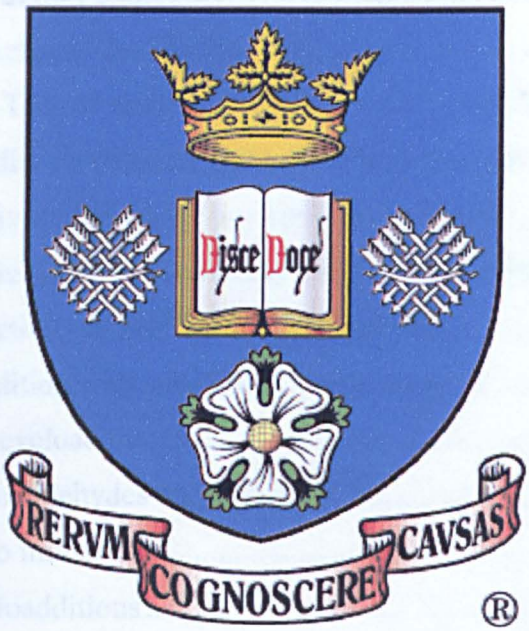
New and Efficient Strategies in Stereoselective Heterocycle Synthesis



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Doctor of Philosophy

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Abstract

This thesis describes the development and the application of three different [3+3] annelation strategies for the formation of functionalised piperidines. Initially, the scope of the [3+3] cycloaddition reaction of Pd-trimethylenemethane and aziridines towards functionalised piperidines was investigated for its application to silyl ether substituted aziridines. These substrates appeared to be very challenging, undergoing the cycloaddition only under very rigorous conditions. Since this methodology was not trivial to repeat, a two-step strategy was explored that involved the addition of a Grignard reagent to the aziridines followed by ring-closure to the corresponding piperidines. These two procedures were found to be enantiospecific, providing good routes for the synthesis of enantiopure piperidines. The functionalisation of the *exo*-alkene group of these piperidines was also investigated with particular regard to the reaction diastereoselectivity. A third [3+3] annelation reaction towards the synthesis of the piperidine core has also been employed, which invoked the addition of the Büchi Grignard reagent to the enantiopure silyl ether substituted aziridine **(*R*)-139** to provide the corresponding acetal **263** in good yield. Acid catalysed cyclisation of the acetal produced the corresponding enantiopure tetrahydropyridine **264**. The last section of this work focused on the applicability of these methods for the synthesis of natural products and highlights our attempts towards the synthesis of quinolizidine alkaloid (-)217A.

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me, for our nights out, for chats about life and my immaturity... You've been such a good friend!

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Abbreviations

Ac	Acetyl
Acac	acetylacetonate
ADDP	1,1'-(Azodicarbonyl)dipiperidine
aq.	aqueous
Ar	Aryl
Atm	Atmosphere (pressure)
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
b.p.	Boiling point
Br	Broad
^{n}Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
C	Concentration
calcd.	Calculated
cat.	Catalyst or catalytic
Cbz	Carboxybenzyloxy
Chloramine-T	*N*-Chloro-4-toluenesulfonamide sodium salt
CI	Chemical Ionisation
COSY	Correlated spectroscopy
Cp	Cyclopentadienyl
d	Doublet (NMR); day(s) (reaction time)
D	Dextrorotatory
δ	Chemical shift
Dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DIBAL	Di-*iso*-butylaluminium hydride
DMAP	4-[*N*,*N*-Dimethylamino]pyridine

DMDO	Dimethyldioxirane
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
EI	Electron impact
eq. or equiv.	Equivalent(s)
ES	Electrospray (mass spectroscopy)
Et	Ethyl
Et_2O	Diethyl ether
EWG	Electron-withdrawing group
FTIR	Fourier transform infra-red
G	gram(s)
h or hrs	Hour(s)
HMPT	Hexamethylphosphorotriamide
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infra-red
J	Coupling constant
L	Litre, ligand
L	Laevorotatory
LDA	Lithium di-*iso*-propylamide
LG	Leaving group
$LiAlH_4$ or LAH	Lithium aluminium hydride
Lit.	Literature
M	Molar, metal
M	Multiplet (NMR); medium (FTIR)
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Min	Minute(s)
Mol. Sieves or MS	Molecular sieves
m.p.	Melting point

Ms or mesyl	Methanesulfonyl
NaOH	Sodium hydroxide
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
Ns	4-Nitrobenzenesulfonyl
Nu	Nucleophile
P	Protecting group
Pd-TMM	Palladium-trimethylenemethane
Pent.	*n*-Pentyl
Ph	Phenyl
PMBS	*para*-Methoxybenzenesulfonyl
ppm	Parts per million
^{i}Pr	*iso*-Propyl
^{n}Pr	*n*-Propyl
Pyr	Pyridine
Q	Quartet
RCM	Ring closing metathesis
Rt	Room temperature
S	Singlet (NMR); strong (IR)
S	Solvent
SM	Starting material
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Temp	Temperature
Tf or triflate	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMEDA	*N,N,N,N*-Tetramethylethylenediamine
TMM	Trimethylenemethane
TMS	Trimethylsilyl
Ts or tosyl	4-Toluenesulfonyl
w	Weak (IR)
w/v	Weight per volume

Chapter I - Introduction

The formation of five- and six-membered rings constitutes a great area of interest to the organic chemist due to their presence in a huge variety of natural products. Indeed, an abundance of natural products contain a core of cyclopentane skeleta such as prostaglandins and triquinanes. The power of cycloadditions for ring formation derives from the potential for chemo-, regio-, and enantioselectivity. Cycloaddition strategies have been employed in the formation of five-membered rings, using reactions such as the 1,3-dipolar cycloaddition, but although this method was successful in the synthesis of certain heterocycles it could not be extended to carbocyclic systems. The Diels-Alder reaction is an established way to form six-membered rings and in close analogy to it, a [3+2] strategy for formation of five-membered rings is conceivable.

1.Trimethylenemethane Complexes

The trimethylenemethane (TMM) unit and its equivalents are very reactive organic species. They are potentially interesting four-carbon fragments for cycloadditions and could provide an efficient route towards five-membered rings. TMM can be represented in either a zwitterionic or a diradical form (Figure 1):

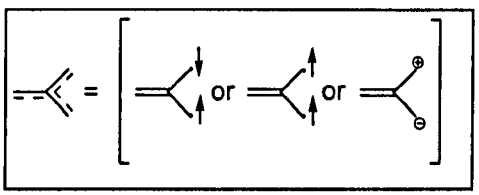
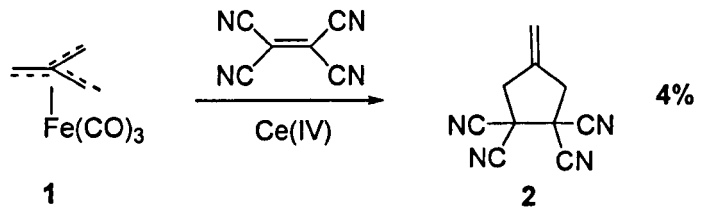


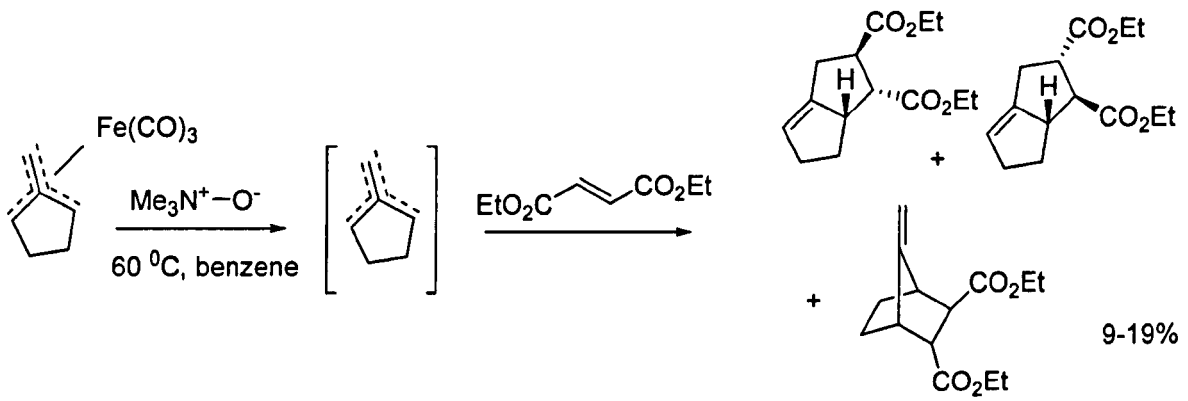
Figure 1

The TMM synthon can be stabilized by coordination of a metal complex. Emerson et al[1] were the first researchers to report the synthesis of one of these complexes, $Fe[\eta^4\text{-}C(CH_2)_3](CO)_3$. Since this time, some other TMM complexes have been synthesised with molybdenum and chromium[2], as well as complexes of iridium, rhodium, osmium and ruthenium[3]. Although the possible use of metal complexed TMM systems in organic syntheses appeared promising, their poor

reactivity in cycloadditions make them less interesting for that purpose. The reactivity had been lowered so much that these species would not undergo cycloaddition reactions. As highlighted in Schemes 1 and 2, even when the Fe-TMM complex **1** was reacted with a very much activated alkene, only a low yield of cycloadduct **2** was obtained[2, 4].



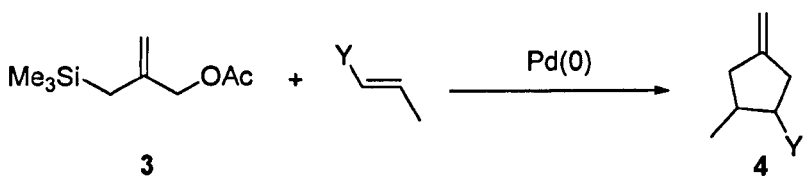
Scheme 1



Scheme 2

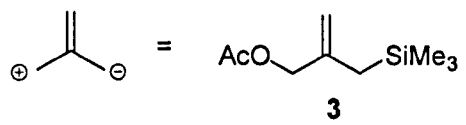
1.1.Palladium-Trimethylenemethane (Pd-TMM) complexes

In 1979, Trost and Chan[4, 5] reported that 2-acetoxymethyl-3-allyltrimethylsilane **3** served as a novel annulating agent with olefins bearing electron withdrawing groups in the presence of a palladium(0) catalyst to generate cyclopentanes **4** (Scheme 3).



Scheme 3

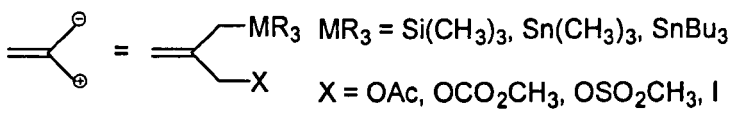
Their reasoning was based on the fact that, to be reactive in cycloadditions, the TMM equivalent must exist in a zwitterionic form with synthons for a carbocation and carbanion that do not self-annihilate. In the case above, silyl group serves as carbanion equivalent and carboxylate as carbocation equivalent (Scheme 4).



3

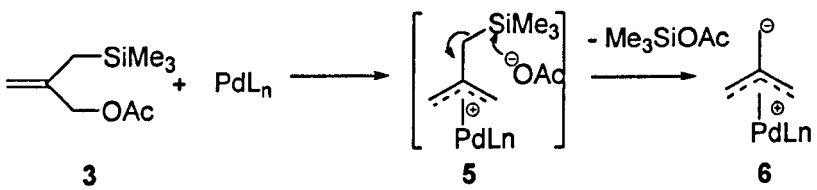
Scheme 4

Other groups can also be considered as illustrated in Scheme 5.



Scheme 5

However, all of these synthons need an activator: palladium (0) complexes serve as such activators because they can readily effect the ionization of even poor leaving groups. In the presence of a palladium (0) catalyst, a π-allyl palladium species **6** is formed via the oxidative insertion of Pd(0) into the carbon-oxygen bond of **3**. The proximal positive charge weakens the carbon – silicon bond and facilitates the loss of $SiMe_3$, forming the palladium-TMM complex as a reactive intermediate[6]. This complex contains both the required nucleophilic and electrophilic centres (Scheme 6).

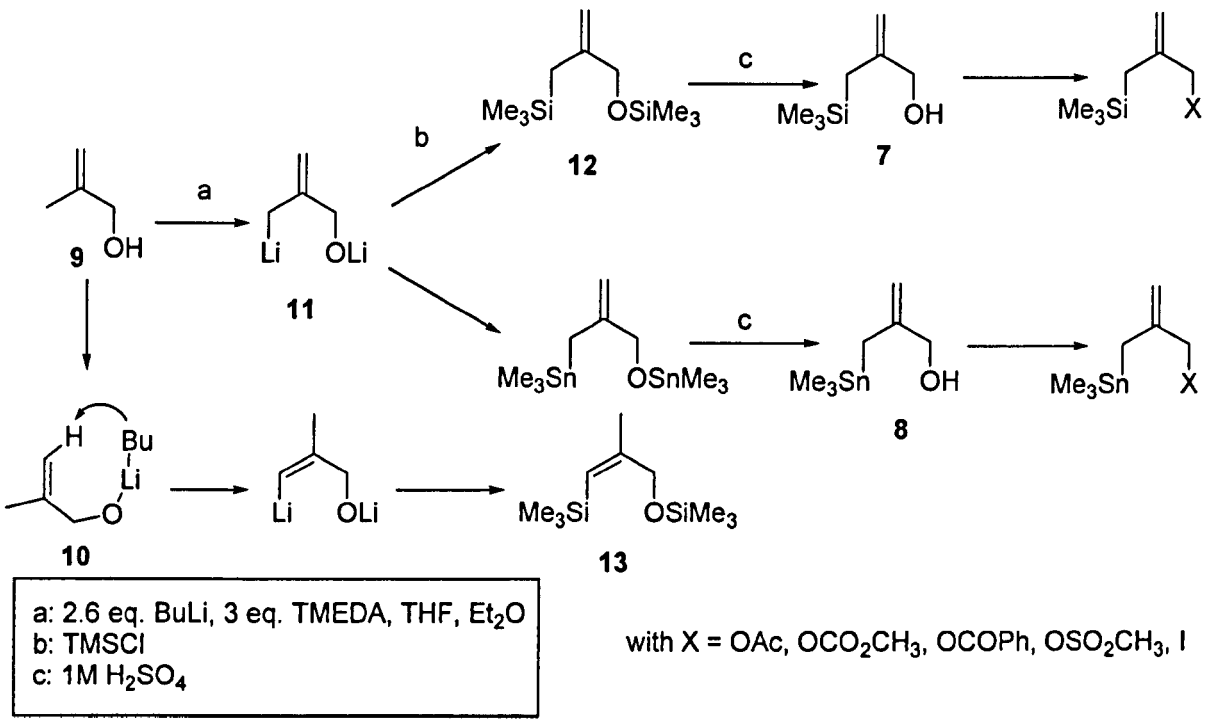


3 **5** **6**

Scheme 6

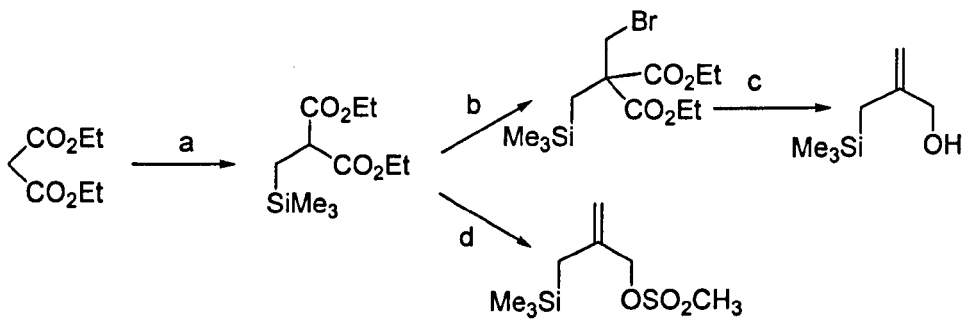
1.1.1.Synthesis of TMM and conjunctive reagents

In 1983, Trost and co-workers[7] described a convenient two-step route to 2-(hydroxymethyl)allyltrimethylsilane **7** using inexpensive reagents (Scheme 7). A similar route can be used to make the stannyl derivate **8**. Firstly methallyl alcohol **9** was doubly deprotonated with butyllithium in the presence of TMEDA. The efficiency of this process appeared to be very dependant on the polarity of the reaction medium, in that when the reaction was run in hexane, a significant amount (up to 50%) of an isomeric alkene was produced, thought to be **13**, as judged by ^{1}H NMR spectroscopy. In the non-polar solvent, complexation of the lithium alkoxide with the lithiating agent (**10**) increases the acidity of the *syn* proton of the alkene and this internal activation leads to the by-product **13**. Indeed, changing to a more polar solvent (i.e. removing the hexane from the butyllithium solution and replacing this with ether or THF) did lead to a significant decrease in the amount of by-product **13** formed, presumably due to suppression of the internal coordination. Use of ether gave ~15% **13** and 60-70% of the desired vinyl silane **12**. In THF, conversion was low but only the *exo*-methylene product **12** was formed, probably due to the instability of THF in the presence of strong base, so in practise a ~1.5:1 ratio of ether:THF was used. A 1:1 ratio of BuLi:TMEDA was also found to be optimal. The dianion **11** was quenched with TMSCl, and then selective hydrolysis of the TMS-ether using dilute sulphuric acid yielded the allylic alcohol **7**. This allylic alcohol can then be functionalised with various groups.



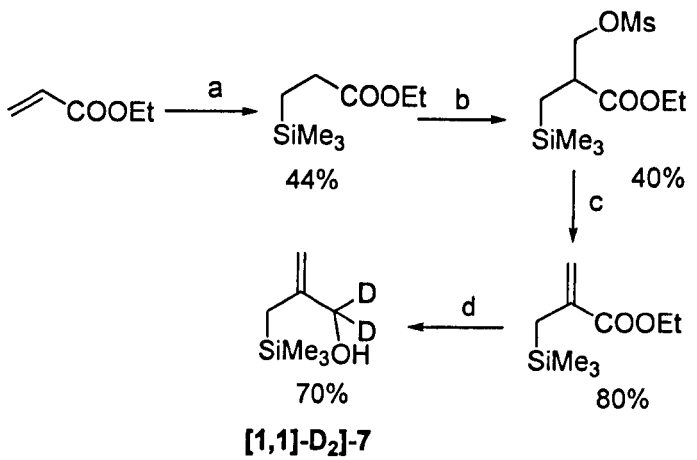
Scheme 7

Alternatively, two routes from diethyl malonate using (chloromethyl)- or (iodomethyl)trimethylsilane also provide reagents of type **7** (Scheme 8)[8, 9].



Scheme 8

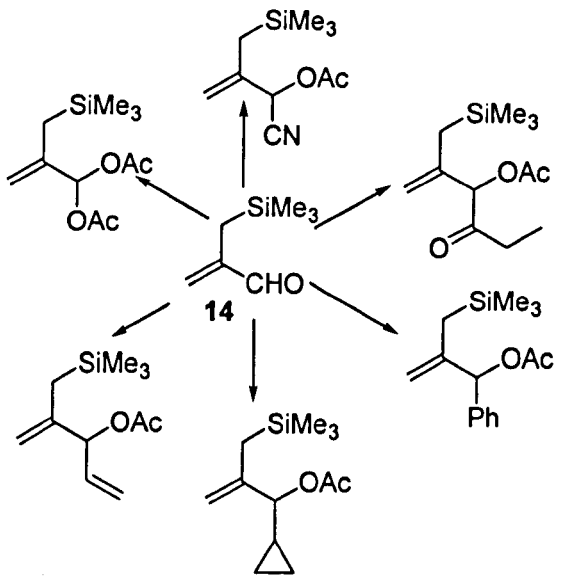
Ethyl acrylate also serves as a readily available starting material in a route where the silicon source is again the inexpensive chlorotrimethylsilane. Scheme 9 outlines this route to a 1,1-dideutero analogue of **7**[10, 11].



a, Me_3SiCl/Li;
b, 1. $LiN(iPr)_2$, THF; 2. $(CH_2O)n$, 3. CH_3SO_2Cl/Et_3N;
c, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), RT Et_2O;
d, $LiAlD_4$, -25 °C, Et_2O

Scheme 9

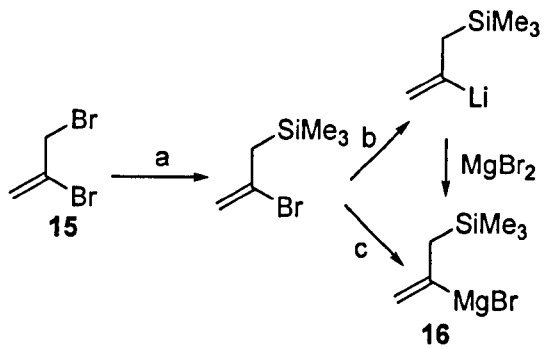
Various 1,3-disubstituted TMM precursors (Scheme 10) can be synthesised thanks to the ready availability of the aldehyde **14**, prepared by Swern oxidation of the alcohol **7**[12, 13].



Scheme 10

The Grignard reagent, 1-[(trimethylsilyl)methyl]ethenylmagnesium bromide **16**, synthesised starting from the isopropenyl bromide **15** can also be used to create

the 1,3-bifunctional units required for cycloaddition (Scheme 11)[14-16]. The Grignard reagent **16** shows good chemoselectivity in its addition to aldehydes and ketones.

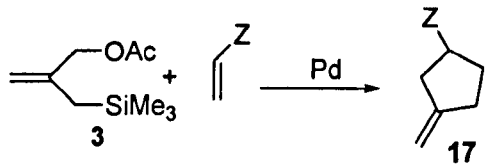


a, (2 Me_3SiLi + 3 CuCN), 0°C, THF/HMPA or 1. $HSiCl_3/Et_3N$, CuCl, 2. 3 CH_3MgBr, Et_2O;
b, ^tBuLi, -78 °C, Et_2O
c, Mg turnings

Scheme 11

2.[3+2] Cycloadditions with unsubstituted TMM reagents

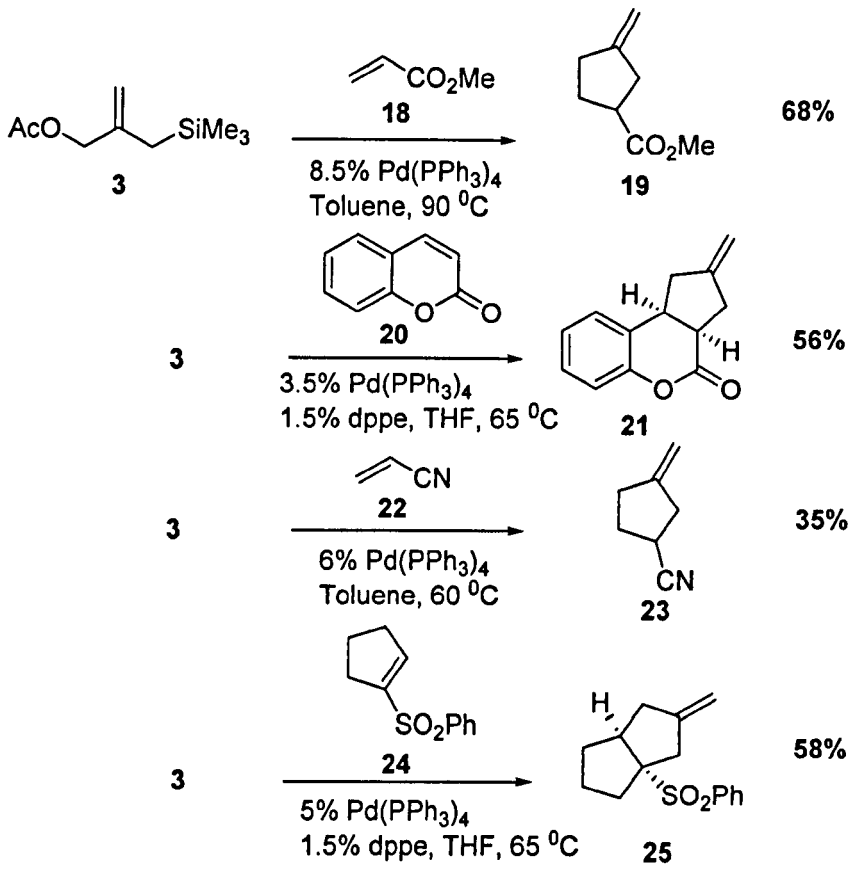
The TMM unit **3** is able to undergo a [3+2] cycloaddition with electron deficient alkenes in the presence of palladium-catalyst to give methylenecyclopentanes **17** (Scheme 12)[10].



Z = electron withdrawing group

Scheme 12

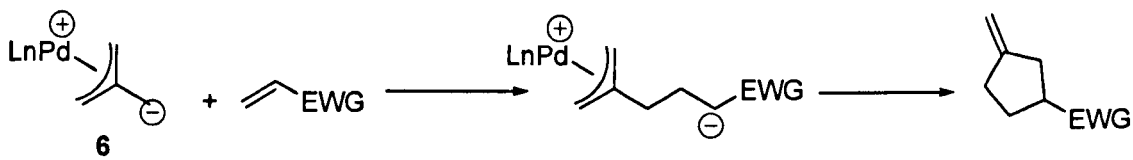
The acceptor requires an electron-withdrawing group, similar to a dienophile in a Diels Alder reaction. Various electron-withdrawing groups (EWG) such as ester[10], cyano[6, 10] and sulfone[6, 10] groups in addition to a ketone carbonyl group can be used as activators of the olefinic bond (Scheme 13). Any EWG that activates an olefin in terms of a Michael reaction should function similarly.



Scheme 13

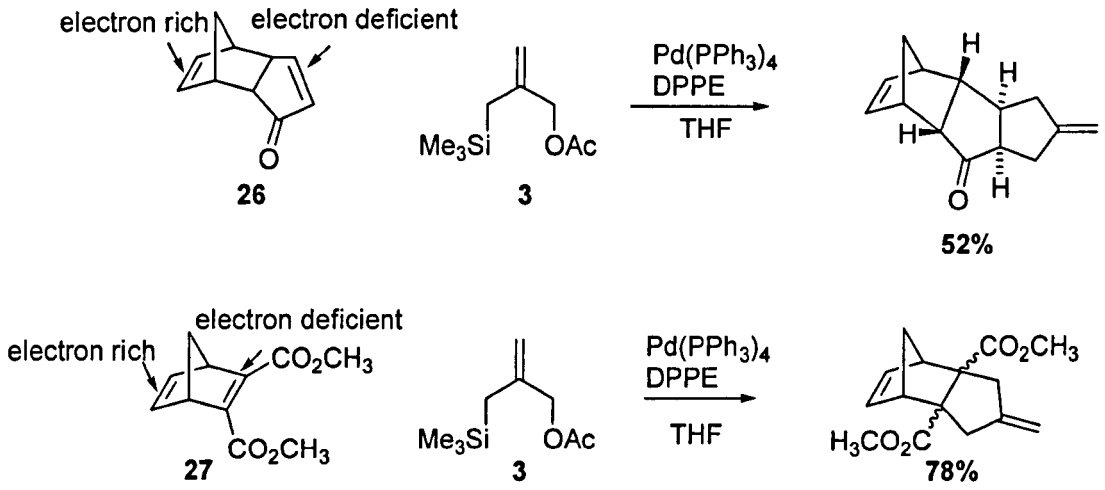
2.1.Mechanistic studies on the cycloaddition reaction

The cycloaddition reaction is proposed to proceed *via* a Michael addition of **6** to the double bond followed by palladium catalysed intramolecular allylation of the subsequent carbanion (Scheme 14).



