.7 (C8), 23.9 (q,  $J$  1.9, C5), 22.6 (C12), 14.1 (C13);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -79.70 (d,  $J_{\text{H-F}}$  6.4);  $m/z$  (CI) 251 ( $\text{MH}^+$ , 100), 187 (55), 139 (20); HRMS (EI) Found  $[\text{M}]^+$  250.1541,  $\text{C}_{13}\text{H}_{21}\text{F}_3\text{O}$  requires 250.1539.

**(±)-*cis*-2-Benzyl-6-(trifluoromethyl)-3,6-dihydro-2H-pyran (250c).**



$\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}$   
Mol. Wt.: 242.24

Following the general procedure I, (±)-(*Z*)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247** (92 mg, 0.43 mmol), in the presence of phenylacetaldehyde (52 mg 0.43 mmol), was consumed based on analysis by TLC after 44 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (88% hexane 12% diethyl ether) to give the *title compound* **250c** (44 mg, 0.18 mmol, 42%) as a yellow oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2924, 1742, 1604;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.33-7.18 (5H, m, ArH), 5.85-5.77 (1H, m, H-C4), 5.69-5.62 (1H, m, H-C3), 4.51-4.41 (1H, m, H-C2), 4.00 (1H, dtd,  $J$  16.7, 6.4, 3.6, H-C6), 3.05 (1H, dd,  $J$  13.6, 6.3, H-C7), 2.77 (1H, dd,  $J$  13.6, 7.3, H-C7), 2.40-2.23 (1H, m, H-C5), 2.14-1.90 (1H, m, H-C5).

(±)-*cis*-2-Phenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran (**250d**) and (±)-*trans*-2-Phenyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-pyran (**251d**).



$C_{12}H_{11}F_3O$   
Mol. Wt.: 228.21

Following the general procedure I, (±)-(*Z*)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247** (150 mg, 0.71 mmol), in the presence of benzaldehyde (72  $\mu$ L, 0.71 mmol), was consumed based on analysis by TLC after 42 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (88% hexane 12% diethyl ether) to give the *title compounds* **251d** and **250d** (41 mg, 0.18 mmol, 25%) as a colourless oil.

Data for **251d**:  $\nu_{\max}$ (neat)/ $cm^{-1}$  (mixture) 3066, 2924, 1663;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.48-7.20 (5H, m, ArH), 6.16-6.05 (2H, m, H-C3 and H-C4), 5.43 (1H, s, H-C2), 4.00-3.89 (1H, m, H-C6), 2.55-2.40 (1H, m, H-C5), 2.26-2.08 (1H, m, H-C5);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 139.2 (ArC), 128.5 (ArC), 128.3 (ArC), 127.9 (C3), 127.3 (ArC), 123.5 (C4), 74.3 (C2), 66.5 (q,  $J$  32.1, C6), 23.6 (C5);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -79.14 (d,  $J_{H-F}$  6.4);  $m/z$  (CI) 229 ( $MH^+$ , 100), 228 (70), 151 (60);  $m/z$  (CI) (mixture) 229 ( $MH^+$ , 100), 228 (95), 151 (100); HRMS (ES) Found  $[M+NH_4]^+$  (mixture) 246.1100,  $C_{12}H_{15}F_3NO$  requires 246.1100.

Data for **250d**:  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.48-7.20 (5H, m, ArH), 5.97-5.91 (1H, m, H-C4), 5.80 (1H, d,  $J$  10.3, H-C3), 5.30 (1H, s, H-C2), 4.27-4.16 (1H, m, H-C6), 2.55-2.40 (1H, m, H-C5), 2.26-2.08 (1H, m, H-C5);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 139.8 (ArC), 130.1 (ArC), 128.6 (ArC), 128.2 (C3), 127.0 (ArC), 122.0 (C4), 77.9 (C2), 72.3 (q,  $J$  32.2, C6), 23.6 (C5);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -79.55 (d,  $J_{H-F}$  6.1).

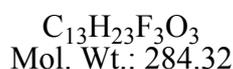
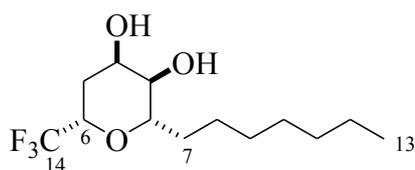
#### General procedure J: *syn* di-hydroxylation of olefins on 29.37 mmol scale.

An olefin derivative (29.37 mmol, 1.00 eq.) was placed into a round-bottomed flask and dissolved in tetrahydrofuran (195 mL) and water (83 mL). The resulting solution was stirred at room temperature and 4-methylmorpholine *N*-oxide (9.74 g, 58.73 mmol, 2 eq.) added in one portion, followed by a 0.1 M aqueous solution of osmium tetroxide (14.68 mL, 1.47 mmol, 0.05 eq.). The reaction was then stirred at room temperature for 72 hours, allowed to cool to 0  $^{\circ}C$ , a saturated aqueous solution of sodium bisulfite (190 mL) added

*Experimental*

slowly and after 10 minutes of stirring at 0 °C, the solution was warmed to room temperature while being stirred for 30 minutes. The solution was diluted with ethyl acetate (190 mL), the organic layer separated, the aqueous layer extracted with ethyl acetate (3 x 80 mL), the combined organic layers were washed with a saturated aqueous solution of sodium chloride (2 x 200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*.

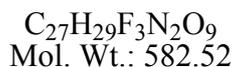
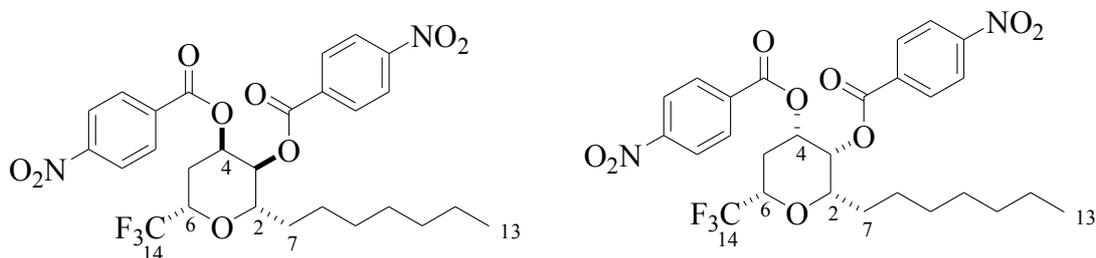
**(2*S*\*,3*R*\*,4*R*\*,6*S*\*)-2-Heptyl-6-(trifluoromethyl)-tetrahydro-2*H*-pyran-3,4-diol (**253**).**



Following the general procedure J, ( $\pm$ )-*cis*-6-heptyl-2-(trifluoromethyl)-3,6-dihydro-2*H*-pyran **250b** (175 mg, 0.70 mmol) afforded the *title compound* **253** (165 mg, 0.58 mmol, 83%) as a colourless oil which was used in the next step without any further purification.

$\nu_{\max}$ (neat)/ $cm^{-1}$  3401, 2928, 1709, 1637;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 4.19-4.13 (1H, m, H-C2), 4.14-4.05 (1H, m, H-C6), 3.60-3.51 (1H, m, H-C4), 3.40-3.32 (1H, m, H-C3), 2.86 (1H, bs, H-OH), 2.61 (1H, bs, H-OH), 2.08-1.99 (1H, m, H-C5), 1.87-1.75 (1H, m, H-C5), 1.82-1.71 (1H, m, H-C7), 1.63-1.46 (1H, m, H-C7), 1.45-1.17 (10H, m, H-C8 to H-C12), 0.87 (3H, t,  $J$  6.6, H-C13);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 124.3 (q,  $J$  279.1, C14), 75.7 (C3), 71.0 (C4), 69.7 (q,  $J$  32.0, C6), 66.5 (C2), 31.8 (C9), 31.8 (C7), 31.1 (C5), 29.5 (C9), 29.2 (C10), 25.2 (C8), 22.6 (C12), 14.0 (C13);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -79.01 (d,  $J_{H-F}$  6.4);  $m/z$  (CI) 285 ( $MH^+$ , 20), 267 (100), 249 (22).

(2*S*\*,3*R*\*,4*S*\*,6*S*\*)-2-Heptyl-6-(trifluoromethyl)-tetrahydro-2*H*-pyran-3,4-diyl bis(4-nitrobenzoate) (**255**), (2*S*\*,3*S*\*,4*R*\*,6*S*\*)-2-Heptyl-6-(trifluoromethyl)-tetrahydro-2*H*-pyran-3,4-diyl bis(4-nitrobenzoate) (**256**).



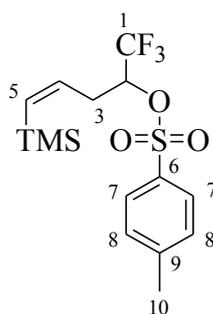
A round-bottomed flask was charged with (2*S*,3*R*,4*R*,6*S*)-2-heptyl-6-(trifluoromethyl)-tetrahydro-2*H*-pyran-3,4-diol **253** and (2*R*,3*S*,4*S*,6*R*)-2-Heptyl-6-(trifluoromethyl)-tetrahydro-2*H*-pyran-3,4-diol **253** (81 mg, 0.30 mmol, 1.00 eq.), pyridine (4.5 mL) and 4-dimethylaminopyridine (4 mg, 0.03 mmol, 0.1 eq.). The resulting solution was cooled to 0 °C and 4-nitrobenzoyl chloride (1.17 g, 6.28 mmol, 21.00 eq.) in dichloromethane (1.5 mL) was added dropwise. The resulting solution was warmed to room temperature and stirred for 24 hours. To this solution was added water (0.3 mL) and dichloromethane (90 mL) and the resulting mixture was washed with water (3 x 90 mL), a saturated aqueous solution of sodium hydrogen carbonate (90 mL), and water (90 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a yellow solid which was purified by flash column chromatography (90% hexane 10% ethyl acetate) to give the *title compound* **255** and **256** (120 mg, 2.06 mmol, 69%) as a yellow solid.

Data for **255**: M.p. 87-90 °C (mixture);  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  (mixture) 2927, 1736, 1608, 1530;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 8.38-8.32 (2H, m, ArH), 8.25-8.20 (2H, m, ArH), 8.20-8.14 (2H, m, ArH), 8.08-8.00 (2H, m, ArH), 5.99-5.94 (1H, m, H-C4), 5.08 (1H, dd,  $J$  10.1, 2.9, H-C3), 4.37-4.24 (1H, m, H-C6), 4.11-4.01 (1H, m, H-C2), 2.34-2.19 (2H, m, H-C5), 1.76-1.48 (2H, m, H-C7), 1.44-1.16 (10H, m, H-C8 to H-C12), 0.85 (3H, t,  $J$  6.7, H-C13);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 163.5 (C14), 163.4 (C15), 150.9 (ArC), 150.7 (ArC), 134.5 (ArC), 134.4 (ArC), 130.7 (ArC), 130.7 (ArC), 123.9 (ArC), 123.6 (ArC), 77.2 (C3), 74.5 (C2), 70.8 (q,  $J$  33.1, C6), 67.8 (C4), 31.7 (C11), 31.6 (C7), 29.5 (C5), 29.4 (C9), 29.1 (C10), 24.8 (C8), 22.6 (C12), 14.1 (C13);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -78.89 (d,  $J_{\text{H-F}}$  5.9);  $m/z$  (CI) (mixture) 600 ((M+NH<sub>4</sub>)<sup>+</sup>, 100), 540 (40), 404 (50); HRMS (EI) Found [M+H]<sup>+</sup> (mixture) 582.1816, C<sub>27</sub>H<sub>30</sub>F<sub>3</sub>N<sub>2</sub>O<sub>9</sub> requires 582.1820.

*Experimental*

Data for **256**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 8.38-8.33 (2H, m, ArH), 8.25-8.21 (2H, m, ArH), 8.20-8.14 (2H, m, ArH), 8.05-8.00 (2H, m, ArH), 5.64 (1H, d,  $J$  2.8, H-C3), 5.43 (1H, ddd,  $J$  10.2, 7.7, 2.8, H-C4), 4.09-4.02 (1H, m, H-C6), 3.77 (1H, dd,  $J$  7.7, 4.7, H-C2), 2.34-2.23 (2H, m, H-C5), 1.87-1.51 (2H, m, H-C7), 1.45-1.22 (10H, m, H-C8 to H-C12), 0.92-0.84 (3H, m, H-C13);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -79.13 (d,  $J_{\text{H-F}}$  5.7).

**(±)-(Z)-1,1,1-Trifluoro-5-(trimethylsilyl)pent-4-en-2-yl-4-methylbenzenesulfonate (257).**



$\text{C}_{15}\text{H}_{21}\text{F}_3\text{O}_3\text{SSi}$   
Mol. Wt.: 366.47

Following the general procedure A, (±)-(Z)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247** (3.50 g, 16.48 mmol) was consumed based on analysis by TLC after 20 hours of stirring at 0 °C. The work-up afforded a pale yellow oil, which was purified by flash column chromatography (75% hexane, 25% diethyl ether) to give the *title compound* **257** (3.01 g, 8.21 mmol, 50%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3036, 2956, 1960, 1815, 1599;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.79 (2H, d,  $J$  8.4, H-C7), 7.34 (2H, d,  $J$  8.4, H-C8), 6.12 (1H, td,  $J$  14.2, 7.2, H-C4), 5.69-5.62 (1H, m, H-C5), 4.94-4.82 (1H, m, H-C2), 2.66-2.58 (2H, m, H-C3), 2.45 (3H, s, H-C10), 0.08 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 145.4 (ArC), 138.4 (C4), 135.0 (ArC), 133.1 (C5), 129.8 (ArC), 128.0 (ArC), 76.6 (q,  $J$  32.7, C2), 32.3 (q,  $J$  1.3, C3), 21.7 (C10), -0.1 (CTMS);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -76.74 (d,  $J_{\text{H-F}}$  6.0);  $m/z$  (CI) 367 ( $\text{MH}^+$ , 100), 245 (65), 155 (40); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  384.1268,  $\text{C}_{15}\text{H}_{25}\text{F}_3\text{NO}_3\text{SSi}$  requires 384.1271.

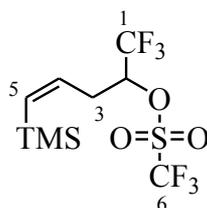
**General Procedure K: Triflate protection of an alcohol on 3.41 mmol scale.**

A round-bottomed flask was charged with pyridine (6.8 mL) and dichloromethane (25 mL). The mixture was stirred and cooled to 0 °C and trifluoromethanesulfonic anhydride (861  $\mu\text{l}$ , 5.12 mmol, 1.50 eq.) added dropwise followed by an alcohol derivative (3.41

*Experimental*

mmol, 1.00 eq.) in dichloromethane (3 mL). The resulting solution was stirred at 0 °C for 4 hours and 15% hydrochloric acid (10 mL) was added dropwise, followed by ice-water (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water until a neutral pH was reached and then dried over magnesium sulfate, filtered, and concentrated *in vacuo*.

**(±)-(Z)-1,1,1-Trifluoro-5-(trimethylsilyl)pent-4-en-2-yl trifluoromethanesulfonate (259).**

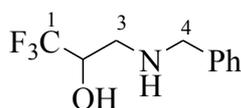


$C_9H_{14}F_6O_3SSi$   
Mol. Wt.: 344.35

Following the general procedure K, (±)-(Z)-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-ol **247** (724 mg, 3.41 mmol) afforded a pale pink oil, which was purified by flash column chromatography (75% hexane, 25% diethyl ether) to give the *title compound* **259** (774 mg, 2.25 mmol, 66%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2960, 1614, 840;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.19 (1H, td,  $J$  14.3, 7.2, H-C4), 5.95-5.87 (1H, m, H-C5), 5.09-4.98 (1H, m, H-C2), 2.84-2.75 (2H, m, H-C3), 0.15 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 137.4 (C4), 136.4 (C5), 122.1 (q,  $J$  254.4, C1), 81.1 (q,  $J$  34.0, C2), 32.1 (q,  $J$  0.9, C3), -0.2 (CTMS);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -74.56 (d,  $J_{\text{H-F}}$  3.0).

**(±)-3-(Benzylamino)-1,1,1-trifluoropropan-2-ol (260).**



$C_{10}H_{12}F_3NO$   
Mol. Wt.: 219.2

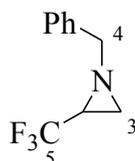
A round-bottomed flask was charged with benzylamine (2.08 g, 19.40 mmol, 0.97 eq.) and acetonitrile (5 mL). The resulting solution was stirred, cooled to 0 °C and (±)-2-(trifluoromethyl)oxirane **248** (1.72 mL, 20.00 mmol, 1.00 eq.) added dropwise. The

*Experimental*

mixture was warmed to room temperature and stirred for 48 hours, concentrated *in vacuo*, filtered and the precipitate washed with ice-cold hexane (20 mL). This gave the *title compound 260* (3.59 g, 16.40 mmol, 82%) as a white solid which was used in the next step without any further purification.

M.p. 94-96 °C (Lit.: 78°C in diethyl ether);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.38-7.22 (5H, m, Ar-H), 4.03-3.91 (1H, m, H-C2), 3.79 (2H, s, H-C3), 3.50 (2H, bs, H-OH and H-NH), 2.90 (1H, dd,  $J$  12.8, 6.9, H-C4), 2.83 (1H, dd,  $J$  12.8, 4.5, H-C4);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 138.6 (ArC), 128.7 (ArC), 128.2 (ArC), 127.5 (ArC), 124.9 (q,  $J$  282.1, C1), 67.6 (q,  $J$  30.6, C2), 53.6 (C4), 46.8 (q,  $J$  1.7, C3);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -78.95 (d,  $J_{\text{H-F}}$  7.1). Data in agreement with literature values.

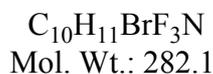
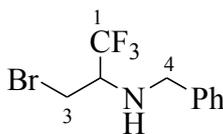
**(±)-1-Benzyl-2-(trifluoromethyl)aziridine (261).**



$\text{C}_{10}\text{H}_{10}\text{F}_3\text{N}$   
Mol Wt.: 201.19

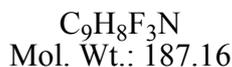
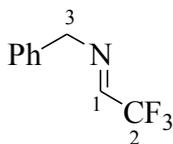
A round-bottomed flask equipped with a reflux condenser was charged with dichlorotriphenylphosphorane (4.39 g, 13.57 mmol, 1.00 eq.) and acetonitrile (3 mL). The resulting solution was stirred at room temperature and (±)-3-(benzylamino)-1,1,1-trifluoropropan-2-ol **260** (2.98 g, 13.57 mmol, 1.00 eq.) in acetonitrile (2 mL) added dropwise. The mixture was then heated at reflux temperature for 30 minutes and then cooled to 0 °C. To the mixture was added triethylamine (2.35 mL, 16.96 mmol, 1.25 eq.) dropwise and then the reaction mixture was slowly warmed to reflux temperature and stirred overnight. The mixture was then cooled to room temperature and concentrated *in vacuo*. This afforded a white solid, which was purified by distillation under reduced pressure (120 °C, 20 mmHg) to give the *title compound 261* (1.86 g, 9.23 mmol, 68%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.43-7.27 (5H, m, Ar-H), 4.00 (1H, d,  $J$  13.1, H-C4), 3.93 (1H, d,  $J$  13.1, H-C4), 3.78 (1H, dd,  $J$  11.9, 3.9, H-C3), 3.64 (1H, dd,  $J$  11.9, 6.4, H-C3), 3.45-3.33 (1H, m, H-C2);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -73.41 (d,  $J_{\text{H-F}}$  7.0);  $m/z$  (ES) 202 ( $\text{MH}^+$ , 100), 133 (30), 124 (18). Data in agreement with literature values.

**(±)-N-Benzyl-3-bromo-1,1,1-trifluoropropan-2-amine (262).**

A round-bottomed flask was charged with a 48% hydrobromic acid (3.70 mL, 33.67 mmol, 20.41 eq.) and the solution was cooled to 0 °C. To this was added (±)-1-benzyl-2-(trifluoromethyl)aziridine **261** (333 mg, 1.65 mmol, 1.00 eq.) dropwise, the mixture warmed to room temperature and stirred for 16 hours. After this, a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and diethyl ether (10 mL) was added. The organic layer was separated, the aqueous layer extracted with diethyl ether (2 x 10 mL), the combined organic layers dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a pale yellow oil which was purified by flash column chromatography (83% hexane 17% diethyl ether) to afford the *title compound* **262** (189 mg, 0.67 mmol, 41%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.46-7.27 (5H, m, Ar-H), 4.06 (1H, d,  $J$  13.1, H-C4), 3.98 (1H, d,  $J$  13.1, H-C4), 3.65 (1H, dd,  $J$  11.0, 3.8, H-C2), 3.56-3.38 (2H, m, H-C3), 1.94 (1H, bs, N-NH);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -68.89 (d,  $J_{\text{H-F}}$  6.6);  $m/z$  (ES) 283 ( $\text{MH}^+$ , 55), 282 (100), 204 (50). Data in agreement with literature values.

**(E)-Phenyl-N-(2,2,2-trifluoroethylidene)methanamine (263).**

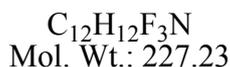
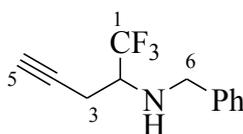
A round-bottomed flask equipped with a dropping funnel and a Dean and Stark distillation apparatus fitted with a reflux condenser was charged with a 90% aqueous solution of (±)-1-ethoxy-2,2,2-trifluoroethanol **187** (4.25 mL, 32.95 mmol, 1.00 eq.) and toluene (27 mL). The resulting solution was stirred at room temperature and benzylamine (3.53 g, 32.95 mmol, 1.00 eq.) was added dropwise. The mixture was then heated slowly to 140 °C for 2 hours so that the distillate was trapped and the aqueous layer separated. The mixture was then dried over 4Å molecular sieves, filtered and concentrated *in vacuo*.

### Experimental

This afforded a pale yellow oil, which was purified by distillation under reduced pressure (45 °C, 1.25 mmHg) to give the *title compound* **263** (3.93 g, 20.97 mmol, 64%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.61-7.55 (1H, m, H-C1), 7.36-7.25 (3H, m, Ar-H), 7.24-7.18 (2H, m, Ar-H), 4.77 (2H, s, H-C3);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 150.0 (q,  $J$  38.2, C1), 139.5 (ArC), 128.5 (ArC), 128.1 (ArC), 127.2 (ArC), 63.5 (C3);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -71.93 (d,  $J_{\text{H-F}}$  1.7). Data in agreement with literature values.

### (±)-*N*-Benzyl-1,1,1-trifluoropent-4-yn-2-amine (264).

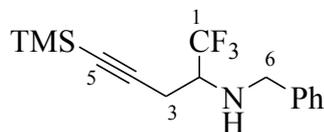


A round-bottomed flask was charged with (*E*)-phenyl-*N*-(2,2,2-trifluoroethylidene)methanamine **263** (2.00 g, 10.69 mmol, 1.00 eq.), an 80 % w/v solution of 3-bromoprop-1-yne in toluene (2.06 g, 13.92 mmol, 1.30 eq.) and *N,N*-dimethylformamide (19 mL). The resulting solution was cooled to 0 °C and coarse zinc powder (911 mg) added portionwise, followed by chlorotrimethylsilane (10 drops) dropwise. The resulting suspension was warmed to room temperature and stirred for 2 hours. The mixture was then cooled to 0 °C and a saturated aqueous solution of ammonium chloride (40 mL) was added dropwise followed by diethyl ether (40 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (60 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a yellow oil which was purified by flash column chromatography (90% hexane 10% ethyl acetate) to afford the *title compound* **264** (1.44 g, 6.35 mmol, 59%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.41-7.26 (5H, m, ArH), 4.04 (1H, dd,  $J$  13.2, 4.8, H-C6), 3.96 (1H, dd,  $J$  13.2, 4.4, H-C6), 3.34-3.19 (1H, m, H-C2), 2.65 (1H, ddd,  $J$  17.2, 4.6, 2.7, H-C3), 2.50 (1H, ddd,  $J$  17.2, 7.6, 2.7, H-C3), 2.07 (1H, t,  $J$  2.7), 1.82 (1H, bs, H-NH);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 139.1 (ArC), 128.5 (ArC), 128.3 (ArC), 127.4 (ArC), 78.6 (C4), 71.3 (C5), 57.42 (q,  $J$  28.0, C2), 52.38 (C6), 19.85 (q,  $J$  3.0, C3);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -75.12 (d,

$J_{H-F}$  7.0);  $m/z$  (CI) 228 ( $MH^+$ , 100), 188 (82), 158 (34). Data in agreement with literature values.

**(±)-*N*-Benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-yn-2-amine (265).**



$C_{15}H_{20}F_3NSi$   
Mol. Wt.: 299.41

Following the general procedure O, (±)-*N*-benzyl-1,1,1-trifluoropent-4-yn-2-amine **264** (1.44 g, 6.35 mmol) afforded a yellow oil, which was purified by flash column chromatography (95% hexane, 5% ethyl acetate) to give the *title compound* **265** (1.24 g, 4.13 mmol, 65%) as a colourless oil.

$\nu_{max}$ (neat)/ $cm^{-1}$  3352, 3089, 2960, 2181, 1924, 1890;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.33-7.14 (5H, m, ArH), 3.84 (1H, d,  $J$  13.1, H-C6), 3.76 (1H, d,  $J$  13.1, H-C6), 3.24-3.10 (1H, m, H-C2), 2.60 (1H, dd,  $J$  17.3, 4.3, H-C3), 2.43 (1H, dd,  $J$  17.3, 8.5, H-C3), 1.72 (1H, bs, H-NH), 0.09 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 139.2 (ArC), 128.5 (ArC), 128.3 (ArC), 127.3 (ArC), 100.9 (C5), 88.1 (C4), 57.19 (q,  $J$  28.0, C2), 52.21 (C6), 20.76 (q,  $J$  3.0, C3), -0.1 (CTMS);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -75.36 (d,  $J_{H-F}$  6.9);  $m/z$  (CI) 300 ( $MH^+$ , 100), 226 (44), 188 (43); HRMS (ES) Found  $[M+H]^+$  300.1380,  $C_{15}H_{21}F_3NSi$  requires 300.1390.

**(±)-(*Z*)-*N*-Benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine (258) and (±)-(*E*)-*N*-Benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine (266).**



$C_{15}H_{22}F_3NSi$   
Mol. Wt.: 301.42

Following the general procedure H, *N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-yn-2-amine **265** (0.62 g, 2.07 mmol) afforded a yellow oil, which was purified by flash column chromatography (98% hexane, 1% ethyl acetate, 1% triethylamine) to give the *title compound* **258** and **266** (280 mg, 0.93 mmol, 45%) as a colourless oil.

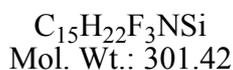
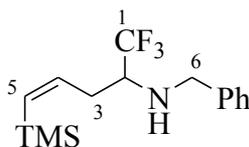
### Experimental

Data for **266**:  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  (mixture) 3359, 3091, 2956, 1924, 1889, 1607;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.36-7.23 (5H, m, ArH), 5.89-5.78 (2H, m, H-C4 and H-C5), 3.99 (1H, d,  $J$  13.3, H-C6), 3.82 (1H, d,  $J$  13.3, H-C6), 3.19-3.02 (1H, m, H-C2), 2.60-2.48 (1H, m, H-C3), 2.25 (1H, ddd,  $J$  14.5, 9.7, 6.7, H-C3), 0.07 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 140.7 (C4), 139.5 (ArC), 135.6 (C5), 128.5 (ArC), 128.3 (ArC), 127.3 (ArC), 57.4 (q,  $J$  27.4, C2), 52.2 (C6), 36.1 (q,  $J$  2.1, C3), -1.4 (CTMS);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -75.21 (d,  $J_{\text{H-F}}$  7.2);  $m/z$  (CI) 302 ( $\text{MH}^+$ , 100), 228 (40), 188 (55); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  (mixture) 302.1548,  $\text{C}_{15}\text{H}_{23}\text{F}_3\text{NSi}$  requires 302.1546.

Data for **258**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.38-7.22 (5H, m, ArH), 6.25-6.14 (1H, m, H-C4), 5.73-5.67 (1H, m, H-C5), 4.01 (1H, d,  $J$  13.3, H-C6), 3.83 (1H, d,  $J$  13.3, H-C6), 3.17-3.03 (1H, m, H-C2), 2.58-2.48 (1H, m, H-C3), 2.32 (1H, dddd,  $J$  14.8, 9.5, 8.0, 1.2, H-C3), 0.12 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 142.3 (C4), 139.5 (ArC), 133.7 (C5), 128.4 (ArC), 128.2 (ArC), 127.2 (ArC), 58.2 (q,  $J$  27.3, C2), 52.3 (C6), 32.5 (q,  $J$  2.1, C3), 0.1 (CTMS);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -75.09 (d,  $J_{\text{H-F}}$  7.1);  $m/z$  (CI) 302 ( $\text{MH}^+$ , 64), 228 (25), 188 (100).

### General procedure L: hydrotitanation of alkynylsilanes on 3.57 mmol scale.

A three-necked flask fitted with a dropping funnel and a thermometer, was charged with an alkynylsilane (3.57 mmol, 1.00 eq.) and diethyl ether (70 mL). The solution was then cooled to  $-78\text{ }^{\circ}\text{C}$  before adding dropwise titanium(IV) isopropoxide (5.36 mL, 18.11 mmol, 5.07 eq.), and a 2.0 M solution of isopropylmagnesium chloride in diethyl ether (18.12 mL, 36.19 mmol, 10.13 eq.). The resulting solution was then warmed slowly to  $-60\text{ }^{\circ}\text{C}$  until GCMS showed complete consumption of starting material. To this solution was added dropwise, a saturated aqueous solution of ammonium chloride (150 mL) and ethyl acetate (150 mL) and the reaction mixture was slowly warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*.

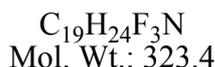
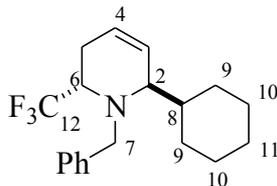
**(±)-(Z)-N-Benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine (258).**

Following the general procedure L, *N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **265** (22 mg, 0.073 mmol) afforded a yellow oil, which was purified by flash column chromatography (95% hexane, 5% ethyl acetate) to give the *title compound* **258** (11 mg, 0.037 mmol, 51%) as a colourless oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3359, 2958, 1924, 1889, 1607; HRMS (ES) Found  $[\text{M}+\text{H}]^+$  302.1548,  $\text{C}_{15}\text{H}_{23}\text{F}_3\text{NSi}$  requires 302.1546.

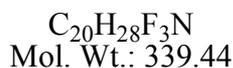
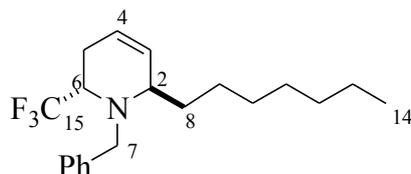
**General procedure M: the Aza-silyl-Prins reaction on 0.70 mmol scale.** Unless otherwise stated, a round-bottomed flask equipped, with a condenser, was charged with indium trichloride (145 mg, 0.70 mmol, 1.00 eq.), an aldehyde derivative (0.70 mmol, 1.00 eq.) and acetonitrile (2.5 mL). The resulting suspension was stirred at room temperature for 15 minutes and a solution of a homoallylic amine (0.70 mmol, 1.00 eq.) in acetonitrile (1 mL) was added dropwise. The reaction was then heated to reflux temperature. Once TLC showed full consumption of the starting material, the solution was cooled to room temperature, poured into dichloromethane (5 mL), 1.0 M aqueous sodium hydroxide (5 mL) added and the resulting biphasic solution stirred for a further 30 minutes at room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*.

(±)-*trans*-1-Benzyl-2-cyclohexyl-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine  
(**267a**).



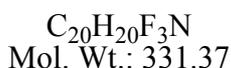
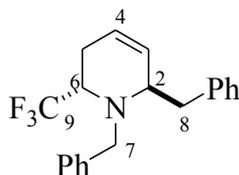
Following the general procedure M, A 1:1 mixture of (±)-(*Z*)-*N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **258** and (±)-(*E*)-*N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **266** (150 mg, 0.50 mmol), in the presence of cyclohexanecarbaldehyde (56 mg, 0.50 mmol), was consumed based on analysis by TLC after 48 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (99% hexane 1% ethyl acetate) to give the *title compound* **267a** (24 mg, 0.07 mmol, 15%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3032, 2925, 1604;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.37-7.19 (5H, m, ArH), 5.92-5.84 (1H, m, H-C4), 5.83-5.76 (1H, m, H-C3), 3.94 (1H, d,  $J$  13.7, H-C7), 3.64-3.50 (1H, m, H-C6), 3.48 (1H, d,  $J$  13.7, H-C7), 2.66-2.59 (1H, m, H-C2), 2.45-2.32 (1H, m, H-C5), 2.17-2.05 (1H, m, H-C5), 2.06-1.95 (1H, m, H-C9), 1.75-1.53 (3H, m, H-C9), 1.49-1.31 (1H, m, H-C8), 1.22-0.94 (3H, m, H-C9), 0.93-0.70 (2H, m, H-C9 and H-C10), 0.62-0.44 (1H, m, H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 139.4 (ArC), 129.1 (C3), 128.3 (ArC), 128.0 (ArC), 126.8 (ArC), 123.5 (C4), 62.8 (C2), 54.7 (q,  $J$  29.4, C6), 51.8 (q,  $J$  2.2, C7), 41.6 (C8), 30.3 (C9), 29.7 (C9), 26.4 (C11), 26.2 (C10), 26.1 (C10), 20.2 (q,  $J$  1.6, C5);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -70.2 (d,  $J_{\text{H-F}}$  8.9);  $m/z$  (CI) 324 ( $\text{MH}^+$ , 43), 240 (100), 133 (43); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  324.1931,  $C_{19}H_{25}F_3N$  requires 324.1934.

**(±)-trans-1-Benzyl-2-heptyl-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (267b).**

Following the general procedure M, A 1:1 mixture of (±)-(Z)-N-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **258** and (±)-(E)-N-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **266** (92 mg, 0.43 mmol), in the presence of octanal (43 mg, 0.14 mmol), was consumed based on analysis by TLC after 48 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (99% hexane 1% ethyl acetate) to give the *title compound* **267b** (63 mg, 0.18 mmol, 43%) as a colourless oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3032, 2955, 1741;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.39-7.20 (5H, m, ArH), 5.86-5.78 (1H, m, H-C4), 5.69-5.60 (1H, m, H-C3), 3.93 (1H, d,  $J$  13.8, H-C7), 3.58 (1H, d,  $J$  13.8, H-C7), 3.56-3.46 (1H, m, H-C6), 3.07 (1H, s, H-C2), 2.45-2.28 (1H, m, H-C5), 2.20-2.08 (1H, m, H-C5), 1.47-1.35 (2H, m, H-C8), 1.33-1.19 (4H, m, H-C9 and H-C10), 1.20-0.95 (6H, m, H-C11 to H-C13), 0.86 (3H, t,  $J$  6.9, H-C14);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 139.4 (ArC), 130.1 (C2), 128.8 (ArC), 128.1 (ArC), 126.9 (ArC), 122.8 (C4), 57.2 (C2), 54.5 (q,  $J$  26.1, C6), 52.0 (q,  $J$  2.2, C7), 33.5 (C8), 31.8 (C12), 29.3 (C10), 29.2 (C11), 25.4 (C9), 22.6 (C13), 21.2 (q,  $J$  1.7, C5), 14.1 (C14);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -69.60 (d,  $J_{\text{H-F}}$  9.0);  $m/z$  (CI) 340 ( $\text{MH}^+$ , 55), 240 (100), 133 (50); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  340.2247,  $\text{C}_{20}\text{H}_{29}\text{F}_3\text{N}$  requires 340.2247.

**(±)-trans-1,2-Dibenzyl-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (267c).**

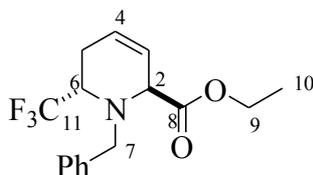
Following the general procedure M, A 1:1 mixture of (±)-(Z)-N-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **258** and (±)-(E)-N-benzyl-1,1,1-trifluoro-5-

*Experimental*

(trimethylsilyl)pent-4-en-2-amine **266** (29 mg, 0.09 mmol), in the presence of phenylacetaldehyde (12 mg, 0.09 mmol), was consumed based on analysis by TLC after 48 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (99% hexane 1% ethyl acetate) to give the *title compound* **267c** (16 mg, 0.05 mmol, 50%) as a yellow oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3028, 2924, 1889, 1729;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.22-6.96 (10H, m, Ar-H), 5.92-5.79 (1H, m, H-C4), 5.65-5.57 (1H, m, H-C3), 3.95 (1H, d,  $J$  14.1, H-C7), 3.73-3.60 (1H, m, H-C6), 3.61 (1H, d,  $J$  14.1, H-C7), 3.33-3.24 (1H, m, H-C2), 2.84 (1H, dd,  $J$  13.5, 7.5, H-C8), 2.63 (1H, dd,  $J$  13.5, 6.9, H-C8), 2.48-2.26 (1H, m, H-C5), 2.24-2.10 (1H, m, H-C5);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -69.59 (d,  $J_{\text{H-F}}$  8.9);  $m/z$  (CI) 332 ( $\text{MH}^+$ , 100), 240 (70), 133 (36); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  332.1618,  $\text{C}_{20}\text{H}_{21}\text{F}_3\text{N}$  requires 332.1621.

**(±)-*trans*-Ethyl-1-benzyl-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate (267d).**



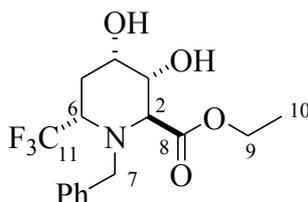
$\text{C}_{16}\text{H}_{18}\text{F}_3\text{NO}_2$   
Mol. Wt.: 313.31

Following the general procedure M, A 1:1 mixture of (±)-(*Z*)-*N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **258** and (±)-(*E*)-*N*-benzyl-1,1,1-trifluoro-5-(trimethylsilyl)pent-4-en-2-amine **266** (150 mg, 0.50 mmol), in the presence of a pre-heated 38% solution of ethyl 2-oxoacetate in toluene (127 mg, 0.50 mmol, 1.00 eq.), was consumed based on analysis by TLC after 17 hours of stirring at reflux temperature. The work-up gave a yellow oil, which was purified by flash column chromatography (95% hexane 5% ethyl acetate) to give the *title compound* **267d** (101 mg, 0.32 mmol, 65%) as a pale yellow oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3031, 2928, 1748, 1668;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.47-7.40 (2H, m, Ar-H), 7.37-7.22 (2H, m, Ar-H), 7.20-7.14 (1H, m, Ar-H), 6.01-5.82 (1H, m, H-C3), 5.79-5.72 (1H, m, H-C4), 4.24-4.13 (2H, m, H-C9), 4.14-4.07 (1H, m, H-C2), 3.97 (1H, d,  $J$  13.5, H-C7), 3.81 (1H, d,  $J$  13.5, H-C7), 3.71-3.57 (1H, m, H-C6), 2.54-2.18 (2H, m, H-C5), 1.26 (3H, t,  $J$  7.1, H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 171.8 (C8), 137.7 (ArC), 128.9 (C3), 128.4 (ArC), 127.4 (ArC), 125.1 (ArC), 123.7 (C4), 61.1 (C2), 58.5 (C9), 54.5 (q,  $J$  1.8,

C7), 53.3 (q,  $J$  27.8, C6), 23.3 (q,  $J$  2.1, C5), 14.2 (C10);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -68.20 (d,  $J_{H-F}$  8.6);  $m/z$  (CI) 314 ( $MH^+$ , 96), 240 (100), 133 (40); HRMS (ES) Found  $[M+H]^+$  314.1363,  $C_{16}H_{19}F_3NO_2$  requires 314.1362.

**(2*S*\*,3*R*\*,4*S*\*,6*S*\*)-Ethyl-1-benzyl-3,4-dihydroxy-6-(trifluoromethyl)piperidine-2-carboxylate (271).**



$C_{16}H_{20}F_3NO_4$   
Mol. Wt.: 347.33

Following the general procedure J, ( $\pm$ )-*trans*-ethyl-1-benzyl-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-2-carboxylate **267d** (64 mg, 0.20 mmol) afforded the *title compound* **271** (58 mg, 0.17 mmol, 83%) as a pale yellow oil which was used in the next step without any further purification.

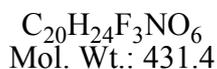
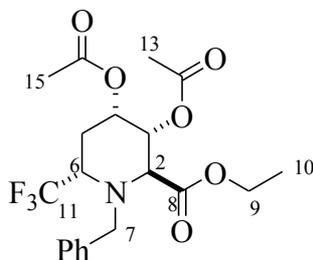
$\nu_{max}$ (neat)/ $cm^{-1}$  3393, 2955, 2854, 1732;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.40-7.24 (5H, m, ArH), 4.20 (2H, ddd,  $J$  14.0, 6.9, 3.7, H-C9), 4.19-4.13 (1H, m, H-C3), 4.10-4.03 (1H, m, H-C6), 4.01 (1H, d,  $J$  13.0, H-C7), 3.82 (1H, d,  $J$  13.0, H-C7), 3.74-3.68 (1H, m, H-C4), 3.70-3.64 (1H, m, H-C2), 2.06-1.93 (1H, m, H-C5), 1.84-1.68 (1H, m, H-C5), 1.32-1.25 (3H, m, H-C10);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -69.39 (d,  $J_{H-F}$  7.1);  $m/z$  (CI) 346 ( $(M-H)^+$ , 5), 304 (100), 214 (7).

**General procedure N: di-acetylation of diols on 0.06 mmol scale.**

A round-bottomed flask was charged with a diol derivative (0.06 mmol, 1.00 eq.) and dichloromethane (300  $\mu$ L) and the resulting solution stirred at room temperature. Acetic anhydride (27  $\mu$ L, 0.29 mmol, 5.00 eq.) was added dropwise, followed by 4-dimethylaminopyridine (1 mg, 0.006 mmol, 0.10 eq.) in one portion and the reaction was allowed to stir for 24 hours at room temperature. After this time, the reaction was quenched by adding a saturated solution of sodium hydrogen carbonate (2 mL), dichloromethane (2 mL) was added and the resulting biphasic solution stirred for 15 minutes at room temperature. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 2 mL). The combined organic layers were washed

with a saturated solution of sodium chloride (4 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*.

**(2*S*\*,3*R*\*,4*S*\*,6*S*\*)-Ethyl-3,4-diacetoxy-1-benzyl-6-(trifluoromethyl)piperidine-2-carboxylate (**272**).**

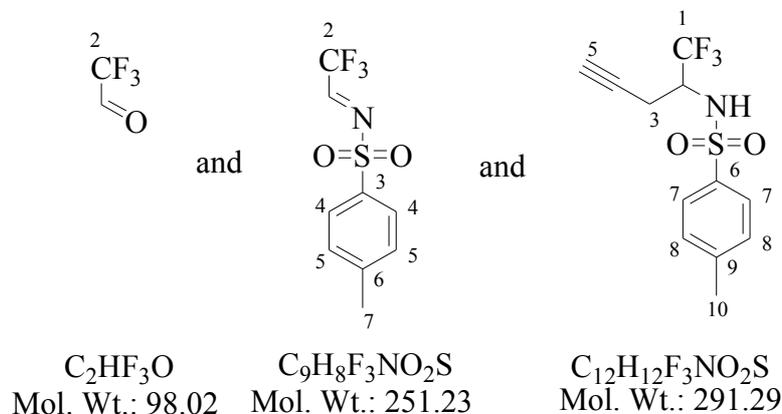


Following the general procedure N, (2*S*,3*R*,4*S*,6*S*)-ethyl-1-benzyl-3,4-dihydroxy-6-(trifluoromethyl)piperidine-2-carboxylate **271** and (2*R*,3*S*,4*R*,6*R*)-ethyl-1-benzyl-3,4-dihydroxy-6-(trifluoromethyl)piperidine-2-carboxylate **271** (20 mg, 0.06 mmol) afforded a yellow oil, which was purified by preparative TLC (90% hexane, 10% ethyl acetate) to give the *title compound* **272** (13 mg, 0.03 mmol, 50%) as a pale yellow solid.

M.p. 84-86 °C;  $\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3030, 2926, 1791, 1749;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.32-7.24 (5H, m, Ar-H), 5.36-5.32 (1H, m, H-C3), 5.02 (1H, ddd,  $J$  10.7, 4.4, 3.2, H-C4), 4.28-4.14 (2H, m, H-C9), 4.14 (1H, d,  $J$  14.3, H-C7), 4.04-3.93 (1H, m, H-C6), 3.74-3.72 (1H, m, H-C2), 3.74 (1H, d,  $J$  14.3, H-C7), 2.19-2.04 (2H, m, H-C5), 2.03 (3H, s, H-C13), 1.96 (3H, s, H-C15), 1.22 (3H, t,  $J$  7.2, H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 169.9 (C12), 169.9 (C14), 169.6 (C8), 137.7 (ArC), 128.4 (ArC), 128.3 (ArC), 127.6 (ArC), 67.9 (C3), 66.7 (C4), 61.4 (C2), 61.2 (C9), 60.4 (C7), 53.9 (C6), 25.6 (q,  $J$  2.4, C5), 20.8 (C13 and C15), 14.2 (C10);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -68.61 (d,  $J_{\text{H-F}}$  6.8);  $m/z$  (CI) 432 ( $\text{MH}^+$ , 100), 358 (30), 298 (62); HRMS(ES) Found  $[\text{M}+\text{H}]^+$  432.1626,  $\text{C}_{20}\text{H}_{25}\text{F}_3\text{NO}_6$  requires 432.1628.

*Experimental*

**2,2,2-Trifluoroacetaldehyde (535) and (E)-4-Methyl-N-(2,2,2-trifluoroethylidene)benzenesulfonamide (273) and (±)-4-Methyl-N-(1,1,1-trifluoropent-4-yn-2-yl)benzenesulfonamide (274).**



A round-bottomed flask was equipped with a dropping funnel and a reflux condenser fitted with a collection flask immersed in a  $-78\text{ }^\circ\text{C}$  cold bath. The flask was charged with a 90% aqueous solution of (±)-1-ethoxy-2,2,2-trifluoroethanol **187** (3.3 mL, 25.58 mmol, 2.19 eq.) and heated to  $80\text{ }^\circ\text{C}$ . To this solution was added a 98% sulphuric acid (6.2 mL) dropwise and the mixture stirred for 30 minutes at  $80\text{ }^\circ\text{C}$ . This process produced a grey gas, which was condensed to afford the *title compound* **535** as a colourless oil which was used in the next step immediately. A sealed vessel was charged with 4-methylbenzenesulfonamide (2.00 g, 11.70 mmol, 1.00 eq.), tetrahydrofuran (10 mL) and pyridine (45  $\mu\text{L}$ ). The resulting solution was stirred at room temperature and an excess amount of 2,2,2-trifluoroacetaldehyde **535** added dropwise. The vessel was sealed and stirred at room temperature for 48 hours. The mixture was concentrated *in vacuo* and thionyl chloride (2 mL) and benzene (5 mL) added. A reflux condenser was fitted to the flask and the mixture heated at reflux temperature for 5 hours. The mixture was concentrated *in vacuo* to afford the *title compound* **273** (2.64 g, 10.55 mmol, 90%) as a sticky yellow oil which was used in the next step immediately. A round-bottomed flask was charged with (E)-4-methyl-N-(2,2,2-trifluoroethylidene)benzenesulfonamide **273** (2.64 g, 10.55 mmol, 1.00 eq.), a 80 % w/v solution of 3-bromoprop-1-yne in toluene (2.06 g, 13.76 mmol, 1.30 eq.) and *N,N*-dimethylformamide (19 mL). The resulting solution was cooled to  $0\text{ }^\circ\text{C}$  and coarse zinc powder (899 mg) was added portionwise, followed by chlorotrimethylsilane (4 drops) dropwise. The resulting suspension was warmed to room temperature and stirred for 2 hours. The mixture was then cooled to  $0\text{ }^\circ\text{C}$  and a saturated aqueous solution of ammonium chloride (40 mL) was added dropwise

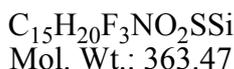
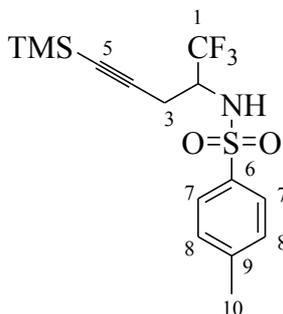
*Experimental*

followed by diethyl ether (40 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (60 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a yellow oil which was purified by flash column chromatography (90% hexane 10% ethyl acetate) to afford the *title compound 274* (757 mg, 2.60 mmol, 22%) as a white solid.