Scheme 14

Trost and Chan[14] performed some experiments to study the mechanism of this [3+2] cycloaddition. They tested susbtrates that possessed both electron rich and electron deficient olefins to see if any chemoselectivity could be achieved.

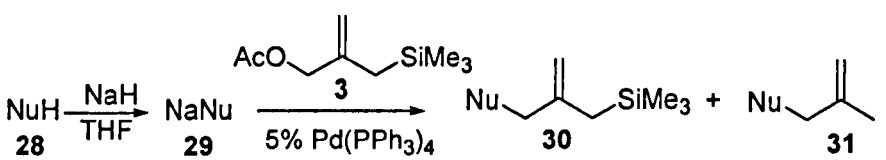


Scheme 15

The ambident traps **26** and **27** chemoselectively led to products derived from exclusive reaction at the electron-deficient double bond. Cycloadducts resulting from attack of Pd-TMM **5** at the electron rich alkene were not observed.

2.2.Mechanistic studies on the nature of Pd-TMM complexes

The Pd-TMM complex **6** is described as a η^3-allylpalladium fragment. A series of experiments were performed by Trost and Chan[17] to provide evidence for the existence of this moiety. Sodium salts of nucleophiles **29** were generated with 1 equivalent of the conjugate acid **28** and 0.8 equivalent NaH. These anions **29** were then treated with **3** in the presence of a Pd(0) catalyst (Scheme 16).



Scheme 16

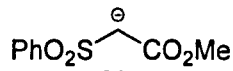
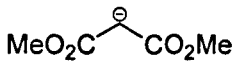
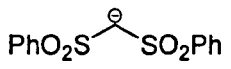
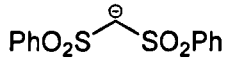
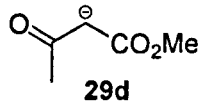
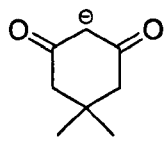
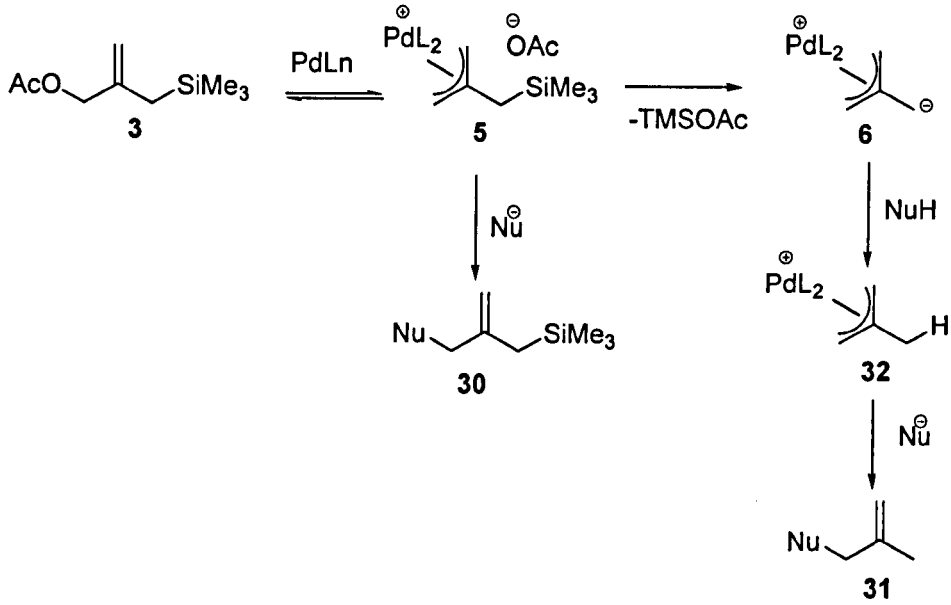
Entry	Nu	Temp	Yield **30**	Yield **31**
1	 **29a**	25°C	72%	
2	 **29b**	25	73%	
3	 **29c**	65	54%	18%
4	 **29c**	25		17%
5	 **29d**	25		44%
6	 **29e**	25		74%

Table 1

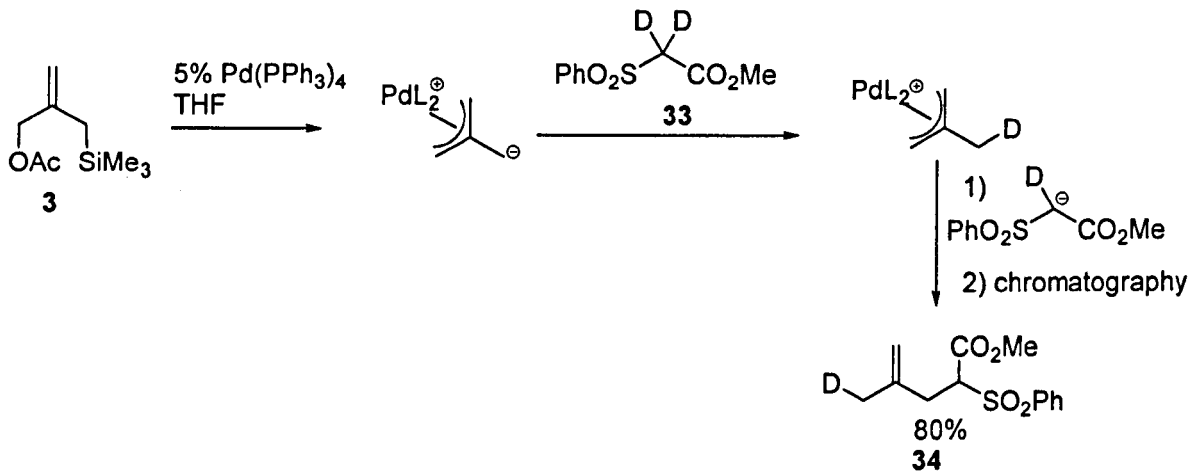
For strong nucleophiles (Table 1, entries 1 and 2), the expected alkylation product **30** is isolated in good yield. However, if more stabilised anions are used (generally pKa less than 12, entries 3-6), desilylated alkylation product **31** is instead obtained. These results can be explained as follows in Scheme 17: more reactive **29a** and **29b** react with the π-allylpalladium moiety very quickly, and thus the π-allylpalladium species **5** is trapped to produce silylated product **30**. The use of less reactive nucleophiles **29c, 29d** and **29e** means that intermediate **5** is not trapped as quickly and therefore has a longer lifetime and can undergo desilylation with acetate anion to produce Pd-TMM complex **6**. Pd-TMM complex **6** can be protonated by any conjugate acid of the nucleophile **28** that is present[a]. The nucleophilic anion **29** now reacts with the π-allylpalladium moiety of **32** in this case, and desilylated product **31** is observed.

[a] Trost considers that Pd-TMM complex **6** has a pK_a included between 21 and 25, since it can abstract a proton from acetophenone but not from esters.



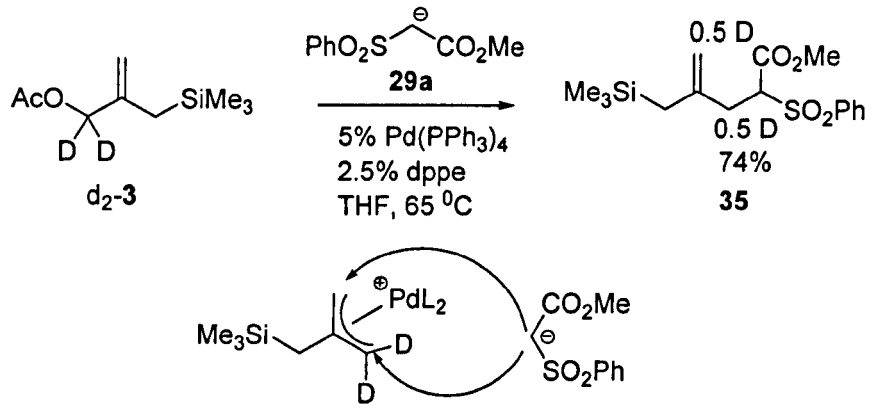
Scheme 17

The existence of a proton transfer step was confirmed by the use of 95% deuterium labelled **33** which provided deuterated product **34** in excellent yield with 91% deuterium incorporation (Scheme 18).



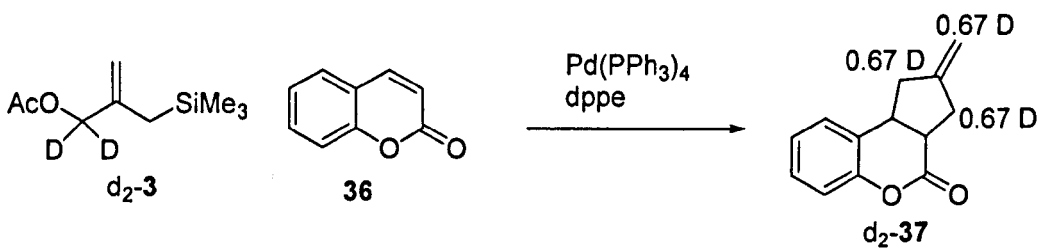
Scheme 18

Alkylation of a deuterium labelled TMM precursor d_2-**3** with **29a** shows that the deuterium label is incorporated in two of the carbons of the product **35**. A symmetrical π-allyl palladium species must be present, which is attacked equally at either terminus by reactive nucleophiles (Schemes 19).



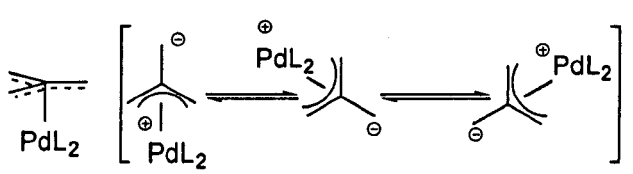
Scheme 19

However, with less reactive nucleophiles, an equal distribution of labels is found in the product. This implies that the palladium-TMM is unsymmetrical but capable of symmetrising at a rate comparable to that of cycloaddition reaction with the nucleophile (Scheme 20).



Scheme 20

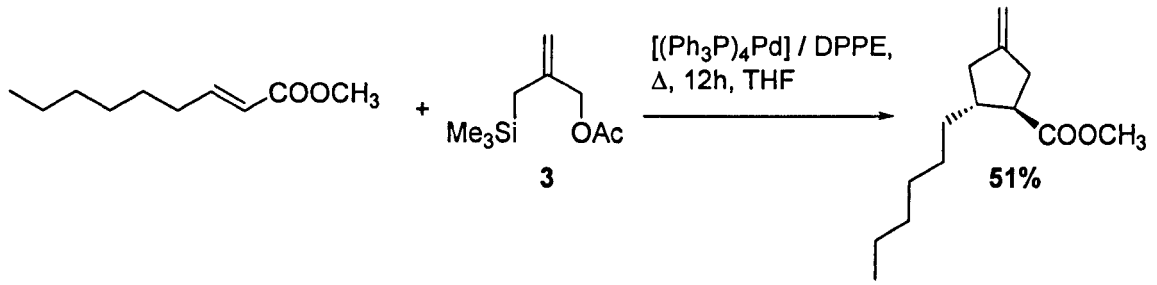
While d^6 metals tend to form η^4-TMM complexes[1, 3], theoretical calculations have shown that a η^3-TMM species is more likely for d^8 metals[18, 19]. Indeed, a crystal structure of $Pd[\eta^3\text{-}CH_2C((CO_2Me)_2)CH_2](PPh_3)_2$ has been published by Chen[20] that provides evidence of this bonding pattern.



Scheme 21

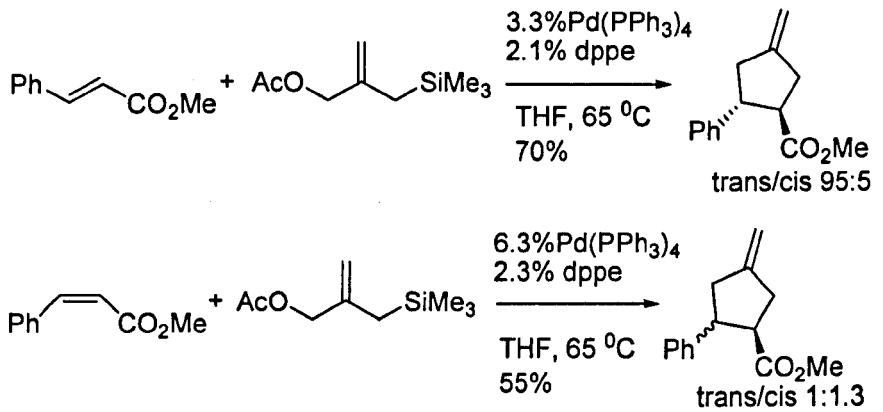
2.3.Stereoselectivity of Pd-TMM Cycloaddition

The stereoselectivity of the cycloaddition normally is very high; the geometry of (*E*)-olefins is retained in the product, as illustrated in Scheme 22[7, 17]:



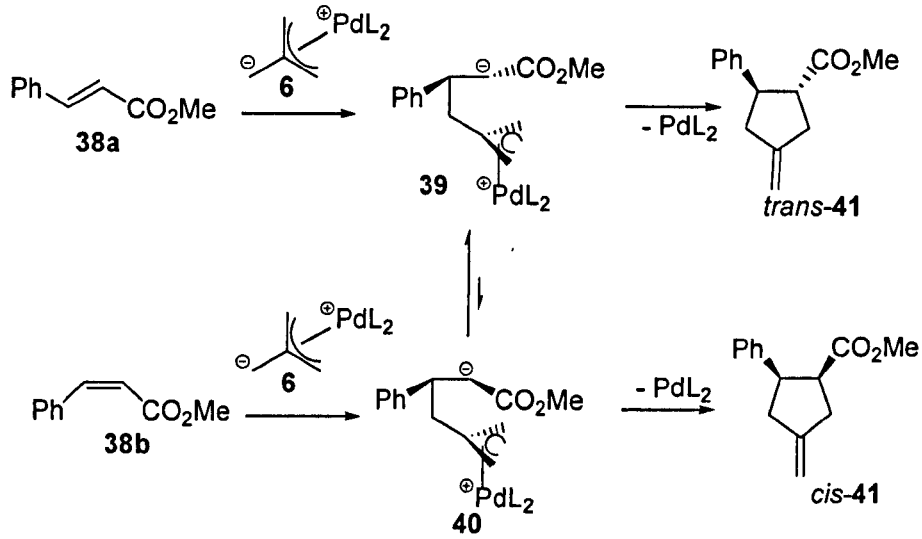
Scheme 22

A comparison of isomeric cinnamate was carried out as highlighted in Scheme 23. From *E*-olefin, *E*-adduct was mainly obtained. On the other hand, *Z*-olefin produced a mixture of *E*- and *Z*-methylenecyclopentanes.



Scheme 23

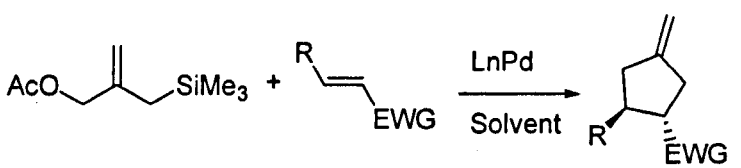
Partial loss of stereochemistry in the case of *Z*-olefinic acceptors arises from isomerization of the zwitterionic intermediate under the reaction conditions (Scheme 24).



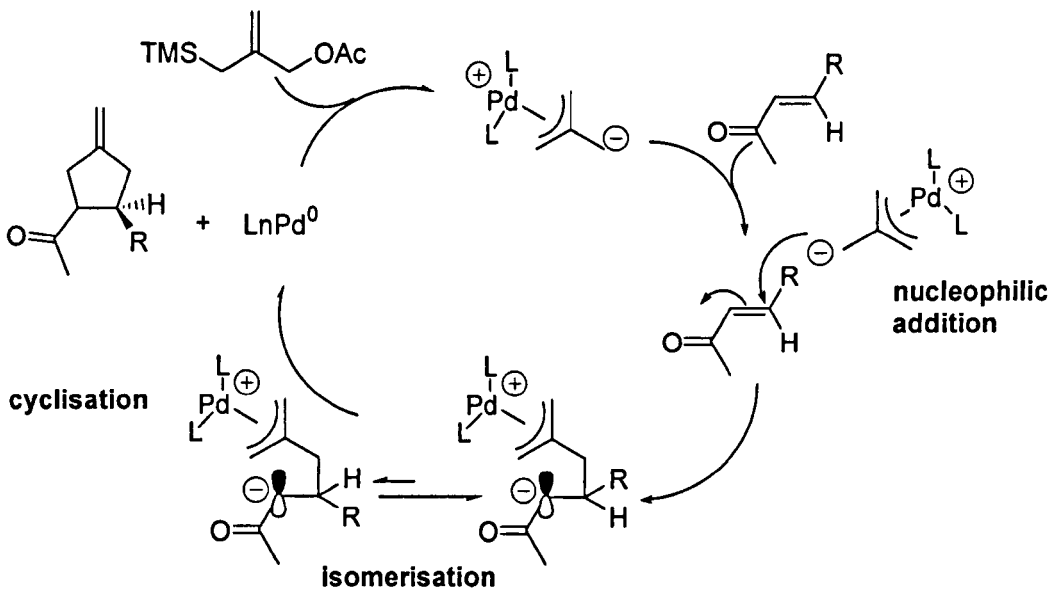
Scheme 24

This provides good evidence that the cycloaddition reaction proceeds *via* a stepwise, non-concerted addition mechanism. Zwitterionic intermediate **39** is formed from reaction of Pd-TMM **6** with *trans*-alkene **38a**, and ring closure to *trans*-**41** is rapid due to the neutralisation of charges providing a strong driving force for the normally slow 5-*endo*-trig ring closure[21] and thus stereochemistry is maintained from **38a** to the product *trans*-**41**[b]. In the case of *cis*-alkene **38b**, the mechanism goes through the intermediate **40**: here the bond rotation of **40** to **39** competes with cyclisation to *cis*-**41**, resulting in a loss of stereospecificity.

The difficulty in designing a catalyst for the asymmetric Pd-TMM cycloaddition reaction is illustrated by the following stepwise mechanism proposed by Trost and co-workers[22] (Scheme 25).

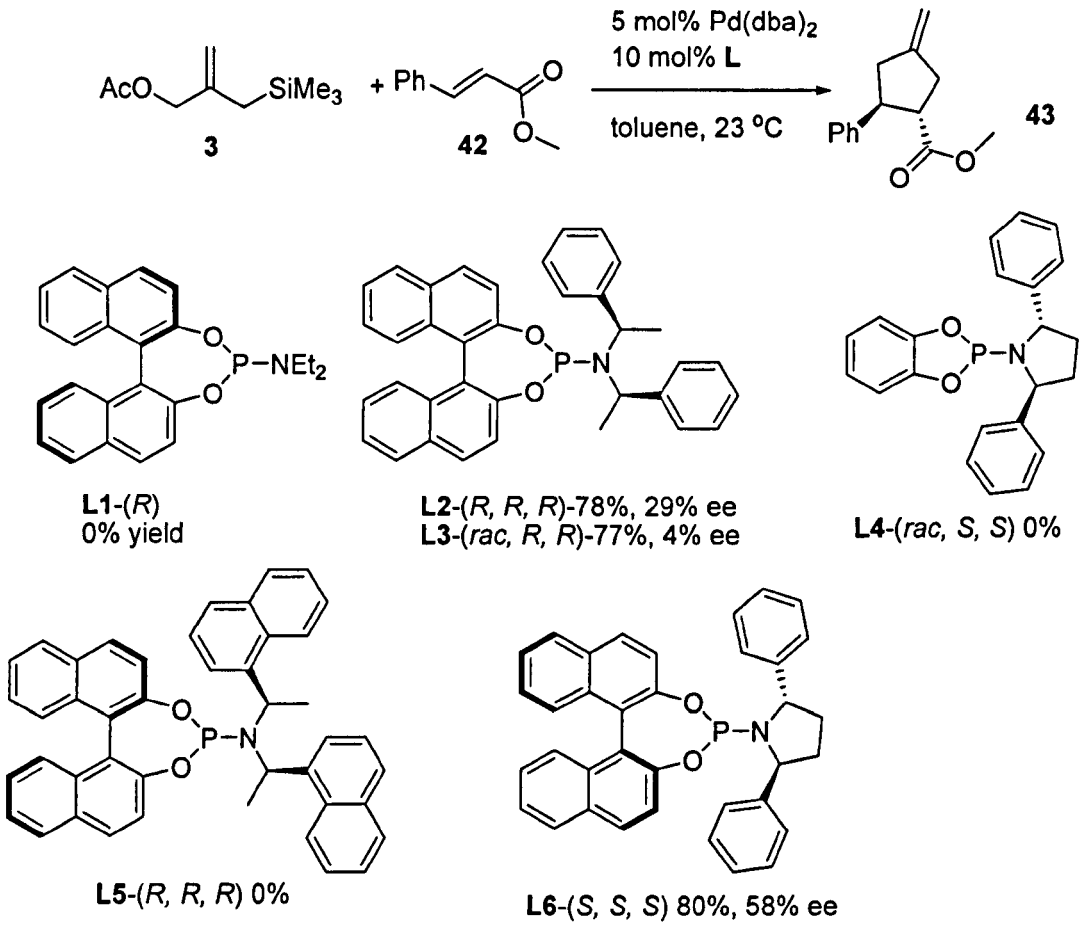


[b] According to Baldwin's rules, 5-*endo*-trig ring closure is disfavoured



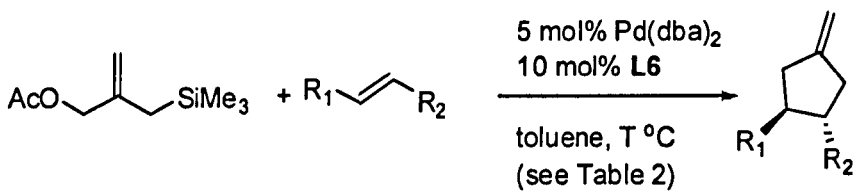
Scheme 25

The formation of the zwitterionic intermediate is generated by insertion of LnPd into the C-O bond followed by attack of the displaced acetate anion onto the trimethylsilyl group, which deposits its electrons onto the TMM fragment. The enantiodetermining step is most likely the initial nucleophilic attack. This step occurs distal to the set of coordinated chiral ligands. Nonetheless, Trost and his collaborators examined the reaction of **3** with methyl cinnamate **42** in the presence of 5 mol% of $Pd(dba)_2$ and 10 mol% of various chiral phosphoramidites as ligands in toluene at 23 °C. As highlighted in Scheme 26, these conditions provided an asymmetric catalytic cycloaddition reaction, providing cyclopentane **43** with modest enentioselectivity.



Scheme 26

Using the optimized catalytic conditions, they investigated the scope of the TMM accepting olefin. All cyclopentane products were formed in >19:1 *trans:cis* selectivity, with good enantiocontrol (Scheme 27, Table 2).



Scheme 27

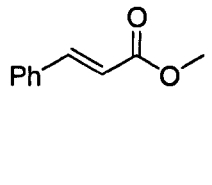
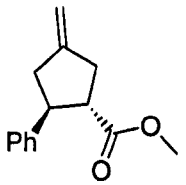
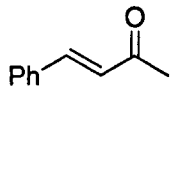
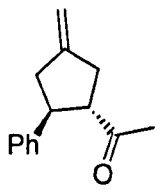
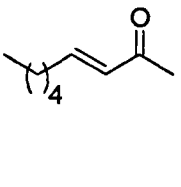
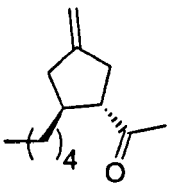
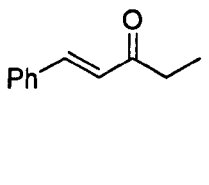
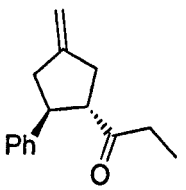
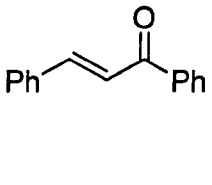
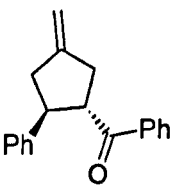
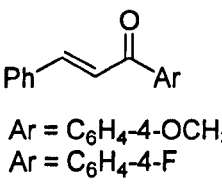
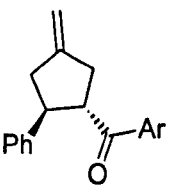
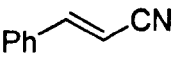
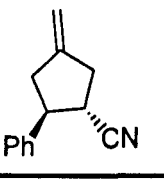
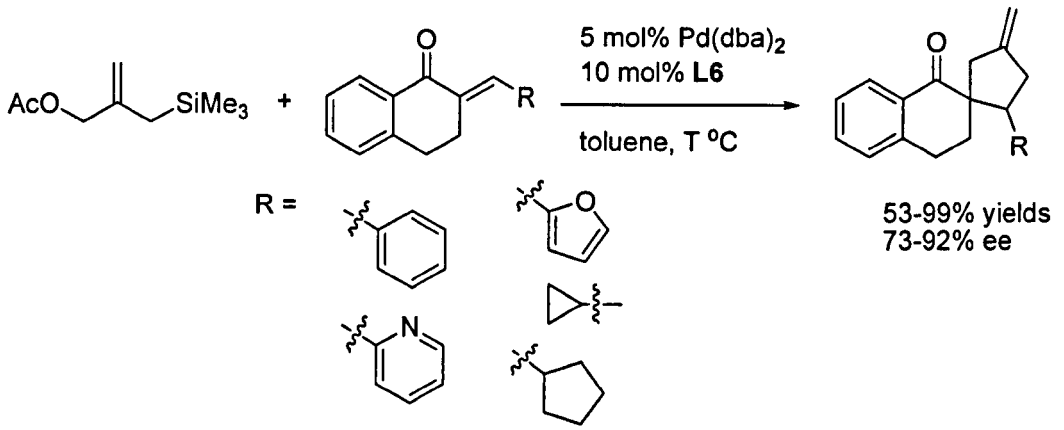
Entry	Substrate	Product	Temp (°C)	Yield (%)	ee (%)
1			23	80	58
			0	81	62
2			23	76	72
			-25	63	82
3			23	72	73
			-25	79	84
4			23	84	73
			-25	72	83
5			-25	83	80
6	 a: Ar = C_6H_4-4-OCH_3 b: Ar = C_6H_4-4-F		a: -25	73	72
			b: -25	80	74
7			0	78	58

Table 2

The reaction of **3** was also tested with various tetralone derivatives in the presence of $Pd(dba)_2$ and **L6** with success, as the corresponding *exo*-

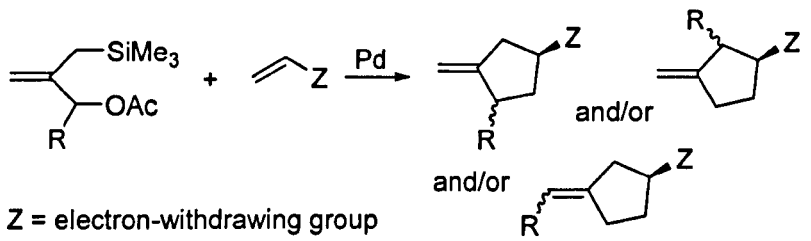
methylenecyclopentanes were obtained in high yields and enantiomeric excesses (Scheme 28).