M.p. 108-111 °C;  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3296, 3296, 3043, 2930, 2359, 1598;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.77 (2H, d,  $J$  8.4, H-C7), 7.31 (2H, d,  $J$  8.4, H-C8), 5.30 (1H, d,  $J$  9.9, H-NH), 4.11-3.99 (1H, m, H-C2), 2.57 (2H, dd,  $J$  5.4, 2.7, H-C3), 2.43 (3H, s, H-C10), 2.04 (1H, t,  $J$  2.7, H-C5);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 144.1 (C9), 137.2 (C6), 129.7 (C8), 127.1 (C7), 76.0 (C4), 73.0 (C5), 52.9 (q,  $J$  31.4, C2), 21.6 (C10), 19.9 (q,  $J$  2.3, C3);  $\delta_{\text{F}}$  (282 MHz,  $\text{CDCl}_3$ ) -75.43 (d,  $J_{\text{H-F}}$  6.9);  $m/z$  (CI) 292 ( $\text{MH}^+$ , 100), 252 (13), 138 (34); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  309.0881,  $\text{C}_{12}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2\text{S}$  requires 309.0879.

**General procedure O: alkyne silylation on 25.00 mmol scale.** To a stirred solution of an alkyne derivative (25.00 mmol, 1.00 eq.) in tetrahydrofuran (40 mL) at  $-78$  °C was added dropwise, a 2.5 M solution of *n*-butyllithium in hexane (20 mL, 50.00 mmol, 2.00 eq.) over 30 minutes. The resulting solution was stirred at  $-78$  °C for a further 1 hour and 30 minutes. After this time, trimethylsilyl chloride (6.35 mL, 50.00 mmol, 2.00 eq.) was added dropwise to the solution, the cold bath removed and the reaction stirred for 1 hour while being allowed to warm to room temperature. A 1.0 M solution of hydrochloric acid (50 mL) was then added and the reaction was stirred at room temperature for a further 45 minutes. The aqueous layer was then extracted with diethyl ether (3 x 25 mL), the combined organic layers were washed with ice cold water (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*.

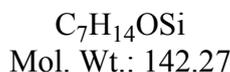
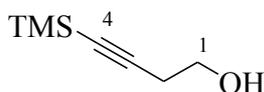
(±)-4-Methyl-*N*-(1,1,1-trifluoro-5-(trimethylsilyl)pent-4-yn-2-yl)benzenesulfonamide (275).



Following the general procedure O, (±)-4-methyl-*N*-(1,1,1-trifluoropent-4-yn-2-yl)benzenesulfonamide **274** (857 mg, 2.94 mmol) afforded a brown oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound* **275** (485 g, 1.33 mmol, 45%) as a white solid.

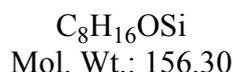
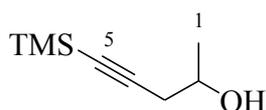
M.p. 128-129 °C;  $\nu_{\max}$ (nujol)/ $cm^{-1}$  3314, 3278, 2954;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 7.77 (2H, d,  $J$  8.3, H-C7), 7.32 (2H, d,  $J$  8.3, H-C8), 5.10 (1H, d,  $J$  9.7, H-NH), 4.08-3.94 (1H, m, H-C2), 2.62-2.58 (2H, m, H-C3), 2.44 (3H, s, H-C10), 0.17 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 144.1 (C9), 137.2 (C6), 129.8 (C8), 127.0 (C7), 99.9 (C5), 97.6 (C4), 53.0 (q,  $J$  32.5, C2), 21.6 (C10), 21.4 (q,  $J$  2.0, C3), -0.2 (CTMS);  $\delta_F$  (282 MHz,  $CDCl_3$ ) -75.18 (d,  $J_{H-F}$  6.9);  $m/z$  (CI) 364 ( $MH^+$ , 100), 209 (35), 125 (44); HRMS (ES) Found  $[M+NH_4]^+$  381.1273,  $C_{15}H_{24}F_3N_2O_2SSi$  requires 381.1274.

4-(Trimethylsilyl)but-3-yn-1-ol (250).



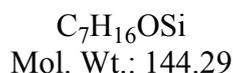
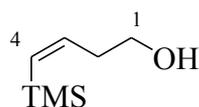
Following the general procedure O, 3-butyn-1-ol **248** (1.75 g, 25.00 mmol) gave a pale yellow oil, which was purified by distillation under reduced pressure (29 °C, 0.2 mmHg) to give the *title compound* **250** (2.16 g, 14.90 mmol, 61%) as a colourless oil.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 3.73 (2H, t,  $J$  9.2, H-C1), 2.52 (2H, t,  $J$  9.2, H-C2), 1.31 (1H, bs, H-OH), 0.17 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 103.2 (C3), 87.0 (C4), 60.8 (C1), 24.2 (C2), 0.0 (CTMS). Data in agreement with literature values.

**(±)-5-Trimethylsilyl-4-pentyn-2-ol (251).**

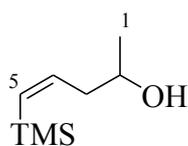
Following the general procedure O, (±)-4-pentyn-2-ol **249** (2.10 g, 25.00 mmol) gave a pale yellow oil, which was purified by distillation under reduced pressure (70°C, 5 mmHg) to give the *title compound* **251** (3.10 g, 19.27 mmol, 79%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 3.99-3.89 (1H, m, H-C2), 2.44 (1H, dd,  $J$  5.1, 16.8, H-C3), 2.35 (1H, dd,  $J$  6.6, 16.8, H-C3), 1.82 (1H, bs, H-OH), 1.26 (3H, d,  $J$  6.0, H-C1), 0.16 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 103.3 (C4), 87.7 (C5), 66.2 (C2), 30.4 (C3), 22.2 (C1), 0.0 (CTMS). Data in agreement with literature values.

**(Z)-4-Trimethylsilyl-3-buten-1-ol (252).**

Following the general procedure H, 4-trimethylsilyl-3-buten-1-ol **249** (2.12 g, 14.90 mmol) afforded a pale yellow oil, which was purified by distillation under reduced pressure (64 °C, 0.7 mmHg) to give the *title compound* **252** (1.39 g, 9.62 mmol, 65%) as a colourless oil.

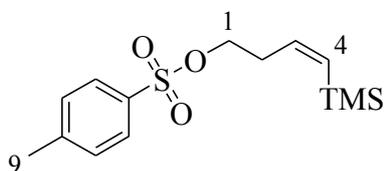
$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.30 (1H, td,  $J$  7.5, 15.0, H-C3), 5.70 (1H, d,  $J$  15.0, H-C4), 3.69 (2H, t,  $J$  7.5, H-C1), 2.42 (2H, dt,  $J$  7.5, 7.5, H-C2), 1.43 (1H, bs, H-OH), 0.14 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.9 (C3), 132.8 (C4), 61.9 (C1), 36.4 (C2), 0.0 (CTMS). Data in agreement with literature values.

**(±)-(Z)-5-Trimethylsilyl-4-penten-2-ol (253).**

$C_8H_{18}OSi$   
Mol. Wt.: 158.31

Following the general procedure H, (±)-5-trimethylsilyl-4-pentyn-2-ol **251** (3.01 g, 19.27 mmol) gave a pale yellow oil, which was purified by distillation under reduced pressure (24 °C, 0.15 mmHg) to give the *title compound* **253** (2.00 g, 12.64 mmol, 66%) as a colourless oil.

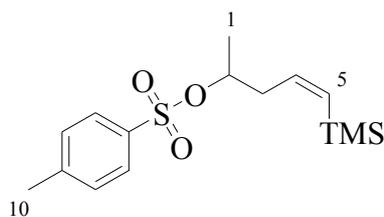
$\delta_H$  (300 MHz;  $CDCl_3$ ) 6.33 (1H, ddd,  $J$  7.0, 7.0, 14.1, H-C4), 5.70 (1H, ddd,  $J$  1.2, 1.2, 14.1, H-C5), 3.91-3.82 (1H, m, H-C2), 2.33-2.28 (2H, m, H-C3), 1.54 (1H, bs, H-OH), 1.23 (3H, d,  $J$  6.2, H-C1), 0.14 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 144.2 (C4), 132.8 (C5), 67.5 (C2), 43.0 (C3), 22.9 (C1), 0.3 (CTMS). Data in agreement with literature values.

**(Z)-4-(Trimethylsilyl)but-3-enyl 4-methylbenzenesulfonate (254).**

$C_{14}H_{22}O_3SSi$   
Mol. Wt.: 298.47

Following the general procedure A, (Z)-4-trimethylsilyl-3-buten-1-ol **252** (1.39g, 9.62 mmol) gave after 5 hours of stirring, a yellow oil which was purified by flash column chromatography (90% petroleum ether 10% ethyl acetate) to give the *title compound* **254** (2.50 g, 8.39 mmol, 87%) as a colourless oil.

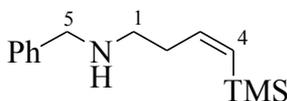
$\delta_H$  (300 MHz;  $CDCl_3$ ) 7.80 (2H, d,  $J$  8.3, H-C6), 7.36 (2H, d,  $J$  8.3, H-C7) 6.12 (1H, td,  $J$  7.2, 14.4, H-C3), 5.65 (1H, td,  $J$  1.3, 14.3, H-C4), 4.04 (2H, t,  $J$  7.2, H-C1), 2.48 (2H, ddt,  $J$  1.3, 7.2, 7.2 H-C2), 2.45 (3H, s, H-C9), 0.07 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 144.9 (C8), 141.2 (C3), 133.8 (C4), 133.1 (C5), 129.8 (C7), 127.9 (C6), 69.5 (C1), 32.7 (C2), 21.7 (C9), 0.0 (CTMS). Data in agreement with literature values.

**(±)-(Z)-5-(Trimethylsilyl)pent-4-en-2-yl 4-methylbenzenesulfonate (255).**

C<sub>15</sub>H<sub>24</sub>O<sub>3</sub>SSi  
Mol. Wt.: 312.5

Following the general procedure A, (±)-(Z)-5-trimethylsilyl-4-penten-2-ol **253** (2.00 g, 12.64 mmol) gave after overnight stirring a yellow oil which was purified by flash column chromatography (90% petroleum ether 10% ethyl acetate) to give the *title compound* **255** (2.26 g, 7.23 mmol, 57%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.80 (2H, d,  $J$  8.1, H-C7), 7.34 (2H, d,  $J$  8.1, H-C8), 6.07 (1H, ddd,  $J$  7.0, 7.0, 14.1, H-C4), 5.57 (1H, d,  $J$  14.1, H-C5), 4.66-4.60 (1H, m, H-C2), 2.51-2.30 (2H, m, H-C3), 2.45 (3H, s, H-C10), 1.28 (3H, d,  $J$  6.4, H-C1), 0.07 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 144.6 (C9), 141.3 (C4), 133.2 (C6), 132.2 (C5), 129.7 (C8), 127.8 (C7), 79.5 (C2), 40.8 (C3), 21.6 (C10), 20.4 (C1), 0.0 (CTMS). Data in agreement with literature values.

**(Z)-N-Benzyl-4-(trimethylsilyl)but-3-en-1-amine (256).**

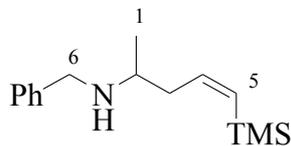
C<sub>14</sub>H<sub>23</sub>NSi  
Mol. Wt.: 233.42

Following the general procedure B, (±)-(Z)-4-(trimethylsilyl)but-3-enyl(4-methylbenzene)sulfonate **254** (2.50 g, 8.39 mmol), in the presence of benzylamine (4.50 g, 41.95 mmol), was consumed based on analysis by TLC after 5 hours of stirring and heating. The excess of benzylamine was distilled (50 °C, 2 mmHg) and the work-up gave a yellow oil, which was purified by flash column chromatography (90% petroleum ether 9% ethyl acetate 1% triethylamine) to give the *title compound* **256** (1.53 g, 6.56 mmol, 78%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.39-7.23 (5H, m, ArH), 6.30 (1H, td,  $J$  7.0, 14.1, H-C3), 5.60 (1H, td,  $J$  1.2, 14.1, H-C4) 3.81 (2H, s, H-C5), 2.72 (2H, t,  $J$  7.0, H-C1), 2.37 (2H, ddt,  $J$  1.2, 7.0, 7.0 H-C2), 1.34 (1H, bs, H-NH) 0.13 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 145.8

(C3), 140.5 (ArC), 131.1 (C4), 128.2 (ArC), 127.9 (ArC), 126.8 (ArC), 53.6 (C5), 48.7 (C1), 33.6 (C2), 0.0 (CTMS). Data in agreement with literature values.

**(Z)-N-Benzyl-5-(trimethylsilyl)pent-4-en-2-amine (257).**

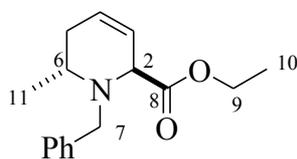


$C_{15}H_{25}NSi$   
Mol. Wt.: 247.45

Following the general procedure B, ( $\pm$ )-(Z)-5-(trimethylsilyl)pent-4-en-2-yl(4-methylbenzene)sulfonate **255** (2.26 g, 7.23 mmol), in the presence of benzylamine (3.88 g, 36.15 mmol), was consumed based on analysis by TLC after 5 hours of stirring and heating. The excess of benzylamine was distilled (50 °C, 2 mmHg) and the work-up gave a yellow oil, which was purified by flash column chromatography (90% petroleum ether 9% ethyl acetate 1% triethylamine) to give the *title compound* **257** (1.92 g, 7.74 mmol, 100 %) as a colourless oil.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 7.39-7.24 (5H, m, ArH), 6.29 (1H, ddd,  $J$  7.1, 7.1, 14.2, H-C4), 5.63 (1H, ddd,  $J$  1.4, 1.4, 14.2, H-C5), 3.90 (1H, d,  $J$  13.2, H-C6), 3.80 (1H, d,  $J$  13.2, H-C6), 2.80 (1H, ddq,  $J$  6.4, 6.4, 6.4, H-C2), 2.45-2.33 (1H, m, H-C3), 2.31-2.19 (1H, m, H-C3), 1.68 (1H, bs, H-NH), 1.15 (3H, d,  $J$  6.4, H-C1), 0.14 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 145.7 (C4), 140.7 (ArC), 131.3 (C5), 128.2 (ArC), 127.9 (ArC), 126.7 (ArC), 52.3 (C2), 51.1 (C6), 40.3 (C3), 19.9 (C1), 0.0 (CTMS). Data in agreement with literature values.

**( $\pm$ )-trans-Ethyl 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate (258).**



$C_{16}H_{21}NO_2$   
Mol. Wt.: 259.34

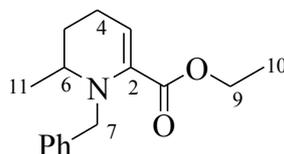
Following the general procedure M, (Z)-N-benzyl-5-(trimethylsilyl)pent-4-en-2-amine **257** (604 mg, 2.44 mmol), in the presence of a pre-heated 42% solution of ethyl 2-oxoacetate in toluene (558 mg, 2.44 mmol, 1.00 eq.), was consumed based on analysis by TLC after 48 hours of stirring at room temperature instead of reflux. The work-up gave a

*Experimental*

yellow oil, which was purified by flash column chromatography (90% hexane 10% ethyl acetate) to give the *title compound 258* (468 mg, 1.81 mmol, 74%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2964, 1737, 1453, 1273;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.48-7.42 (2H, m, ArH), 7.35-7.23 (3H, m, ArH), 5.94-5.86 (1H, m, H-C4), 5.76-5.66 (1H, m, H-C3), 4.23-4.07 (2H, m, H-C9), 3.88 (1H, d,  $J$  13.6, H-C7), 3.83 (1H, m, H-C2), 3.80 (1H, d,  $J$  13.6, H-C7), 3.37-3.32 (1H, m, H-C6), 2.27-2.21 (1H, m, H-C5), 2.00-1.88 (1H, m, H-C5), 1.28 (3H, t,  $J$  7.1, H-C10), 1.16 (3H, d,  $J$  6.6, H-C11);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 172.8 (C9), 139.6 (ArC), 128.8 (ArC), 128.4 (ArC), 127.0 (ArC), 126.4 (C4), 123.2 (C3), 60.7 (C9), 57.1 (C2), 53.2 (C7), 51.0 (C6), 31.8 (C5), 15.6 (C11), 14.3 (C10);  $m/z$  (CI) 260 ( $\text{MH}^+$ , 100), 186 (44); HRMS (CI) Found  $[\text{M}]^+$  259.1574,  $\text{C}_{16}\text{H}_{21}\text{NO}_2$  requires 259.1572.

**(±)-Ethyl 1-benzyl-6-methyl-1,4,5,6-tetrahydropyridine-2-carboxylate (259).**

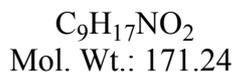
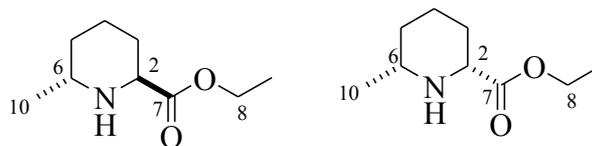


$\text{C}_{16}\text{H}_{21}\text{NO}_2$   
Mol. Wt.: 259.34

A round-bottomed flask was charged with (±)-*trans*-ethyl 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate **258** (69 mg, 0.27 mmol, 1.0 eq.) and methanol (3 mL). The resulting solution was stirred at room temperature and a 1.0 M aqueous solution of lithium hydroxide (0.72 mL) added dropwise. The mixture was stirred at room temperature overnight, water (5 mL) and dichloromethane (5 mL) added, the organic layer separated and the aqueous layer extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. This gave the *title compound 259* (40 mg, 0.15 mmol, 58%) as a colourless oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.52-7.26 (5H, m, Ar-H), 6.16-6.12 (1H, m, H-C3), 4.32-4.19 (3H, m, H-C9 and H-C7), 3.73 (1H, d,  $J$  14.4, H-C7), 3.15-3.06 (1H, m, H-C6), 2.18-2.12 (2H, m, H-C4), 1.65-1.52 (1H, m, H-C5), 1.47-1.38 (1H, m, H-C5), 1.34 (3H, t,  $J$  7.3, H-C10), 0.91 (3H, d,  $J$  6.3, H-C11);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 166.2 (C8), 139.7 (C2), 137.1 (ArC), 128.3 (ArC), 128.1 (ArC), 126.8 (ArC), 117.1 (C3), 60.6 (C9), 56.7 (C7), 49.5 (C6), 22.3 (C5), 19.4 (C4), 17.3 (C11), 14.2 (C10);  $m/z$  (CI) 260 ( $\text{MH}^+$ , 100), 217 (18), 143 (10).

(±)-*trans*-Ethyl 6-methylpiperidine-2-carboxylate (**262**) and (±)-*cis*-Ethyl 6-methylpiperidine-2-carboxylate (**263**).

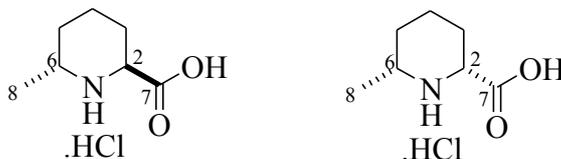


A solution of (±)-*trans*-ethyl 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate **258** (125 mg, 0.48 mmol) in absolute ethanol (3 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of 20% palladium hydroxide (70 mg, 10% weight) in absolute ethanol (2 mL). The hydrogenation was complete in 5 hours. The mixture was filtered through celite, which was washed with diethyl ether (10 mL) and concentrated *in vacuo* to afford the *title compounds* **262** and **263** (72 mg, 0.42 mmol, 87%) as a colourless oil.

Data for **262**:  $\delta_H$  (300 MHz;  $CDCl_3$ ) 4.19 (2H, q,  $J$  7.1, H-C8), 3.72 (1H, dd,  $J$  4.8, 3.0, H-C2), 2.98-2.85 (1H, m, H-C6), 2.57 (1H, bs, H-NH), 2.13-2.03 (1H, m, H-C3), 1.81-1.71 (1H, m, H-C3), 1.64-1.60 (1H, m, H-C4), 1.59-1.54 (1H, m, H-C5), 1.37-1.30 (1H, m, H-C4), 1.27 (3H, t,  $J$  7.1, H-C9), 1.22-1.17 (1H, m, H-C5), 1.07 (3H, d,  $J$  6.3, H-C10);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 173.9 (C7), 60.8 (C2), 55.9 (C8), 47.8 (C6), 33.0 (C5), 26.1 (C10), 22.5 (C3), 21.3 (C9), 14.3 (C4);  $m/z$  (CI) (mixture) 172 ( $MH^+$ , 100), 170 (15). Data in agreement with literature values.

Data for **263**:  $\delta_H$  (300 MHz;  $CDCl_3$ ) 4.19 (2H, q,  $J$  7.1, H-C8), 3.34 (1H, dd,  $J$  11.3, 2.8, H-C2), 2.72-2.57 (1H, m, H-C6), 2.57 (1H, s, N-NH), 2.02-1.93 (1H, m, H-C3), 1.90-1.81 (1H, m, H-C4), 1.71-1.64 (1H, m, H-C4), 1.44-1.37 (1H, m, H-C3), 1.36-1.32 (1H, m, H-C5), 1.25 (3H, t,  $J$  7.1, H-C9), 1.18-1.13 (1H, m, H-C5), 1.12 (3H, d,  $J$  6.3, H-C10);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 173.2 (C7), 60.9 (C2), 59.3 (C8), 51.9 (C6), 33.6 (C5), 28.8 (C10), 24.5 (C3), 22.7 (C9), 14.2 (C4). Data in agreement with literature values.

(±)-*trans*-6-Methylpiperidine-2-carboxylic acid hydrochloride (**264**) and (±)-*cis*-6-Methylpiperidine-2-carboxylic acid hydrochloride (**265**).

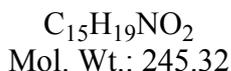
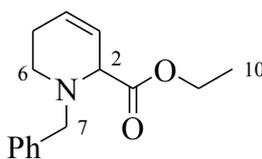


A round-bottomed flask fitted with a condenser was charged with a 2:1 mixture of (±)-*trans*-ethyl 6-methylpiperidine-2-carboxylate **262** and (±)-*cis*-ethyl 6-methylpiperidine-2-carboxylate **263** (40 mg, 0.23 mmol, 1.00 eq.). To this was added 10.15 M hydrochloric acid (3 mL) and the resulting mixture was heated to reflux temperature for 2 hours. The resulting solution was concentrated *in vacuo* and then freeze dried to afford the *title compound* **264** and **265** (34 mg, 0.19 mmol, 83%) as a pale yellow solid.

Data for **265**: M.p. (mixture) >250 °C decomposes (Lit.: >250 °C decomposes);  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  (mixture) 3390, 2945, 1731;  $\delta_{\text{H}}$  (300 MHz; D<sub>2</sub>O) 3.78 (1H, dd, *J* 12.0, 2.9, H-C2), 3.31-3.16 (1H, m, H-C6), 2.31-2.21 (1H, m, H-C3), 1.98-1.81 (2H, m, H-C5), 1.66-1.53 (2H, m, H-C4), 1.45-1.34 (1H, m, H-C3), 1.32 (3H, d, *J* 6.4, H-C8);  $\delta_{\text{C}}$  (75.5 MHz; D<sub>2</sub>O) 173.1 (C7), 59.2 (C2), 53.8 (C6), 30.2 (C5), 26.4 (C3), 22.8 (C4), 19.2 (C8). Data in agreement with literature values.

Data for **264**:  $\delta_{\text{H}}$  (300 MHz; D<sub>2</sub>O) 4.13 (1H, t, *J* 5.2, H-C2), 3.66-3.54 (1H, m, H-C6), 2.16-2.00 (1H, m, H-C3), 1.94-1.81 (2H, m, H-C5), 1.80-1.69 (1H, m, H-C3), 1.54-1.44 (2H, m, H-C4), 1.31 (3H, d, *J* 6.7, H-C8);  $\delta_{\text{C}}$  (75.5 MHz; D<sub>2</sub>O) 173.0 (C7), 55.3 (C2), 50.6 (C6), 29.5 (C5), 25.5 (C3), 19.0 (C4), 17.7 (C8). Data in agreement with literature values.

(±)-Ethyl 1-benzyl-1,2,5,6-tetrahydropyridine-2-carboxylate (**268**).<sup>7</sup>



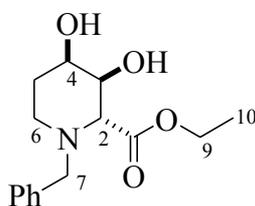
Following the general procedure M, (*Z*)-*N*-benzyl-4-(trimethylsilyl)but-3-en-1-amine **256** (162 mg, 0.70 mmol), was consumed based on analysis by TLC after 15 hours of stirring at reflux. The work up gave a yellow oil, which was purified by flash column

*Experimental*

chromatography (90% hexane 10% ethyl acetate) to give the *title compound* **268** (120 mg, 0.49 mmol, 70%) as a colourless oil.

$\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.38-7.27 (5H, m, ArH), 5.97-5.95 (1H, m, H-C4), 5.72-5.67 (1H, m, H-C5), 4.26-4.16 (2H, m, H-C9), 3.88 (1H, d,  $J$  13.8, H-C7), 3.85 (1H, bs, H-C6), 3.64 (1H, d,  $J$  13.8, H-C7), 3.13 (1H, m, H-C2), 2.53 (1H, m, H-C2), 2.15 (2H, m, H-C3), 1.27 (3H, t,  $J$  7.2, H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 172.3 (C8), 138.5 (ArC), 129.5 (ArCH), 128.8 (ArCH), 128.7 (ArCH), 127.6 (C5), 123.9 (C4), 63.1 (C6), 61.1 (C9), 59.8 (C7), 45.3 (C2), 25.6 (C3), 14.7 (C10). Data in agreement with literature values.

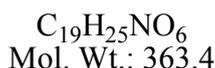
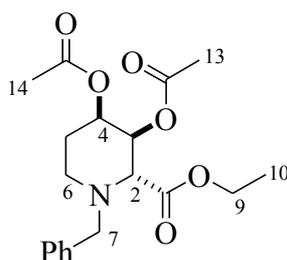
**(2*R*\*,3*S*\*,4*R*\*)-Ethyl 1-benzyl-3,4-dihydropiperidine-2-carboxylate (269).**



$\text{C}_{15}\text{H}_{21}\text{NO}_4$   
Mol. Wt.: 279.33

Following the general procedure J, ethyl 1-benzyl-1,2,5,6-tetrahydropyridine-2-carboxylate **268** (36 mg, 0.15 mmol) afforded the *title compound* **269** (15 mg, 0.05 mmol, 36%) as a pale yellow oil which was used in the next step without any further purification.

$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3413, 2958, 2850, 1732, 1657;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.39-7.26 (5H, m, Ar-H), 4.29-4.26 (2H, q,  $J$  7.1, H-C9), 4.11-4.08 (1H, m, H-C3), 3.93 (1H, d,  $J$  14.5, H-C7), 3.88-3.82 (1H, m, H-C4), 3.73 (1H, d,  $J$  14.5, H-C7), 3.55 (1H, d,  $J$  6.0, H-C2), 2.95-2.85 (1H, m, H-C6), 2.64-2.57 (1H, m, H-C6), 1.89-1.75 (2H, m, H-C5), 1.25 (3H, t,  $J$  7.1, H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 169.7 (C8), 129.2 (ArC), 128.5 (ArC), 128.5 (ArC), 127.7 (ArC), 70.1 (C4), 67.0 (C3), 64.9 (C2), 60.1 (C9), 58.1 (C7), 44.9 (C6), 28.9 (C5), 14.2 (C10).

**(2*R*\*,3*S*\*,4*R*\*)-Ethyl 3,4-diacetoxy-1-benzylpiperidine-2-carboxylate (270).**

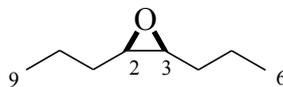
Following the general procedure N, (2*R*,3*S*,4*R*)-ethyl 1-benzyl-3,4-dihydropiperidine-2-carboxylate **269** and (2*S*,3*R*,4*S*)-ethyl 1-benzyl-3,4-dihydropiperidine-2-carboxylate **269** (9 mg, 0.03 mmol) afforded a pale yellow oil, which was purified by preparatory TLC (90% hexane, 10% ethyl acetate) to give the *title compound* **270** (8 mg, 0.02 mmol, 69 %) as a sticky pale yellow oil.

$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  2958, 2853, 1745, 1651;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.37-7.27 (5H, m, Ar-H), 5.30 (1H, dd,  $J$  7.1, 3.1, H-C3), 5.22 (1H, td,  $J$  6.7, 3.1, H-C4), 4.25-4.16 (2H, m, H-C9), 3.82 (2H, d,  $J$  13.6, H-C7), 3.54 (2H, d,  $J$  13.6, H-C7), 3.53 (1H, d,  $J$  7.1, H-C2), 2.92-2.80 (1H, m, H-C6), 2.53-2.42 (1H, m, H-C6), 2.06 (3H, s, H-C13), 2.06 (3H, s, H-C14), 1.95-1.76 (2H, m, H-C5), 1.32-1.26 (3H, m, H-C10);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 170.4 (C8), 170.1 (C11), 169.8 (C12), 128.7 (ArC), 128.3 (ArC), 128.3 (ArC), 127.3 (ArC), 70.4 (C3), 67.7 (C4), 64.8 (C2), 61.1 (C9), 59.3 (C7), 45.3 (C6), 29.7 (C5), 21.1 (C13), 20.8 (C14), 14.2 (C10);  $m/z$  (CI) 364 ( $\text{MH}^+$ , 100), 304 (15), 290 (25); HRMS (FI) Found  $[\text{M}]^+$  363.1676,  $\text{C}_{19}\text{H}_{25}\text{NO}_6$  requires 363.1682.

**General procedure P: Epoxidation of alkenes with *meta*-chloroperbenzoic acid on 53.48 mmol scale.** A round-bottomed flask was charged with 77% *meta*-chloroperbenzoic acid in water (23.98 g, 106.95 mmol, 2.00 eq.), sodium hydrogen carbonate (18.02 g, 213.90 mmol, 4.00 eq.) and dichloromethane (230 mL). The resulting suspension was stirred and cooled to 0 °C and an alkene derivative (53.48 mmol, 1.00 eq.) in dichloromethane was added dropwise. The mixture was stirred vigorously until NMR showed complete consumption of starting material and a saturated aqueous solution of sodium hydrogen carbonate (200 mL) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with a saturated solution of sodium sulfite (2 x 100 mL), a saturated

aqueous solution of sodium hydrogen carbonate (100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*.

**(±)-(2,3-*cis*)-2,3-Dipropyloxirane (298).**

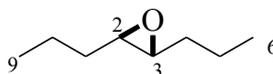


$C_8H_{16}O$   
Mol. Wt.: 128.21

Following the general procedure P, (*Z*)-oct-4-ene **298** (6.00 g, 53.48 mmol), was consumed based on analysis by NMR after 72 hours of stirring at 0 °C. The work-up afforded a pale yellow oil, which was purified by distillation under reduced pressure (28 °C, 2mmHg) to give the *title compound* **298** (5.69 g, 44.41 mmol, 83%) as a colourless oil.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 2.95-2.87 (2H, m, H-C2 and H-C3), 1.58-1.41 (8H, m, H-C4, H-C5, H-C7 and H-C8), 1.02-0.93 (6H, m, H-C6 and H-C9);  $m/z$  (CI) 129 ( $MH^+$ , 64), 111 (100). Data in agreement with literature values.

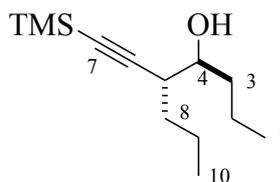
**(±)-(2,3-*trans*)-2,3-Dipropyloxirane (301).**



$C_8H_{16}O$   
Mol. Wt.: 128.21

Following the general procedure P, (*E*)-oct-4-ene **299** (3.93 g, 35.00 mmol), was consumed based on analysis by NMR after 92 hours of stirring at 0 °C. The work-up afforded a pale yellow oil, which was purified by distillation under reduced pressure (20 °C, 1.5 mmHg) to give the *title compound* **301** (3.02 g, 23.53 mmol, 67%) as a colourless oil.

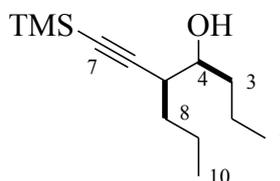
$\delta_H$  (300 MHz;  $CDCl_3$ ) 2.68-2.62 (2H, m, H-C2 and H-C3), 1.55-1.39 (8H, m, H-C4, H-C5, H-C7 and H-C8), 0.98-0.90 (6H, m, H-C6 and H-C9);  $m/z$  (CI) 129 ( $MH^+$ , 98), 111 (100). Data in agreement with literature values.

**(±)-(4,5-*syn*)-5-((Trimethylsilyl)ethynyl)octan-4-ol (302).**

$C_{13}H_{26}OSi$   
Mol. Wt.: 226.43

Following the general procedure G, (±)-(2,3-*cis*)-2,3-dipropyloxirane **300** (2.33 g, 18.18 mmol) afforded a pale yellow oil, which was purified by flash column chromatography (97% hexane, 3% ethyl acetate) to give the *title compound* **302** (822 mg, 3.63 mmol, 20%) as a colourless oil.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 3.50-3.39 (1H, m, H-4), 2.44 (1H, td,  $J$  9.2, 4.7, H-C5), 1.73 (1H, d,  $J$  7.7, H-OH), 1.66-1.25 (8H, m, H-C3 and H-C2, H-C8 and H-C9), 0.98-0.88 (6H, m, H-C1 and H-C10), 0.16 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 106.4 (C7), 88.6 (C6), 72.6 (C4), 40.0 (C3), 37.7 (C5), 33.8 (C8), 20.7 (C9), 19.0 (C2), 14.1 (C1), 13.9 (C10), 0.2 (CTMS). Data in agreement with literature values.

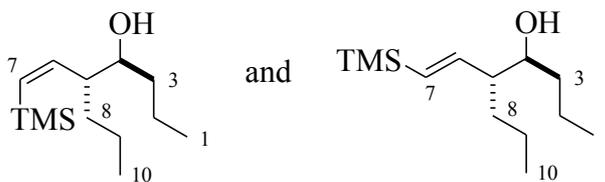
**(±)-(4,5-*anti*)-5-((Trimethylsilyl)ethynyl)octan-4-ol (303).**

$C_{13}H_{26}OSi$   
Mol. Wt.: 226.43

Following the general procedure G, (±)-(2,3-*trans*)-2,3-dipropyloxirane **301** (1.37 g, 10.67 mmol) afforded a pale yellow oil, which was purified by flash column chromatography (95% hexane, 5% ethyl acetate) to give the *title compound* **303** (1.23 g, 5.43 mmol, 51%) as a colourless oil.

$\delta_H$  (300 MHz;  $CDCl_3$ ) 3.57-3.49 (1H, m, H-C4), 2.49 (1H, td,  $J$  9.8, 5.1, H-C5), 1.90 (1H, bs, H-OH), 1.61-1.44 (4H, m, H-C3 and H-C8), 1.44-1.24 (4H, m, H-C2 and H-C9), 0.95-0.86 (6H, m, H-C1 and H-C10), 0.12 (9H, s, H-CTMS);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 107.5 (C7), 87.7 (C6), 73.0 (C4), 40.0 (C3), 35.8 (C5), 32.1 (C8), 20.6 (C9), 19.0 (C2), 14.0 (C1), 13.9 (C10), 0.1 (CTMS). Data in agreement with literature values.

(±)-(4,5-*syn,Z*)-5-(2-(Trimethylsilyl)vinyl)octan-4-ol (**304**) and (±)-(4,5-*syn,E*)-5-(2-(Trimethylsilyl)vinyl)octan-4-ol (**305**).



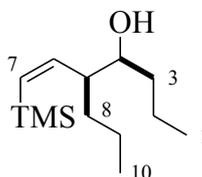
$C_{13}H_{28}OSi$   
Mol. Wt.: 228.45

Following the general procedure H, (±)-(4,5-*syn*)-5-((trimethylsilyl)ethynyl)octan-4-ol **302** (812 mg, 3.57 mmol) afforded a yellow oil, which was purified by flash column chromatography (97% hexane, 3% ethyl acetate) to give the *title compounds* **304** and **305** (227 mg, 0.99 mmol, 28%) as a colourless oil.

Data for **304**:  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  (mixture) 3435, 2958, 1672, 1608;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.07 (1H, dd,  $J$  14.2, 10.6, H-C6), 5.71 (1H, d,  $J$  14.2, H-C7), 3.50-3.33 (1H, m, H-C4), 2.09-1.95 (1H, m, H-C5), 1.61-1.13 (8H, m, H-C3 and H-C2 and H-C8 and H-C9), 0.98-0.84 (6H, m, H-C1 and H-C10), 0.06 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 146.9 (C6), 134.4 (C7), 73.1 (C4), 53.1 (C5), 36.8 (C3), 32.8 (C8), 20.5 (C9), 18.9 (C2), 14.6 (C1), 14.2 (C10), -1.1 (CTMS);  $m/z$  (CI) 229 ( $\text{MH}^+$ , 4), 211 (70), 156 (50).

Data for **305**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.01-5.74 (2H, m, H-C6 and H-C7), 3.50-3.33 (1H, m, H-C4), 2.29-2.14 (1H, m, H-C5), 1.61-1.13 (8H, m, H-C3 and H-C2 and H-C8 and H-C9), 0.98-0.84 (6H, m, H-C1 and H-C10), 0.13 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 149.3 (C6), 132.9 (C7), 73.0 (C4), 49.4 (C5), 36.3 (C3), 33.3 (C8), 20.7 (C9), 18.8 (C2), 14.5 (C1), 14.2 (C10), 0.5 (CTMS).

(±)-(4,5-*anti,Z*)-5-(2-(Trimethylsilyl)vinyl)octan-4-ol (**306**).



$C_{13}H_{28}OSi$   
Mol. Wt.: 228.45

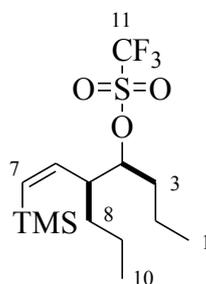
Following the general procedure H, (±)-(4,5-*anti*)-5-((trimethylsilyl)ethynyl)octan-4-ol **303** (1.23 g, 5.40 mmol) afforded after 48 hours at reflux temperature a pale yellow oil,

*Experimental*

which was purified by flash column chromatography (94% hexane, 6% ethyl acetate) to give the *title compound 306* (860 mg, 3.76 mmol, 70%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3352, 2957, 1608;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.08 (1H, dd,  $J$  14.2, 10.6, H-C6), 5.63 (1H, d,  $J$  14.2, H-C7), 3.52-3.43 (1H, m, H-C4), 2.35-2.24 (1H, m, H-C5), 1.63-1.41 (2H, m, H-C3), 1.40-1.11 (6H, m, H-C2 and H-C8 and H-C9), 0.95-0.86 (6H, m, H-C1 and H-C10), 0.12 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 149.5 (C6), 131.7 (C7), 74.6 (C4), 49.4 (C5), 36.3 (C3), 32.9 (C8), 20.6 (C9), 19.5 (C2), 14.6 (C1), 14.0 (C10), 0.6 (CTMS);  $m/z$  (CI) 229 ( $\text{MH}^+$ , 30), 211 (97), 137 (100).

**(±)-(4,5-*anti*)-5-((*Z*)-2-(Trimethylsilyl)vinyl)octan-4-yl trifluoromethanesulfonate (308).**

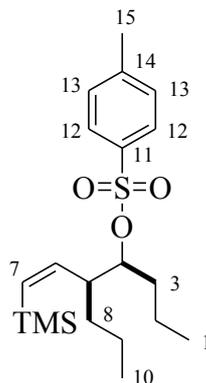


$\text{C}_{14}\text{H}_{27}\text{F}_3\text{O}_3\text{SSi}$   
Mol. Wt.: 360.51

Following the general procedure K, (±)-(4,5-*anti,Z*)-5-(2-(trimethylsilyl)vinyl)octan-4-ol **306** (100 mg, 0.44 mmol) afforded a pale pink oil, which was purified by flash column chromatography (90% dichloromethane, 10% methanol) to give the *title compound 308* (91 mg, 0.25 mmol, 58%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2959, 1605, 837;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.97 (1H, dd,  $J$  14.0, 10.1, H-C6), 5.34 (1H, d,  $J$  14.0, H-C7), 5.22-5.11 (1H, m, H-C4), 2.79-2.66 (1H, m, H-C5), 1.95-1.84 (2H, m, H-C3), 1.37-1.09 (6H, m, H-C2 and H-C8 and H-C9), 0.86 (3H, t,  $J$  7.4, H-C1), 0.81-0.75 (3H, m, H-C10), 0.01 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 152.1 (C6), 131.7 (C7), 131.4 (C4), 127.3 (C5), 46.3 (C3), 37.8 (C8), 25.7 (C9), 20.3 (C2), 14.2 (C1), 13.9 (C10), 0.4 (CTMS).

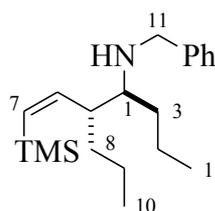
(±)-(4,5-*anti*)-5-((*Z*)-2-(Trimethylsilyl)vinyl)octan-4-yl 4-methylbenzenesulfonate  
(307).



$C_{20}H_{34}O_3SSi$   
Mol. Wt.: 382.63

Following the general procedure A, (±)-(4,5-*anti,Z*)-5-(2-(trimethylsilyl)vinyl)octan-4-ol **306** (482 mg, 2.11 mmol) was consumed based on analysis by TLC after 48 hours of stirring at 0 °C. The work-up afforded a yellow oil, which was purified by flash column chromatography (97% petroleum ether, 3% ethyl acetate) to give the *title compound* **307** (246 mg, 0.64 mmol, 30%) as a colourless oil.

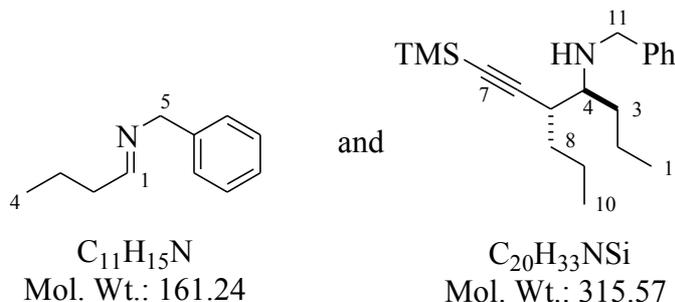
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2959, 2873, 1609;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.78 (2H, d,  $J$  8.2, H-C12), 7.31 (2H, d,  $J$  8.2, H-C13), 5.84 (1H, dd,  $J$  14.3, 10.4, H-C6), 5.43 (1H, d,  $J$  14.3, H-C7), 4.49 (1H, dd,  $J$  11.9, 5.8, H-C4), 2.49-2.42 (1H, m, H-C5), 2.43 (3H, s, H-C15), 1.75-1.51 (2H, m, H-C3), 1.49-1.01 (6H, m, H-C2 and H-C8 and H-C9), 0.82 (3H, t,  $J$  7.3, H-C1), 0.84-0.79 (6H, m, H-C10 and H-C15), 0.07 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 147.3 (C6), 144.3 (C14), 134.6 (C11), 131.5 (C7), 129.5 (C13), 127.8 (C12), 87.0 (C4), 46.1 (C5), 34.5 (C3), 32.1 (C8), 21.6 (C15), 20.2 (C9), 18.4 (C2), 14.3 (C1), 13.8 (C10), 0.3 (CTMS).

**(±)-(4,5-*syn,Z*)-*N*-Benzyl-5-(2-(trimethylsilyl)vinyl)octan-4-amine(309).**

$C_{20}H_{35}NSi$   
Mol. Wt.: 317.58

Following the general procedure B, (±)-(4,5-*anti*)-5-((*Z*)-2-(trimethylsilyl)vinyl)octan-4-yl 4-methylbenzenesulfonate **307** (156 mg, 0.41 mmol), in the presence of benzylamine (214 mg, 2.00 mmol), was consumed based on analysis by TLC after 20 hours of stirring and heating. The excess of benzylamine was distilled (104 °C, 245 mmHg) and the work-up gave a yellow oil, which was purified by flash column chromatography (94% hexane 5% ethyl acetate 1% triethylamine) to give the *title compound* **309** (22 mg, 0.07 mmol, 17%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3327, 2956, 1604;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.38-7.19 (5H, m, Ar-H), 6.12 (1H, dd,  $J$  14.2, 10.4, H-C6), 5.58 (1H, d,  $J$  14.2, H-C7), 3.81 (1H, d,  $J$  13.0, H-C11), 3.74 (1H, d,  $J$  13.0, H-C11), 2.48 (1H, dd,  $J$  9.9, 4.9, H-C4), 2.35 (1H, ddd,  $J$  14.2, 9.6, 4.9, H-C5), 1.58-1.25 (6H, m, H-C3 and H-C8 and H-C2), 1.23-1.06 (2H, m, H-C9), 0.93-0.84 (6H, m, H-C1 and H-C10), 0.11 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 150.9 (C6), 141.3 (ArC), 130.8 (C7), 128.3 (ArC), 127.9 (ArC), 126.8 (ArC), 60.3 (C4), 52.2 (C11), 46.0 (C5), 33.3 (C3), 33.0 (C8), 20.8 (C9), 19.1 (C2), 14.6 (C1), 14.4 (C10), 0.5 (CTMS);  $m/z$  (CI) 318 ( $\text{MH}^+$ , 20), 162 (100); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  318.2614,  $C_{20}H_{36}NSi$  requires 318.2612.

**(*E*)-*N*-Butylidene(phenyl)methanamine (314) and (±)-(4,5-*anti*)-*N*-Benzyl-5-((trimethylsilyl)ethynyl)octan-4-amine (315).**

A round-bottomed flask was charged with magnesium sulfate (120.36 g, 277.20 mmol, 4.00 eq.), benzylamine (7.42 g, 69.30 mmol, 1.00 eq.) and dichloromethane (200 mL).

### Experimental

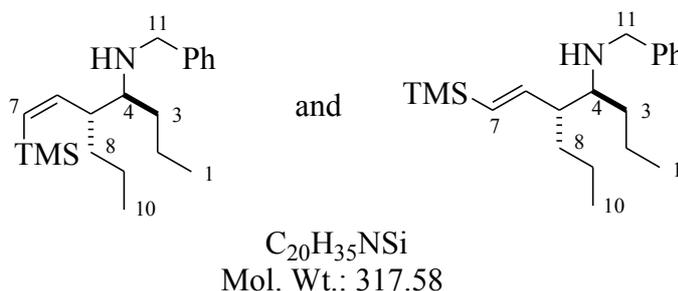
The resulting suspension was stirred at room temperature and butyraldehyde **313** (6.21 mL, 69.30 mmol, 1.00 eq.) added dropwise. The mixture was stirred overnight at room temperature, filtered and concentrated *in vacuo* to afford a pale yellow oil. This was purified by distillation under reduced pressure (130 °C, 20 mmHg) to give the *title compound* **314** (2.10 g, 13.02 mmol, 19%) as a colourless oil which was used in the next step immediately.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.79 (1H, t,  $J$  4.9, H-C1), 7.38-7.21 (5H, m, Ar-H), 4.57 (2H, s, H-C5), 2.34-2.24 (2H, m, H-C2), 1.67-1.53 (2H, m, H-C3), 0.97 (3H, t,  $J$  7.4, H-C4). Data in agreement with literature values.

A three-necked round-bottomed flask equipped with a dropping funnel and a thermometer was charged with hex-1-ynyltrimethylsilane **311** (308 mg, 2.00 mmol, 1.00 eq.) and tetrahydrofuran (10 mL). The resulting solution was stirred and cooled to  $-40$  °C and a 1.4 M solution of *sec*-butyllithium in cyclohexane (1.57 mL, 2.20 mmol, 1.10 eq.) was added dropwise. The mixture was slowly warmed to 0 °C for 1 hour, cooled to  $-20$  °C and a 1.0 M solution of anhydrous zinc (II) bromide in tetrahydrofuran (2.20 mL, 2.20 mmol, 1.10 eq.) added dropwise, which gave a colourless solution. This solution was then cooled to  $-70$  °C and **314** (322 mg, 2.00 mmol, 1.00 eq.) in tetrahydrofuran (5 mL) added dropwise over 10 minutes. The mixture was then stirred at  $-70$  °C for 1 hour, warmed slowly to 0 °C, and a solution of 2 parts saturated aqueous solution of ammonium chloride to 1 part 30% aqueous solution of ammonia (10 mL) was added dropwise. Also to the mixture was added water (10 mL) and diethyl ether (10 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic layers were washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This afforded a yellow oil, which was purified by flash column chromatography (95% hexane, 5% ethyl acetate) to give the *title compound* **315** (410 mg, 1.30 mmol, 65%) as a pale yellow oil.

$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3340, 2958, 2164, 1604;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.39-7.19 (5H, m, Ar-H), 3.92-3.69 (2H, m, H-C11), 2.62-2.47 (2H, m, H-C4 and H-C5), 1.68-1.19 (8H, m, H-C3 and H-C2 and H-C8 and H-C9), 1.02-0.84 (6H, m, H-C1 and H-C10), 0.14 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 141.1 (ArC), 128.2 (ArC), 128.1 (ArC), 126.7 (ArC), 108.9 (C7), 86.7 (C6), 59.1 (C4), 51.2 (C11), 36.7 (C5), 34.1 (C3), 33.0 (C8), 21.0 (C9), 19.3 (C2), 14.3 (C1), 14.0 (C10), 0.2 (CTMS);  $m/z$  (CI) 316 ( $\text{MH}^+$ , 65), 162 (100); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  316.2458,  $\text{C}_{20}\text{H}_{34}\text{NSi}$  requires 316.2455.