Scheme 28

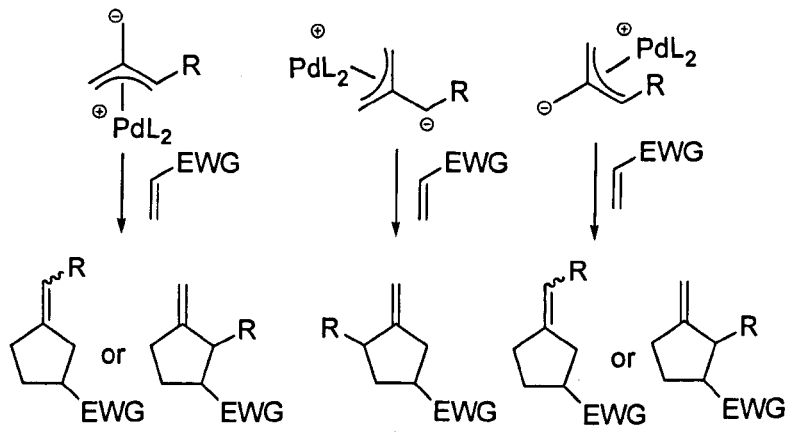
3.[3+2] Cycloaddition with substituted TMM reagents

Substituted TMM precursors can also be used in cycloadditions but since the reaction proceeds *via* a π-allyl intermediate, questions of regiochemistry arise. If we combine the three possible regioisomers with the two diastereoisomers that are possible in each case, we obtain a total of six possible products (Scheme 29).



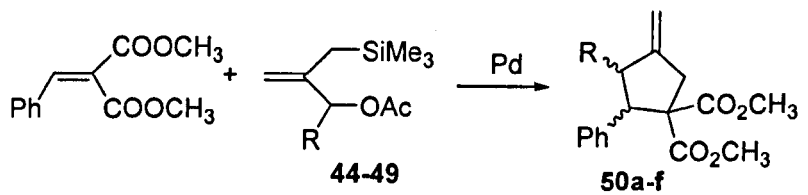
Scheme 29

In Scheme 30, all the various possible products that can be obtained from the different mesomeric forms of the Pd-substituted TMM complex are shown:



Scheme 30

Trost and co-workers decided to carry out some experiments to see if any chemoselectivity is observed during cycloadditions with substituted TMM-Pd precursors[6, 14-16] (Scheme 31, Table 3).



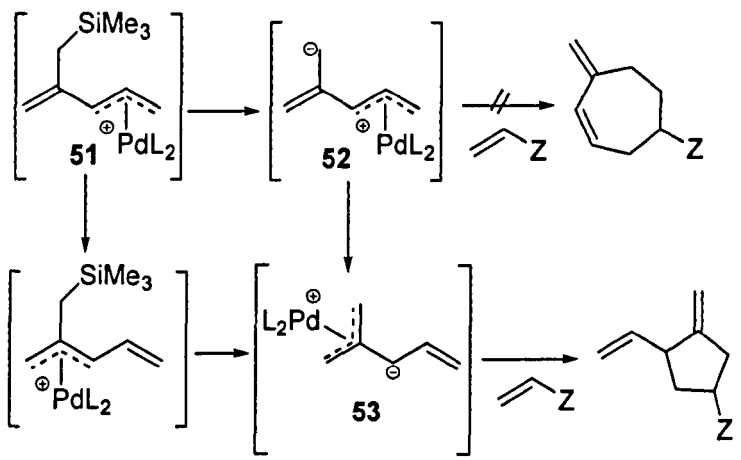
Scheme 31

Reagent	Product	R	Yield %	
44	**50a**	CN	54	trans
45	**50b**	COEt	59	trans
46	**50c**	Ph	[a]	cis + trans
47	**50d**	cyclopropyl	61	cis + trans
48	**50e**	$CH{=}CH_2$	89	cis + trans
49	**50f**	OAc	86	cis + trans

[a] yield not reported

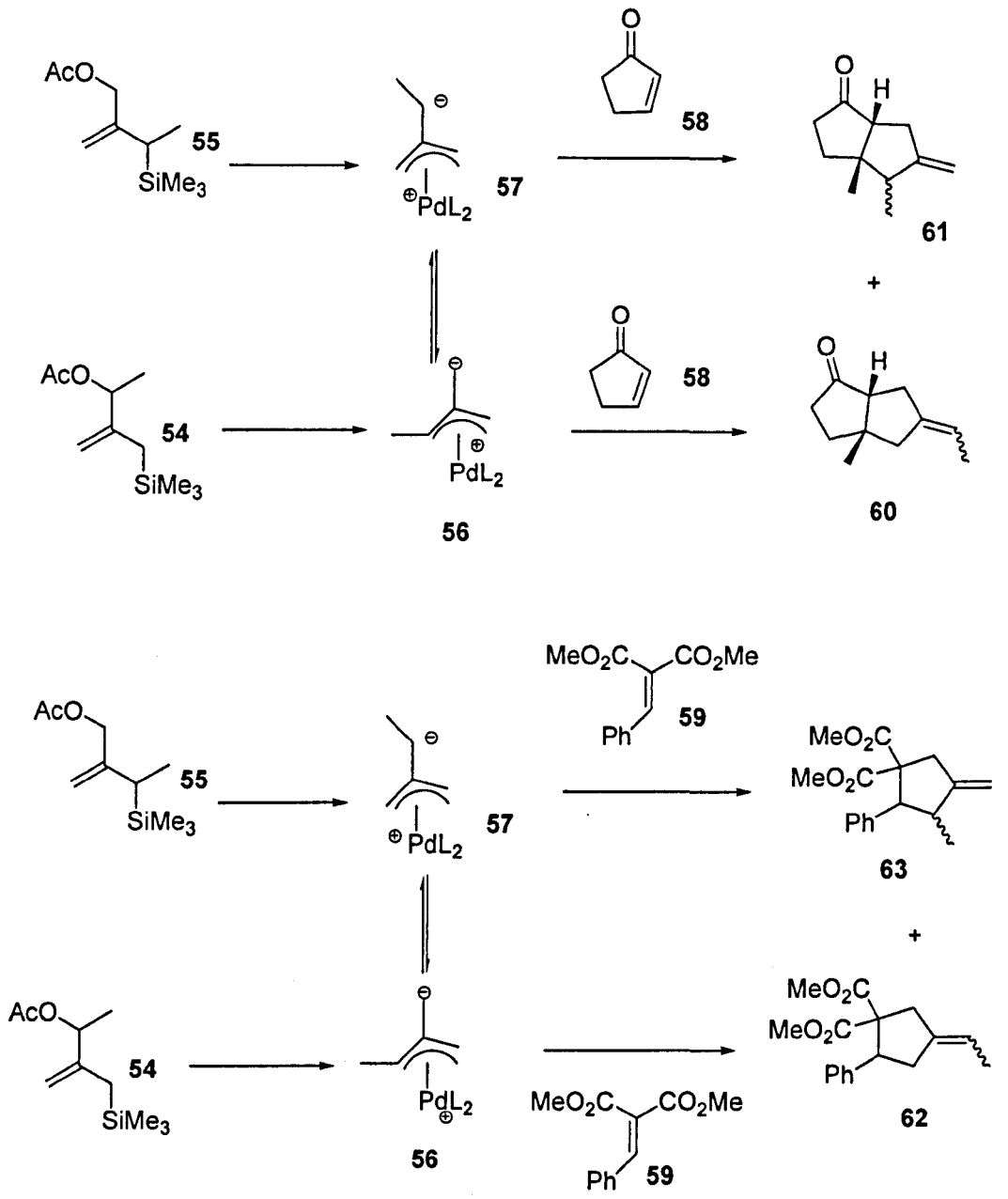
Table 3

As can be seen from Table 3, when R is an electron withdrawing group, only the trans isomer is obtained, although this selectivity is not observed with other R-groups. The formation of only five-membered ring products with the vinyl derivative **48** suggests that the kinetically favored π-allylpalladium cation **51**, which should produce seven membered-ring products via the zwitterion **52**, is not a product-determining intermediate. All intermediates funnel through **53**, which is presumably the product-determining intermediate (Scheme 27).



Scheme 32

These experiments suggested that the unsymmetrical TMM complexes equilibrate faster than they undergo cycloaddition. To investigate this, Trost[23, 24] and co-workers used two isomeric methyl-TMM precursors **54** and **55** with a view to trapping them with the appropriate olefin acceptors (Scheme 33 and Table 4). First they used 2-cyclopentenone **58** and both precursors gave identical product mixtures, in which **61** predominated over **60**. On the other hand, they used dimethyl benzylidenemalonate **59** as a trapping agent, and observed that, even if a slightly larger amount of adduct **62** was formed from **54** than from **55**, in both cases adducts derived from **57** were favoured. The results indicate that the regioselectivity of the cycloaddition is independent of the regiochemistry of the precursors.

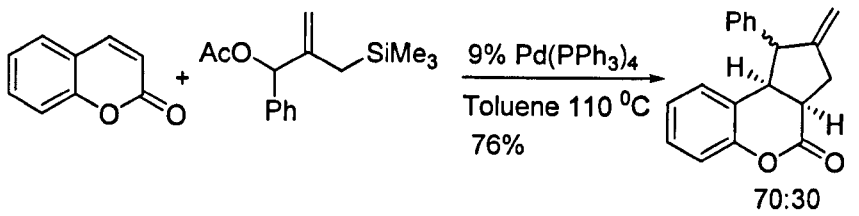


Scheme 33

Reactants	Products	Yield	Selectivity
54+58	**60+61**	52%	<5:>95
55+58	**60+61**	45%	<5:>95
54+59	**62+63**	82%	23:77
55+59	**62+63**	90%	13:87

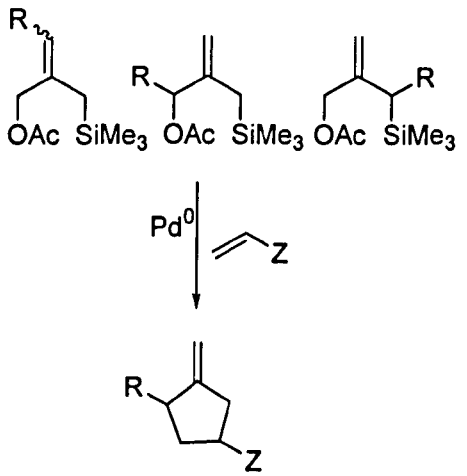
Table 4

The example below confirms the previous results: only a single regioisomer is obtained (Scheme 34)[13-16].



Scheme 34

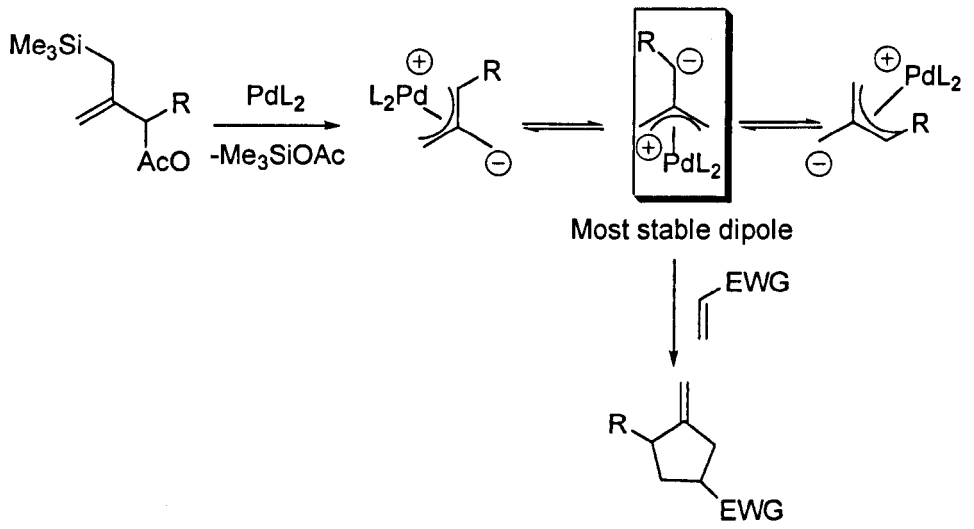
The regioselectivity of these reactions is remarkable. All substituents tested to date, electron donating or electron withdrawing, end up preferentially at the carbon in the product that becomes bonded to the β carbon of the acceptor i.e. all the substituted TMM precursors lead to the same methylenecyclopentane, as shown in Scheme 35.



Scheme 35

The regioselectivity can be rationalised as being due to nucleophilic attack of the most negatively charged carbon atom. This implies that the negative charge prefers to sit on the more substituted carbon atom of the TMM species: this is quite surprising when R is a methyl group or an electron-donating group but it can

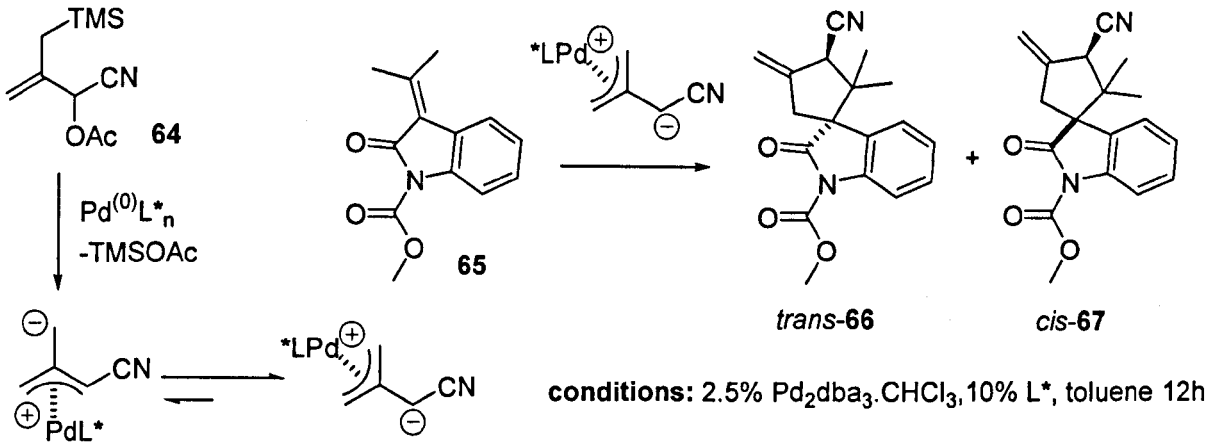
be explained by invoking a strong interaction between the HOMO of the TMM carbanion and the LUMO of the Pd-π-allyl moiety (Scheme 36).



Scheme 36

In their efforts to develop an efficient asymmetric process to make enantiopure cyclopentanes using the transition metal-catalyzed [3+2] trimethylenemethane cycloaddition, Trost and co-workers[25] recently investigated the reactivity of 3-alkylidene-oxindoline-2-ones **65** toward Pd-TMM complexes. They chose the cyano-substituted TMM-precursor **64**, thinking it could enhance the asymmetric induction.

Initial experiments with hexamethylphosphorus triamide (HMPT) as ligand for palladium showed that the desired cycloadduct formed in excellent yield as a *cis/trans* mixture (Scheme 37, Table 5 and Figure 2).



Scheme 37

Ligand	Temp (°C)	Yield (%)	**66/67**	**66** ee (%)	**67** ee (%)
HMPT	23	99	2:1		
L1	0	93	1:3	80	97
L3	0	97	4.3:1	92	95
L2	-20	97	1:6.2	96	99

Table 5

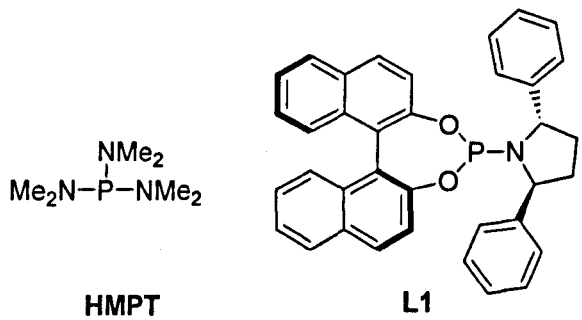
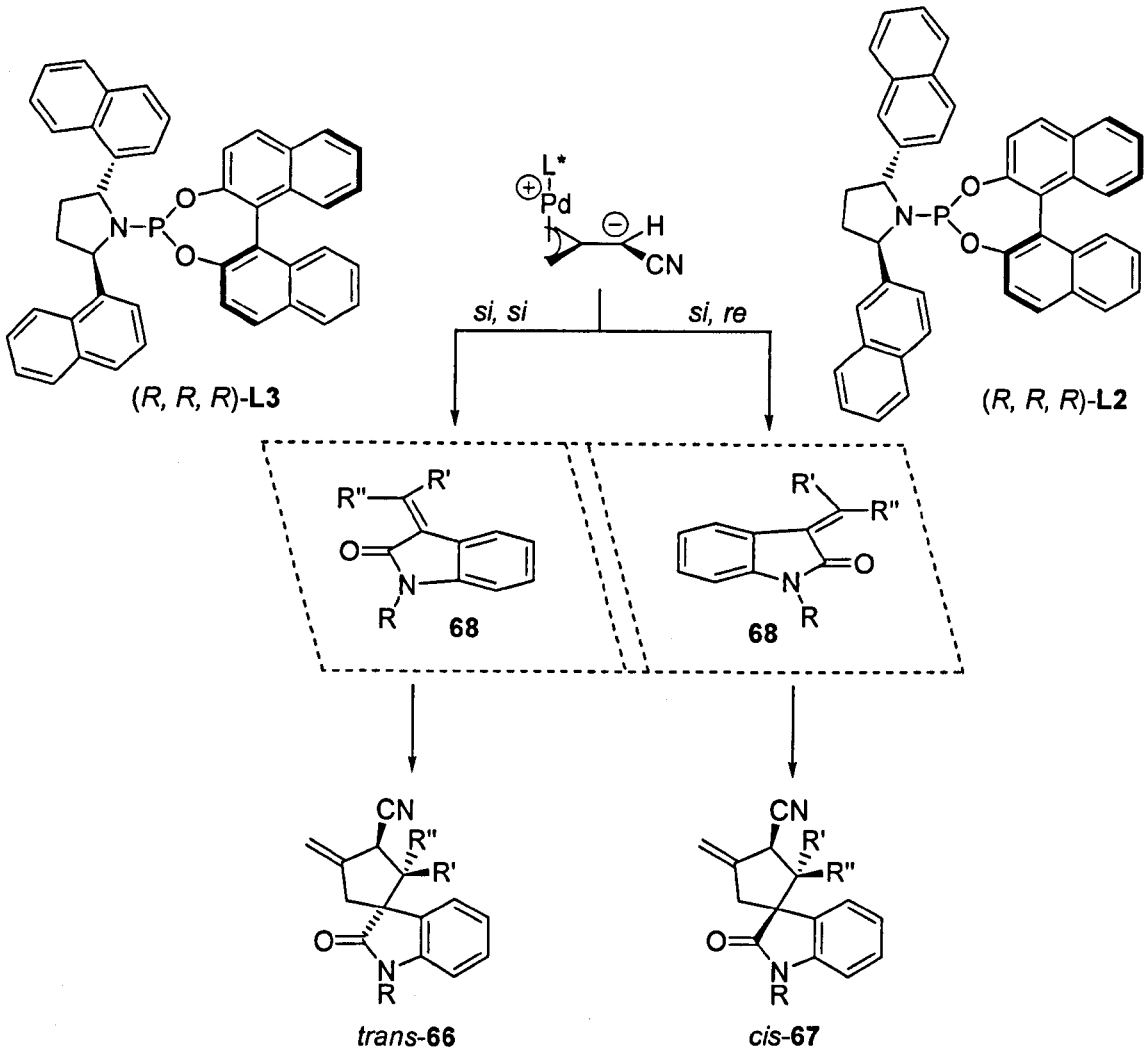


Figure 2

As highlighted in Table 5, **L1** gave mainly the *cis*-cyclopentane **X**. This contrasts the reaction with HMPT as ligand, where a 2:1 ratio favouring the corresponding *trans* product **66** was observed. Attempts to optimize the conditions for the formation of both diastereoisomers resulted in good diastereo- and excellent

enantioselectivities for either *trans*-**66** (92% ee and 4.3:1 dr with **L3**) and *cis*-**67** (99% ee and 1:6.2 dr with **L2**).



Scheme 38

The bulky 1-naphthyl-substituents of **L3** preferentially orient the aromatic oxindole part of the substrate **68** under the BINOL portion of the ligand. The 2-naphthyl-substituents of **L2** are shielding an area closer to the phosphorus centre of the ligand, favouring an orientation of the oxindole benzene ring away from the BINOL portion of the ligand (Scheme 38). Notably, variation of the substituents of the oxindole portion had little influence on the ee.

In the same paper, Trost and his collaborators also explored the influence of an unsymmetrical substitution pattern on both sides of the double bond of the oxindole. The cycloaddition proceeds under mild conditions generating the

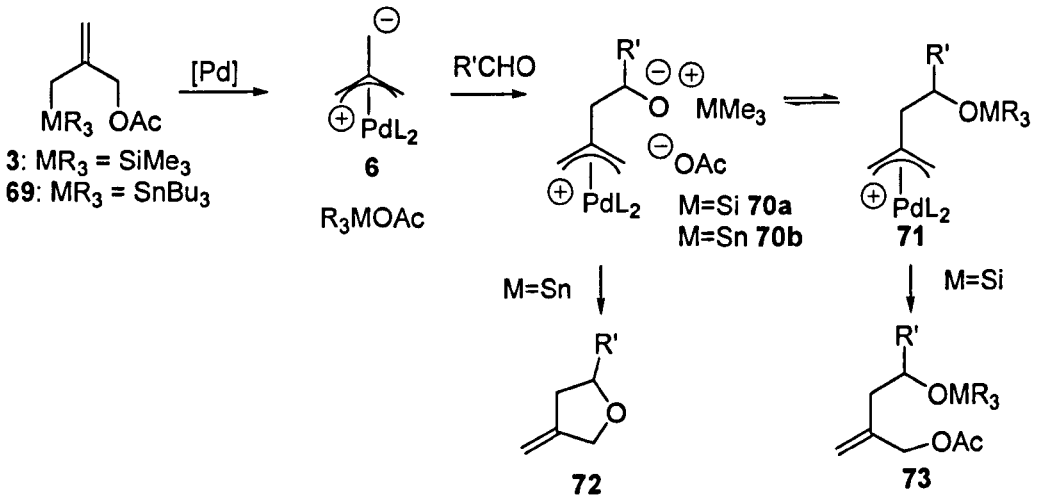
corresponding cycloadducts with up to three stereogenic centres in excellent yields and enantiomeric excesses, especially when **L2** was used.

Whilst palladium-trimethylenemethane is a good reagent for [3+2] cycloadditions to alkenes to form methylenecyclopentanes, but it has also been successfully used in addition to aldehydes, ketones and imines. These processes will be described in the following section.

4.Other types of cycloadditions

4.1.Addition to aldehydes and ketones[26, 27]

In theory, the palladium-TMM complex can act as a nucleophile towards a ketone or aldehyde leaving an oxyanion **70**, which would then cyclise to form the methylene tetrahydrofuran **72**. In practice, however, this cycloaddition with aldehydes and ketones occurs only under specific conditions

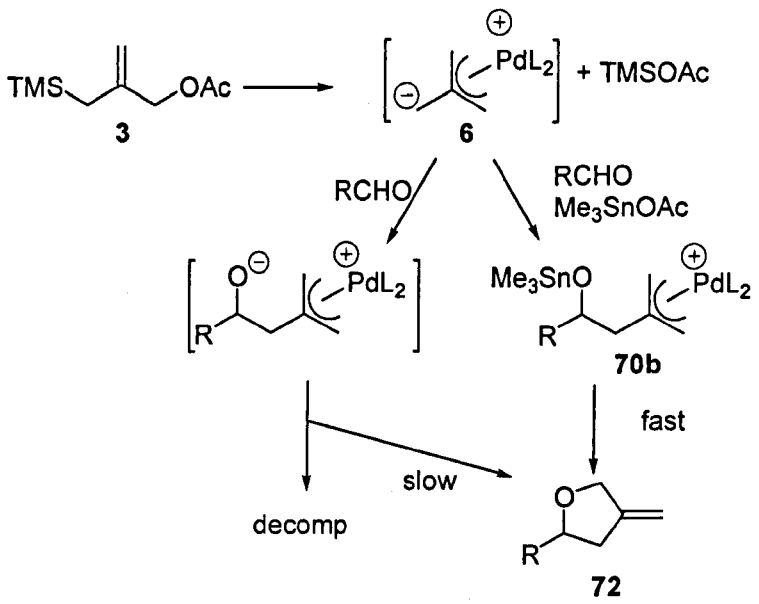


Scheme 39

As shown in Scheme 39, Pd-TMM complex **6** is formed from precursor **3** or **69** in the presence of a Pd(0) catalyst with associated Me_3SiOAc or Me_3SnOAc. Addition of Pd-TMM **6** to aldehyde provides **70** and the product **72** or **73** and this

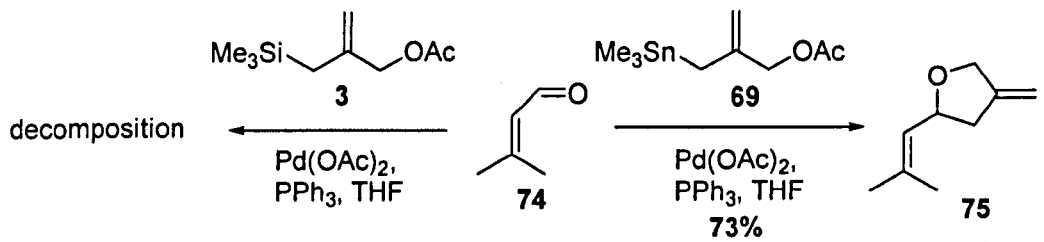
is determined by the nature of the Me_3M^+ counter-anion. The alkoxide **70a** is a poor nucleophile for the π-allylpalladium moiety, and hence ring closure to **72** is slow and competitive reaction with acetate generates **73**.

A rationale for the effect of tin cocatalysis is described in Scheme 40. The stannyl ether is a more long-lived species than alkoxide and reacts very well with the π-allyl palladium cation whereas alkoxides are poor nucleophiles for these electrophiles. This means that formation of the stannyl ether intermediate promotes the cyclisation reaction to the methylene tetrahydrofuran since this cyclises quickly in comparison to the alkoxide.



Scheme 40

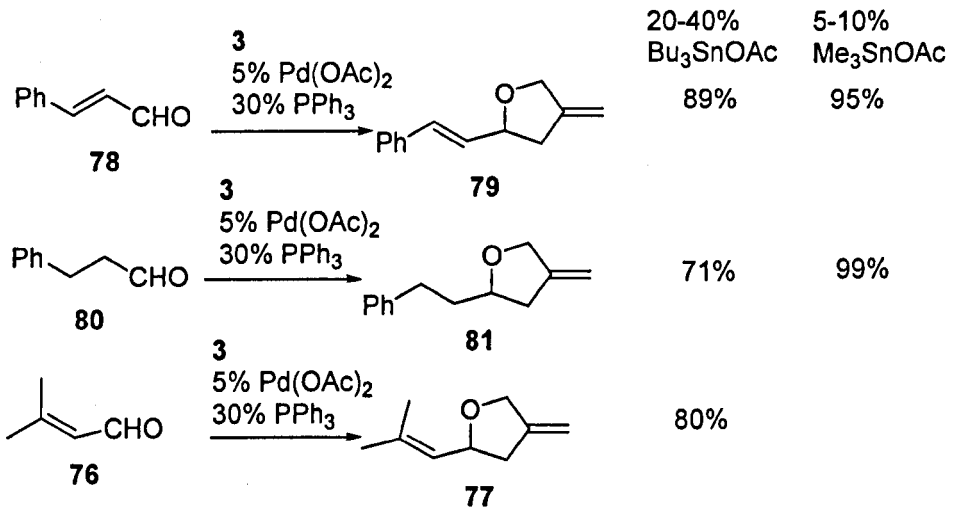
A summary of this reactivity profile is given in Scheme 41.



Scheme 41

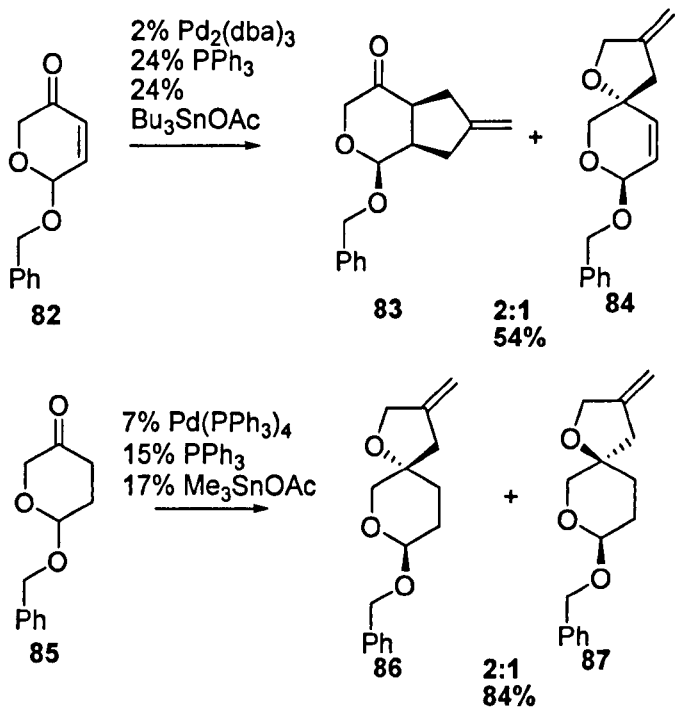
Since it has been shown that [3+2] cycloaddition on aldehydes occurs in presence of tin, Trost and co-workers had the idea to use tin acetate as a co-catalyst in presence of TMM.

In an experiment to further establish the origin of this tin effect, **3** and 10-20 mol% trialkyltin acetate were used in reaction with various aldehydes **76**, **78**, and **80** and cycloaddition to form the desired tetrahydrofurans **77**, **79** and **81** was accomplished in high yields in all cases (Scheme 42).



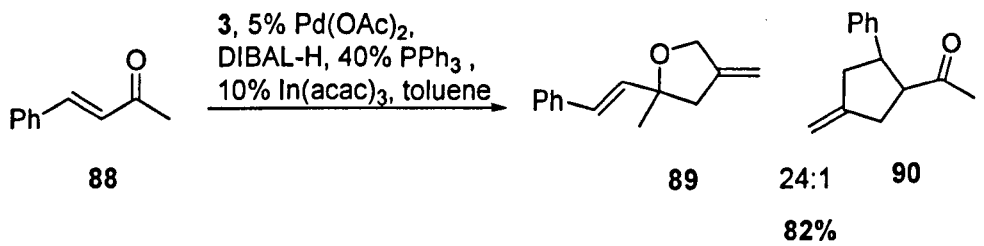
Scheme 42

Notably, this method can also be applied to ketones. α,β-Unsaturated ketones undergo cycloaddition preferentially on the olefin forming a 2:1 mixture of **83**:**84** (Scheme 43). Rapid decomposition was seen without the tributyltin acetate cocatalyst. In the absence of the olefin moiety, the cycloaddition takes place smoothly at the carbonyl of ketone **85**, forming isomers **86** and **87**. This occurs in much enhanced yield when trimethyltin acetate (84%) is used in comparison to tributyltin acetate (52%).



Scheme 43

As well as tin compounds, the use of electropositive indium complexes as co-catalysts has also shown application for the [3+2] cycloaddition to aldehydes, and these can even undergo addition to the carbonyl moiety of enones such as **88** (Scheme 44). Without $In(acac)_3$, the reaction proceeds *via* an almost exclusive 1,4-addition **90**[28].

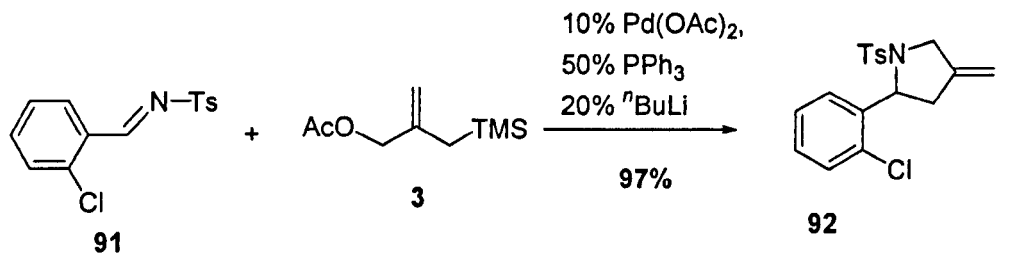


Scheme 44

Trost proposed that In^{3+} co-ordinates to the carbonyl in order to increase the electrophilicity of the carbonyl group and promote attack at this site. In^{3+} may also modulate the activity of the alkoxide nucleophile onto the π-allylpalladium moiety as for the stannyl ether.

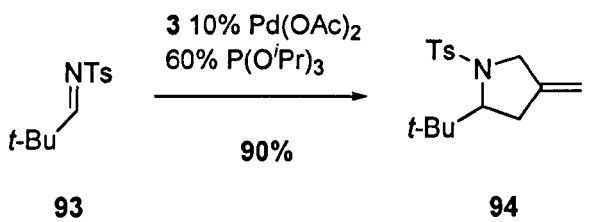
4.2.Addition to imines

In 1993, Trost's investigations[29] on cycloadditions to imines *via* Pd-catalyzed TMM reactions led to the conclusion that, whereas simple imines fail to react, imines possessing an electron-withdrawing group at either the carbon or nitrogen enhance the electrophilicity of the imine sufficiently to make it an excellent acceptor. This represents a good way to synthesize pyrrolidines. For a variety of aromatic groups, yields of 95-98% were achieved (Scheme 45).



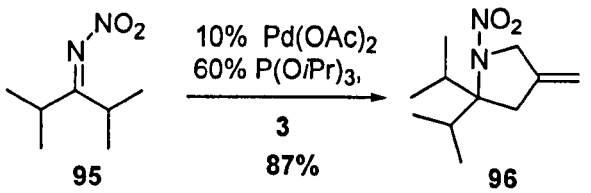
Scheme 45

The reaction also worked for aliphatic tosylimines as long as they were derived from non-enolisable aldehydes or ketones, an example of which is shown below in Scheme 46. The sterically hindered, non-enolisable 'butyl imine gave a high yield of methylene pyrrolidine.



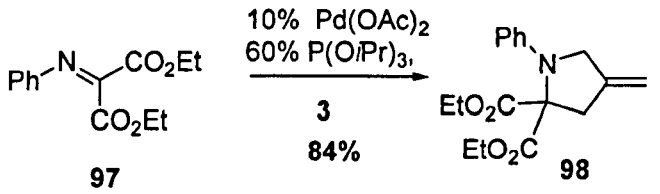
Scheme 46

Other activating groups were also used (Scheme 47). The electron withdrawing nitro group was effective as an alternative to a tosyl group on nitrogen for hindered imines such as the bis *iso*-propyl substituted example **95** but was unsuccessful with less hindered imines, due to possible enolisation.



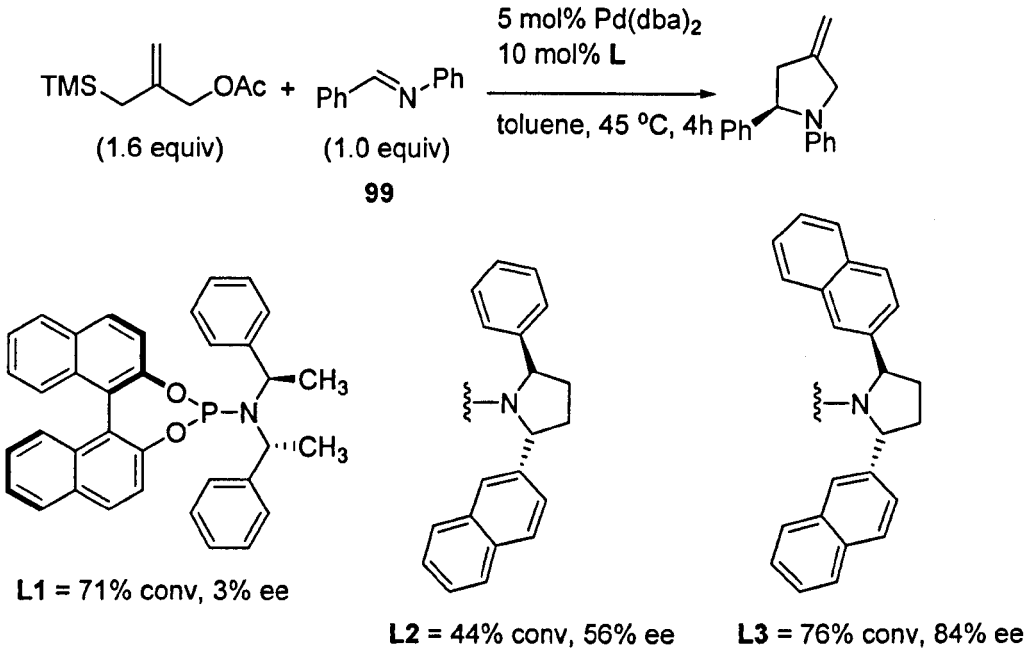
Scheme 47

Activating groups were also used effectively on the carbon of the imine, demonstrated by the diester **97** which underwent cycloaddition easily, forming a pyrrolidine armed with two ester groups **98** (Scheme 48).



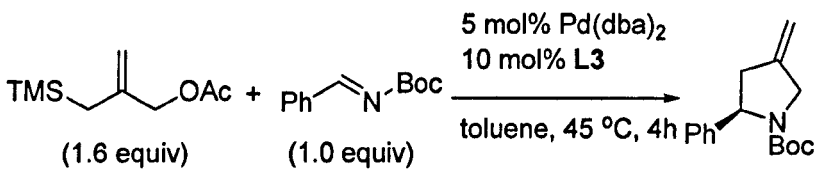
Scheme 48

In 2007, Trost and co-workers[30] reported their work on an asymmetric [3+2] cycloaddition with imines. Initial studies focused on the reaction of benzylidene aniline **99** under the previously developed conditions (5 mol% $Pd(dba)_2$, 10 mol% ligand, 1.6 equiv TMS propenyl acetate) at 45 °C (Scheme 49).



Scheme 49

Ligand **L1** gave only 3% ee at 71% conversion but adjusting the nature of the chiral space by increasing the size of the aryl groups led to replacement of one phenyl group with a 2-naphthyl group (**L2**), which did increase the ee. Bis-2-naphthyl ligand **L3** gave the best results with a 76% conversion and 84% ee. Using the optimized ligand **L3**, they determined the best class of imine for this reaction. Keeping in mind that they wanted to use a group which could provide high enantiomeric excess but would be easy to remove, they screened benzyl, phosphonyl, Fmoc and Cbz imines but it turned out that the use of the *N*-Boc imine gave excellent results with the protected pyrrolidine being obtained in 98% yield and 87% ee (Scheme 50).

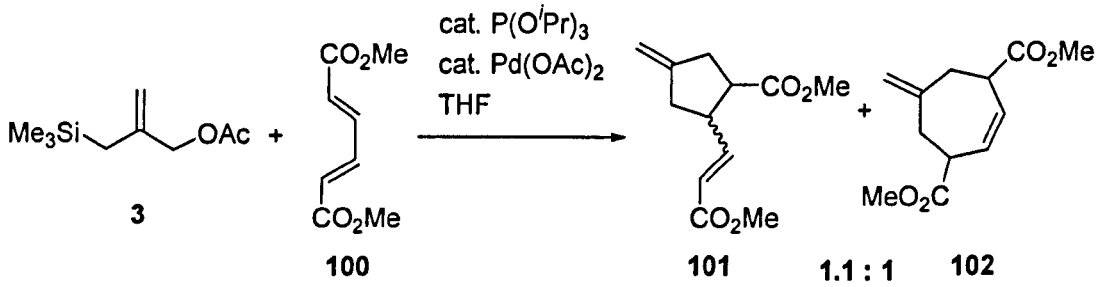


Scheme 50

The reaction using both *N*-Boc and *N*-aryl imines was also investigated. The reaction worked well when the *N*-bound aryl ring bore electron donating groups or withdrawing groups (80-87% yields, 83-84% ee). On the C-bound ring, electron withdrawing groups significantly enhanced reactivity. However, the use of Boc-imines provided a broader reaction scope, this class being more reactive than the substituted benzylidene anilines.

4.3.[4+3] Cycloadditions

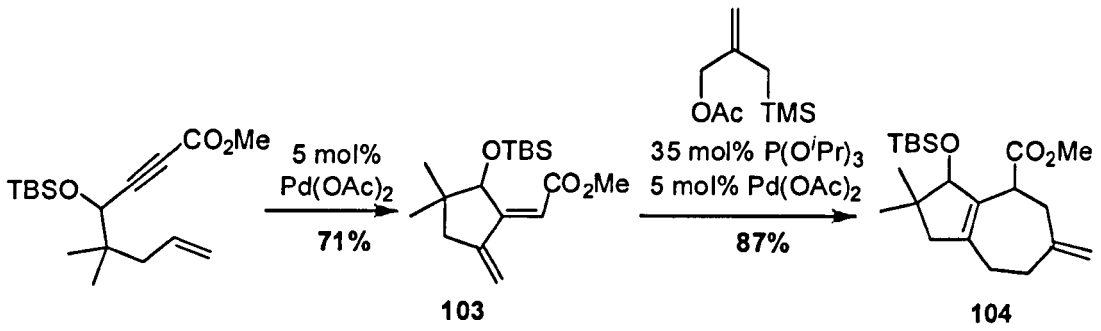
The TMM-precursor **3** can also be used in a [4+3] cycloaddition with dienes to form seven-membered rings[31, 32]. The diene **100** can either react at one alkene only in a [3+2] cycloaddition giving cyclopentane **101** or in a [4+3] reaction to give cycloheptene **102** (Scheme 51).



Scheme 51

In the event, little selectivity was seen between [3+2] and [4+3] cycloadducts, with a 1.1:1 ratio of **101** to **102** being obtained. The proposed solution to this was to restrict the diene to a cisoid conformation thus promoting the opportunity for seven-membered ring formation.

For example, the diene **103** was formed by a palladium-catalysed enyne cycloisomerisation reaction and a subsequent palladium catalysed [4+3] cycloaddition reaction gave the seven-membered ring **104** as the only product. Increased steric hindrance by increased substitution on the ring of the diene enhanced the selectivity for seven-membered ring formation (Scheme 52).



Scheme 52

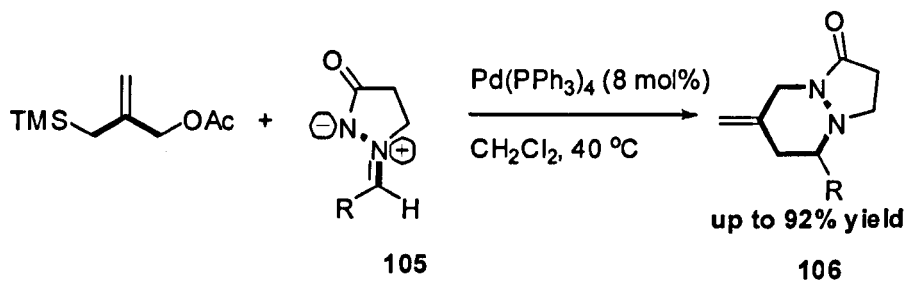
This approach was successful for highly substituted substrates and moderately successful for less substituted substrates but it was still limited to geometrically constrained molecules and so is far from being general.

4.4.[3+3] Cycloadditions

4.4.1.[3+3] Cycloaddition with Azomethine imines

Although a [3+3] cycloaddition strategy is a legitimate approach toward the formation of six-membered rings, it has been much less studied than the corresponding [4+2] approach[33-36] and only a few examples of transition-metal-catalyzed [3+3] cycloadditions have been reported to date[37-45].

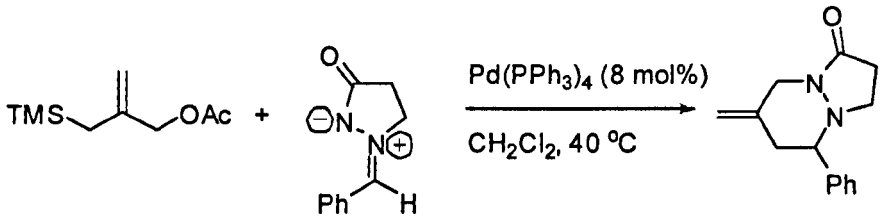
In 2006, Shintani and Hayashi[46] described the development of a new palladium-catalyzed [3+3] cycloaddition of TMM with azomethine imines **105** to produce highly functionalized hexahydropyridazine derivatives **106** under simple and mild conditions (Scheme 53).



Scheme 53

1-Alkylidene-3-oxopyrazolidin-1-ium-2-ides **105** developed by Dorn and Otto in 1968[47, 48], are isolable and stable azomethine imines and have been used as 1,3-dipoles in the context of [3+2] cycloadditions, giving five-membered nitrogen-containing heterocycles[49-52].

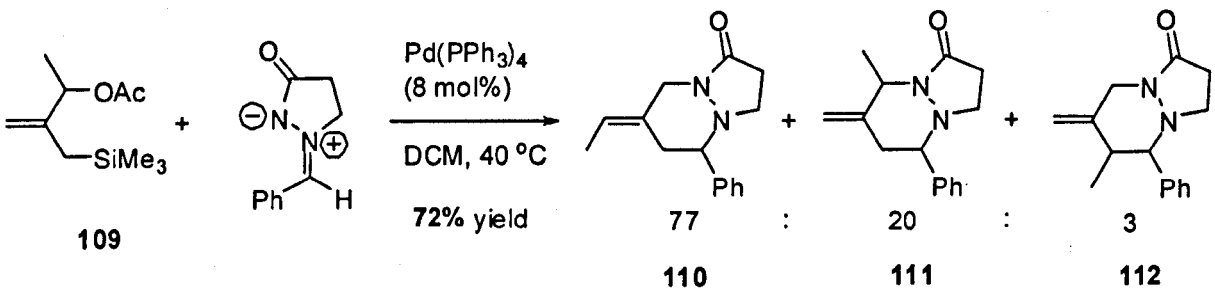
Initially, they examined the reaction of **3** with azomethine imine **107** in the presence of a catalytic amount of $Pd(PPh_3)_4$ at 40 °C and found that the choice of solvent has a significant impact on the reaction progress (Scheme 54). Thus, desired [3+3] cycloadduct **108** was obtained in high yield by the use of dichloromethane (82% yield).



Scheme 54

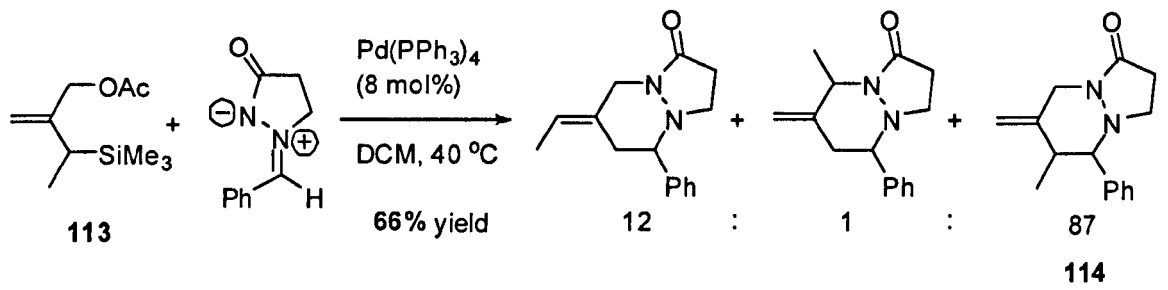
With respect to the substituents on the alkylidene portion, a variety of aryl groups as well as heteroaryl and alkenyl groups can be tolerated, furnishing [3+3] cycloadducts in high yield (70-92% yield). However, substrates with an alkyl substituent are less effective for this [3+3] cycloaddition.

They also investigated the reactions using substituted TMM precursors (Scheme 55). Compound **109** mainly furnished two different products **110** and **111**, with traces of a third compound **112** (77 : 20 : 3).



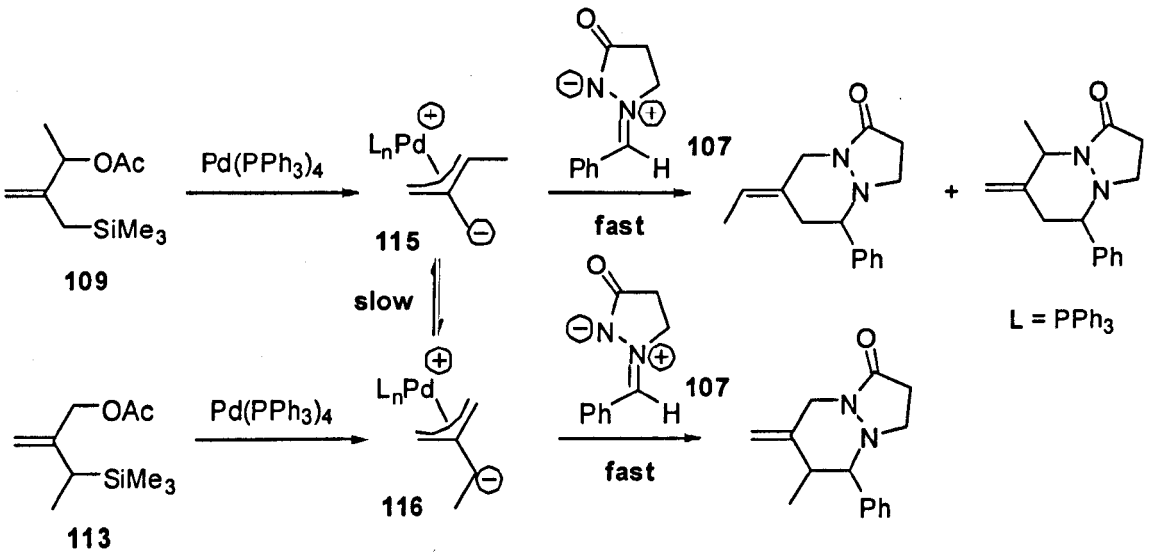
Scheme 55

In contrast, the use of structural isomer **113** generated **114** as the major product (Scheme 56).



Scheme 56

These results showed that the substitution pattern of the TMM precursor is reflected in the product distribution in the [3+3] cycloaddition with azomethine imine **107**, indicating that the cycloaddition occurs without significant equilibration between intermediates **115** and **116** (Scheme 57).



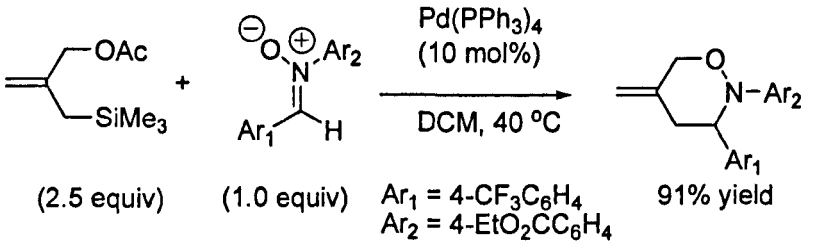
Scheme 57

This observation contrasts to the palladium-catalyzed [3+2] cycloadditions of **109** or **113** with electron-deficient olefins described by Trost, which preferentially afford five-membered cyclic compounds derived from intermediate **116** regardless

of the starting TMM precursor (**109** or **113**) due to the fast equilibration between **115** and **116** prior to the cycloaddition[23].

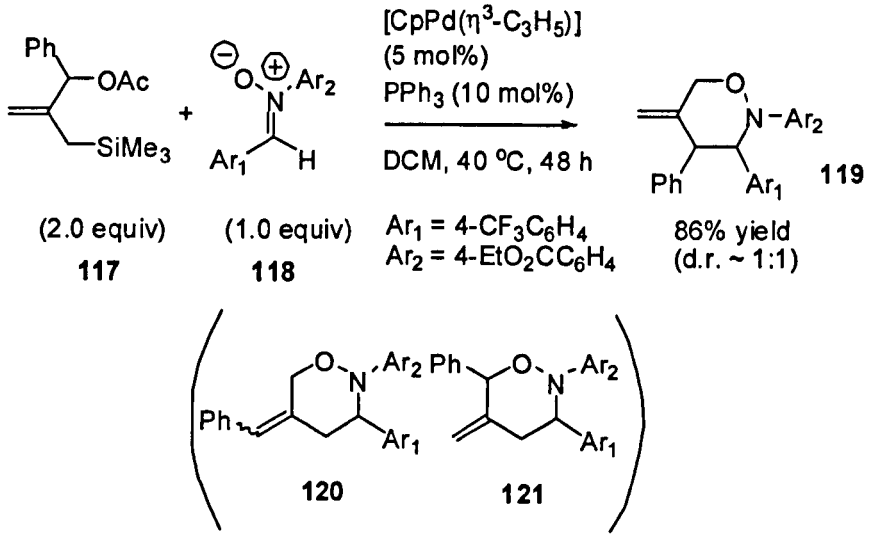
4.4.2.[3+3] Cycloaddition with Nitrones

[3+3] cycloadditions can also be extended to the couplings with nitrones as shown by Shintani and Hayashi[46] (Scheme 58).