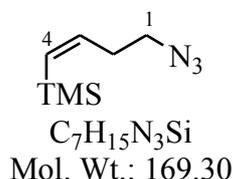
(±)-(4,5-*syn,Z*)-*N*-Benzyl-5-(2-(trimethylsilyl)vinyl)octan-4-amine (**316**) and (±)-(4,5-*syn,E*)-*N*-Benzyl-5-(2-(trimethylsilyl)vinyl)octan-4-amine (**317**).



Following the general procedure H, (±)-(4,5-*anti*)-*N*-benzyl-5-((trimethylsilyl)ethynyl)octan-4-amine **315** (1.23 g, 3.90 mmol) afforded a pale yellow oil, which was purified by flash column chromatography (98% dichloromethane, 2% methanol) to give the *title compound* **316** (124 mg, 0.39 mmol, 10%) as a colourless oil. Further elution (98% dichloromethane, 2% methanol) provided the other *title compound* **317** (250 mg, 0.79 mmol, 20%) as a colourless oil.

Data for **317**:  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3328, 3027, 2956, 1605;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.39-7.19 (5H, m, Ar-H), 5.86-5.60 (2H, m, H-C6 and H-C7), 3.80 (1H, d,  $J$  12.9, H-C11), 3.68 (1H, d,  $J$  12.9, H-C11), 2.50-2.37 (1H, m, H-C4), 2.21-2.06 (1H, m, H-C5), 1.56-1.07 (8H, m, H-C3 and H-C2 and H-C8 and H-C9), 0.93-0.82 (6H, m, H-C1 and H-C10), 0.04 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 148.9 (C6), 132.3 (ArC), 128.3 (C7), 128.3 (ArC), 128.2 (ArC), 126.7 (ArC), 59.7 (C4), 51.8 (C11), 49.9 (C5), 33.4 (C3), 32.4 (C8), 20.7 (C9), 18.8 (C2), 14.5 (C1), 14.2 (C10), -1.1 (CTMS);  $m/z$  (CI) 318 ( $\text{MH}^+$ , 80), 162 (100); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  318.2615,  $C_{20}H_{36}NSi$  requires 318.2612.

**(Z)-(1-Azidobut-3-enyl)trimethylsilane (361).**

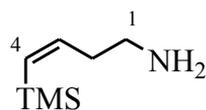


A round-bottomed flask equipped with a reflux condenser was charged with (*Z*)-4-(trimethylsilyl)but-3-enyl 4-methylbenzenesulfonate **254** (9.13 g, 30.59 mmol, 1.00 eq.) and *N,N*-dimethylformamide (61 mL). Sodium azide (5.98 g, 91.78 mmol, 3.00 eq.) was added portionwise and the resulting solution was allowed to warm to 60 °C, stirred at this temperature for 4 hour and poured into a mixture of diethyl ether:water (200 mL, 3:7, v/v). The resulting biphasic solution was stirred for 30 minutes at room temperature, the

aqueous layer separated and the organic layer washed with water (3 x 30 mL). The combined aqueous layers were extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. This afforded a pale yellow oil which was purified by flash column chromatography (95% hexane 5% diethyl ether) to afford the *title compound* **361** (4.26 g, 25.16 mmol, 82%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.25 (1H, td,  $J$  13.7, 6.7, H-C3), 5.67 (1H, d,  $J$  13.7, H-C4), 3.30 (2H, t,  $J$  6.9, H-C1), 2.42 (2H, td,  $J$  6.9, 6.7, H-C2), 0.13 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.5 (C3), 133.1 (C4), 51.2 (C1), 33.0 (C2), 0.2 (CTMS). Data in agreement with literature values.

**(Z)-4-(Trimethylsilyl)but-3-en-1-amine (322).**



$\text{C}_7\text{H}_{17}\text{NSi}$   
Mol. Wt.: 143.3

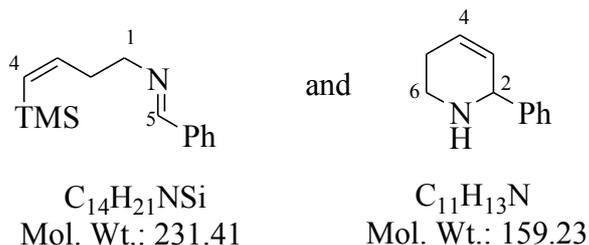
A round-bottomed flask connected to a syringe pump was charged with lithium aluminium hydride (1.00 g, 26.43 mmol, 1.05 eq.) and tetrahydrofuran (106 mL). The resulting suspension was allowed to cool to 0 °C and stirred before adding a solution of (Z)-(1-azidobut-3-enyl)trimethylsilane **361** (4.26 g, 25.17 mmol, 1.00 eq.) in tetrahydrofuran (25 mL) dropwise over 2 hours. The reaction was then stirred for a further 30 minutes at 0 °C, carefully quenched at 0 °C by addition of a saturated aqueous solution of sodium chloride (100 mL), and then diethyl ether (100 mL) was added and the resulting mixture allowed to warm to room temperature whilst being stirred for 30 minutes. The mixture was filtered through a pad of celite, the organic layer separated and the aqueous layer extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. This afforded a pale yellow oil, which was purified by distillation under reduced pressure (110 °C, 90 mmHg) to give the *title compound* **322** (2.42 g, 16.86 mmol, 67%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.17 (1H, td,  $J$  14.3, 7.4, H-C3), 5.52 (1H, td,  $J$  14.3, 1.2, H-C4), 2.67 (2H, t,  $J$  6.9, H-C1), 2.18 (2H, dq,  $J$  6.9, 1.2, H-C2), 1.17 (2H, bs, H-NH<sub>2</sub>), 0.03 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 145.9 (C3), 131.5 (C4), 42.0 (C1), 37.6 (C2), 0.2 (CTMS). Data in agreement with literature values.

**General Procedure Q: imine formation followed by imine-vinylsilane cyclisation and benzyloxyl carbonyl protection:** A round-bottomed flask was charged with magnesium sulfate (2.0 g) and an aldehyde derivative (1.40 mmol, 1.00 eq.) in dichloromethane (5 mL). To the resulting suspension was added a primary amine (200 mg, 1.40 mmol, 1.00 eq.) in dichloromethane (1 mL) dropwise and the mixture was stirred vigorously at room temperature overnight. The mixture was filtered and concentrated *in vacuo*. This afforded an imine derivative, which was used in the next step without further purification. A round-bottomed flask equipped with a reflux condenser was charged with scandium(III) trifluoromethanesulfonate (268 mg, 0.55 mmol, 2.00 eq.) and acetonitrile (1.5 mL). To the resulting suspension was added an imine derivative (0.28 mmol, 1.00 eq.) in acetonitrile (0.5 mL) and the mixture was heated to reflux temperature until NMR showed complete consumption of starting material. The solution was cooled to room temperature, water (5 mL) and dichloromethane (5 mL) were added and the resulting biphasic solution was stirred for 30 minutes at room temperature. The organic layer was separated and the aqueous layers were extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a 2-substituted tetrahydropyridine derivative, which was used in the next step without further purification. A round-bottomed flask was charged with a 2-substituted tetrahydropyridine derivative (0.40 mmol, 1.00 eq.), water (1.0 mL) and tetrahydrofuran (1.0 mL). The resulting biphasic solution was stirred and cooled to 0 °C, then sodium hydrogen carbonate (155 mg, 1.19 mmol, 3.00 eq.) was added portionwise, followed by benzyloxycarbonyl chloride (78 µL, 0.55 mmol, 1.40 eq.) dropwise. The mixture was allowed to warm slowly to room temperature and stirred until GCMS showed complete consumption of starting material. The solution was then diluted with ethyl acetate (5 mL), the organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (5 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*.

*Experimental*

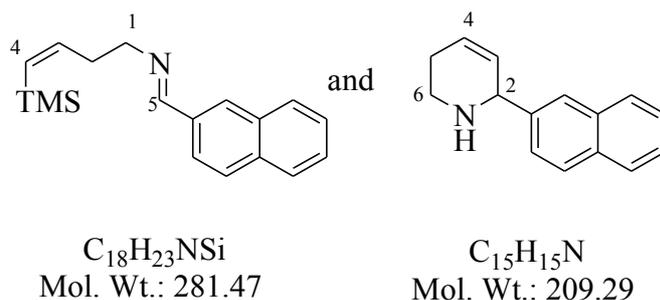
**(3Z)-N-Benzylidene-4-(trimethylsilyl)but-3-en-1-amine (362) and (±)-2-Phenyl-1,2,5,6-tetrahydropyridine (369).**



Following the general procedure Q, (Z)-4-(trimethylsilyl)but-3-en-1-amine **322** (350 mg, 2.44 mmol) in the presence of benzaldehyde (259 mg, 2.44 mmol), afforded the *title compound* **362** (706 mg, 2.44 mmol, *quantitative*) as a yellow oil which was used in the next step without any further purification. The (3Z)-N-benzylidene-4-(trimethylsilyl)but-3-en-1-amine **362** (45 mg, 0.20 mmol) after 240 hours at reflux was consumed based on analysis by NMR to afford a yellow oil, which was purified by flash column chromatography (95% dichloromethane, 5% methanol) to give the *title compound* **369** (16 mg, 0.10 mmol, 50%) as a pale yellow oil.

$\delta_H$  (400 MHz;  $CDCl_3$ ) 7.38-7.24 (5H, m, Ar-H), 5.99-5.94 (1H, m, H-C4), 5.77-5.73 (1H, m, H-C3), 4.50-4.47 (1H, m, H-C2), 3.14-3.08 (1H, m, H-C6), 3.01-2.94 (1H, m, H-C6), 2.30-2.21 (1H, m, H-C5), 2.13-2.07 (1H, m, H-C5);  $m/z$  (ES) 160 ( $MH^+$ , 100). Data in agreement with literature values.

**(3Z)-N-(Naphthalen-2-ylmethylene)-4-(trimethylsilyl)but-3-en-1-amine (363) and (±)-2-(Naphthalen-2-yl)-1,2,5,6-tetrahydropyridine (371a).**



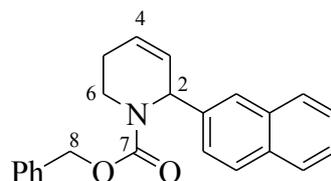
Following the general procedure Q, (Z)-4-(trimethylsilyl)but-3-en-1-amine **322** (350 mg, 2.44 mmol) in the presence of 2-naphthaldehyde (381 mg, 2.44 mmol), afforded the *title compound* **363** (706 mg, 2.44 mmol, *quantitative*) as a yellow oil which was used in the next step without any further purification. The (3Z)-N-(naphthalen-2-ylmethylene)-4-(trimethylsilyl)but-3-en-1-amine **363** (40 mg, 0.14 mmol) after 120 hours at reflux was consumed based on analysis by NMR to afford a yellow oil, which was purified by flash

*Experimental*

column chromatography (95% dichloromethane, 5% methanol) to give the *title compound* **370** (14 mg, 0.07 mmol, 48%) as a pale yellow oil.

$\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.84-7.79 (4H, m, Ar-H), 7.56-7.43 (3H, m, Ar-H), 6.14-6.12 (1H, m, H-C4), 5.79 (1H, dd,  $J$  10.4, 2.0, H-C3), 4.96 (1H, bs, H-C2), 3.01-2.90 (2H, m, H-C6), 2.39-2.35 (1H, m, H-C5), 2.19-2.14 (1H, m, H-C5);  $m/z$  (ES) 210 ( $\text{MH}^+$ , 95), 181 (100).

**(±)-Benzyl 2-(naphthalen-2-yl)-1,2,5,6-tetrahydropyridine-1-carboxylate (372a).**

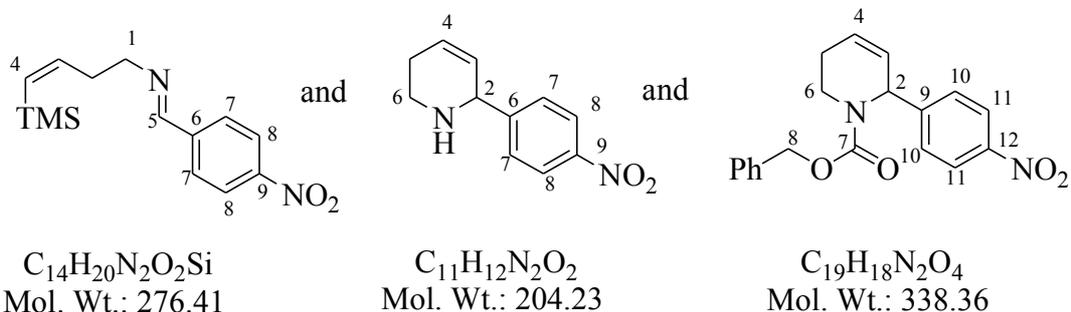


$\text{C}_{23}\text{H}_{21}\text{NO}_2$   
Mol. Wt.: 343.42

Following the general procedure Q, 2-(naphthalen-2-yl)-1,2,5,6-tetrahydropyridine **371a** (10 mg, 0.05 mmol) afforded a yellow oil, which was purified by preparative high performance liquid chromatography to give the *title compound* **372a** (7 mg, 0.22 mmol, 43%) as a sticky colourless oil.

$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3057, 2896, 1698, 1600;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.88-7.67 (4H, m, Ar-H), 7.54-7.40 (3H, m, Ar-H), 7.39-7.28 (5H, m, Ar-H), 6.16-6.05 (1H, m, H-C4), 6.03-5.88 (1H, m, H-C3), 5.93-5.65 (1H, m, H-C2), 5.23 (1H, d,  $J$  12.3, H-C8), 5.14 (1H, d,  $J$  12.3, H-C8), 4.35-3.98 (1H, m, H-C6), 3.04 (1H, ddd,  $J$  13.3, 12.2, 4.0, H-C6), 2.49-2.26 (1H, m, H-C5), 2.18-2.03 (1H, m, H-C5);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 155.3 (C7), 138.1 (ArC), 133.1 (ArC), 128.5 (ArC), 128.2 (ArC), 128.0 (ArC), 128.0 (ArC), 127.6 (ArC), 126.9 (C4), 126.7 (C3), 126.1 (ArC), 125.9 (ArC), 67.2 (C8), 55.0 (C2), 37.2 (C6), 24.9 (C5);  $m/z$  (CI) 344 ( $\text{MH}^+$ , 60), 252 (27), 126 (100); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  344.1649,  $\text{C}_{23}\text{H}_{22}\text{NO}_2$  requires 344.1645.

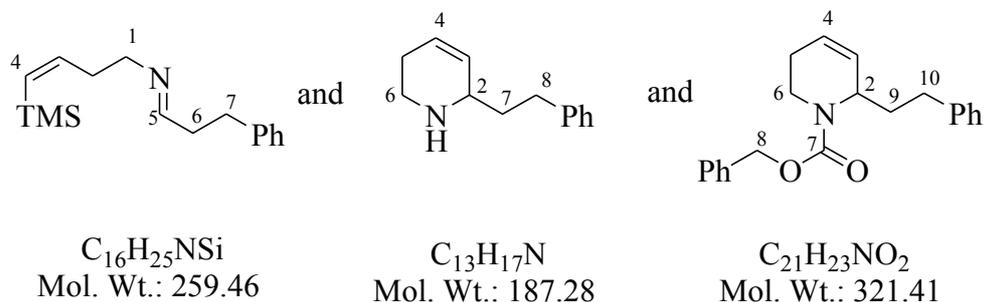
**(3Z)-N-(4-Nitrobenzylidene)-4-(trimethylsilyl)but-3-en-1-amine (364)** and **(±)-2-(4-Nitrophenyl)-1,2,5,6-tetrahydropyridine (371b)** and **(±)-Benzyl 2-(4-nitrophenyl)-1,2,5,6-tetrahydropyridine-1-carboxylate (372b)**.



Following the general procedure Q, (Z)-4-(trimethylsilyl)but-3-en-1-amine **322** (150 mg, 1.05 mmol) in the presence of 4-nitrobenzaldehyde (158 mg, 1.05 mmol), afforded the *title compound* **364** (288 mg, 1.04 mmol, *quantitative*) as a yellow oil, which was used in the next step without any further purification. The (3Z)-N-(4-nitrobenzylidene)-4-(trimethylsilyl)but-3-en-1-amine **364** (190 mg, 0.69 mmol) after 17 hours at reflux was consumed based on analysis by NMR to afford the *title compound* **371b** (121 mg, 0.59 mmol, 86%) as a yellow oil which was used in the next step without any further purification. Then 2-(4-nitrophenyl)-1,2,5,6-tetrahydropyridine **371b** (121 mg, 0.59 mmol) afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **372b** (124 mg, 0.37 mmol, 62%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3034, 2930, 1694, 1346;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 8.15 (2H, d,  $J$  6.7, H-C11), 7.67-7.39 (2H, m, H-C10), 7.40-7.24 (5H, m, Ar-H), 6.15-6.06 (1H, m, H-C4), 5.93-5.75 (1H, m, H-C3), 5.77-5.52 (1H, m, H-C2), 5.20 (1H, d,  $J$  12.2, H-C8), 5.11 (1H, d,  $J$  12.2, H-C8), 4.39-4.04 (1H, m, H-C6), 2.95 (1H, ddd,  $J$  13.5, 11.6, 4.1, H-C6), 2.45-2.28 (1H, m, H-C5), 2.18-2.05 (1H, m, H-C5);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 155.1 (C7), 148.0 (C12), 147.2 (C9), 136.3 (ArC), 128.5 (C10), 128.1 (ArC), 128.0 (ArC), 127.5 (C4), 126.9 (ArC), 125.6 (C3), 123.6 (C11), 67.4 (C8), 54.4 (C2), 37.4 (C6), 24.7 (C5);  $m/z$  (CI) 339 ( $\text{MH}^+$ , 100), 247 (25), 216 (35); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  339.1340,  $C_{19}H_{19}N_2O_4$  requires 339.1339.

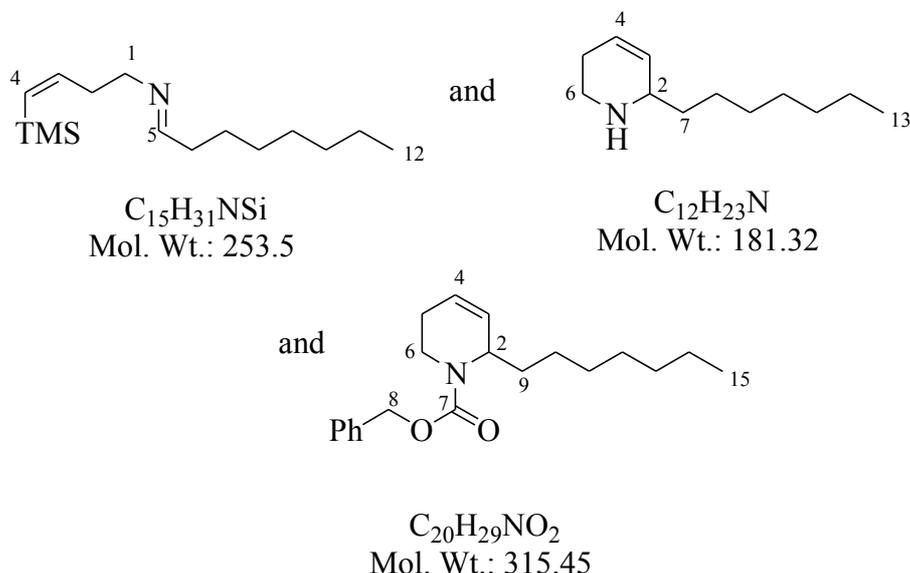
**(3Z)-N-(3-Phenylpropylidene)-4-(trimethylsilyl)but-3-en-1-amine (365)** and **(±)-2-Phenethyl-1,2,5,6-tetrahydropyridine (371c)** and **(±)-Benzyl 2-phenethyl-1,2,5,6-tetrahydropyridine-1-carboxylate(372c)**.



Following the general procedure Q, (Z)-4-(trimethylsilyl)but-3-en-1-amine **322** (150 mg, 1.05 mmol) in the presence of 3-phenylpropanal (141 mg, 1.05 mmol), afforded the *title compound* **365** (262 mg, 1.01 mmol, 96%) as a yellow solid which was used in the next step without any further purification. The (3Z)-N-(3-phenylpropylidene)-4-(trimethylsilyl)but-3-en-1-amine **365** (142 mg, 0.55 mmol) after 17 hours at reflux was consumed based on analysis by NMR to afford the *title compound* **371c** (58 mg, 0.31 mmol, 57%) as a yellow oil which was used in the next step without any further purification. Then 2-phenethyl-1,2,5,6-tetrahydropyridine **371c** (58 mg, 0.31 mmol) afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **372c** (55 mg, 0.17 mmol, 55%) as a colourless oil.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3030, 2925, 1698;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.41-7.08 (10H, m, Ar-H), 5.90-5.77 (1H, m, H-C4), 5.77-5.64 (1H, m, H-C3), 5.19 (1H, d,  $J$  12.3, H-C8), 5.15-5.08 (1H, m, H-C8), 4.64-4.39 (1H, m, H-C2), 4.33-4.07 (1H, m, H-C6), 3.07-2.88 (1H, m, H-C6), 2.73-2.57 (2H, m, H-C10), 2.38-2.16 (1H, m, H-C5), 2.06-1.93 (1H, m, H-C5), 1.95-1.81 (2H, m, H-C9);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 155.3 (C7), 143.2 (ArC), 141.6 (ArC), 136.7 (ArC), 129.6 (C3), 128.4 (ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (ArC), 127.9 (ArC), 127.0 (ArC), 125.8 (C4), 67.0 (C8), 51.9 (C2), 37.0 (C9), 35.8 (C6), 32.4 (C10), 24.8 (C5);  $m/z$  (CI) 322 ( $\text{MH}^+$ , 100), 216 (20), 188 (30); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  322.1796,  $\text{C}_{21}\text{H}_{24}\text{NO}_2$  requires 322.1802.

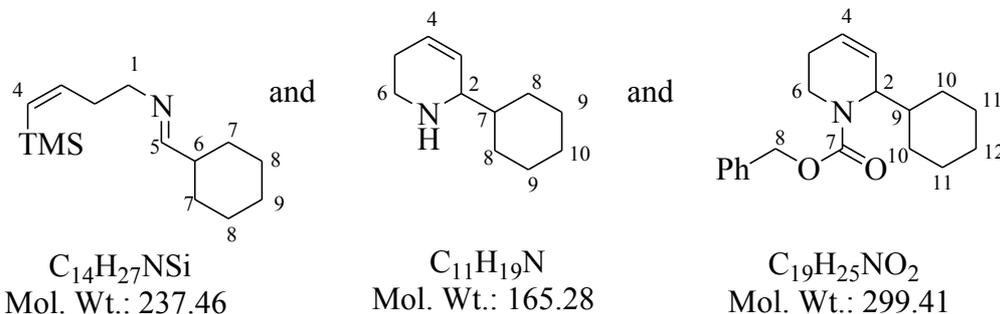
**(3Z)-N-Octylidene-4-(trimethylsilyl)but-3-en-1-amine (366)** and **(±)-2-Heptyl-1,2,5,6-tetrahydropyridine (371d)** and **(±)-Benzyl 2-heptyl-1,2,5,6-tetrahydropyridine-1-carboxylate (372d)**.



Following the general procedure Q, (Z)-4-(trimethylsilyl)but-3-en-1-amine **322** (150 mg, 1.05 mmol) in the presence of octanal (134 mg, 1.05 mmol), afforded the *title compound* **366** (232 mg, 0.92 mmol, 87%) as a yellow oil which was used in the next step without any further purification. The (3Z)-N-octylidene-4-(trimethylsilyl)but-3-en-1-amine **366** (143 mg, 0.56 mmol) after 17 hours at reflux was consumed based on analysis by NMR to afford the *title compound* **371d** (85 mg, 0.47 mmol, 83%) as a yellow oil which was used in the next step without any further purification. Then 2-heptyl-1,2,5,6-tetrahydropyridine **371d** (85 mg, 0.47 mmol) afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **372d** (74 mg, 0.23 mmol, 50%) as a colourless oil.