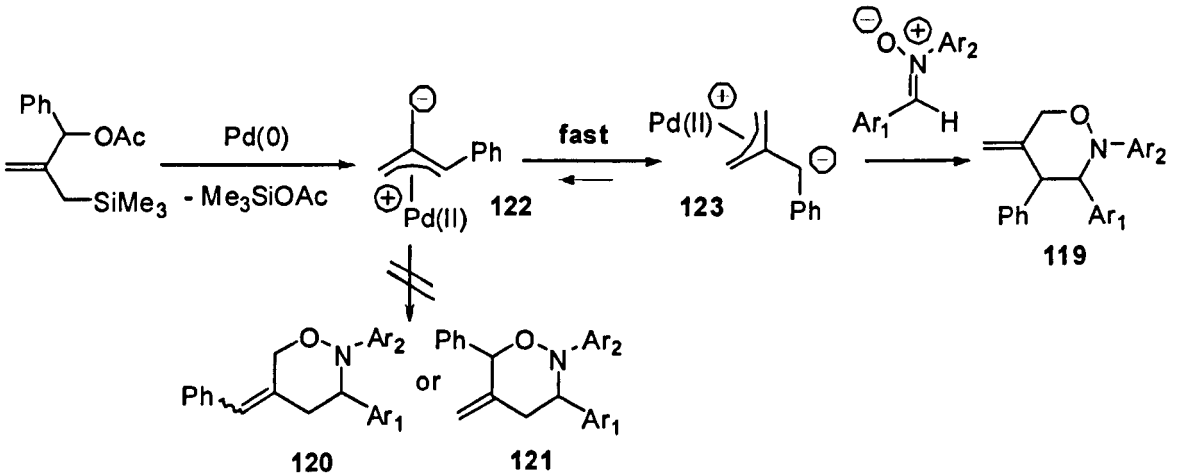
Scheme 58

More recent work by the same group proved that trimethylenemethane derivatives could be used in a palladium-catalyzed asymmetric [3+3] cycloaddition with nitrones to produce six-membered heterocycles with high stereoselectivity[53].
In an initial investigation, they performed a reaction of the TMM precursor **117** with nitrone **118** in the presence of 5 mol % [CpPd(η^3-C_3H_5)] and 10 mol % PPh_3 at 40 °C, and found that product **119** was obtained in 86% yield as a mixture of two diastereoisomers (d.r.~ 1:1), with almost no formation of the structural isomers **120** and **121** (Scheme 59).



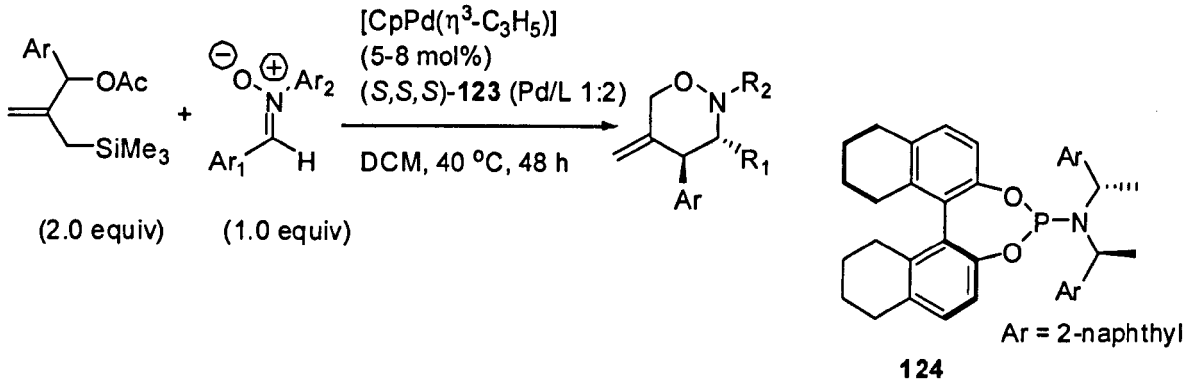
Scheme 59

The observed high selectivity to form **119** over isomers **120** or **121** proves that the initially formed Pd-TMM intermediate **122** rapidly isomerizes to Pd-TMM intermediate **123**, which bears a more stable benzylic anion, leading to the product **119** (Scheme 60).



Scheme 60

After having investigated different ligands used in various transition metal-catalyzed cycloadditions such as (*S*)-MeO-mop[54, 55], (*S*)-binap[56] or phosphoramidites[57], they investigated the scope of this asymmetric [3+3] cycloaddition reaction using (*S,S,S*)-**124** as the ligand (Scheme 61).



Scheme 61

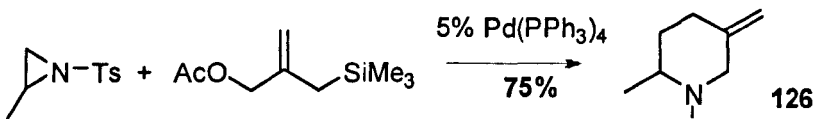
It was found that various aryl groups can be tolerated on the electrophilic carbon atom of the nitrone, with the corresponding 1,2-oxazines obtained in excellent yield (92-99%), relatively high diastereoselectivity (*trans/cis* 76:24-89:11) and high enantioselectivity (91-92% ee)[c]. Several TMM precursors with different aryl groups can also be used in the [3+3] cycloaddition reaction with similarly high efficiency. Unfortunately, the use of unsubstituted TMM precursor **3** gives the cycloadduct with almost no enantioselectivity.

4.4.3.[3+3] Cycloaddition with Aziridines

Prior to work in the Harrity group[37-39, 58], there was a single example in the literature of the use of 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** in reaction with *N*-tosyl methyl aziridine **125** in a [3+3] cycloaddition reaction in order to form a functionalised piperidine **126**[40] (Scheme 62). Presumably, as with the imines, the presence of the electron withdrawing tosyl group activates the aziridine towards nucleophilic attack. Nucleophilic attack took place specifically at the less hindered, unsubstituted carbon. The mechanism was assumed to be analogous to all those shown above and the route was attractive in that if enantiomerically pure aziridines were to be used then the stereochemistry would be retained in the product as this centre is not directly affected by the

[c] Alkyl-substituted nitrones are not suitable substrates under these reaction conditions; they give little or no cycloadducts.

cycloaddition reaction. This would be an efficient entry into the formation of enantiomerically pure functionalised piperidines.

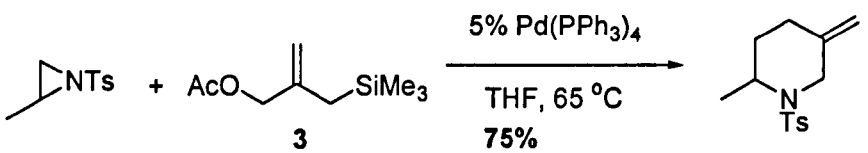


Scheme 62

Chapter II - Palladium-Trimethylenemethane complexes and their applications in [3+3] Cycloadditions towards the Piperidine nucleus

The presence of the piperidine nucleus in a myriad of natural products and biologically active compounds is reflected in the continued interest in developing new and efficient routes to this motif. As described in the introduction, our approach to piperidines is based on Trost's [3+2] cycloaddition to five-membered rings *via* trimethylenemethane (TMM) and its equivalents[5].

In 1989, Kemmit and Bambal[40] reported the first metal-catalysed cycloaddition of 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** to the aziridine ring system (Scheme 63). They used the complex $[Pd(PPh_3)_4]$ to catalyse the cycloaddition of trimethylenemethane to activated aziridines to give 5-methylenepiperidines in good yields. The mechanism was proposed to proceed *via* an analogous stepwise process to the [3+2] cycloaddition described by Trost.

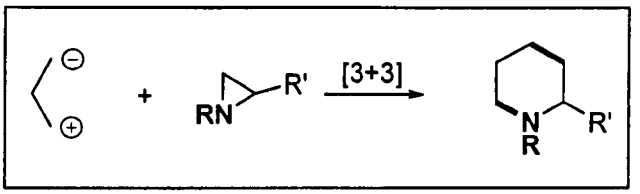


Scheme 63

The route is attractive in that, if enantiomerically pure aziridines (which are readily available) were to be used, then the stereochemistry would be retained in the product, as this centre is not directly affected by the cycloaddition reaction. This would therefore represent an efficient entry into the formation of enantiomerically pure functionalised piperidines.

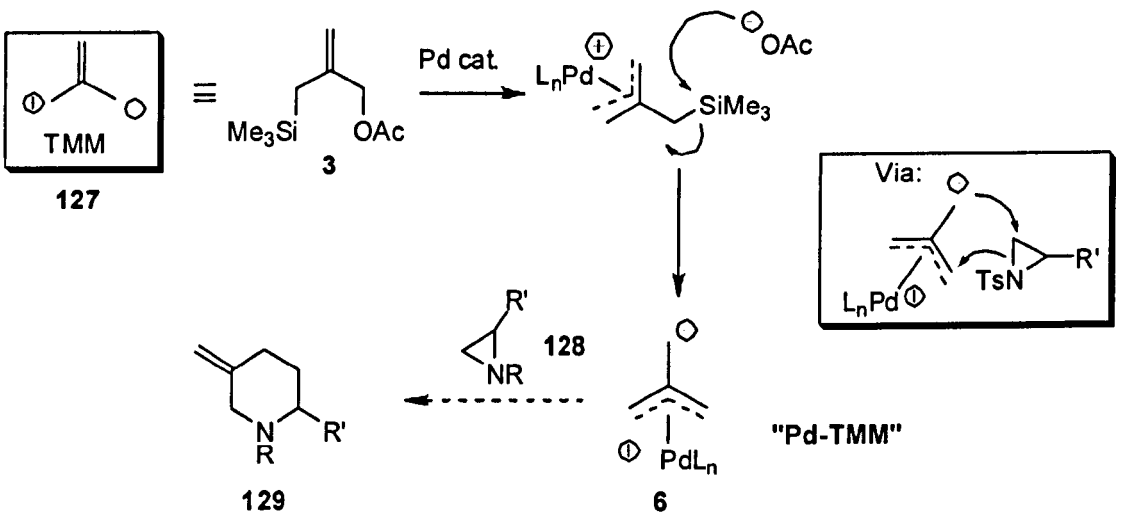
1.Previous studies

In the Harrity group, the application of TMM-metal complexes in [3+3] cycloadditions towards the preparation of enantiomerically pure piperidine products has been investigated for the last few years[33, 38, 39] (Scheme 64).



Scheme 64

A 1,3-dipole **127** was required for this transformation, and Trost's TMM precursor **3** was chosen as the synthetic equivalent[5] (Scheme 65). Not only would this result in the construction of the heterocycle in a single step from readily available starting materials, it would also furnish the product **129** with an exocyclic methylene group, which can be further functionalised.



Scheme 65

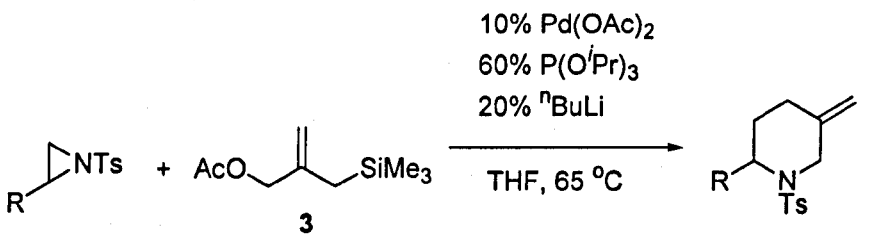
The R group attached to the aziridine nitrogen atom has to be a protecting group capable of activating the aziridine **128** towards nucleophilic attack, and should be

easy to remove. The nature of the palladium species needed for efficient catalysis was previously investigated in the group and it turned out that $Pd(OAc)_2$, together with $P(O^iPr)_3$ and *n*-BuLi as a reductant, provided the best catalyst for the [3+3] cycloaddition. The tosyl group was initially employed because of its electron withdrawing nature. Another advantage is that according to the method of Craig[59], enantiomerically pure tosyl aziridines can be synthesised in high yield from the corresponding amino acid.

Preliminary experiments have demonstrated that this technique permits the synthesis of these compounds in enantiomerically pure form from the corresponding aziridines.

1.1.Cycloaddition Reactions of Monosubstituted Aziridines[38]

Since ring opening reactions of aziridines require either an electron-withdrawing activating group attached to the nitrogen or catalysis by Lewis or protic acids, previous studies focused on the *p*-toluenesulfonyl (Ts) as the *N*-substituent (Scheme 66). The presence of the electron withdrawing tosyl group activates the aziridine towards nucleophilic attack. Nucleophilic attack takes place generally at the less hindered, unsubstituted carbon. After having tested a range of solvents and catalyst systems, optimal conditions were identified for the [3+3] cycloaddition reaction and a range of substituted tosylaziridines were screened as outlined in Table 6 below.



Scheme 66

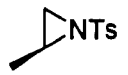
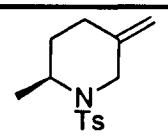
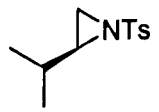
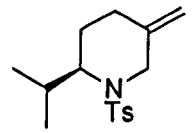
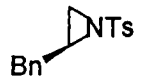
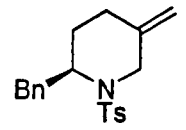
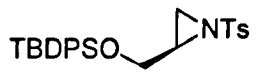
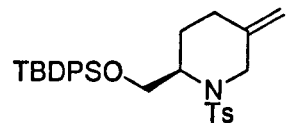
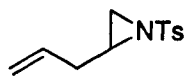
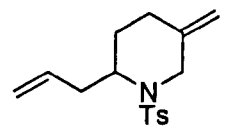
Entry	Aziridine	Product	Yield
1			82%
2			72%
3			79%
4			62%
5			65%

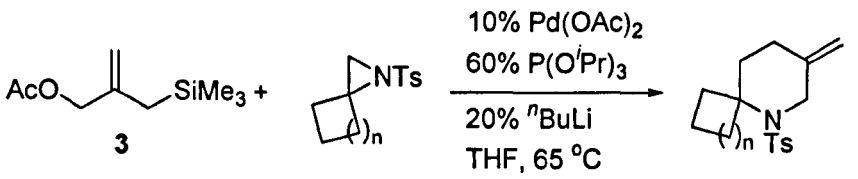
Table 6

We notice that, in all the cases tested, piperidines were obtained in good yields and with complete retention of enantiopurity. Groups that could be useful in further transformations (OTBDPS and allyl) were tolerated under the reaction conditions. All piperidines formed were substituted by an exocyclic methylene, which provided further possible functionalisation.

1.2.Cycloaddition Reactions of 2,2-Disubstituted Aziridines[38]

Given that 2,5-disubstituted piperidines were prepared in good yields and in excellent enantiomeric purity, the substrate scope was expanded to include 2,2-

disubstituted aziridines (Scheme 67). This was successful and spiropiperidines were obtained in good yields (Table 7).



Scheme 67

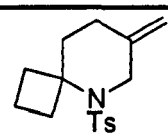
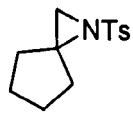
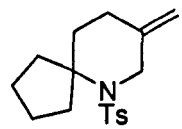
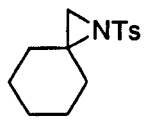
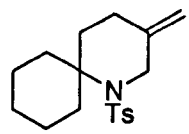
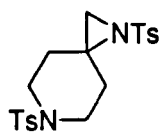
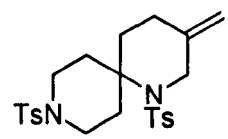
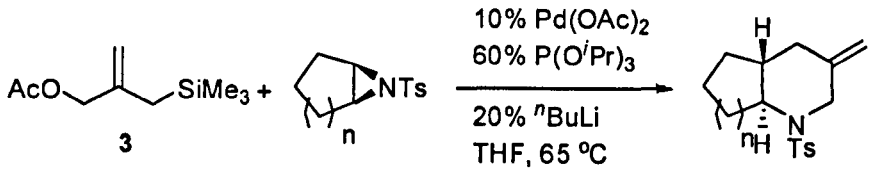
Entry	Aziridine	Product	Yield
1			74%
2			54%
3			70%
4			43%

Table 7

1.3.Cycloaddition Reactions of 2,3-Disubstituted Aziridines[38]

A final class of substrates that were investigated were the bicyclic aziridines (Scheme 68). The reactions were found to be slow and the yields low. However, piperidines with five- and six-membered rings were isolated (Table 8). In contrast, the seven-membered ring piperidine could not be isolated.



Scheme 68

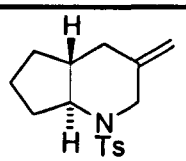
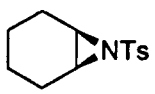
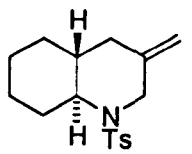
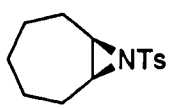
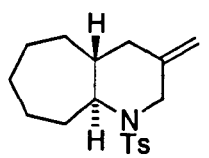
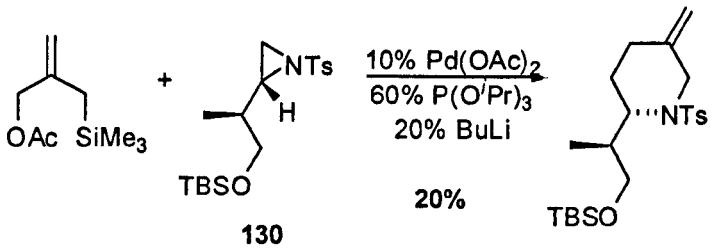
Entry	Aziridine	Product	Yield
1			15%
2			29%
3			0%

Table 8

Thus a wide variety of piperidines could be prepared, mostly in good yields, from readily available aziridine substrates. The door was open for the application of this technique to the synthesis of various natural products with a piperidine core. The possibility of formation of bicyclic or spirocyclic piperidines was especially encouraging due to their presence in a wide range of natural products.

2.Background

During the application of this chemistry in target synthesis, a surprisingly inefficient [3+3] cycloaddition was observed when aziridine **130** was employed (Scheme 69). The reaction could not be optimized to any great extent after screening many catalyst systems and conditions.

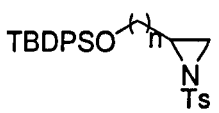


130

Scheme 69

We decided to further explore this observation, in particular we wished to investigate whether there was any particular silylether effect on the [3+3] cycloaddition.

That's the reason why part of our project was focused on the silylether-substituted aziridines and our investigation led us to the question whether there was any particular silylether effect on the [3+3] cycloaddition. Specifically, we chose to study the effect of the side chain on the cycloadditon, using the aziridines described below (Figure 3).



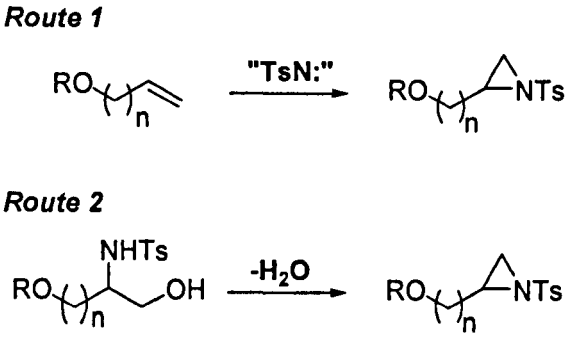
n = 1, 2, 3, 4

Figure 3

3.Synthesis of aziridine precursors

Two different routes have been considered to synthesise the required aziridines (Scheme 70):

- Aziridination of an alkene *via* a nitrene addition **(Route 1)**
- Dehydration using amino-acids *via* a Mitsunobu reaction **(Route 2)**

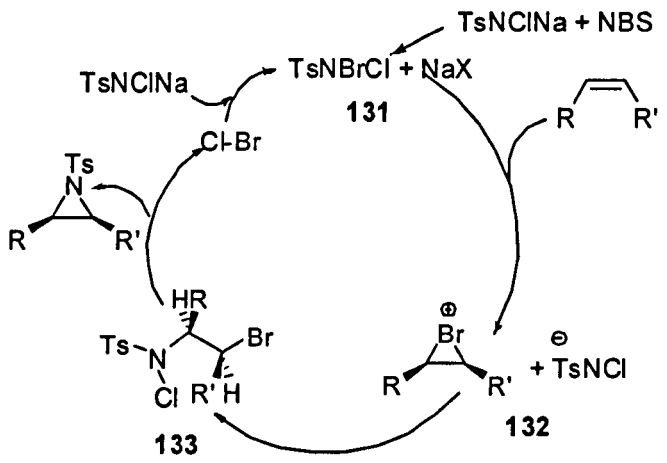


Scheme 70

3.1.Aziridination *via* a nitrene addition

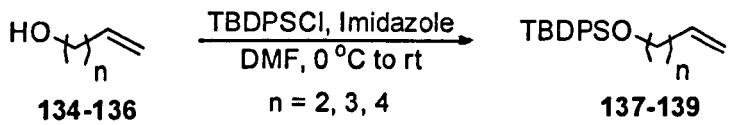
Various routes towards the aziridine synthesis *via* a nitrene addition have been reported in the literature. Amongst them, chloramine-T coupled with various catalysts (phenyltrimethylammonium tribromide $PhMe_3^+Br_3^-$ or PTAB[60], pyridinium hydrobromide perbromide $py.HBr_3$[61], *N*-bromosuccinimide[62] *NBS*) have attracted a lot of interest. In our case, we used the route described by Sudalai and Thakur[62], which is a modification of the Sharpless[60] aziridination that uses *N*-bromosuccinimide and chloramine-T.

The mechanism of the aziridination remains unclear but some elements are proposed (Scheme 43). Firstly, bromide catalyst acts as a source of Br^+. Secondly, it is believed that it reacts with chloramine-T to produce **131** which then reacts with the olefin to afford the bromonium ion **132**. The ion can then undergo stereoselective opening by $TsNCl^-$ species to produce **133** and then undergo cyclisation to yield the aziridine and regenerate the species **131** by reaction between chloramine-T and Br-Cl.



Scheme 71

We anticipated that we could prepare the desired silyl ether containing aziridines from the commercially available hydroxyalkenes **134-136**. Initial efforts to prepare the aziridine from the unprotected hydroxyalkene failed, therefore, we decided to protect the hydroxyl group using *tert*-butyldiphenylsilyl (TBDPS) group (Scheme 72). We obtained the expected protected hydroxyalkenes **137-139** in excellent yields (Table 9).

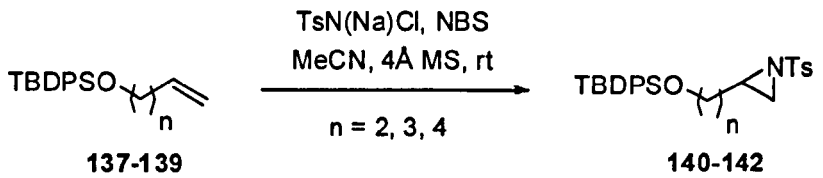


Scheme 72

n	Yield %
2	93
3	99
4	95

Table 9

Then, we proceeded to study the aziridination of the alkenes **137-139** (Scheme 73). Unfortunately, we only obtained the desired products in poor to moderate yields (Table 10).



Scheme 73

n	Yield %
2	16
3	25
4	48

Table 10

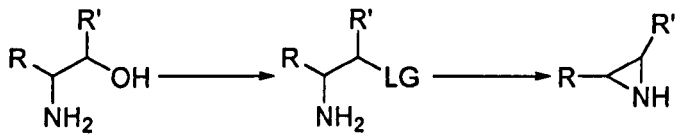
We can highlight an effect of the length of the side chain, since the longer the chain, the better the yield. It can be explained by the inductive effect of the silyl ether group; it makes the alkene less electron rich and therefore makes the bromination step slower. Since the closer the silyl ether group to the double bond, the stronger the inductive effect, this might explain the increasing of the yields when increasing the chain from n=2 to n=4.

Whilst this route was not especially efficient, the reagents are cheap, easy to use and in each case we recover useful quantities of product together with the starting material.

3.2.Amino acid route

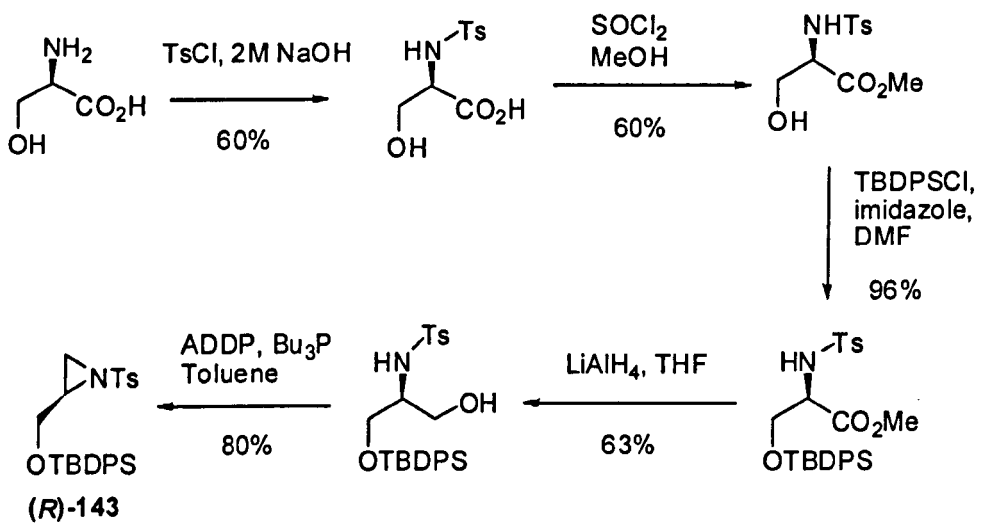
Since the product yields were quite low for compounds **140** and **141**, we investigated an alternative route to synthesise these aziridines. Enantiomerically

pure aziridines can be obtained from enantiomerically pure amino acids by the method of Craig[59], which uses tosylation of the nitrogen before reduction of the acid functionality. Tosylation of the alcohol moiety generates a good leaving group, which permits ring closure to furnish the corresponding enantiomerically pure aziridine in high yield. The general pathway for the synthesis of aziridines starting with an amino alcohol (or amino acid when the alcohol is not available) is shown in Scheme 74.



Scheme 74

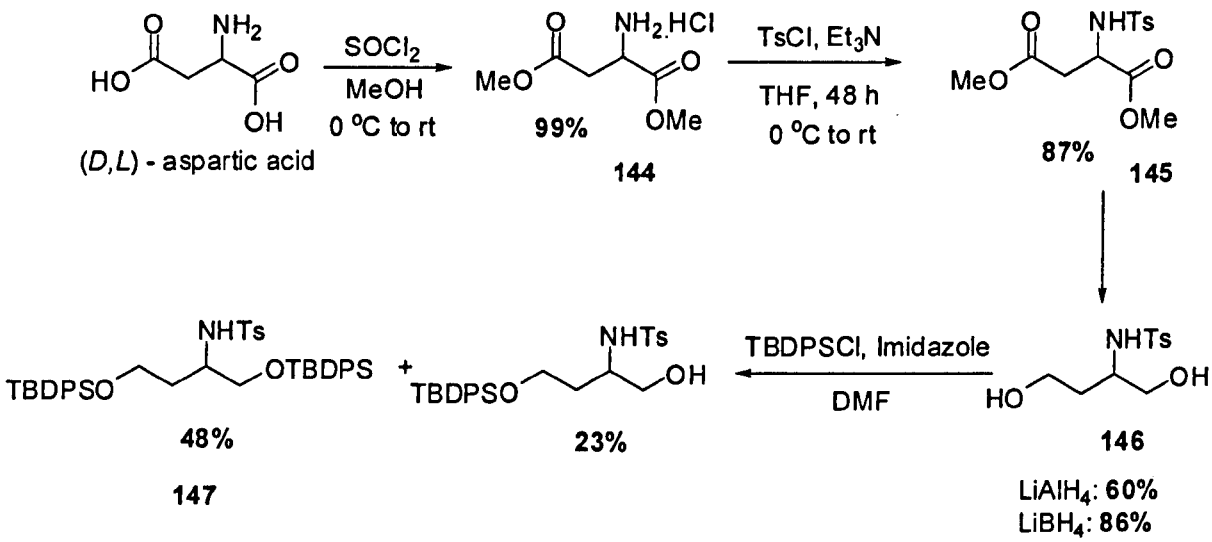
This approach had already been investigated in the group towards the synthesis of a siloxymethyl aziridine (Scheme 75). This route started from the enantiopure and commercially available (*D*)-serine.