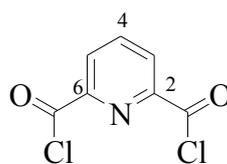
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  2926, 1702, 1425;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.41-7.28 (5H, m, Ar-H), 5.85-5.74 (1H, m, H-C4), 5.74-5.59 (1H, m, H-C3), 5.23-5.07 (2H, m, H-C8), 4.54-4.31 (1H, m, H-C2), 4.30-4.04 (1H, m, H-C6), 3.08-2.80 (1H, m, H-C6), 2.35-2.09 (1H, m, H-C5), 2.04-1.83 (1H, m, H-C5), 1.66-1.45 (2H, m, H-C9), 1.43-1.11 (10H, m, H-C10 to H-C14), 0.88 (3H, t,  $J$  6.7, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 155.0 (C7), 136.9 (ArC), 129.0 (C3), 128.4 (ArC), 128.3 (ArC), 127.8 (ArC), 124.6 (C4), 66.9 (C8), 52.2 (C2), 36.9 (C6), 34.3 (C9), 31.8 (C13), 29.4 (C11 and C12), 26.1 (C10), 24.8 (C5), 22.6 (C14), 14.1 (C15);  $m/z$  (CI) 316 ( $\text{MH}^+$ , 100), 216 (34), 111 (35); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  316.2268,  $\text{C}_{20}\text{H}_{30}\text{NO}_2$  requires 316.2271.

**(3Z)-N-(Cyclohexylmethylene)-4-(trimethylsilyl)but-3-en-1-amine (367) and (±)-2-Cyclohexyl-1,2,5,6-tetrahydropyridine (371e) and (±)-Benzyl 2-cyclohexyl-1,2,5,6-tetrahydropyridine-1-carboxylate(372e).**



Following the general procedure Q, (Z)-4-(trimethylsilyl)but-3-en-1-amine **322** (200 mg, 1.40 mmol) in the presence of cyclohexanecarbaldehyde (156 mg, 1.40 mmol), afforded the *title compound* **367** (332 mg, 1.40 mmol, *quantitative*) as a yellow oil which was used in the next step without any further purification. The (3Z)-N-(cyclohexylmethylene)-4-(trimethylsilyl)but-3-en-1-amine **367** (66 mg, 0.28 mmol) after 17 hours at reflux was consumed based on analysis by NMR to afford the *title compound* **371e** (40 mg, 0.24 mmol, 88%) as a yellow oil which was used in the next step without any further purification. Then 2-cyclohexyl-1,2,5,6-tetrahydropyridine **371e** (40 mg, 0.24 mmol) afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **372e** (32 mg, 0.11 mmol, 44%) as a colourless oil.

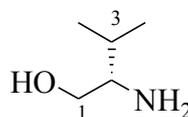
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3034, 2927, 1697, 1651;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.40-7.27 (5H, m, Ar-H), 5.84-5.78 (1H, m, H-C4), 5.82-5.71 (1H, m, H-C3), 5.17 (1H, d,  $J$  12.5, H-C8), 5.11 (1H, d,  $J$  12.5, H-C8), 4.32-4.19 (1H, m, H-C2), 4.20-4.06 (1H, m, H-C6), 3.06-2.84 (1H, m, H-C6), 2.38-2.06 (1H, m, H-C5), 2.05-1.83 (1H, m, H-C5), 1.84-1.45 (5H, m, H-C9 and H-C10), 1.38-0.94 (6H, m, H-C11 and H-C12);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 155.6 (C7), 136.9 (ArC), 128.4 (ArC), 127.8 (ArC), 127.7 (ArC), 127.3 (C3), 125.4 (C4), 66.9 (C8), 56.9 (C2), 42.6 (C9), 38.1 (C6), 29.9 (C10), 29.8 (C10), 26.3 (C11), 26.2 (C11 and C12), 24.9 (C5);  $m/z$  (CI) 300 ( $\text{MH}^+$ , 100), 216 (30), 166 (12); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  300.1957,  $C_{19}H_{26}NO_2$  requires 300.1958.

**Pyridine-2,6-dicarbonyl dichloride (374).**

$C_7H_3Cl_2NO_2$   
Mol. Wt.: 204.01

A round-bottomed flask equipped with a reflux condenser was charged with pyridine-2,6-dicarboxylic acid **373** (8.40 g, 50.26 mmol, 1.00 eq.) and redistilled thionyl chloride (54 mL) added dropwise. The resulting solution was stirred and heated to reflux temperature overnight, cooled to room temperature and concentrated *in vacuo*. This afforded the *title compound* **374** (10.20 g, 50.02 mmol, quantitative) as a cream solid, which was used in the next step without further purification.

M.p. 63-65 °C (Lit.: 60 °C in benzene);  $\delta_H$  (300 MHz;  $CDCl_3$ ) 8.37 (2H, d, *J* 7.9, H-C3 and H-C5), 8.19-8.13 (1H, m, H-C4); *m/z* (CI) 204 ( $M^+$ , 100), 168 (64), 142 (22). Data in agreement with literature values.

**(S)-2-Amino-3-methylbutan-1-ol (376).**

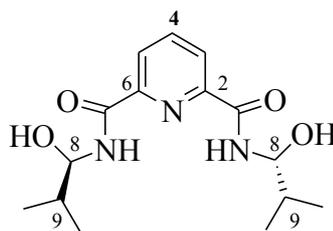
$C_5H_{13}NO$   
Mol. Wt.: 103.16

A round-bottomed flask equipped with a reflux condenser was charged with lithium aluminium hydride (10.63 g, 280.00 mmol, 2.00 eq.) and tetrahydrofuran (425 mL). The resulting suspension was stirred and cooled to 0 °C before adding slowly (*S*)-2-amino-3-methyl-butyric acid **375** (16.40 g, 140 mmol, 1 eq.) portionwise. The reaction was then stirred for an additional 1 hour at 0 °C, slowly warmed to room temperature and heated at reflux temperature overnight. After cooling to room temperature and then to 0 °C, a 2.0 M solution of sodium hydroxide (100 mL) was added dropwise to the reaction mixture, the organic layer separated and the precipitate extracted with boiling tetrahydrofuran (100 mL) for 1 hour. The combined organic layers were concentrated *in vacuo*, the solution diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium chloride (40 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the *title compound* **376** (11.18 g, 108 mmol, 77%) as a colourless oil which was used in the next step without any further purification.

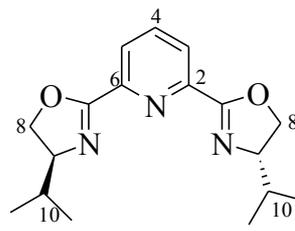
Experimental

$[\alpha]_D^{26} = +26.0$  ( $c$  1.0,  $\text{CDCl}_3$ ), (Lit.:  $[\alpha]_D^{18} = +22.9$  ( $c$  0.6,  $\text{EtOH}$ ));  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 3.62-3.57 (1H, m, H-C1), 3.30-3.24 (1H, m, H-C1), 2.56-2.50 (1H, m, H-C2), 2.36 (3H, bs, H-OH and H-NH<sub>2</sub>) 1.61-1.49 (1H, m, H-C3), 0.89-0.86 (6H, m, H-C4);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 64.9 (C1), 58.8 (C2), 31.6 (C3), 19.7 (C4), 18.8 (C4). Data in agreement with literature values.

***N,N*-bis((*R*)-1-hydroxy-2-methylpropyl)pyridine-2,6-dicarboxamide (377) and 2,6-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]pyridine (349).**



$\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_4$   
Mol. Wt.: 309.36



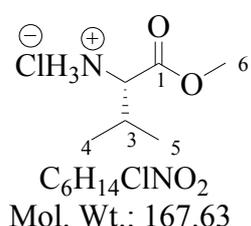
$\text{C}_{17}\text{H}_{23}\text{N}_3\text{O}_2$   
Mol. Wt.: 301.38

A round-bottomed flask equipped with a reflux condenser was charged with (*S*)-(+)-2-amino-3-methylbutan-1-ol **376** (7.60 g, 73.90 mmol), triethylamine (28 mL, 201.50 mmol) and chloroform (133 mL) and the resulting solution was stirred at 0 °C. To this solution was added dropwise, a solution of pyridine-2,6-dicarbonyl chloride **374** (6.85 g, 33.58 mmol) in chloroform (66 mL) over 45 minutes. The resulting suspension was stirred and warmed to room temperature for 18 hours, thionyl chloride (24.80 mL) was added and the mixture heated to reflux temperature for 2 hours. The reaction mixture was slowly poured onto ice water (100 mL), the organic layer separated, washed with saturated aqueous sodium chloride (50 mL), a 1.0 M aqueous solution of potassium carbonate (50 mL), and the aqueous layer extracted with chloroform (50 mL). The combined organic layers were dried over sodium sulphate, filtered, and concentrated *in vacuo* to give a brown solid which was purified by flash column chromatography (60% chloroform 40% ether) to afford the dihydrochloride salt of the *title compound* **377** as a light brown solid. A round-bottomed flask was charged with the dihydrochloride salt **377** (12.63 g) a solution of sodium hydroxide (9.25 g) in water (123 mL) and methanol (262 mL). The resulting suspension was stirred at room temperature for 72 hours, diluted with chloroform (420 mL), the organic layer was separated and washed with saturated aqueous sodium chloride (100 mL). The organic layer was dried over sodium sulphate, filtered, and concentrated *in vacuo* to afford a brown solid which was purified by recrystallization

(hexane / ethyl acetate) to afford the *title compound 349* (3.40 g, 11.00 mmol, 22%) as a white solid.

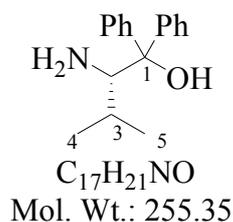
M.p. 148-150 °C (Lit.: 151-154 °C;  $[\alpha]_D^{21} = -114.0$  ( $c$  1.0, CH<sub>2</sub>Cl<sub>2</sub>), (Lit.:  $[\alpha]_D^{20} = -110.0$  ( $c$  0.7, CH<sub>2</sub>Cl<sub>2</sub>));  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 8.22 (2H, d,  $J$  7.8, H-C3 and H-C5), 7.88 (1H, t,  $J$  7.8, H-C4), 4.55 (2H, dd,  $J$  8.3, 9.5, H-C8), 4.24 (2H, t,  $J$  8.3, H-C8), 4.16 (2H, ddd,  $J$  6.6, 8.3, 9.5, H-C9), 1.94-1.83 (2H, m, H-C10), 1.06 (6H, d,  $J$  6.6, H-C11), 0.95 (6H, m, H-C11). Data in agreement with literature values.

**(S)-Valine methyl ester hydrochloride (378).**



A round-bottomed flask equipped with a reflux condenser was charged with methanol (208 mL). This was stirred and cooled to -10 °C and re-distilled thionyl chloride (18.25 mL, 250.00 mmol, 2.00 eq.) was added dropwise over 15 minutes. The resulting solution was stirred for a further 10 minutes and (S)-2-amino-3-methylbutanoic acid **375** (14.64 g, 125.00 mmol, 1.00 eq.) added portionwise. The mixture was slowly warmed to room temperature and then heated to reflux temperature for 20 hours. The mixture was cooled to room temperature and filtered to afford the *title compound 378* (14.42 g, 86.02 mmol, 69%) as a white solid which was used in the next step without further purification.

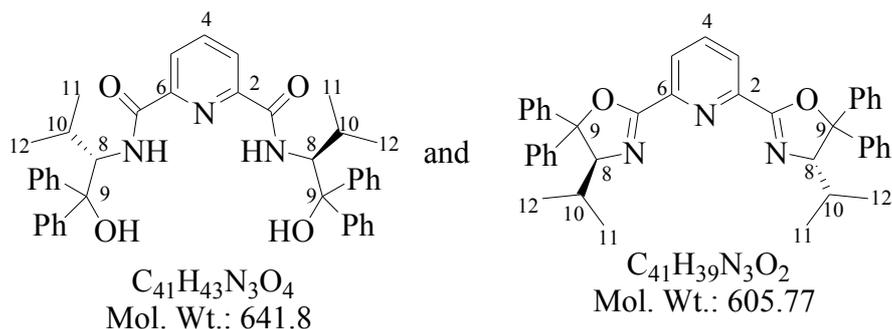
M.p. 165-168 °C (Lit.: 168-170 °C);  $[\alpha]_D^{25} + 14.1$  ( $c$  1.0, H<sub>2</sub>O), (Lit.:  $[\alpha]_D^{25} + 24.2$  ( $c$  1.0, MeOH));  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 8.84 (3H, s, H-NH<sub>2</sub><sup>+</sup>), 4.04-3.90 (1H, m, H-C2), 3.81 (3H, s, H-C6), 2.53-2.40 (1H, m, H-C3), 1.14 (3H, d,  $J$  4.5, H-C5), 1.12 (3H, d,  $J$  4.4, H-C4);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>) 168.7 (C1), 58.6 (C2), 52.9 (C6), 29.8 (C3), 18.3 (C5), 18.3 (C4). Data in agreement with literature values.

**(S)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (379).**

A round-bottomed flask equipped with a reflux condenser and a dropping funnel was charged with magnesium (4.80 g, 198.00 mmol, 5.50 eq.). Then bromobenzene (10.00 g, 63.83 mmol, 1.77 eq.) was added dropwise and the resulting suspension was stirred and heated to 45 °C for 15 minutes. To the mixture was added bromobenzene (18.2 g, 114.89 mmol, 3.19 eq.) in tetrahydrofuran (150 mL) at a dropwise rate that allowed steady reflux over 1 hour. The mixture was heated to 65 °C for 1 hour, cooled to 0 °C and (*S*)-valine methyl ester hydrochloride **378** (6.00 g, 36.00 mmol, 1.00 eq.) added portionwise. The mixture was heated to 65 °C, stirred overnight, cooled to room temperature and diluted with diethyl ether (100 mL). To the mixture was added dropwise a saturated aqueous solution of ammonium chloride (100 mL), the organic layer was separated and washed with a saturated aqueous solution of sodium chloride (100 mL). The organic layer was dried over sodium carbonate, filtered and concentrated *in vacuo*. This afforded a yellow oil which was purified by flash column chromatography (67% hexane 33% ethyl acetate) to afford the *title compound* **379** (7.01 g, 27.45 mmol, 76%) as a white solid.

M.p. 91-92 °C (Lit.: 94-95 °C);  $[\alpha]_D^{25}$  - 127.0 (*c* 0.9, CHCl<sub>3</sub>), (Lit.:  $[\alpha]_D^{25}$  - 113.1 (*c* 1.0, CHCl<sub>3</sub>));  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.62 (2H, d, *J* 7.6, Ar-H), 7.49 (2H, d, *J* 7.6, Ar-H), 7.35-7.24 (4H, m, Ar-H), 7.23-7.12 (2H, m, Ar-H), 3.85 (1H, d, *J* 1.9, H-C2), 1.83-1.67 (1H, m, H-C3), 0.93 (3H, d, *J* 7.0, H-C5), 0.89 (3H, d, *J* 6.8, H-C4); *m/z* (CI) 238 (M(-OH)<sup>+</sup>, 100), 182 (50), 105 (60). Data in agreement with literature values.

*N,N*-Bis((*S*)-1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)pyridine-2,6-dicarboxamide (**380**) and 2,6-Bis((*S*)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (**348**).



A round-bottomed flask was charged with (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol **379** (6.83 g, 26.75 mmol, 2.00 eq.) and dichloromethane (80 mL). The resulting solution was stirred and cooled to 0 °C, triethylamine (9.32 mL, 66.88 mmol, 5.00 eq.) was added dropwise followed by a solution of pyridine-2,6-dicarbonyl dichloride **374** (2.73 g, 13.37 mmol, 1.00 eq.) in dichloromethane (13 mL) dropwise. The resulting solution was warmed to room temperature and stirred for 20 hours, diluted with dichloromethane (50 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL), water (50 mL) and a saturated aqueous solution of sodium chloride (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a pale yellow oil which was purified by flash column chromatography (67% hexane 33% ethyl acetate) to afford the *title compound* **380** (3.23 g, 5.03 mmol, 38%) as a sticky pale yellow oil which was used immediately in the next step.

$[\alpha]_D^{25}$  - 46.2 (*c* 1.0,  $CHCl_3$ ), (Lit.:  $[\alpha]_D^{25}$  - 50.3 (*c* 1.0,  $CHCl_3$ ));  $\delta_H$  (300 MHz;  $CDCl_3$ ) 8.28 (2H, d, *J* 10.2, H-NH), 8.20 (2H, d, *J* 7.7, H-C3 and H-C5), 8.00-7.93 (1H, m, H-C4), 7.57-7.49 (8H, m, Ar-H), 7.38 (4H, t, *J* 7.6, Ar-H), 7.25-7.16 (6H, m, Ar-H), 7.13-7.05 (2H, m, Ar-H), 5.09 (2H, dd, *J* 10.2, 1.7, H-C8), 1.98-1.86 (2H, m, H-C10), 1.13 (3H, d, *J* 6.1, H-C11), 0.93 (3H, d, *J* 6.9, H-C11), 0.92 (6H, d, *J* 6.7, H-C12). Data in agreement with literature values.

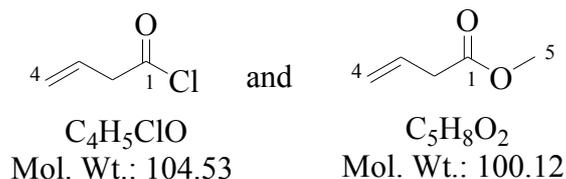
A round-bottomed flask equipped with a reflux condenser was charged with *N,N*-bis((*S*)-1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)pyridine-2,6-dicarboxamide **380** (3.23 g, 5.03 mmol, 1.00 eq.) and dichloromethane (90 mL). The resulting solution was stirred at room temperature and powdered calcium hydride (636 mg, 15.10 mmol, 3.00 eq.) was added portionwise, followed by addition of methanesulfonic acid (1.96 mL, 30.21 mmol, 6.00 eq.) dropwise. The resulting suspension was heated to reflux temperature for 6 hours, the mixture cooled to room temperature, diluted with dichloromethane (90 mL) and a saturated aqueous solution of sodium hydrogen carbonate (90 mL) was added. The

*Experimental*

organic layer was separated and washed with water (100 mL) and a saturated aqueous solution of sodium chloride (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a pale yellow oil which was purified by flash column chromatography (80% hexane 20% ethyl acetate) to afford the *title compound* **348** (2.29 g, 3.77 mmol, 75%) as a pale yellow solid.

M.p. 87-88 °C (Lit.: 65-66 °C);  $[\alpha]_D^{25}$  -233.2 (*c* 2.7, CHCl<sub>3</sub>), (Lit.:  $[\alpha]_D^{25}$  -386.2 (*c* 1.1, CHCl<sub>3</sub>));  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 8.23 (2H, d, *J* 7.8, H-C3 and H-C5), 7.99-7.89 (1H, m, H-C4), 7.63 (4H, d, *J* 8.0, Ar-H), 7.41-7.34 (8H, m, Ar-H), 7.34-7.25 (8H, m, Ar-H), 4.90 (2H, d, *J* 4.9, H-C8), 2.01-1.83 (2H, m, H-C10), 1.07 (6H, d, *J* 6.8, H-C12), 0.69 (6H, d, *J* 6.5, H-C11);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>) 160.5 (C7), 147.1 (C2 and C6), 145.2 (ArC), 140.5 (C4), 128.3 (ArC), 127.8 (ArC), 127.7 (ArC), 127.3 (ArC), 127.0 (ArC), 126.3 (ArC), 125.5 (C3 and C5), 93.5 (C9), 80.5 (C8), 30.3 (C10), 22.0 (C12), 17.3 (C11). Data in agreement with literature values.

**But-3-enoyl chloride (497) and methyl but-3-enoate (484).**



A round-bottomed flask equipped with a reflux condenser was charged with but-3-enoic acid **496** (25.00 g, 290.00 mmol, 1.00 eq.). With stirring, redistilled thionyl chloride (42.50 mL, 600.00 mmol, 2.07 eq.) was added dropwise and the resulting solution was heated to 40 °C for 3 hours. The mixture was cooled to room temperature and the excess thionyl chloride was removed by distillation under reduced pressure to afford the *title compound* **497** (30.31 g, 290.00 mmol, 100%) as a pale yellow oil which was used in the next step without further purification.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>) 5.87 (1H, tdd, *J* 17.0, 10.3, 6.8, H-C3), 5.30 (1H, ddd, *J* 13.2, 2.5, 1.3, H-C4), 5.24 (1H, ddd, *J* 13.2, 2.5, 1.3, H-C4), 3.60 (2H, td, *J* 6.8, 1.3, H-C2). Data in agreement with literature values.

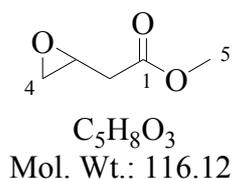
A round-bottomed flask was charged with methanol (300 mL), cooled to 0 °C and **497** (30.31 g, 290.00 mmol, 1.00 eq.) added dropwise. The resulting solution was slowly warmed to room temperature and stirred for 1 hour, water (100 mL) and dichloromethane (100 mL) added and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were washed with a

*Experimental*

saturated aqueous solution of sodium chloride (200 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a pale yellow oil. This was purified by distillation under reduced pressure (80 °C, 250 mmHg) to give the *title compound 484* (12.49 g, 125.00 mmol, 43%) as a colourless oil.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.89-5.68 (1H, m, H-C3), 5.09-4.99 (2H, m, H-C4), 3.60-3.54 (3H, m, H-C5), 2.98 (2H, d,  $J$  6.9, H-C2);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 171.5 (C1), 130.0 (C3), 118.1 (C4), 51.4 (C5), 38.5 (C2). Data in agreement with literature values.

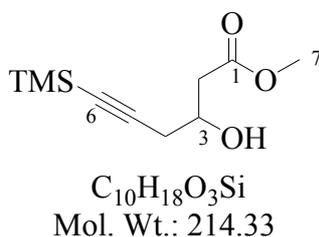
**(±)-Methyl 2-(oxiran-2-yl)acetate (485).**



Following the general procedure P, albeit without the use of sodium hydrogen carbonate, methyl but-3-enoate **484** (10.24 g, 102.27 mmol), was consumed based on analysis by NMR after 24 hours of stirring at 0 °C. The work up gave the *title compound 485* (10.46 g, 90.08 mmol, 88%) as a colourless oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 3.73 (3H, s, H-C5), 3.34-3.25 (1H, m, H-C3), 2.87-2.83 (1H, m, H-C4), 2.59-2.56 (2H, m, H-C2), 2.58-2.55 (1H, m, H-C4);  $m/z$  (CI) 117 ( $\text{MH}^+$ , 100). Data in agreement with literature values.

**(±)-Methyl 3-hydroxy-6-(trimethylsilyl)hex-5-ynoate (486).**



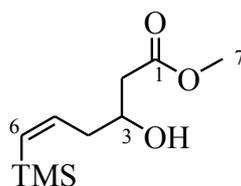
Following the general procedure G, methyl 2-(oxiran-2-yl)acetate **485** (1.79 g, 15.40 mmol) afforded a pale yellow oil, which was purified by flash column chromatography (80% hexane, 20% ethyl acetate) to give the *title compound 486* (1.70 g, 7.94 mmol, 52%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  3469, 2958, 2176, 1738;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 4.25-4.06 (1H, m, H-C3), 3.73 (3H, s, H-C7), 2.97 (1H, d,  $J$  4.5, H-OH), 2.70 (1H, dd,  $J$  16.5, 3.6, H-C2), 2.54

*Experimental*

(1H, dd,  $J$  16.5, 8.5, H-C2), 2.53-2.46 (2H, m, H-C4), 0.15 (9H, s, H-CTMS);  $\delta_c$  (75.5 MHz; CDCl<sub>3</sub>) 172.8 (C1), 102.0 (C6), 87.9 (C5), 66.5 (C3), 51.9 (C7), 39.9 (C2), 27.8 (C4), -0.0 (CTMS);  $m/z$  (CI) 215 (MH<sup>+</sup>, 65), 197 (100), 183 (55); HRMS (ES) Found [M+H]<sup>+</sup> 215.1096, C<sub>10</sub>H<sub>19</sub>O<sub>3</sub>Si requires 215.1098.

**(±)-(Z)-Methyl 3-hydroxy-6-(trimethylsilyl)hex-5-enoate (487).**

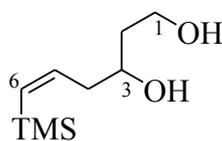


C<sub>10</sub>H<sub>20</sub>O<sub>3</sub>Si  
Mol. Wt.: 216.35

Following the general procedure L, (±)-methyl 3-hydroxy-6-(trimethylsilyl)hex-5-ynoate **486** (765 mg, 3.57 mmol) afforded a yellow oil, which was purified by flash column chromatography (95% hexane, 5% ethyl acetate) to give the *title compound* **487** (315 mg, 1.46 mmol, 41%) as pale yellow oil.