Scheme 75

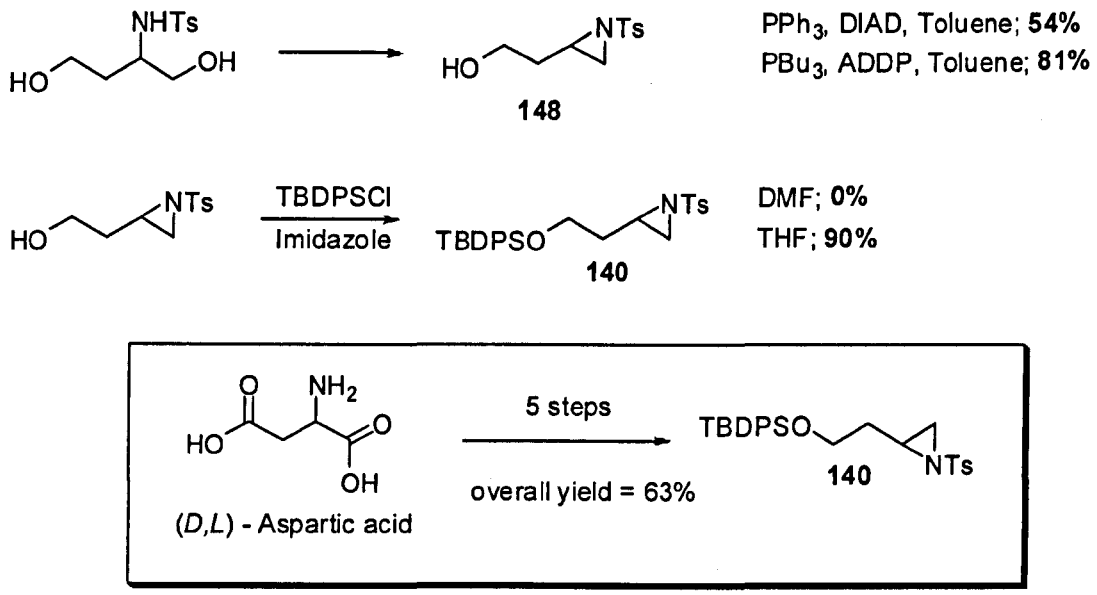
An advantage of this method is that the first two steps do not require chromatographic purification so aziridine (***R***)-**143** can be easily obtained on a large scale.

Since this route provided good yields of aziridine, we applied this method to the required homologous aziridines. Starting from the racemic (*D,L*)-aspartic acid, we performed the esterification, then the tosylation of the nitrogen and the reduction of diester **145** into corresponding diol **146**, all these three steps proceeded in very good yields (Scheme 76). At this point, we tried to protect one of the two hydroxyl groups but unfortunately, we got mainly the diprotected alcohol **147**.



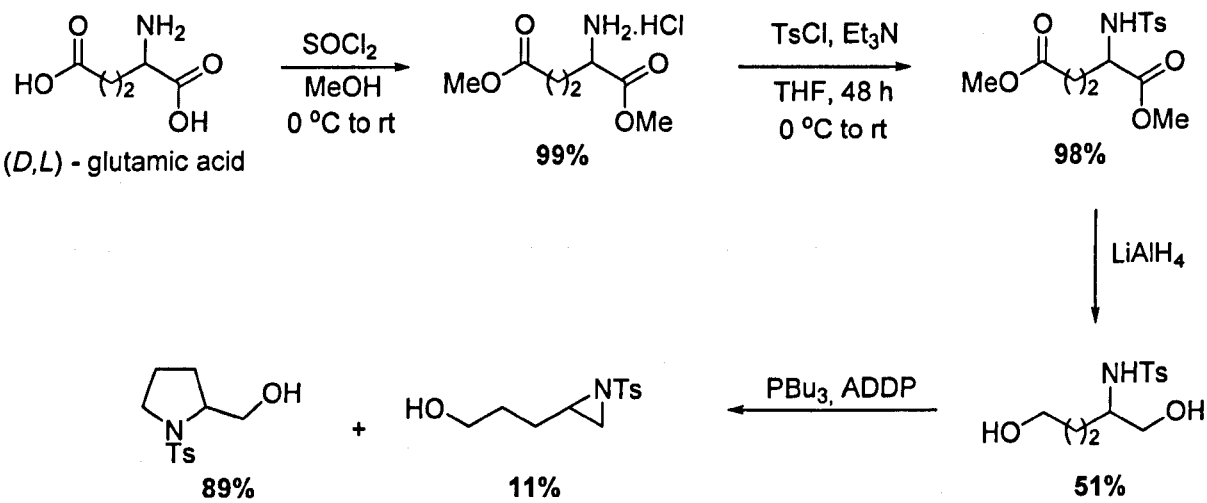
Scheme 76

Therefore, we decided to perform the Mitsunobu reaction, which worked better using PBu_3 and ADDP than using PPh_3 and DIAD (Scheme 77). As desired, the unprotected aziridine **148** was obtained in good yield. Then, we protected the alcohol using TBDPSCl in THF. We noticed a solvent effect for the protection step, the use of DMF resulted in addition of water to the aziridine. Finally, using THF, the desired aziridine **140** was synthesised in a good overall yield. This route is particularly interesting, since it has the potential to access enantiomerically pure aziridines.



Scheme 77

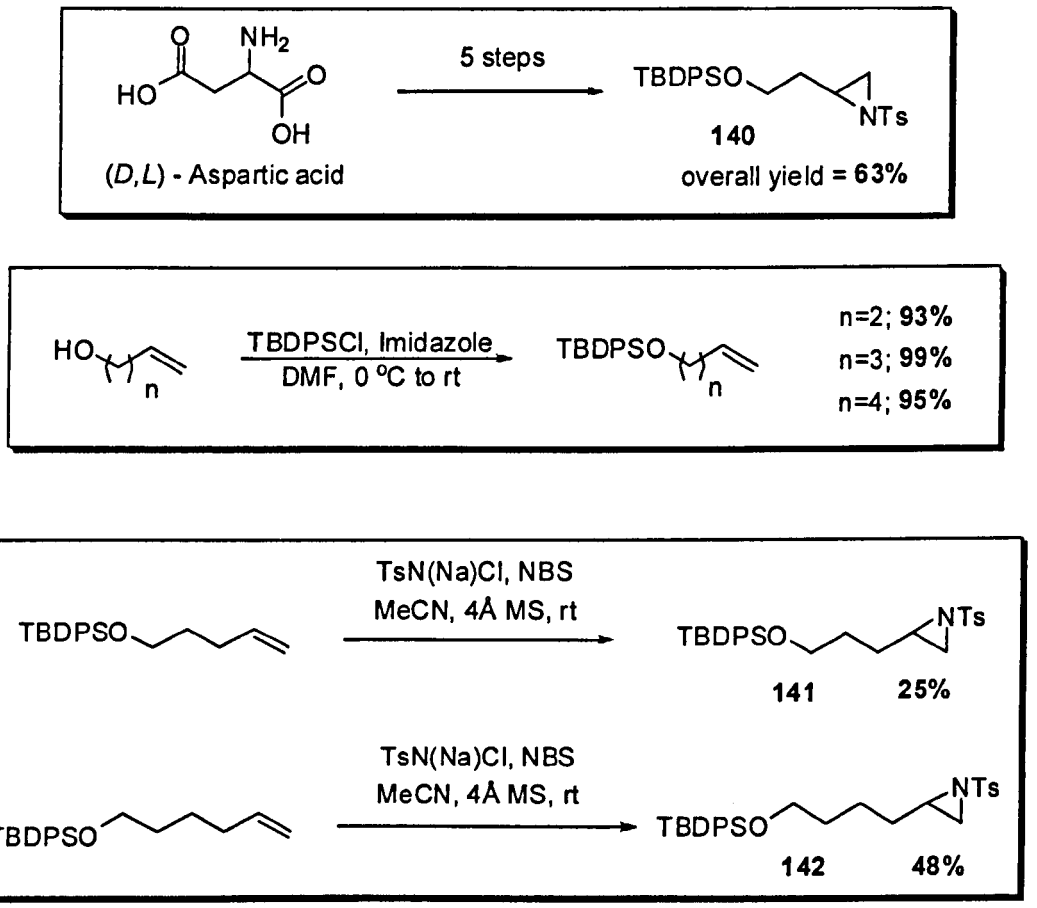
Based upon these good results, we used this methodology for the homologous aziridine, starting from racemic glutamic acid. Unfortunately, we mainly formed the five-membered pyrolidine in the final Mitsunobu ring closure step (Scheme 78).



Scheme 78

The previous results have been summarized in Scheme 79:

- ✓ We used the amino acid route for the synthesis of siloxyethyl aziridine **140**, which represents a good way of preparing enantiopure aziridines.
- ✓ We used the nitrene addition route for siloxypropyl and siloxybutyl aziridines **141** and **142** synthesis, which comprises a cheap and easy route.

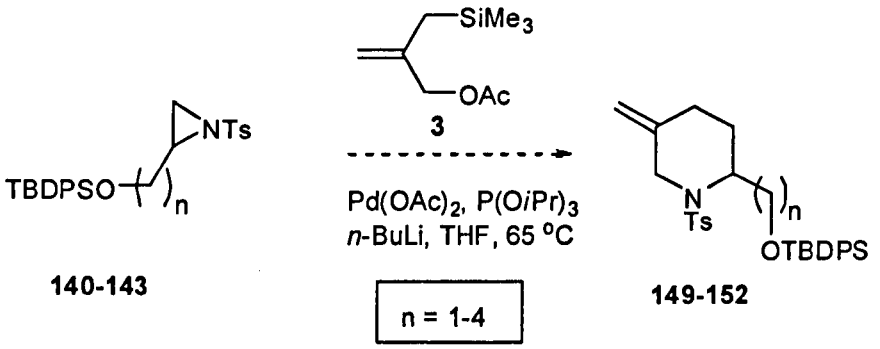


Scheme 79

4.[3+3] Cycloaddition

Previous work in the group established optimum conditions for the [3+3] cycloaddition[38]. Although this method is capable of giving good results, it is also very capricious and to obtain high yields of product requires rigorous drying of recrystallised aziridine, distillation of the triisopropylphosphite from sodium and

the complete exclusion of air and moisture. Our proposed cycloaddition under these optimal conditions is summarized in Scheme 80.



Scheme 80

Additionally, by consideration of the proposed catalytic cycle for this reaction, some deductions can be made about desirable characteristics for the catalyst (Scheme 81):

✓ Initial coordination

An electron deficient ligand would promote this step as it would decrease the electron density at the palladium centre allowing the electron rich olefin to coordinate to the alkene;

✓ Oxidative addition

This would be promoted with electron donating ligands;

✓ Desilylation

An electron withdrawing ligand would make the π-allyl palladium complex formed initially more electrophilic, promoting attack by acetate and thus desilylation;

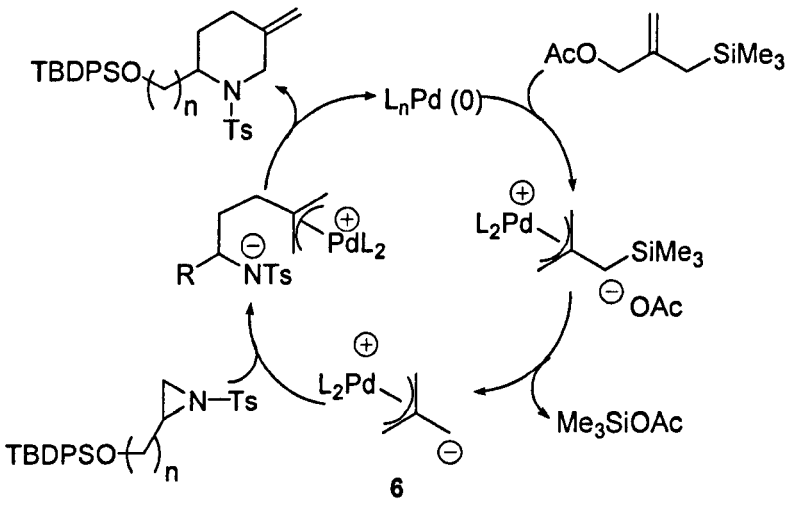
✓ Nucleophilic attack of Pd-TMM complex **6** on aziridine

An electron donating group could be conceived to promote this step as it would increase the electron density and thus the nucleophilicity of the palladium-TMM complex **6**;

✓ Nucleophilic attack of sulfonamide on π-allyl palladium (ring closure).

As with desilylation, this could be aided by electron withdrawing ligands, making the palladium less electron rich and more electrophilic.

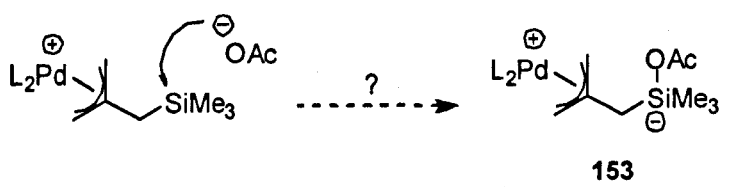
Phosphite ligands appear to provide the best balance of desirable electronic effects. Notably however, phosphite ligands are poor σ-donors so are less capable of stabilising palladium (0), meaning that more equivalents are required to prevent the precipitation of palladium black and concomitant loss of catalytic activity.



Scheme 81

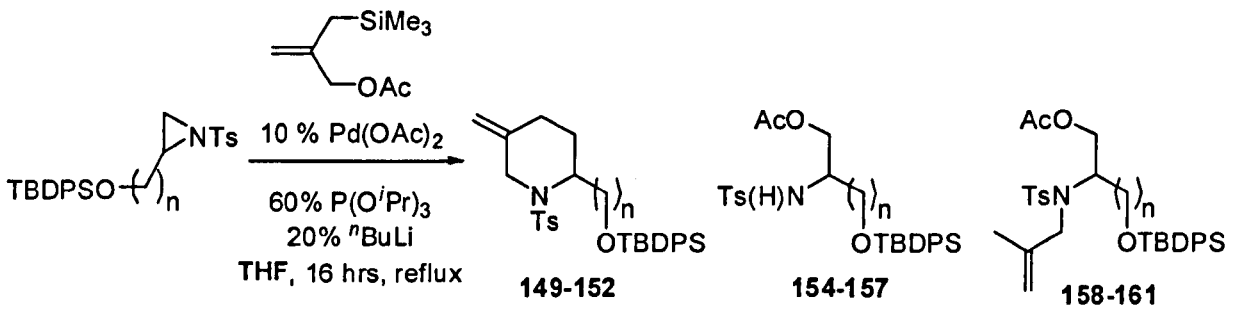
So, depending on the rate determining step, which must be accelerated in order to accelerate the entire reaction, either electron donating or electron withdrawing ligands may help increase the rate.

Another factor is the extent to which the acetate actually removes the TMS group: it may be that a pentacoordinate silicon is present in the intermediate **153**, again changing the electronic requirements for the reaction (Scheme 82).



Scheme 82

We decided to employ the standard conditions used in previous [3+3] cycloadditions, for the reactions of aziridines substituted by a silyl ether group. The results are shown in Table 11.



	149-152	154-157	158-161
n=1	67%	25%	3%
n=2	65%	17%	13%
n=3	20%	25%	9%
n=4	20%	60%	25%

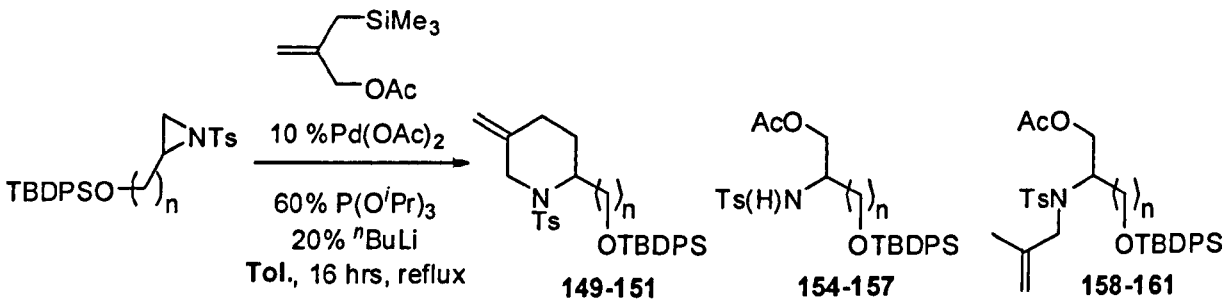
Table 11

The first study was carried out in **THF**. It turns out that not only was the desired piperidine formed, but also by-products resulting from the ring opening of the aziridine by acetate. The ring opened products are then either just protonated to give **154-157** or trapped by the allyl-palladium species to give **158-161**.

- ✓ n=1: we mainly formed the desired product **149**. This reaction was reproducible and we were able to repeat the high yields obtained by co-workers in the group;
- ✓ n=2: this reaction was often low yielding (~20% piperidine **150** and ~60% **155**). Nevertheless, we once managed to obtain the piperidine **150** in a good yield, as shown in Table 11; triisopropylphosphite $P(O^iPr)_3$ had been freshly distilled and we conducted the reaction on a relatively large scale (~200 mg);
- ✓ n=3 and n=4: the yields obtained for the desired piperidines **151** and **152** were consistently poor and we mainly formed the by-products **156** and **157**.

These results are quite difficult to rationalise but there does not appear to be any particular silyl ether effect. This cycloaddition is just very difficult to run and quite capricious and it requires rigorous conditions. We believe that, if we run the reaction more carefully, the cycloaddtion of the aziridines n=3 and n=4 will provide the desired piperidines **151** and **152** in reasonable yields.

However, we wanted to establish if there was a solvent effect, hence we also ran the reaction in a less polar solvent, **toluene** (Table 12).

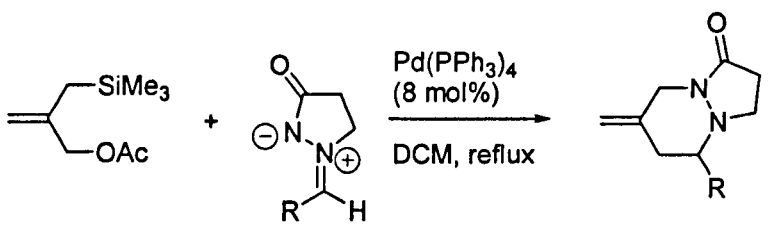


n=1	45%	0%	7%
n=2	49%	Trace	9%

Table 12

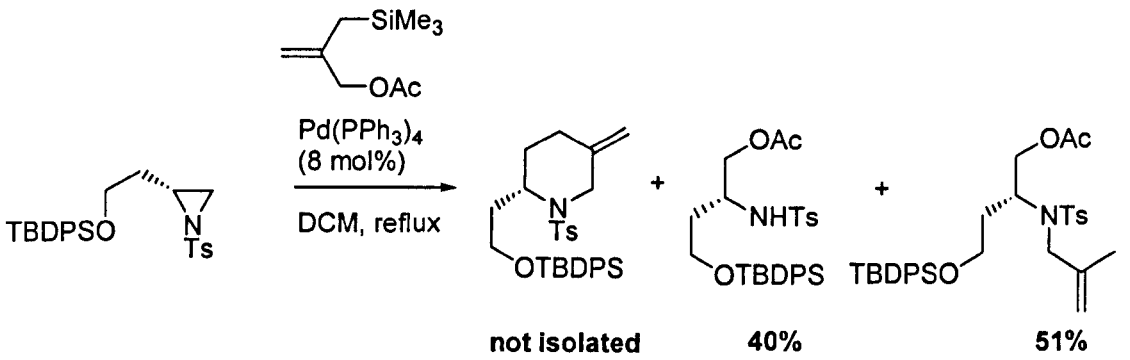
Toluene did not improve the reaction; we obtained moderate yields for **149** and **150** and low yield for **151**. THF appears to be a better solvent for this cycloaddition reaction.

Inspired by Hayashi's work[46] in 2006, we applied the conditions he developed on the cycloaddition of his azomethine imines to our silylether substituted aziridines (Scheme 83).



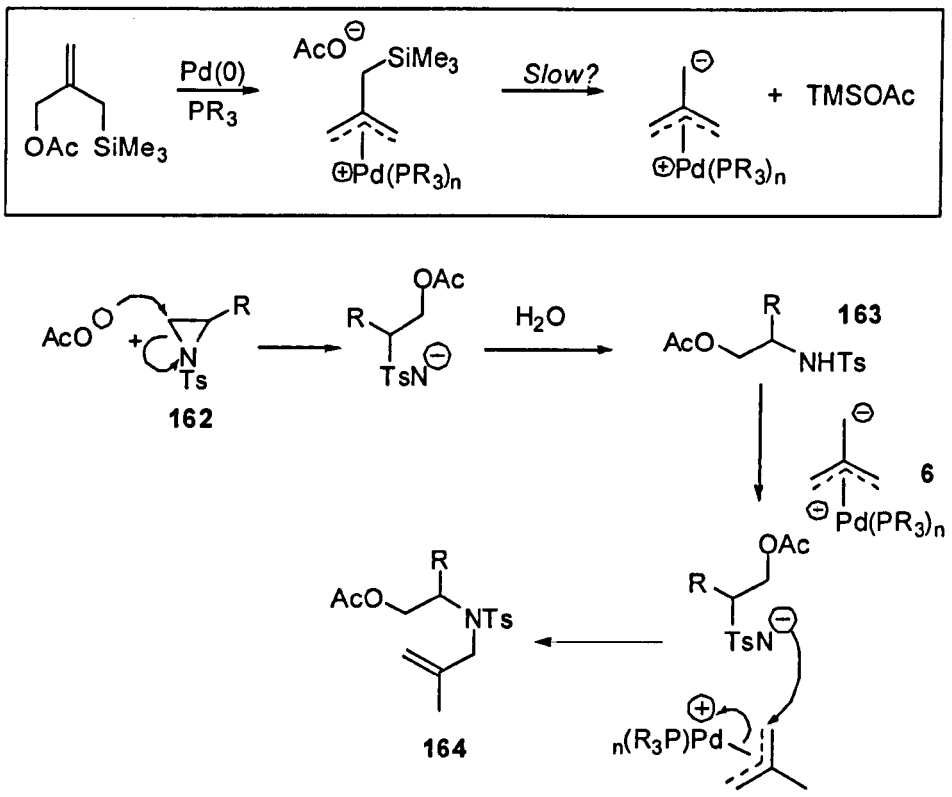
Scheme 83

Unfortunately, the reaction wasn't really successful, leading to a mixture of by-products (Scheme 84).



Scheme 84

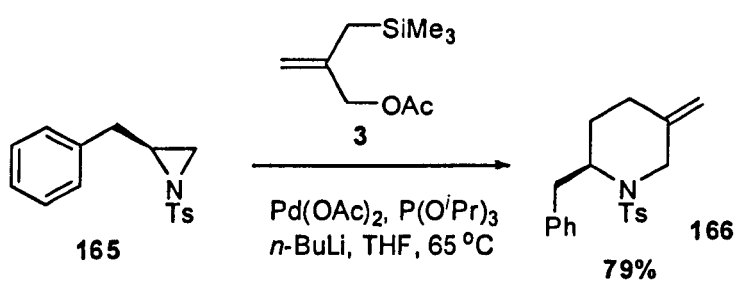
Even though the mechanism of the ring opening by the acetate is unclear, we have made the following hypothesis. We assume that the desilylation is the slow step. The mechanism for formation of acetate opened product **163** must involve the presence of water in the system. The acetate generated from the TMM precursor attacks the aziridine **162** to leave an intermediate which can be protonated (presumably by the presence of small quantities of water) to provide the observed sulphonamide **163**, whilst allylation of this species by Pd-TMM **6** generates the second by-product **164** and releases palladium (Scheme 85).



Scheme 85

5.Investigation of alternative *N*-protecting groups

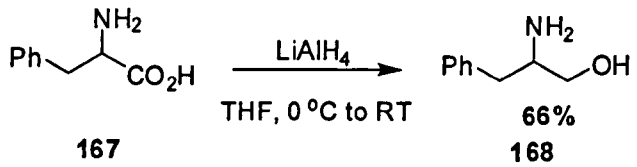
Considering that we were not really successful with the [3+3] cycloaddition on silylether substituted aziridines, we decided to investigate the scope of this cycloaddition by screening different *N*-protecting groups for the aziridine. We decided to employ 2-benzyl substituted aziridines as the *N*-Ts analogue **165** performed consistently well and could therefore be used as a control in parallel with the aziridines under investigation.



Scheme 86

5.1.Aziridine Synthesis

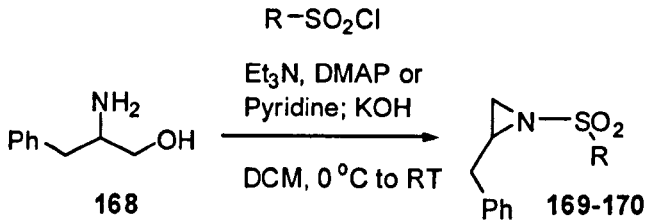
The synthesis of aziridines did not offer any particular problems. The racemic aminoacid phenylalanine **167** was reduced to the aminoalcohol phenylalaninol **168**, which represented a key intermediate for all the aziridines we were interested to test (Scheme 87).



Scheme 87

5.1.1.Sulfonamide aziridines

Starting from the amino alcohol **168**, the synthesis of 1-sulfonamide aziridines can be easily performed using a base and the corresponding sulfonyl chloride, 4-nitrobenzenesulfonyl chloride **169** for the nosyl group and methanesulfonyl chloride **170** for the mesyl group (Scheme 88 and Table 13).