$\nu_{\max}$ (neat)/cm<sup>-1</sup> 3450, 2955, 1738, 1607;  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 6.30 (1H, td,  $J$  14.6, 7.3, H-C5), 5.72-5.65 (1H, m, H-C6), 4.09 (1H, ddt,  $J$  10.1, 6.8, 3.5, H-C3), 3.71 (3H, s, H-C7), 2.91 (1H, d,  $J$  3.6, H-OH), 2.54 (1H, dd,  $J$  16.4, 3.5, H-C2), 2.48-2.40 (1H, m, H-C2), 2.44-2.26 (2H, m, H-C4), 0.12 (9H, s, H-CTMS);  $\delta_c$  (75.5 MHz; CDCl<sub>3</sub>) 173.2 (C1), 143.1 (C5), 133.0 (C6), 67.7 (C3), 51.8 (C7), 40.4 (C2), 40.1 (C4), 0.2 (CTMS);  $m/z$  (CI) 217 (MH<sup>+</sup>, 15), 199 (26), 127 (100); HRMS (ES) Found [M+H]<sup>+</sup> 217.1253, C<sub>10</sub>H<sub>21</sub>O<sub>3</sub>Si requires 217.1254.

**(±)-(Z)-6-(Trimethylsilyl)hex-5-ene-1,3-diol (501).**



C<sub>9</sub>H<sub>20</sub>O<sub>2</sub>Si  
Mol. Wt.: 188.34

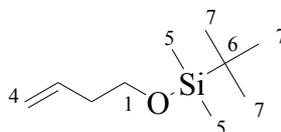
A round-bottomed flask equipped with a dropping funnel was charged with lithium aluminium hydride (70 mg, 1.85 mmol, 2.35 eq.) and tetrahydrofuran (13 mL). The resulting suspension was stirred and cooled to 0 °C and a solution of (±)-(Z)-methyl 3-hydroxy-6-(trimethylsilyl)hex-5-enoate **487** (170 mg, 0.79 mmol, 1.00 eq.) in

*Experimental*

tetrahydrofuran (5 mL) was added dropwise over 30 minutes. The mixture was stirred for a further hour at 0 °C and then warmed to room temperature for 1 hour. Again the mixture was cooled to 0 °C and a saturated aqueous solution of sodium chloride (4 mL) was added dropwise followed by diethyl ether (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were then dried over sodium sulfate, filtered and concentrated *in vacuo*. This gave the *title compound* **501** (121 mg, 0.64 mmol, 81%) as a colourless oil which was used in the next step without any further purification.

$\nu_{\max}$ (neat)/ $\text{cm}^{-1}$  3350, 2954, 1606;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.20 (1H, td,  $J$  14.4, 7.4, H-C5), 5.60 (1H, td,  $J$  14.4, 1.2, H-C6), 3.88-3.78 (1H, m, H-C3), 3.82-3.69 (2H, m, H-C1), 2.33 (1H, bs, H-OH), 2.30-2.21 (2H, m, H-C4), 1.70-1.57 (2H, m, H-C2), 1.54 (1H, bs, H-OH), 0.03 (9H, s, H-CTMS);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 143.6 (C5), 133.4 (C6), 71.6 (C3), 61.9 (C1), 41.5 (C2), 37.8 (C4), 0.2 (CTMS);  $m/z$  (CI) 189 ( $\text{MH}^+$ , 80), 147 (72), 103 (100); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  189.1305,  $\text{C}_9\text{H}_{21}\text{O}_2\text{Si}$  requires 189.1305.

**(But-3-enyloxy)(tert-butyl)dimethylsilane (504).**



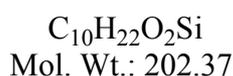
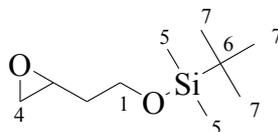
$\text{C}_{10}\text{H}_{22}\text{OSi}$   
Mol. Wt.: 186.37

A round-bottomed flask was charged with *tert*-butylchlorodimethylsilane (5.00 g, 33.00 mmol, 1.00 eq.) and dichloromethane (100 mL). The resulting solution was stirred at room temperature and imidazole (2.25 g, 33.00 mmol, 1.00 eq.) was added followed by 3-buten-1-ol **503** (2.35 g, 32.50 mmol, 0.98 eq.) dropwise. The mixture was stirred for 2 hours at room temperature and diluted with diethyl ether (75 mL). The mixture was washed with water (3 x 50 mL) and a saturated aqueous solution of sodium chloride (1 x 50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. This gave the *title compound* **504** (5.47 g, 29.35 mmol, 90%) as a colourless oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 5.81 (1H, tdd,  $J$  17.1, 10.2, 6.9, H-C3), 5.12-4.98 (2H, m, H-C4), 3.65 (2H, t,  $J$  6.8, H-C1), 2.32-2.23 (2H, m, H-C2), 0.89 (9H, s, H-C7), 0.05 (6H, s, H-C5);  $m/z$  (CI) 187 ( $\text{MH}^+$ , 44), 171 (57), 145(100). Data in agreement with literature

values.

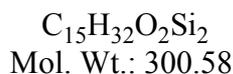
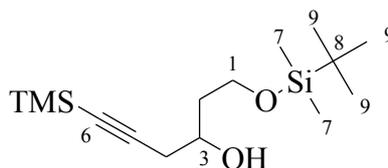
***tert*-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (505).**



Following the general procedure P, albeit without the use of sodium hydrogen carbonate, (but-3-enyloxy)(*tert*-butyl)dimethylsilane **504** (5.47 g, 29.33 mmol), was consumed based on analysis of NMR after 72 hours of stirring at room temperature instead of 0 °C. The work-up gave the *title compound* **505** (5.21 g, 25.74 mmol, 88%) as a colourless oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 3.80-3.75 (2H, m, H-C1), 3.05 (1H, dddd,  $J$  6.6, 5.1, 4.1, 2.8, H-C3), 2.81-2.76 (1H, m, H-C4), 2.52 (1H, dd,  $J$  5.1, 2.8, H-C4), 1.84-1.63 (2H, m, H-C2), 0.90 (9H, s, H-C7), 0.06 (6H, s, H-C5);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 60.0 (C1), 50.1 (C3), 47.2 (C4), 35.9 (C2), 25.9 (C7), 18.3 (C6), -5.4 (C5). Data in agreement with literature values.

**(±)-1-(*tert*-Butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-yn-3-ol (506).**



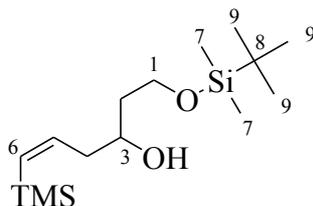
A three-necked round-bottomed flask equipped with a dropping funnel and a thermometer was charged with trimethylsilylacetylene (2.15 g, 22.00 mmol, 1.00 eq.) and tetrahydrofuran (25 ml). The resulting solution was cooled to -78 °C and a 2.5 M solution of *n*-butyllithium in hexane (8.80 mL, 22.00 mmol, 1.47 eq.) was added dropwise. The solution was stirred at this temperature for 1 hour, and then *tert*-butyldimethyl(2-(oxiran-2-yl)ethoxy)silane **505** (3.03 g, 15.00 mmol, 1.00 eq.) in tetrahydrofuran (25 mL) was added dropwise, followed by boron trifluoride etherate (2.74 mL, 22.00 mmol, 1.47 eq.) dropwise. The resulting solution was stirred at -78 °C for 1 hour and then slowly warmed to room temperature for 30 minutes. To the mixture was added a saturated aqueous

*Experimental*

solution of sodium chloride (100 mL) dropwise followed by ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. This afforded a pale yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound 506* (4.15 g, 13.80 mmol, 92%) as a pale yellow oil.

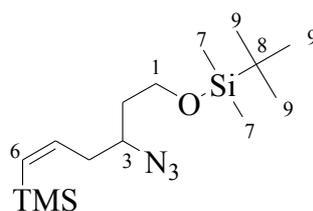
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3430, 2956, 2176, 1642;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 4.03-3.90 (1H, m, H-C3), 3.95-3.79 (2H, m, H-C1), 2.49 (1H, dd,  $J$  16.8, 5.8, H-C4), 2.39 (1H, dd,  $J$  16.8, 7.0, H-C4), 1.91-1.79 (1H, m, H-C2), 1.79-1.65 (1H, m, H-C2), 0.90 (9H, s, H-C9), 0.15 (9H, s, H-CTMS), 0.08 (6H, s, H-C7);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 103.5 (C6), 86.8 (C5), 70.3 (C3), 62.2 (C1), 37.2 (C2), 28.5 (C4), 25.8 (C9), 18.1 (C8), 0.1 (CTMS), -5.5 (C7), -5.5 (C7);  $m/z$  (CI) 301 ( $\text{MH}^+$ , 57), 283 (100), 189 (70); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  301.2017,  $\text{C}_{15}\text{H}_{33}\text{O}_2\text{Si}_2$  requires 254.1209.

**(±)-(Z)-1-(*tert*-Butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ol (502).**



Following the general procedure L, (±)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ol **506** (1.34 g, 4.47 mmol) afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound 502* (807 mg, 2.67 mmol, 60%) as a pale yellow oil.

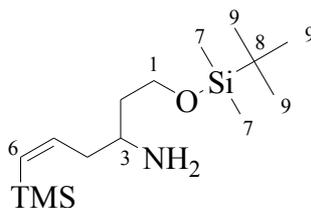
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3367, 2972, 1615;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 6.34 (1H, td,  $J$  14.3, 7.3, H-C5), 5.63 (1H, td,  $J$  14.3, 1.3, H-C6), 3.96-3.86 (2H, m, H-C1), 3.85-3.76 (1H, m, H-C3), 3.43 (1H, bs, H-OH), 2.47-2.23 (2H, m, H-C4), 1.71-1.62 (2H, m, H-C2), 0.90 (9H, s, H-C9), 0.12 (9H, s, H-CTMS), 0.08 (6H, s, H-C7);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 144.5 (C5), 131.8 (C6), 71.9 (C3), 62.8 (C1), 41.2 (C2), 37.8 (C4), 25.8 (C9), 18.1 (C8), 0.2 (CTMS), -5.5 (C7), -5.6 (C7);  $m/z$  (CI) 303 ( $\text{MH}^+$ , 25), 285 (37), 189 (100); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  303.2165,  $\text{C}_{15}\text{H}_{35}\text{O}_2\text{Si}_2$  requires 303.2170.

**(±)-(Z)-(3-Azido-1-(tert-butyldimethylsilyloxy)hex-3-enyl)trimethylsilane (508).**

C<sub>15</sub>H<sub>33</sub>N<sub>3</sub>OSi<sub>2</sub>  
Mol. Wt.: 327.61

A round-bottomed flask was charged with (±)-(Z)-1-(tert-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ol **502** (678 mg, 2.24 mmol, 1.00 eq.) and tetrahydrofuran (27 mL). The resulting solution was stirred at room temperature and triphenylphosphine (1.18 g, 4.48 mmol, 2.00 eq.) was added in one portion, followed by diisopropyl azodicarboxylate (896 μL, 4.48 mmol, 2.00 eq.) dropwise and diphenylphosphoryl azide (964 μL, 4.48 mmol, 2.00 eq.) dropwise. After stirring at room temperature for 1 hour, the mixture was concentrated *in vacuo* and filtered through a pad of celite, washing with 1 part diethyl ether to 1 part pentane (50 mL). The filtrate was concentrated *in vacuo* to afford a pale yellow oil, which was purified by flash column chromatography (95% hexane, 5% ethyl acetate) to give the *title compound* **508** (671 mg, 2.05 mmol, 91%) as a colourless oil.

$\nu_{\max}$ (neat)/cm<sup>-1</sup> 2955, 2100, 1607;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 6.22 (1H, td, *J* 14.3, 7.2, H-C5), 5.62-5.55 (1H, m, H-C6), 3.66-3.58 (2H, m, H-C1), 3.56-3.45 (1H, m, H-C3), 2.33-2.26 (2H, m, H-C4), 1.71-1.58 (1H, m, H-C2), 1.56-1.41 (1H, m, H-C2), 0.79 (9H, s, H-C9), 0.04 (9H, s, H-CTMS), -0.03 (3H, s, H-C7), -0.04 (3H, s, H-C7);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 143.3 (C5), 132.8 (C6), 59.5 (C3), 59.4 (C1), 38.4 (C4), 37.1 (C2), 25.9 (C9), 18.3 (C8), 0.1 (CTMS), -5.4 (C7), -5.4 (C7); *m/z* (CI) 300 (M(-N<sub>2</sub>)H<sup>+</sup>, 100), 285 (65), 286 (37); HRMS (EI) Found [M-N<sub>2</sub>]<sup>+</sup> 299.2092, C<sub>15</sub>H<sub>33</sub>NOSi<sub>2</sub> requires 299.2095.

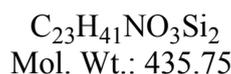
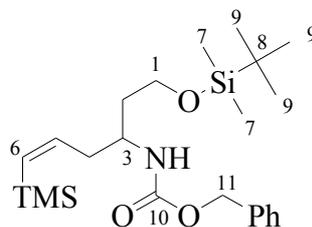
**(±)-(Z)-1-(tert-Butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine (509).**

C<sub>15</sub>H<sub>35</sub>NOSi<sub>2</sub>  
Mol. Wt.: 301.62

A round-bottomed flask equipped with a reflux condenser was charged with (±)-(Z)-(4-azido-6-(tert-butyldimethylsilyloxy)hex-1-enyl)trimethylsilane **508** (1.13 g, 3.45 mmol, 1.00 eq.), water (2.8 mL) and tetrahydrofuran (26 mL). The resulting biphasic solution was stirred at room temperature and triphenylphosphine (994 mg, 3.45 mmol, 1.00 eq.) was added portionwise. The mixture was heated to 60 °C and after 20 hours, GCMS showed complete consumption of starting material. To the solution was added a saturated aqueous solution of sodium chloride (10 mL), the organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. This afforded a yellow oil, which was purified by short flash column chromatography (50% pentane, 50% ethyl acetate) to give the *title compound* **509** (1.04 g, 3.45 mmol, *quantitative*) as a pale yellow oil.

$\nu_{\max}$ (neat)/cm<sup>-1</sup> 3380, 2955, 1605;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 6.19 (1H, td, *J* 14.5, 7.4, H-C5), 5.54-5.46 (1H, m, H-C6), 3.68-3.54 (2H, m, H-C1), 2.93-2.81 (1H, m, H-C3), 2.27-2.09 (1H, m, H-C4), 2.09-1.94 (1H, m, H-C4), 1.64-1.47 (1H, m, H-C2), 1.44-1.30 (1H, m, H-C2), 0.77 (9H, s, H-C9), 0.00 (9H, s, H-CTMS), -0.07 (6H, s, H-C7);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 145.6 (C5), 131.7 (C6), 61.0 (C1), 49.3 (C3), 42.0 (C2), 40.1 (C4), 25.9 (C9), 18.2 (C8), 0.3 (CTMS), -5.4 (C7); *m/z* (CI) 302 (MH<sup>+</sup>, 100), 286 (40), 188 (82); HRMS (ES) Found [M+H]<sup>+</sup> 302.2328, C<sub>15</sub>H<sub>36</sub>NOSi<sub>2</sub> requires 302.2330.

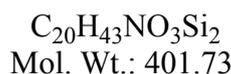
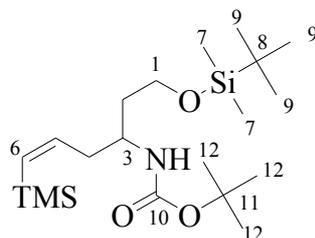
(±)-(Z)-Benzyl-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ylcarbamate (**510**).



A round-bottomed flask was charged with (±)-(Z)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine **509** (1.46 g, 4.84 mmol, 1.00 eq.), water (4.7 mL) and tetrahydrofuran (4.7 mL). The resulting biphasic solution was stirred and cooled to 0 °C, then sodium hydrogen carbonate (1.22g, 14.53 mmol, 3.00 eq.) was added portionwise followed by benzyl chloroformate (968 μL, 6.78 mmol, 1.40 eq.) dropwise. The mixture was allowed to warm slowly to room temperature and stirred for 72 hours. The solution was then diluted with ethyl acetate (10 mL), the organic layer separated and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **510** (1.35 g, 3.10 mmol, 64%) as a colourless oil.

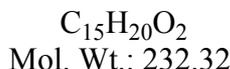
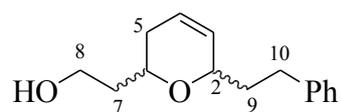
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3332, 3034, 2954, 1712, 1607;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.42-7.27 (5H, m, Ar-H), 6.28 (1H, td, *J* 14.2, 7.2, H-C5), 5.61 (1H, d, *J* 14.2, H-C6), 5.33-5.15 (1H, m, H-NH), 5.08 (2H, s, H-C11), 3.93-3.80 (1H, m, H-C3), 3.79-3.63 (2H, m, H-C1), 2.50-2.27 (2H, m, H-C4), 1.90-1.72 (1H, m, H-C2), 1.71-1.59 (1H, m, H-C2), 0.88 (9H, s, H-C9), 0.11 (9H, s, H-CTMS), 0.04 (3H, s, H-C7), 0.04 (3H, s, H-C7);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 155.8 (C10), 144.0 (C5), 136.7 (ArC), 132.0 (C6), 128.4 (ArC), 127.9 (ArC), 127.9 (ArC), 66.3 (C11), 60.4 (C1), 49.4 (C3), 38.3 (C2), 36.1 (C4), 25.9 (C9), 18.1 (C8), 0.2 (CTMS), -5.5 (C7), -5.5 (C7); *m/z* (CI) 436 (MH<sup>+</sup>, 98), 328 (70), 224 (100);

(±)-(Z)-*tert*-Butyl-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ylcarbamate (**511**).



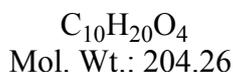
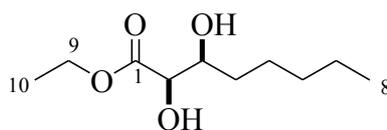
A round-bottomed flask was charged with (±)-(Z)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine **509** (300 mg, 1.00 mmol, 1.00 eq.) and dichloromethane (16 mL). The resulting solution was stirred and cooled to 0 °C, then triethylamine (142  $\mu$  L, 1.00 mmol, 1.00 eq.) added dropwise, followed by a solution of di-*tert*-butyl dicarbonate (267 mg, 1.23 mmol, 1.23 eq.) in dichloromethane (2 mL) dropwise. The mixture was allowed to warm slowly to room temperature and after 1 hour, analysis by GCMS showed complete consumption of starting material. The solution was concentrated *in vacuo* to afford a pale yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **511** (290 mg, 0.72 mmol, 72%) as a colourless oil.

$\nu_{\max}$ (neat)/ $cm^{-1}$  3422, 2263, 2955, 1716, 1606;  $\delta_H$  (300 MHz;  $CDCl_3$ ) 6.24 (1H, td,  $J$  14.4, 7.3, H-C5), 5.59-5.51 (1H, m, H-C6), 4.98 (1H, d,  $J$  6.9, H-NH), 3.78-3.68 (1H, m, H-C3), 3.71-3.59 (2H, m, H-C1), 2.39-2.21 (2H, m, H-C4), 1.82-1.65 (1H, m, H-C2), 1.61-1.46 (1H, m, H-C2), 1.38 (9H, s, H-C12), 0.85 (9H, s, H-C9), 0.07 (9H, s, H-CTMS), 0.01 (6H, s, H-C7);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ) 155.5 (C10), 144.4 (C5), 132.2 (C6), 78.7 (C11), 60.6 (C1), 48.9 (C3), 38.6 (C2), 36.3 (C4), 28.4 (C12), 25.9 (C9), 18.2 (C8), 0.2 (CTMS), -5.5 (C7);  $m/z$  (CI) 402 ( $MH^+$ , 10), 346 (68), 302 (100); HRMS (ES) Found  $[M+H]^+$  402.2853,  $C_{20}H_{44}NO_3Si_2$  requires 402.2854.

**(±)-2-(6-Phenethyl-3,6-dihydro-2H-pyran-2-yl)ethanol (515).**

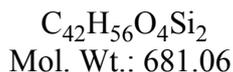
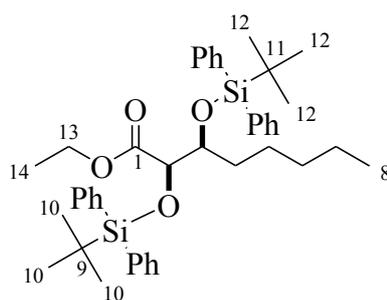
Following the general procedure I, (±)-(Z)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-ol **502** (500 mg, 1.65 mmol) in the presence of 3-phenylpropanal (203 mg, 1.65 mmol), was consumed based on analysis by TLC after 20 hours of stirring at room temperature instead of reflux temperature. The work-up afforded the *title compound* **515** (303 mg, 1.30 mmol, 79%) as a colourless oil which was used in the next step without any further purification.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3401, 3027, 2928, 1603;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.29-7.08 (5H, m, Ar-H), 5.82-5.72 (1H, m, H-C4), 5.57 (1H, tdd,  $J$  10.2, 2.6, 1.3, H-C3), 4.20-4.07 (1H, m, H-C2), 3.84-3.78 (2H, m, H-C8), 3.80-3.73 (1H, m, H-C6), 2.79-2.57 (2H, m, H-C10), 2.17-1.99 (1H, m, H-C7), 1.97-1.80 (1H, m, H-C7), 1.83-1.69 (4H, m, H-C5 and H-C9);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 141.9 (ArC), 129.8 (C3), 128.4 (ArC), 128.3 (ArC), 125.8 (ArC), 124.6 (C4), 74.8 (C6), 74.0 (C2), 61.8 (C8), 37.4 (C9), 37.1 (C5), 31.4 (C10), 31.1 (C7);  $m/z$  (CI) 233 ( $\text{MH}^+$ , 75), 197 (50), 159 (100); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  250.1800,  $\text{C}_{15}\text{H}_{24}\text{NO}_2$  requires 250.1802.

**(±)-(2,3-*syn*)-Ethyl 2,3-dihydroxyoctanoate (517).**

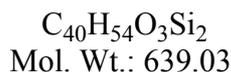
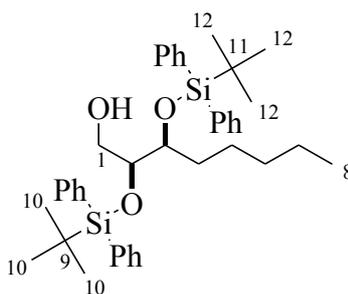
Following the general procedure J, (*E*)-ethyl oct-2-enoate **516** (5.00 g, 29.37 mmol) afforded the *title compound* **517** (5.99 g, 29.37 mmol, *quantitative*) as a colourless oil which was used in the next step without any further purification.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 4.25 (2H, q,  $J$  7.1, H-C9), 4.06 (1H, d,  $J$  2.2, H-C2), 3.89-3.82 (1H, m, H-C3), 2.85 (2H, bs, H-OH), 1.63-1.54 (2H, m, H-C4), 1.53-1.27 (6H, m, H-C5 to H-C7), 1.29 (3H, t,  $J$  7.1, H-C10), 0.90-0.84 (3H, m, H-C8);  $m/z$  (CI) 205 ( $\text{MH}^+$ , 100), 187 (76), 169 (40). Data in agreement with literature values.

**(±)-(2,3-syn)-Ethyl 2,3-bis(*tert*-butyldiphenylsilyloxy)octanoate (518).**

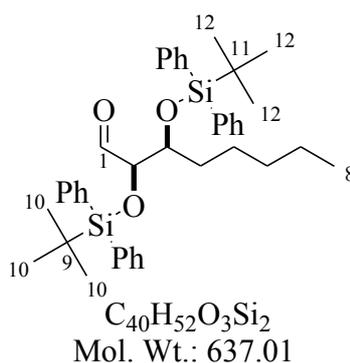
A round-bottomed flask was charged with (±)-(2,3-syn)-ethyl 2,3-dihydroxyoctanoate **517** (2.00 g, 9.79 mmol, 1.00 eq.) and *N,N*-dimethylformamide (20 mL). The resulting solution was stirred at room temperature and imidazole (3.33 g, 48.95 mmol, 5.00 eq.) was added followed by *tert*-butylchlorodiphenylsilane (6.36 mL, 24.47 mmol, 2.50 eq.). The resulting mixture was stirred for 20 hours at room temperature until analysis by GCMS showed complete consumption of starting material. To the mixture was added water (40 mL) followed by ethyl acetate (300 mL). The organic layer was separated and washed with water (100 mL) then a saturated aqueous solution of sodium chloride (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. This afforded a pale yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **518** (5.38 g, 7.90 mmol, 81%) as a sticky colourless oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3071, 2955, 1747;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.73-7.66 (4H, m, Ar-H), 7.65-7.56 (4H, m, Ar-H), 7.43-7.27 (12H, m, Ar-H), 4.31 (1H, d, *J* 3.0, H-C2), 3.97 (1H, dt, *J* 6.4, 3.0, H-C3), 3.93-3.69 (2H, m, H-C13), 1.96-1.72 (1H, m, H-C4), 1.38-1.18 (3H, m, H-C4 and H-C5), 1.06 (9H, s, H-C10), 1.00 (9H, s, H-C12), 0.95 (3H, t, *J* 7.2, H-C14), 0.94-0.83 (4H, m, H-C6 and H-C7), 0.70 (3H, t, *J* 7.0, H-C8);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 171.7 (C1), 136.0 (ArC), 136.0 (ArC), 135.9 (ArC), 135.7 (ArC), 134.3 (ArC), 133.7 (ArC), 133.5 (ArC), 133.4 (ArC), 129.6 (ArC), 129.5 (ArC), 129.5 (ArC), 129.4 (ArC), 127.5 (ArC), 127.4 (ArC), 127.3 (ArC), 127.3 (ArC), 75.5 (C2), 74.7 (C3), 60.4 (C13), 32.6 (C4), 31.4 (C6), 26.9 (C10), 26.8 (C12), 25.3 (C5), 22.3 (C7), 19.6 (C9), 19.4 (C11), 14.1 (C14), 13.9 (C8); *m/z* (CI) 698 ( $\text{MNH}_4^+$ , 15), 623 (30), 603 (100); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  698.4055,  $\text{C}_{42}\text{H}_{60}\text{NO}_4\text{Si}_2$  requires 698.4055.