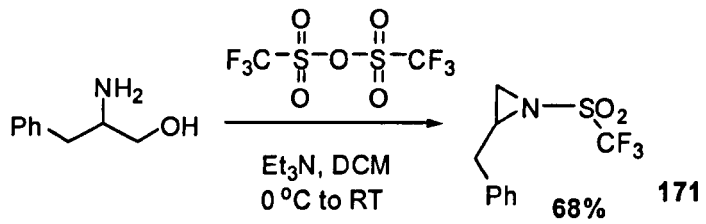
R = CH_3, 4-nitrophenyl

Scheme 88

R	Product
CH_3	43%
4-nitrophenyl	51%

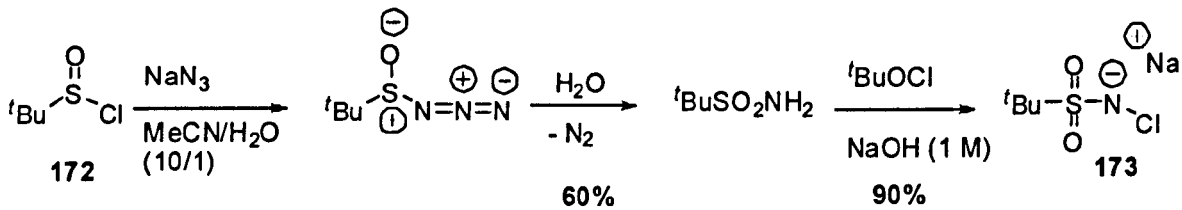
Table 13

To prepare the trifluoromethylsulfonamide aziridine, we used triflic anhydride (Scheme 89). We have to mention that aziridine **171** seems not to be very stable, and therefore it has to be used reasonably soon after preparation.

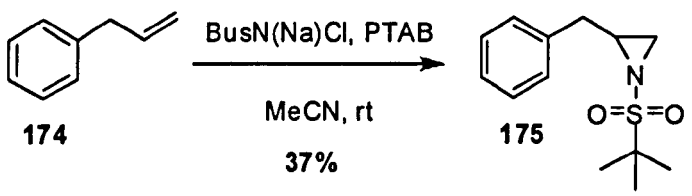


Scheme 89

For the synthesis of the Bus-protected aziridine, we had to make the *N*-chloramine salt of the *tert*-butylsulfonamide **173** from *tert*-butylsulfinyl chloride **172** (Scheme 90) and then performed an aziridation according to Sharpless'conditions using allylbenzene **174** (Scheme 91).



Scheme 90

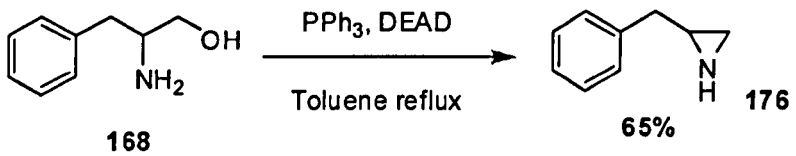


Scheme 91

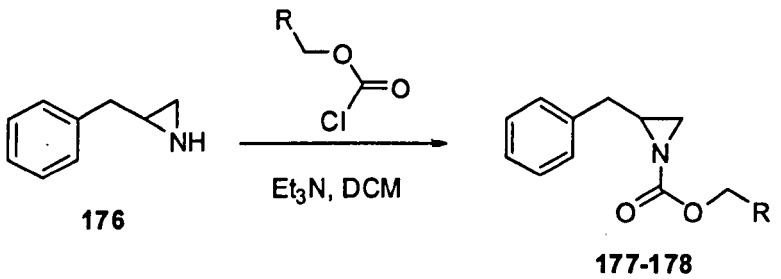
The aziridination proceeded in poor yield but all the reagents are cheap and easy to handle, which makes the reaction easy to set up and easy to scale up.

5.1.2.Carbamate aziridines

We decided to prepare two carbamate-substituted aziridines *via* a Mitsunobu reaction on the aminoalcohol **168** (Scheme 92) followed by protection of the free aziridine **176** using the corresponding chloroformate (Scheme 93 and Table 14).



Scheme 92



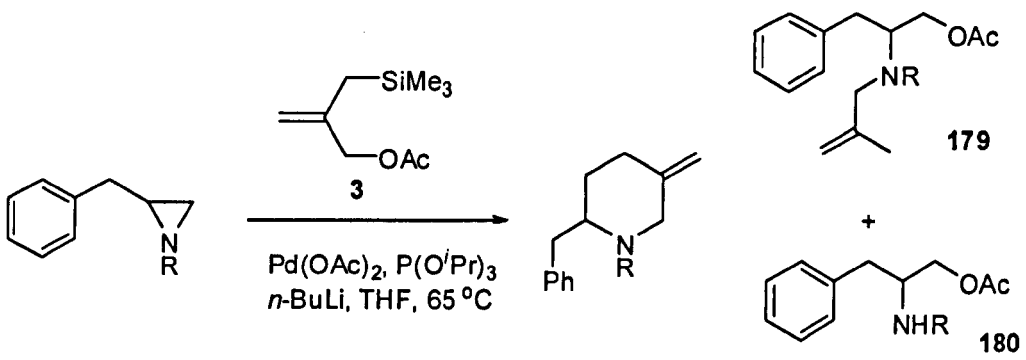
Scheme 93

R	Product
4-nitrophenyl	64%
2-chlorophenyl	99%

Table 14

5.2.[3+3] Cycloaddition

With all these aziridines in hand, we turned our attention to the cycloaddition using the optimum conditions developed in our labs (Scheme 94 and Table 15).



Scheme 94

Entry	R	Product	By-product 1	By-product 2	SM
1	-SO_2CH_3 **169**	-	-	-	89%
2	-SO_2CF_3 **171**	-	-	-	-
3	-$SO_2C(CH_3)_3$ **175**	-	-	-	100%
4	-SO_2(4-nitrobenzene) **170**	-	19% **(178)**	14% **(179)**	39%
5	-CO_2CH_2(4-nitrobenzene) **177**	-	-	-	85%
6	-CO_2CH_2(2-chlorobenzene) **178**	-	-	-	42%

Table 15

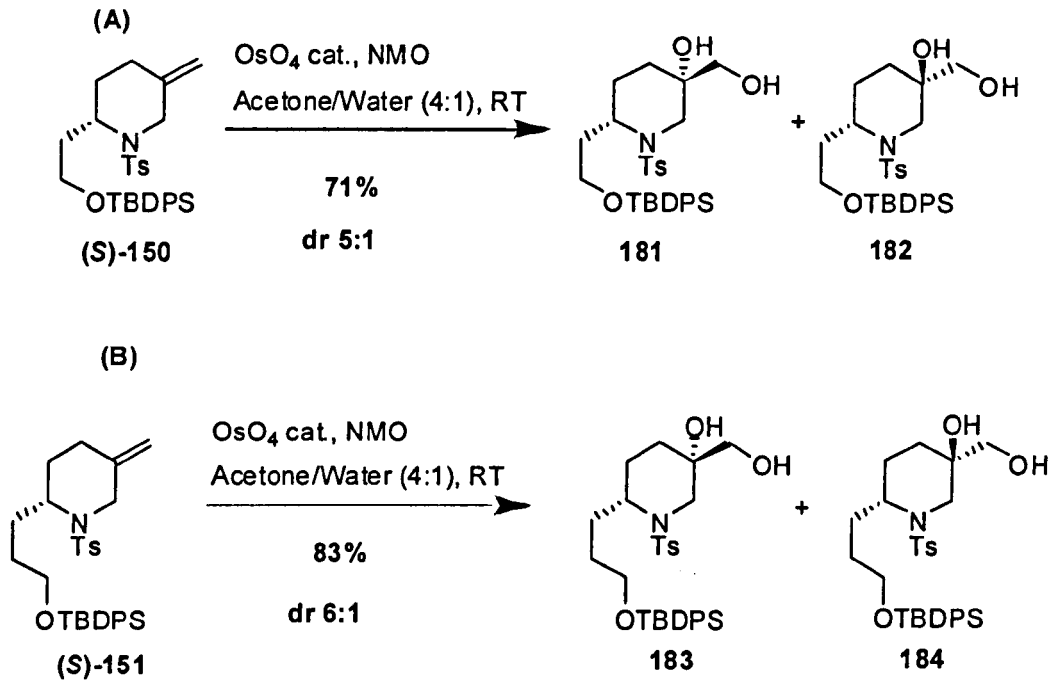
Unfortunately, we quickly realized that we mainly recovered the starting material in most cases (entries 1, 3 and 5, Table 15). It seems that, as for the sulfonamide protecting group, the tosyl group is the protecting group of choice since mesyl and Bus groups **169** and **175** returned starting material, whereas the reaction with the trifluoromethanesulfonyl protected aziridine **171** resulted in a complex mixture with no piperidine having been isolated. We can, however, notice that the TMM precursor reacted with the nosyl protected aziridine **170** to give the two by-products. The carbamate protected aziridines **177** and **178** were not successful either, giving mainly recovered starting material.

6.Functionalisation

With the piperidines **150-152** in hand, we opted to study the functionalisation of the *exo*-alkene group on the piperidines.

6.1.Dihydroxylation

Using the piperidines **(*S*)-150** and **(*S*)-151**, we performed a dihydroxylation reaction with a catalytic amount of osmium tetroxide and NMO (Scheme 95).

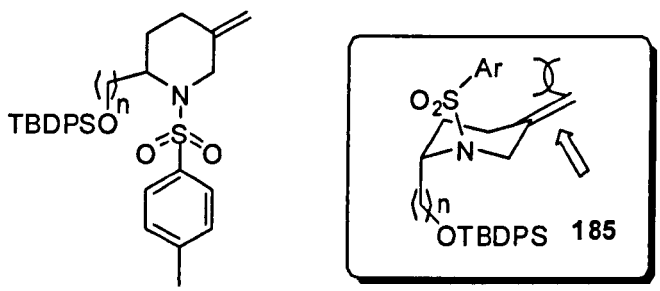


Scheme 95

In both cases, two diastereoisomers were formed but we were unable to separate them by column chromatography or by recrystallisation. The ratios **181/182** and **183/184** were determined by ^1H NMR spectroscopy. However, we have been unable to ascertain which of the diastereoisomers is the major, nonetheless we obtained a good diastereoselectivity in both cases.

It is known that in most circumstances, it is energetically more favourable for a large alkyl group to occupy an equatorial geometry in cyclohexanes in order to avoid unfavourable 1,3-diaxial interactions. However, in the case of piperidines

with a tosyl group attached to nitrogen, the silyl ether group present at C2 should adopt axial geometry in **185** in order to minimise $A_{1,3}$ strain (Scheme 96)[63]. Therefore, any nucleophilic attack should mainly and preferentially occur from the bottom face of the alkene away from the *N*-Ts. This conformation has been confirmed by previous work within the group[39, 64-66].

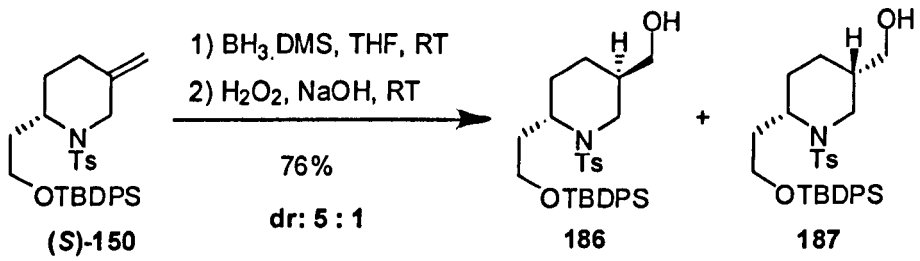


Scheme 96

Once we defined the supposed conformation of the piperidines, we could assume that in **(A)** in Scheme 95, **181** should be the major product, whereas, in **(B)**, it should be **183**. The obtained products are very interesting, since they bear three different hydroxyl groups, two primary alcohol (including a protected one) and one tertiary alcohol.

6.2.Hydroboration

We also considered the hydroboration reaction of the piperidine **(*S*)-150**, using borane dimethylsulfide, hydrogen peroxide and sodium hydroxide (Scheme 97).



Scheme 97

Once again, we obtained two diastereoisomers **186** and **187** in a good yield. We didn't manage to separate them but we determined the diastereoisomeric ratio (dr)

by ^{1}H NMR spectroscopy. Whilst the diastereoselectivity was encouraging, we envisage that this would improve using bulky borane reagents such as 9-BBN.

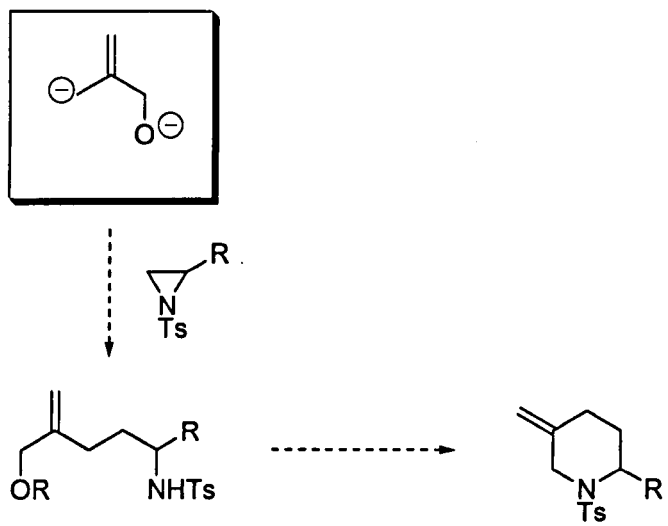
As just shown, the [3+3] cycloaddition has been applied to a particular class of substituted aziridines, the silylether substituted aziridines. It has been proved to be a challenging reaction, difficult to reproduce but good results can be obtained under rigorous conditions.

Since the efficiency of the Pd-TMM technique is quite variable according to the substituent used on the aziridines, an alternative approach has been developed which may avoid the problems of reduced reactivity and potential by-products; this methodology utilised more heavily substituted organomagnesium reagents and is described in the next chapter.

Chapter III - Introduction to Organomagnesium Chemistry

1.Allylalcohol derived organomagnesiun reagent

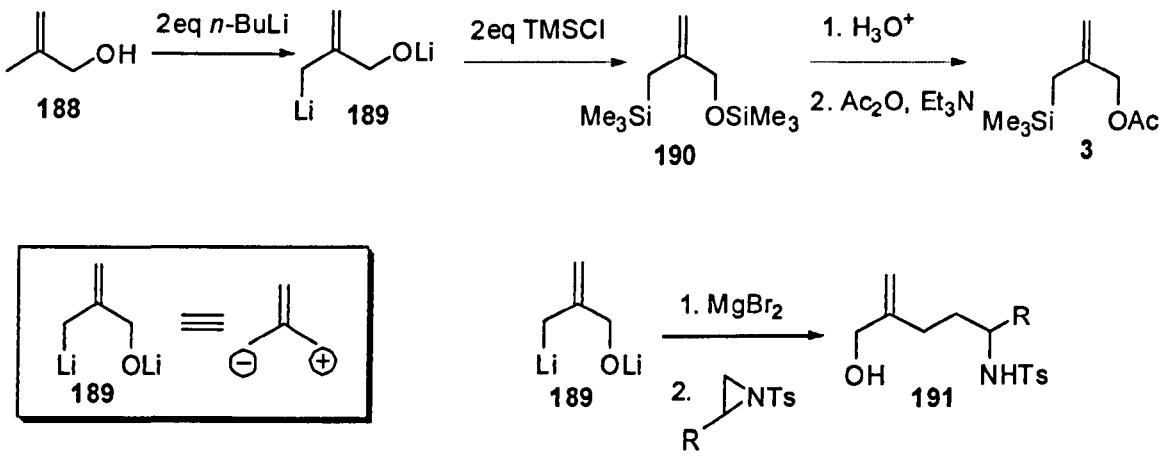
As discussed previously, the [3+3] cycloaddition using Pd-TMM can be a good way to form piperidines but unfortunately it doesn't work in all cases; we have uncovered several instances where the Pd-TMM reagent fails to add to the aziridine or does so with low levels of conversion. We therefore turned our attention to a more nucleophilic alternative in an effort to generate the desired piperidines in high yields for all substrates (Scheme 98).



Scheme 98

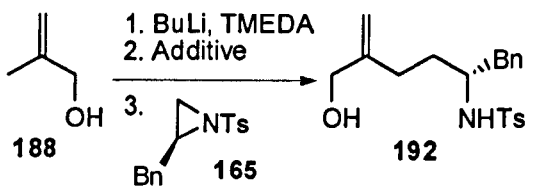
Based on work by Klumpp et al[67-72] and within the group, we investigated the use of Grignard chemistry for the preparation of piperidines. In practice, we have employed Trost's conjunctive reagent (2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate) **3**, which is prepared from methallyl alcohol **188**[7]. As outlined in Scheme 99, double deprotonation of methallyl alcohol **188** provides allyllithium **189** which is quenched by TMSCl to provide allylsilane **190**. The TMM-precursor **3** is finally generated after hydrolysis of **190** and acylation. It is notable that the first step of this sequence furnishes a reactive allyllithium species **189** and we

contemplated employing this intermediate as our "strongly nucleophilic" TMM-equivalent. Accordingly, transmetallation to the corresponding organomagnesium compound furnishes a reagent that will add to aziridines that are inert to our Pd-catalysed [3+3] cycloaddition methodology.



Scheme 99

Preliminary results in the group[58] showed that double deprotonation of methallyl alcohol **188** and addition of the organolithium reagent to **165** only succeeded in furnishing **192** after a large excess of reagent was employed (Scheme 100 and Table 16). Therefore, a transmetallation to the organomagnesium reagent by addition of $MgBr_2$ was performed and addition of the Grignard reagent to **165** provided **192** in moderate yield. Further optimization showed that excellent yields of product could be obtained when aziridine **165** was added to 5 equiv of Grignard reagent and that the reaction was effectively complete within 2 h.



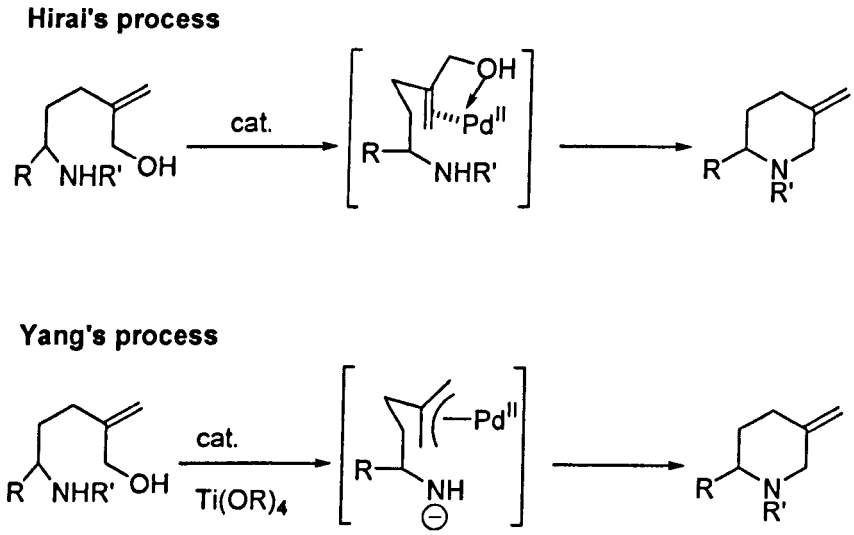
Scheme 100

Equiv of X[a]	additive	conditions	yield
10		25 °C, 2 h	19%
3	$MgBr_2$	25 °C, 18 h	53%
5	$MgBr_2$	25 °C, 18 h	88%
5	$MgBr_2$	25 °C, 2 h	87%

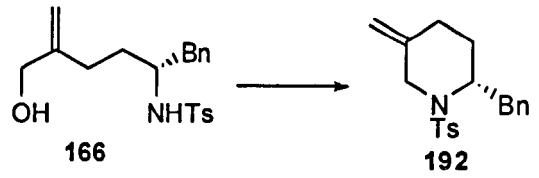
[a] Organomagnesium reagent prepared by addition of TMEDA (2.6 equiv) and *n*-BuLi (3.0 equiv) to **165** followed by $MgBr_2$ (2.6 equiv)

Table 16

Following the investigation on the aziridine ring opening with the Grignard reagent, work in our group was also focused on developing an efficient method for the cyclisation process. Specifically, a transition metal catalysed one-step cyclisation reaction was investigated. Hirai and Makabe have reported that Pd(II) catalysts mediate the closure of carbamates onto allylic alcohols without need for pre-activation of the hydroxyl unit[73] (Scheme 101). Additionally, Yang and Hung have performed a Ti-mediated allylation reaction that proceeds through a Pd π-allyl intermediate and that has been successfully employed on 1,1-disubstituted alkenes[74].



Scheme 101



Scheme 102

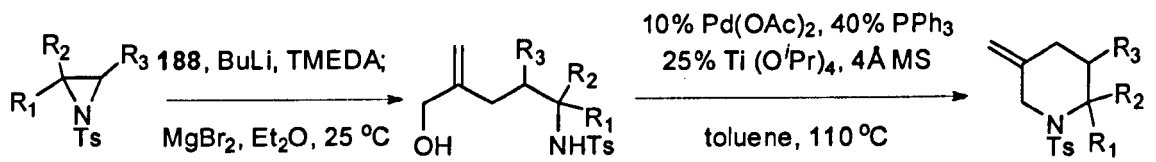
conditions[a]	Yield (%)
i) 5 mol% of $PdCl_2$, THF	0
ii) 5 mol% of $Pd(OAc)_2$, 20 mol% of PBu_3, 60 mol% of Et_3B, THF	75
iii) 5 mol% of $Pd(OAc)_2$, 40 mol% of PPh_3, 25 mol% of $Ti(O^iPr)_4$, 4Å MS, toluene	100

[a]All reactions run at reflux over 18h

Table 17

As shown in Table 17, cyclisation of **166** towards the piperidine **192** using $PdCl_2$ was unsuccessful, and starting material was recovered. In contrast, the B-promoted amination provided the desired piperidine in good yield although presence of the alkene isomerisation product was noticed. The Ti-promoted reaction proceeded smoothly to give piperidine **192** in high yield with the optimal conditions resulting from overnight reflux in toluene.

In the past, the scope of this 2-step piperidine forming reaction was investigated and its efficiency compared with the Pd-TMM cycloaddition process (Scheme 103).



Scheme 103

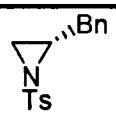
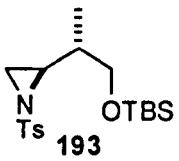
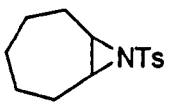
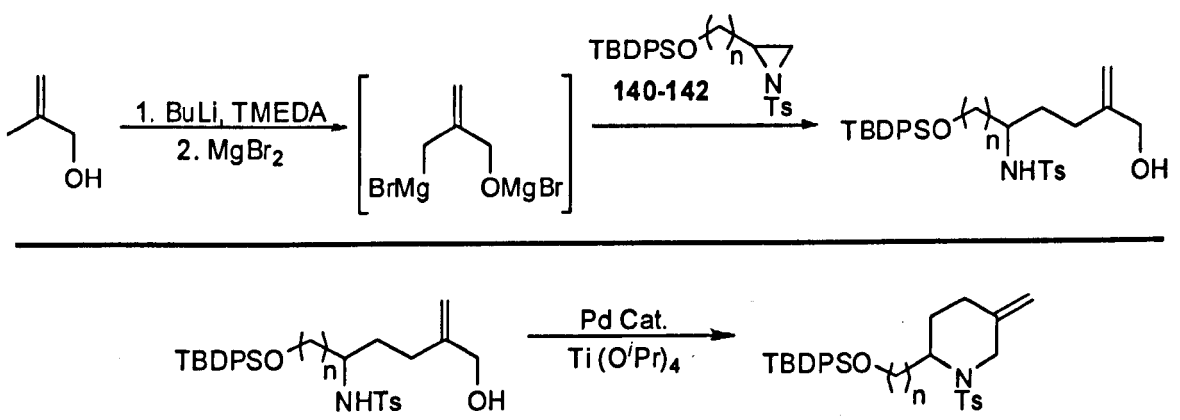
aziridine	Grignard Addition yield	Cyclisation yield	Overall yield	Pd-TMM yield
	87%	100%	87%	79%
	93%	67%	62%	82%
 **193**	92%	81%	74%	15%
 **194**	76%	77%	58%	0%

Table 18

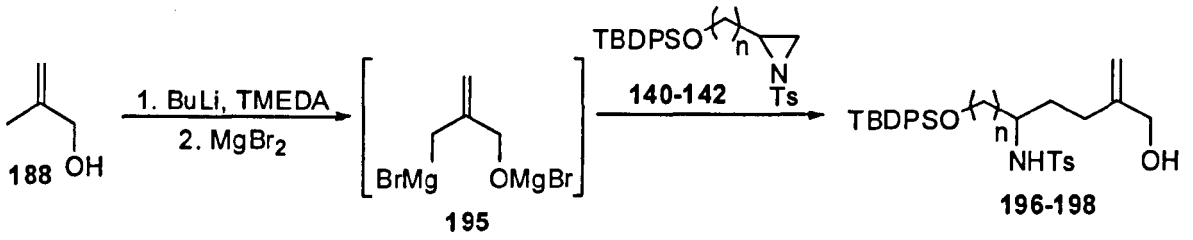
Table 18 highlights that whilst aziridines **193** and **194** had been found to be sluggish in the TMM-mediated [3+3] cycloaddition chemistry, the corresponding piperidines were formed in excellent overall yield using this modified procedure.

Encouraged by these excellent results, we decided to apply this methodology to our aziridines **140-142,** using the pathway outlined in Scheme 104.

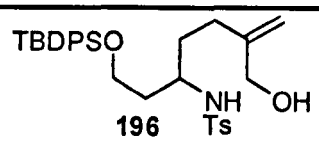
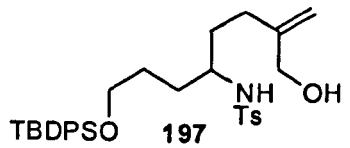
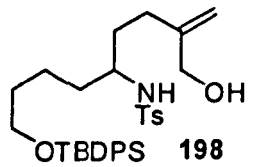


Scheme 104

Starting from commercially available methallyl alcohol, we formed the Grignard reagent and then investigated the ring opening of the aziridines (Scheme 105). As shown in Table 19, we were delighted to find that the desired ring-opened products were formed in good yields.



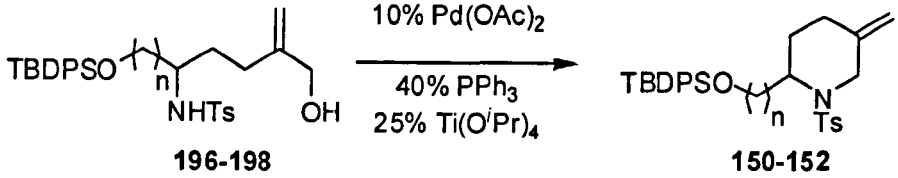
Scheme 105

Entry	n	Product[a]	Yield
1	2	 **196**	76%
2	3	 **197**	73%
3	4	 **198**	99%

[a] Organomagnesium reagent prepared by addition of TMEDA (3.0 equiv) and *n*-BuLi (4.0 equiv) to **188** followed by $MgBr_2$ (2.0 equiv). 5.0 equiv. of this reagent added to aziridine.

Table 19

In addition, we were very pleased to see that the cyclisation worked very well and that we could synthesize the desired piperidines **150-152** in good yields (Scheme 106 and Table 20).