**(±)-(2,3-*syn*)-2,3-Bis(*tert*-butyldiphenylsilyloxy)octan-1-ol (519).**

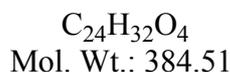
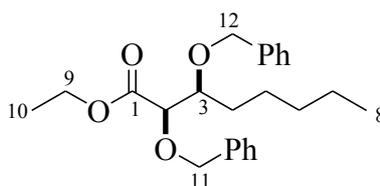
A round-bottomed flask equipped with a dropping funnel and a thermometer was charged with (±)-(2,3-*syn*)-ethyl 2,3-bis(*tert*-butyldiphenylsilyloxy)octanoate **518** (1.00 g, 1.47 mmol, 1.00 eq.) and toluene (8 mL). The resulting solution was stirred and cooled to  $-78$  °C and a 1.0 M solution of diisopropylaluminium hydride in hexane (2.94 mL, 2.94 mmol, 2.00 eq.) was added dropwise. After 2 hours of stirring at  $-78$  °C, TLC showed full consumption of starting material. Water (10 mL) was added dropwise and the resulting suspension was warmed to room temperature for 30 minutes and then filtered through a pad of celite, washing with diethyl ether (50 mL). The filtrate was concentrated *in vacuo* to afford the *title compound* **519** (824 mg, 1.29 mmol, 88%) as a sticky colourless oil which was used in the next step without any further purification.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3584, 3071, 2930;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.59-7.44 (8H, m, Ar-H), 7.44-7.22 (12H, m, Ar-H), 3.95-3.89 (1H, m, H-C2), 3.84-3.74 (1H, m, H-C3), 3.75-3.64 (2H, m, H-C1), 1.98 (1H, dd,  $J$  6.6, 5.7, H-OH), 1.83-1.69 (1H, m, H-C4), 1.51-1.34 (1H, m, H-C4), 1.18-1.01 (6H, m, H-C5 to H-C7), 0.99 (9H, s, H-C10), 0.96 (9H, s, H-C11), 0.74 (3H, t,  $J$  7.1, H-C8);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 135.9 (ArC), 135.8 (ArC), 135.6 (ArC), 133.8 (ArC), 133.6 (ArC), 133.4 (ArC), 133.1 (ArC), 129.7 (ArC), 129.6 (ArC), 129.5 (ArC), 127.7 (ArC), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 75.4 (C3), 74.3 (C2), 63.5 (C1), 31.7 (C4), 31.3 (C6), 26.9 (C10), 26.9 (C12), 25.8 (C5), 22.4 (C7), 19.3 (C9), 19.2 (C11), 13.9 (C8);  $m/z$  (CI) 656 ( $\text{MNH}_4^+$ , 2), 503 (30), 187 (80); HRMS (ES) Found  $[\text{M}+\text{NH}_4]^+$  656.3939,  $\text{C}_{40}\text{H}_{58}\text{NO}_3\text{Si}_2$  requires 656.3950.

**(±)-(2,3-syn)-2,3-Bis(*tert*-butyldiphenylsilyloxy)octanal (520).**

A round-bottomed flask was charged with pyridium chlorochromate (532 mg, 2.47 mmol, 2.04 eq.), 4Å molecular sieves (300 mg) and dichloromethane (10 mL). The resulting suspension was stirred at room temperature and (±)-(2,3-syn)-2,3-bis(*tert*-butyldiphenylsilyloxy)octan-1-ol **519** (774 mg, 1.21 mmol, 1.00 eq) in dichloromethane (2.50 mL) was added dropwise. After stirring for 4 hours at room temperature, analysis by NMR showed full consumption of starting material. The mixture was diluted with diethyl ether (100 mL), filtered twice through Florisil® (2 x 25 g) and concentrated *in vacuo* to afford the *title compound* **520** (491 mg, 0.77 mmol, 64%) as a sticky pale yellow oil which was used in the next step without any further purification.

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$  3049, 2930, 1738;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 9.75 (1H, s, H-C1), 7.62-7.46 (8H, m, Ar-H), 7.41-7.18 (12H, m, Ar-H), 4.08 (1H, d, *J* 3.8, H-C2), 3.89 (1H, dt, *J* 6.3, 3.8, H-C3), 1.83-1.65 (1H, m, H-C4), 1.38-1.21 (1H, m, H-C4), 1.05 (9H, s, H-C10), 0.95 (9H, s, H-C12), 1.00-0.82 (6H, m, H-C5 to H-C7), 0.69 (3H, t, *J* 7.1, H-C8);  $\delta_{\text{C}}$  (75.5 MHz; CDCl<sub>3</sub>) 203.5 (C1), 135.9 (ArC), 135.8 (ArC), 135.7 (ArC), 133.7 (ArC), 133.2 (ArC), 133.0 (ArC), 132.9 (ArC), 129.8 (ArC), 129.8 (ArC), 129.7 (ArC), 129.6 (ArC), 127.6 (ArC), 127.6 (ArC), 127.6 (ArC), 127.4 (ArC), 79.6 (C2), 75.4 (C3), 32.8 (C4), 31.4 (C6), 26.9 (C10), 26.9 (C12), 25.2 (C5), 22.3 (C7), 19.5 (C9), 19.3 (C11), 13.9 (C8); *m/z* (CI) 654 (MNH<sub>4</sub><sup>+</sup>, 10), 381 (30), 339 (100); HRMS (ES) Found [M+NH<sub>4</sub>]<sup>+</sup> 654.3797, C<sub>40</sub>H<sub>56</sub>NO<sub>3</sub>Si<sub>2</sub> requires 654.3793.

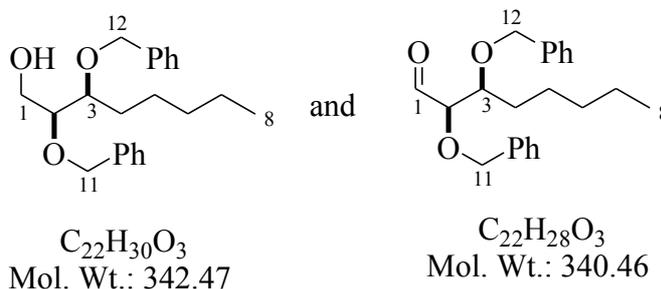
**(±)-(2,3-*syn*)-Ethyl 2,3-bis(benzyloxy)octanoate (521).**

A round-bottomed flask equipped with a dropping funnel was charged with a 60% suspension of sodium hydride in mineral oil (783 mg, 19.58 mmol, 2.00 eq.) and tetrahydrofuran (10 mL). The resulting suspension was cooled to 0 °C and (±)-(2,3-*syn*)-ethyl 2,3-dihydroxyoctanoate **517** (2.00 g, 9.79 mmol, 1.00 eq.) in tetrahydrofuran (7 mL) added dropwise. The resulting mixture was stirred for 1 hour at 0 °C and tetrabutylammonium bromide (634 mg, 1.97 mmol, 0.20 eq.) and 16-crown-6 (5 mg, 0.02 mmol) were added portionwise, followed by benzyl bromide (2.38 mL, 19.58 mmol, 2.00 eq) dropwise. The resulting mixture was warmed to room temperature for 1 hour and 1.0 M hydrochloric acid (10 mL) added dropwise followed by water (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (20 mL), a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. This afforded a yellow oil, which was purified by flash column chromatography (90% hexane, 10% ethyl acetate) to give the *title compound* **521** (1.34 g, 3.48 mmol, 36%) as a pale yellow oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3031, 2930, 1744;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.35-7.19 (10H, m, Ar-H), 4.78 (1H, d,  $J$  12.0, H-C11), 4.57-4.54 (2H, m, H-C12), 4.39 (1H, d,  $J$  12.0, H-C11), 4.21-4.09 (2H, m, H-C9), 3.96 (1H, d,  $J$  4.3, H-C2), 3.70 (1H, dt,  $J$  6.7, 4.3, H-C3), 1.60-1.51 (2H, m, H-C4), 1.29-1.06 (6H, m, H-C5 to H-C7), 1.22 (3H, t,  $J$  7.1, H-C10), 0.85-0.78 (3H, m, H-C8);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 171.2 (C1), 138.4 (ArC), 137.3 (ArC), 128.3 (ArC), 128.3 (ArC), 128.2 (ArC), 128.0 (ArC), 127.9 (ArC), 127.5 (ArC), 79.7 (C2), 79.6 (C3), 72.7 (C11), 72.4 (C12), 60.9 (C9), 31.7 (C6), 30.1 (C4), 25.1 (C5), 22.5 (C7), 14.2 (C10), 14.0 (C8);  $m/z$  (CI) 385 ( $\text{MH}^+$ , 6), 293 (40), 181 (100); HRMS (ES) Found [ $\text{M}+\text{NH}_4$ ] $^+$  402.2642,  $\text{C}_{24}\text{H}_{36}\text{NO}_4$  requires 402.2639.

*Experimental*

(±)-(2,3-*syn*)-2,3-Bis(benzyloxy)octan-1-ol (**522**) and (±)-(2,3-*syn*)-2,3-Bis(benzyloxy)octanal (**523**).



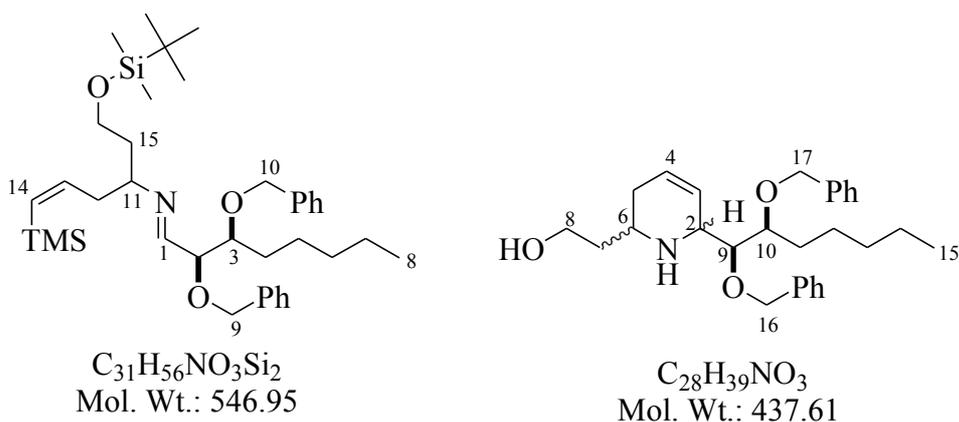
A round-bottomed flask equipped with a dropping funnel and a thermometer was charged with (±)-(2,3-*syn*)-ethyl 2,3-bis(benzyloxy)octanoate **521** (1.26 g, 3.29 mmol, 1.00 eq.) and toluene (18 mL). The resulting solution was stirred and cooled to  $-78\text{ }^{\circ}\text{C}$  and a 1.0 M solution of diisopropylaluminium hydride in hexane (10.20 mL, 10.20 mmol, 3.10 eq.) was added dropwise. After 4 hours of stirring at  $-78\text{ }^{\circ}\text{C}$ , TLC showed full consumption of starting material and water (20 mL) was added dropwise. The resulting suspension was warmed to room temperature for 30 minutes and then filtered through a pad of celite, washing with diethyl ether (70 mL). The filtrate was concentrated *in vacuo* to afford the *title compound* **522** (716 mg, 2.09 mmol, 64%) as a pale yellow oil which was used in the next step without any further purification.

A round-bottomed flask was charged with pyridium chlorochromate (850 mg, 3.95 mmol, 2.04 eq.), 4Å molecular sieves (250 mg) and dichloromethane (16 mL). The resulting suspension was stirred at room temperature and a solution of (±)-(2,3-*syn*)-2,3-bis(benzyloxy)octan-1-ol **522** (676 mg, 1.97 mmol, 1.00 eq) in dichloromethane (3.6 mL) was added dropwise. After stirring for 4 hours at room temperature, NMR showed full consumption of starting material. The mixture was diluted with diethyl ether (100 mL), filtered twice through Florisil® (2 x 25 g) and concentrated *in vacuo* to afford the *title compound* **523** (264 mg, 0.78 mmol, 39%) as a pale yellow oil which was used in the next step without any further purification.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  3064, 2929, 1732;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 9.76 (1H, d,  $J$  1.5, H-C1), 7.41-7.23 (10H, m, Ar-H), 4.80 (1H, d,  $J$  12.0, H-C9), 4.57-4.50 (2H, m, H-C10), 4.53 (1H, d,  $J$  12.0, H-C9), 3.84 (1H, dd,  $J$  3.9, 1.5, H-C2), 3.77-3.68 (1H, m, H-C3), 1.81-1.51 (2H, m, H-C4), 1.34-1.05 (6H, m, H-C5 to H-C7), 0.85 (3H, t,  $J$  6.6, H-C8);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 203.9 (C1), 137.8 (ArC), 134.5 (ArC), 129.0 (ArC), 129.7 (ArC), 128.5 (ArC), 128.3 (ArC), 128.2 (ArC), 128.0 (ArC), 83.7 (C2), 79.3 (C3), 73.1 (C9), 72.4 (C10), 31.7

(C6), 30.1 (C4), 25.2 (C5), 22.5 (C7), 14.0 (C8);  $m/z$  (CI) 358 ( $\text{MNH}_4^+$ , 25), 250 (100), 144 (50).

(±)-(5*Z*)-*N*-(2,3-Bis(benzyloxy)octylidene)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine (**526**) and (±)-6-(2-(1,2-Bis(benzyloxy)heptyl)-1,2,3,6-tetrahydropyridin-6-yl)ethanol (**527**).



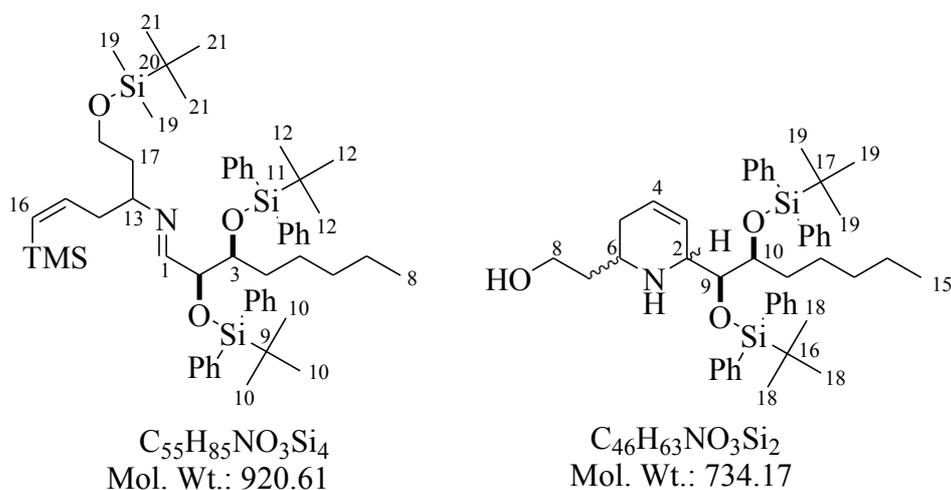
Following the general procedure Q, (±)-(*Z*)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine **509** (233 mg, 0.78 mmol) in the presence of (±)-(2,3-*syn*)-2,3-bis(benzyloxy)octanal **523** (264 mg, 0.78 mmol), afforded the *title compound* **526** (455 mg, 0.73 mmol, 94%) as a yellow oil which was used in the next step without any further purification. Then (±)-(5*Z*)-*N*-(2,3-bis(benzyloxy)octylidene)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine **526** (455 mg, 0.73 mmol) after 17 hours at reflux was consumed, based on analysis by NMR, to afford a orange oil which was purified by flash column chromatography (95% dichloromethane, 5% methanol) to give the *title compound* **527** as a 1.24:1 mixture of two diastereomers **527a** and **527b** (176 mg, 0.40 mmol, 55%) as a pale yellow oil.

Data for **527a**:  $\nu_{\text{max}}$ (neat)/ $\text{cm}^{-1}$  (mixture) 3435, 3063, 2931, 1605;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.34-7.19 (10H, m, Ar-H), 5.90-5.78 (1H, m, H-C4), 5.73-5.64 (1H, m, H-C3), 4.68 (1H, d,  $J$  11.6, H-C16), 4.61-4.58 (2H, m, H-C17), 4.43 (1H, d,  $J$  11.6, H-C16), 3.97-3.87 (1H, m, H-C2), 3.82-3.69 (1H, m, H-C9), 3.79-3.61 (2H, m, H-C8), 3.65-3.51 (1H, m, H-C6), 3.55-3.43 (1H, m, H-C10), 2.30-2.09 (1H, m, H-C5), 2.05-1.89 (2H, m, H-C7), 2.01-1.86 (1H, m, H-C5), 1.68-1.51 (2H, m, H-C11), 1.29-0.99 (6H, m, H-C12 to H-C14), 0.81 (3H, t,  $J$  6.5, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 137.3 (ArC), 136.9 (ArC), 128.5 (ArC), 128.3 (ArC), 128.1 (ArC), 128.0 (ArC), 127.4 (ArC), 126.9 (ArC), 125.8 (C4), 121.6 (C3), 79.0 (C10), 76.8 (C9), 74.0 (C16), 71.6 (C17), 60.8 (C8), 54.1 (C2), 51.4 (C6), 31.6 (C12), 31.7 (C14), 28.7 (C7), 27.8 (C5), 25.5 (C11), 22.4 (C13), 13.9 (C15);  $m/z$  (ES) (mixture)

438 (MH<sup>+</sup>, 100), 278 (5), 150 (8); HRMS (ES) Found [M+H]<sup>+</sup> (mixture) 438.3001, C<sub>28</sub>H<sub>40</sub>NO<sub>3</sub> requires 438.3003.

Data for **527b**: δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 7.35-7.17 (10H, m, Ar-H), 5.90-5.79 (1H, m, H-C4), 5.63-5.54 (1H, m, H-C3), 4.71 (1H, d, *J* 11.4, H-C16), 4.61-4.57 (2H, m, H-C17), 4.45-4.38 (1H, m, H-C2), 4.24 (1H, d, *J* 11.4, H-C16), 3.80-3.71 (2H, m, H-C9), 3.74-3.66 (2H, m, H-C8), 3.62-3.51 (1H, m, H-C6), 3.55-3.43 (1H, m, H-C10), 2.27-2.14 (1H, m, H-C5), 2.02-1.91 (2H, m, H-C7), 1.93-1.86 (1H, m, H-C5), 1.60-1.34 (2H, m, H-C11), 1.27-0.98 (6H, m, H-C12 to H-C14), 0.80 (3H, t, *J* 6.6, H-C15); δ<sub>C</sub> (75.5 MHz; CDCl<sub>3</sub>) 136.8 (ArC), 136.6 (ArC), 128.7 (ArC), 128.5 (ArC), 128.4 (ArC), 128.2 (ArC), 127.6 (ArC), 127.2 (ArC), 125.6 (C4), 120.0 (C3), 79.0 (C10), 75.7 (C9), 72.7 (C16), 71.8 (C17), 60.5 (C8), 51.5 (C6), 50.5 (C2), 31.6 (C12), 31.7 (C14), 28.4 (C7), 27.3 (C5), 25.1 (C11), 22.4 (C13), 13.9 (C15).

**(±)-(5Z)-N-(2,3-Bis(*tert*-butyldiphenylsilyloxy)octylidene)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine (528) and (±)-6-(2-(2,2,9,9-Tetramethyl-6-pentyl-3,3,8,8-tetraphenyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,2,3,6-tetrahydropyridin-6-yl)ethanol (529).**



Following the general procedure Q, (±)-(Z)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine **509** (60 mg, 0.20 mmol) in the presence of (±)-(2,3-*syn*)-2,3-bis(*tert*-butyldiphenylsilyloxy)octanal **520** (127 mg, 0.20 mmol), afforded the *title compound* **528** (150 mg, 0.16 mmol, 82%) as a yellow oil which was used in the next step without any further purification. Then (±)-(5Z)-N-(2,3-bis(*tert*-butyldiphenylsilyloxy)octylidene)-1-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-en-3-amine **528** (150 mg, 0.16 mmol) after 17 hours at reflux was consumed based on analysis by NMR to afford a yellow oil, which was purified by flash column

chromatography (95% dichloromethane, 5% methanol) to give the *title compound* **529** as a 1.25:1 mixture of two diastereomers **529a** and **529b** (44 mg, 0.06 mmol, 38%) as an off-white solid.

Data for **529a**: M.p. 50-52 °C (mixture);  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  (mixture) 3411, 3048, 2931, 1590;  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.59-7.16 (20H, m, Ar-H), 5.83-5.74 (1H, m, H-C4), 5.36-5.27 (1H, m, H-C3), 4.19-4.09 (1H, m, H-C2), 4.00-3.91 (1H, m, H-C9), 3.82-3.73 (1H, m, H-C10), 3.74-3.62 (2H, m, H-C8), 3.43-3.28 (1H, m, H-C6), 2.25-2.09 (2H, m, H-C5), 1.72-1.49 (2H, m, H-C7), 1.48-1.28 (2H, m, H-C11), 1.16-1.00 (6H, m, H-C12 to H-C13), 0.99 (9H, s, H-C18), 0.96 (9H, s, H-C19), 0.77 (3H, t,  $J$  5.7, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 136.2 (ArC), 136.0 (ArC), 135.9 (ArC), 135.8 (ArC), 133.4 (ArC), 133.0 (ArC), 132.5 (ArC), 132.2 (ArC), 130.1 (ArC), 129.8 (ArC), 129.8 (ArC), 129.7 (ArC), 127.8 (ArC), 127.8 (ArC), 127.7 (ArC), 127.5 (ArC), 125.3 (C4), 124.1 (C3), 75.3 (C9), 74.6 (C10), 60.8 (C8), 53.1 (C2), 50.6 (C6), 34.6 (C11), 32.4 (C12), 32.1 (C14), 28.7 (C5), 27.5 (C16), 27.3 (C17), 26.7 (C7), 22.8 (C13), 19.7 (C18), 19.6 (C19), 14.3 (C15);  $m/z$  (ES) (mixture) 734 ( $\text{MH}^+$ , 100), 104 (5), 60 (40); HRMS (ES) Found  $[\text{M}+\text{H}]^+$  (mixture) 734.4429,  $\text{C}_{46}\text{H}_{64}\text{NO}_3\text{Si}_2$  requires 734.4419.

Data for **529b**:  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ) 7.59-7.15 (20H, m, Ar-H), 5.84-5.72 (1H, m, H-C4), 5.36-5.26 (1H, m, H-C3), 4.09-4.00 (1H, m, H-C2), 3.92-3.85 (1H, m, H-C9), 3.81-3.71 (1H, m, H-C10), 3.71-3.62 (2H, m, H-C8), 3.06-2.88 (1H, m, H-C6), 2.10-1.91 (2H, m, H-C5), 1.67-1.49 (2H, m, H-C7), 1.45-1.26 (2H, m, H-C11), 1.15-1.02 (6H, m, H-C12 to H-C14), 0.96 (9H, s, H-C18), 0.92 (9H, s, H-C19), 0.73 (3H, t,  $J$  5.7, H-C15);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ) 136.1 (ArC), 135.9 (ArC), 135.8 (ArC), 135.8 (ArC), 133.0 (ArC), 133.0 (ArC), 132.8 (ArC), 132.1 (ArC), 130.1 (ArC), 130.0 (ArC), 129.8 (ArC), 129.6 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 127.5 (ArC), 125.3 (C4), 124.1 (C3), 77.2 (C9), 75.4 (C10), 61.1 (C7), 52.2 (C2), 50.6 (C6), 32.4 (C12), 32.1 (C14), 31.7 (C11), 28.7 (C5), 27.6 (C16), 27.4 (C17), 26.3 (C7), 22.8 (C13), 19.9 (C18), 19.8 (C19), 14.3 (C15);

## **REFERENCES**