Scheme 106

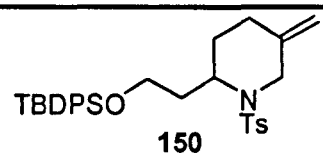
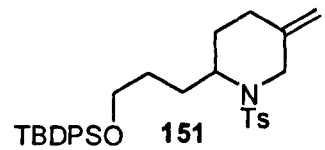
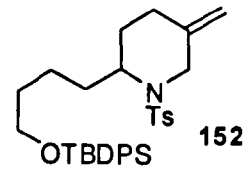
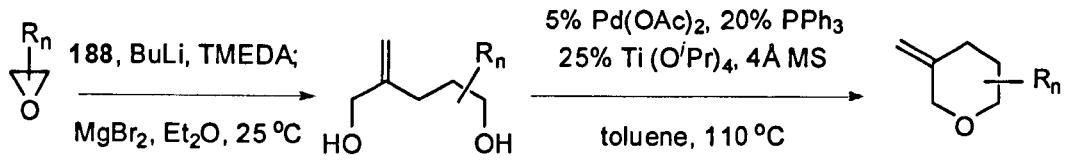
Entry	n	Piperidines	Yield
1	2	 **150**	90%
2	3	 **151**	84%
3	4	 **152**	87%

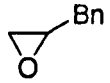
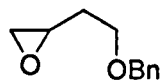
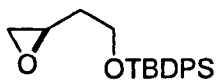
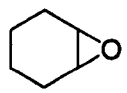
Table 20

This method has great potential for the formation of functionalised piperidines, since we performed the synthesis of the desired piperidines in only two steps. It uses cheap, commercially available reagents and works on the aziridines which had proved to be challenging substrates for the TMM-mediated cycloaddition. The synthesised piperidines are very interesting in terms of functionalisation, since they bear an *exo*-alkyne group and a protected primary alcohol.

Motivated by the fact that pyrans are a common motif to many natural products [75, 76] and in an effort to broaden the scope of this strategy, the use of this allyl-magnesium reagent in addition to epoxides was also investigated within the group by another PhD student and it proved to be also very efficient[77] (Scheme 107 and Table 21).



Scheme 107

epoxide[a]	Grignard Addition yield	Pyran yield	Overall yield
	76%	82%	62%
	74%	85%	63%
	50%	83%	42%
	76%	67%	51%

[a] Organomagnesium reagent prepared by addition of TMEDA (2.1 equiv) and *n*-BuLi (2.1 equiv) to **188** followed by $MgBr_2$ (2.1 equiv)

Table 21

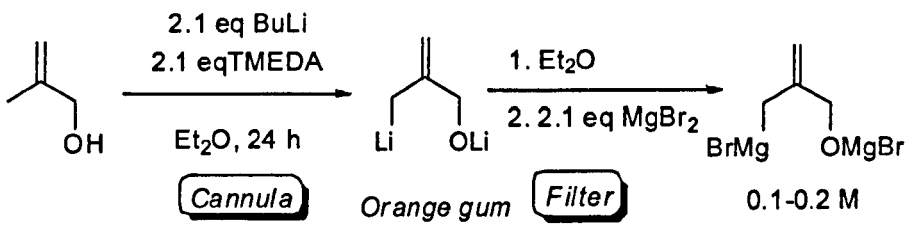
Although we were pleased that the sequence Grignard reaction-cyclisation had been successful with both aziridines and epoxides, a significant drawback of this method was the requirement for 5.0 equivalents of the in situ generated Grignard reagent **195**[78].

One reason for this is that the titration process was not really accurate to assess the concentration of **195**: we used 4.0 equivalents of *n*-BuLi and 2.0 equiv of $MgBr_2$, meaning that 2.0 equiv of butylmagnesium species remained after transmetalation and were also taken into consideration during the titration process. Trost used 2.6 equiv of BuLi[7] for the double deprotonation of **188** therefore we wondered if this could be further reduced without significantly affecting the deprotonation process.

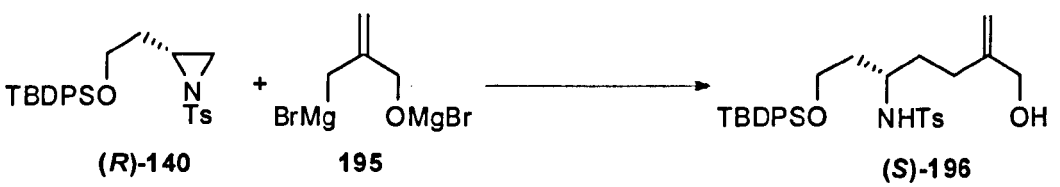
Accordingly, 2.1 equiv each of *n*-BuLi and TMEDA were used and this resulted in formation of a orange gum after stirring at room temperature for 24 h. Removal of the ethereal solution by cannula and addition of fresh ether and freshly prepared $MgBr_2$ (from magnesium turnings and dibromoethane) resulted in the formation of

a white precipitate that was removed from the Grignard reagent by cannula filtration. Titration of the resulting solution generally provided a concentration of active reagent of around 0.1 M (Scheme 108).

With the Grignard reagent in hand, we turned our attention to the study of its addition to our silylether substituted aziridines (Scheme 109). As outlined in Table 22, we were delighted to find that the organomagnesium reagent **195** underwent smooth addition to our aziridine **(*R*)-140**. Moreover, only 2.5 equivalents of reagent were required to achieve complete conversion of each aziridine substrate.



Scheme 108



Scheme 109

Equiv of Grignard	Product Yield
5.0[a]	76%
2.5[b]	85%

[a] Organomagnesium reagent prepared by addition of TMEDA (3.0 equiv) and *n*-BuLi (4.0 equiv) to **188** followed by $MgBr_2$ (2.0 equiv).

[b] Organomagnesium reagent prepared with the improved method: TMEDA (2.1 equiv) and *n*-BuLi (2.1 equiv) to **188** followed by $MgBr_2$ (2.1 equiv).

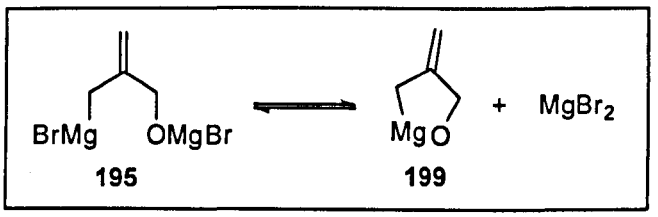
Table 22

This improved method to generate the active Grignard reagent **195** was much more convenient:

- it allowed us to use less equivalents of Grignard **195**;
- the set-up of the reaction was straightforward, since the reagent was directly added *via* syringe to a solution of aziridine in THF;
- the solution could be used several times, as long as it was regularly titrated.

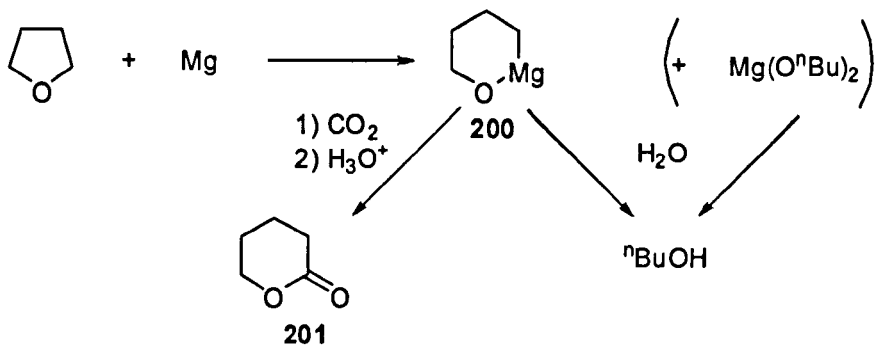
The only disadvantage was that the solution of **195** had to be used within 3 or 4 weeks, the molarity decreasing over this period.

We had assumed in our studies that the organomagnesium reagent had the formula **195**; however, it occurred to us that the reactive reagent could well be the cyclic organomagnesium alkoxide **199** formed by the Schlenk equilibrium[79] (Scheme 110).

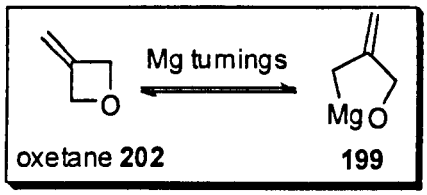


Scheme 110

Experiments carried out in our laboratories suggest that $MgBr_2$ is essential for successful addition of the doubly deprotonated methallyl alcohol to epoxides[78]; however, it is not clear whether the reaction involves Grignard reagent **195**, or is the result of a $MgBr_2$-promoted addition of cyclic magnesium alkoxide **199**.
Inspired by Bartmann's work on the cleavage of tetrahydrofuran by transition-metal activated magnesium[80](Scheme 111), we tried to clarify this issue by preparing cyclic magnesium alkoxide **199** starting from oxetane **202** (Scheme 112).



Scheme 111

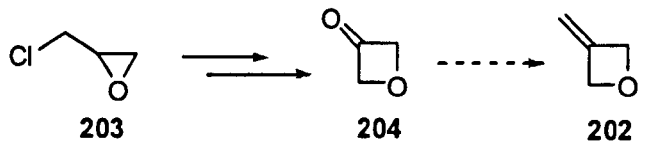


Scheme 112

Bartmann tested a range of transition metal salts ($TiCl_4$, $ZrCl_4$, VCl_4, $NbCl_5$, $CrCl_3$, $MnCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$) for their catalytic activity in THF cleavage. They were usually used in a 10 mole percent ratio to magnesium, in a large excess of THF. Three different types of magnesium were used: commercial magnesium powder; activated magnesium according to Rieke[81]; activated magnesium according to Bogdanovic[82]. The mixtures were heated to reflux and after a certain time the amount of the cyclic organomagnesium compound **200** was determined by quenching of the mixtures with dilute acid and GLC analysis of the yield of butanol formed. The reaction mixtures were occasionally quenched by introduction of carbon dioxide, which converted **200** into δ-valerolactone **201** (Scheme 111). The best results obtained by Bartmann (72% butanol; 35% δ-valerolactone) were when he used $TiCl_4$ as catalyst precursor, with magnesium activated by Rieke's method under reflux for 285 h!

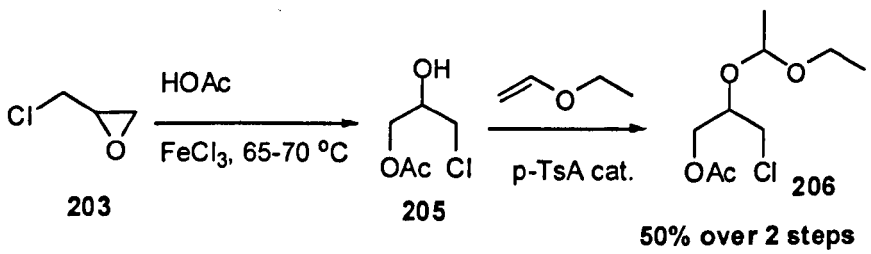
First, we had to focus on the synthesis of the substrate, oxetane **202**, which appeared to be very challenging. Our first idea was to start from epichlorohydrin **203** to make oxetanone **204** using conditions developed by Baum and

collaborators[83] and improved by Kozikowski[84]; then a Wittig reaction should provide us with the desired 3-methylenetrimethylene oxide **202**.



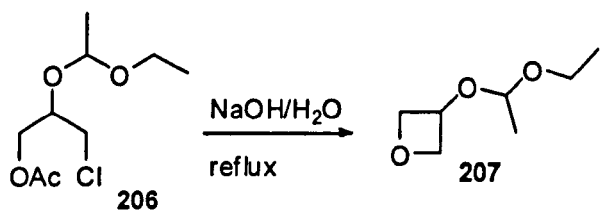
Scheme 113

Ring opening of epichlorohydrin by acetic acid, followed by protection of the resulting secondary alcohol **205** with ethyl vinyl ether offered compound **206** in a good overall yield. No particular purification was made at this stage (Scheme 114).



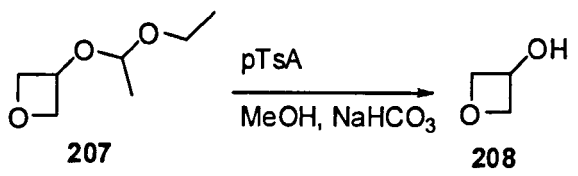
Scheme 114

Then, aqueous sodium hydroxide hydrolysed the ester and also closed the oxetane ring to offer **207**. The crude ^{1}H NMR spectrum being clean, compound **207** was also used without further purification for the next step (Scheme 115).



Scheme 115

Still following Baum's procedure, crude **207** was treated with methanol and a catalytic amount of *p*-toluenesulfonic acid. A distillation under reduced pressure was carried out in order to purify the desired 3-hydroxyoxetane **208** (Scheme 116).



207 208

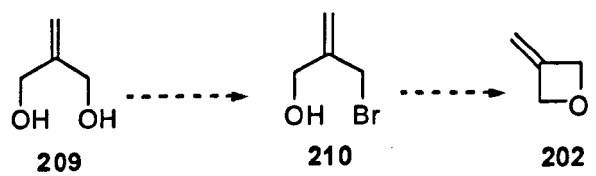
Scheme 116

Unfortunately, even after several distillations, no clean product was obtained; NMR studies carried out on the different fractions seemed to show that the product was decomposed during the distillation, and it probably polymerised. In fact, the desired oxetane **208** has been described in the literature as having a boiling point around 230 °C. Our different distillations were carried out between 120 and 150 °C under 20 mmHg; this could explain why the product had decomposed, or even it polymerised at high temperatures. This sequence of reactions was repeated several times, and in each case, the alcohol deprotection step appeared to be unsuccessful.

We then thought that the reaction might fail due to the deprotection conditions; therefore, we employed two other acids, CSA and PPTs. Unfortunately, in those cases too, we were unable to isolate any desired product **208**.

We then tried to change the protecting group for a silyl ether (TBDPS and TMS). This strategy did not make any difference, the isolation and purification of the oxetane **207** by distillation still being unsuccessful.

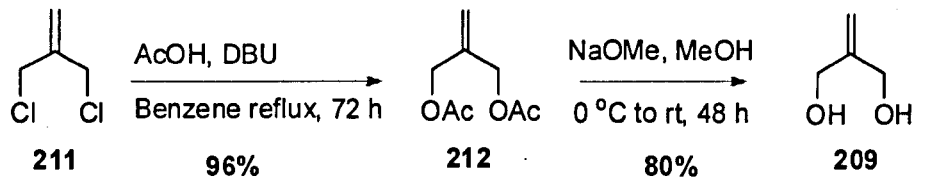
The purification of 3-hydroxyoxetane **208** by distillation appearing to be very challenging, we decided to change our strategy to synthesise oxetane **202** and envisaged a more direct method (Scheme 117).



209 210 202

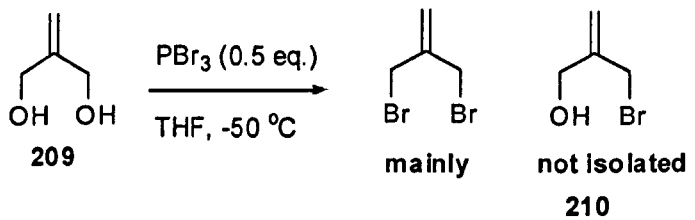
Scheme 117

Diol **209** was readily obtained following Wuest's conditions[85] starting from compound **211** (Scheme 118).



Scheme 118

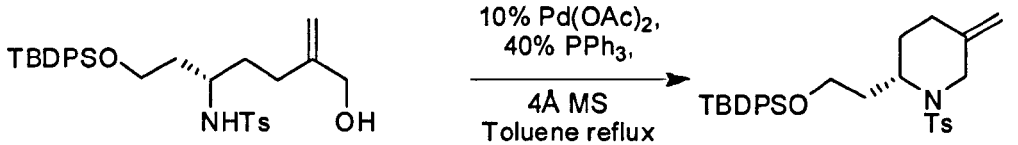
We then submitted diol **209** to bromination conditions, hoping that we could obtain the monobromo derivative **210**. Unfortunately, no desired product could be isolated, only the dibromo derivative was detected by LC/MS spectroscopy (Scheme 119).



Scheme 119

As we experienced many difficulties to synthesise the starting material **202**, we were unable to apply Bartmann's methodology and to carry out further studies on our Grignard reagent.

We also investigated the role of $Ti(^{i}OPr)_4$ in the cyclisation. Originally, we thought that it was there to act as a Lewis acid and it would help to form the Pd-allyl complex by coordinating to the O of the allyl alcohol, making it a better leaving group. However, we later realised that it was not necessary for the reaction to occur (Scheme 120 and Table 23).



(S)-196 (S)-150

Scheme 120

Lewis acid	Product Yield
none	84%
25 %Ti(^{i}OPr)$_4$	90%

Table 23

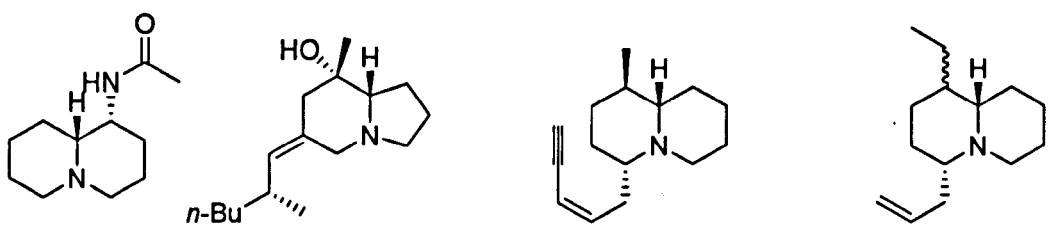
Chapter IV - Application: Natural Product Synthesis

1.Introduction to the Properties and the Synthesis of the Quinolizidine Alkaloids

1.1.Introduction

Alkaloids are nitrogen-containing naturally occurring compounds, produced by a large variety of organisms, including fungi, plants, animals and bacteria. Alkaloids are part of the group of natural products and are chemical derivatives of amino acids or other nitrogen-containing compounds, such as polyamines. They have many biological activities and are usually active in extremely small quantities. Extracts of plants containing alkaloids as the active ingredient have been used as poisons, stimulants and medicines.

Among these alkaloids, we were particularly interested in highly toxic quinolizidine and indolizidine alkaloids isolated from the skin of poisonous amphibians, since they have been reported to be efficient research tools for neurophysiological investigations. For example, quinolizidine alkaloids obtained from marine sources have been recently identified as leading compounds for the development of anticancer, anti-inflammatory and cardiovascular drugs[86] (Scheme121).



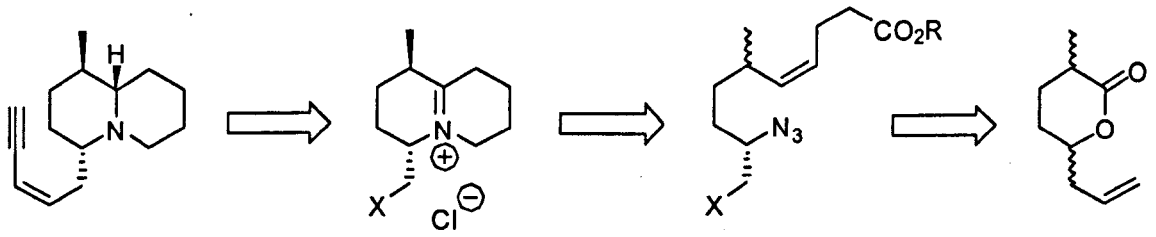
Epiquinamide **(+)-Pumiliotoxin 251D** **Quinolizidine (-)-217A** **Quinolizidine 207I**

Scheme 121

The quinolizidine moiety is incorporated into a vast range of complex plant alkaloids[87], but relatively few quinolizidines (1-azabicyclodecanes) have been isolated. Therefore, we would like to exploit the methodology described in the previous chapters through its employment in target synthesis. As such, we considered to utilise this chemistry to prepare quinolizidine alkaloid (-)217A, an amphibian alkaloid isolated by Daly in 1993 from skin extracts of the Madagascan frog *Mantella baroni*[88].

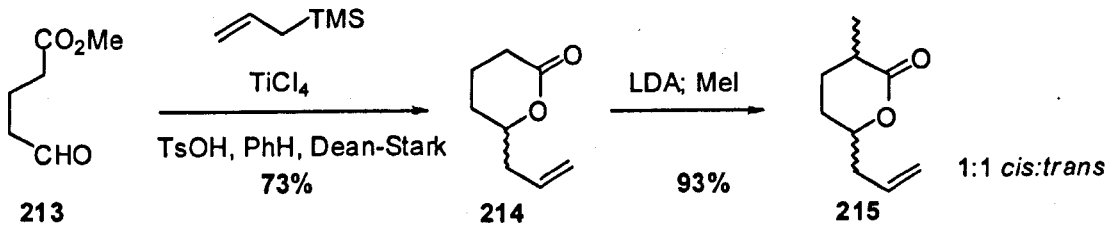
1.2.Previous syntheses

The first total synthesis of quinolizidine alkaloid (-)217A was reported by Pearson and Suga in 1998[89]. After investigating several azide-based routes, they outlined that the cyclisation of an azide onto an ester-bearing alkene yielded a 3,4,5,6-tetrahydropyridine that could be stereoselectively reduced to produce a *cis*-2,6-disubstituted piperidine (Scheme 122).



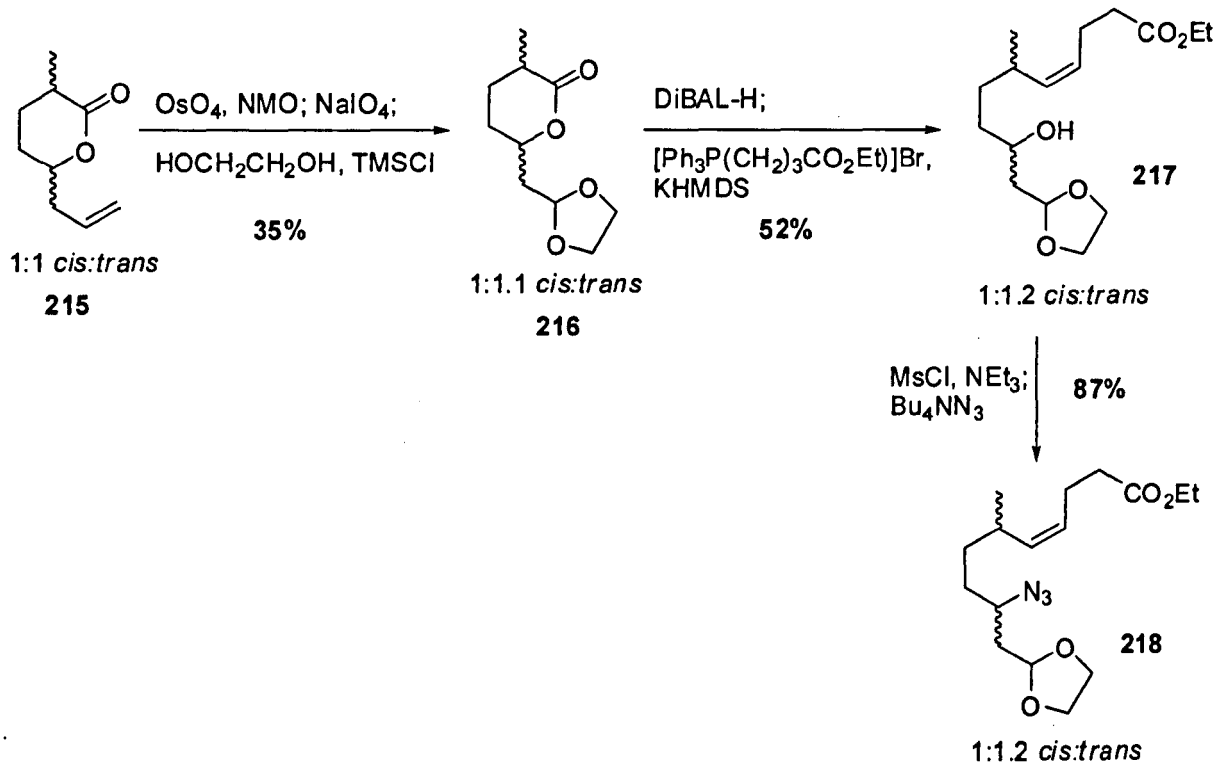
Scheme 122

Accordingly, addition of allyltrimethylsilane to the aldehyde **213**[90-92] followed by cyclisation of the resultant hydroxyester afforded the lactone. After formation of the corresponding enolate, lactone **214** was methylated to produce a 1:1 mixture of diastereomeric lactones **215** (Scheme 123).



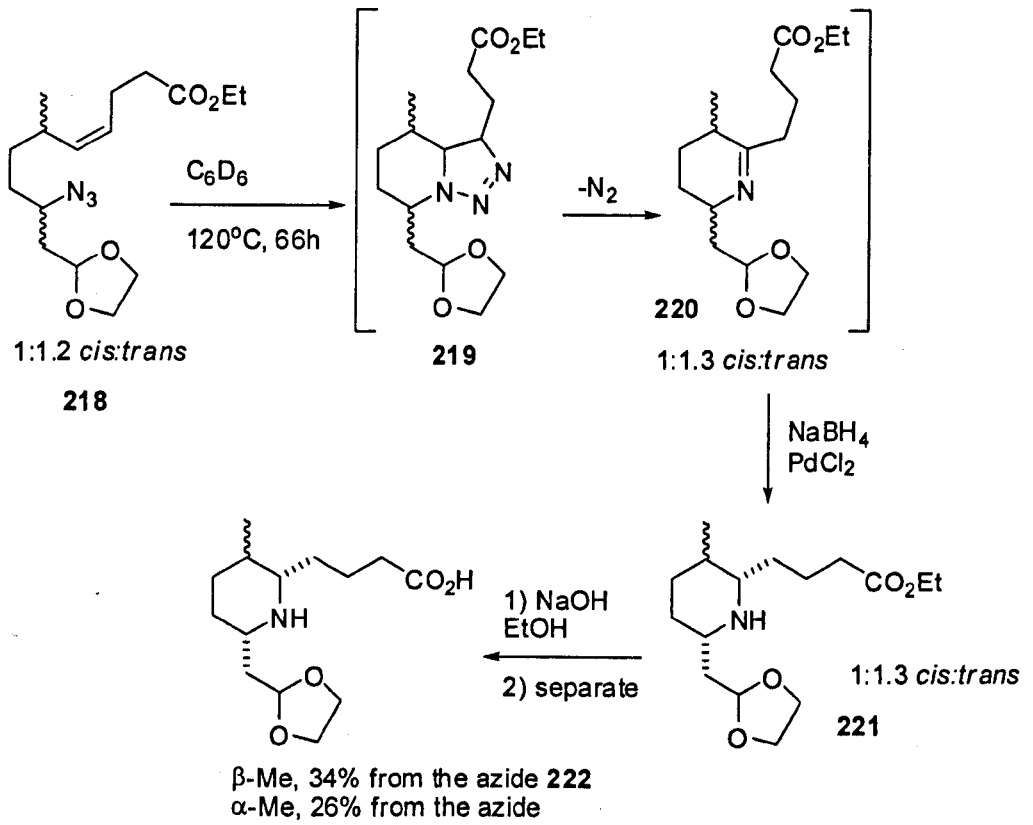
Scheme 123

Based on studies carried out by Cha on cycloaddition of ester-bearing azidoalkenes for the synthesis of indolizidines[93], lactone **215** was then subjected to an oxidative cleavage to give the aldehyde, which was protected to give the acetal **216**; **216** was reduced to the lactol **217** and converted to the alkene **218** after a Wittig reaction (Scheme 124).



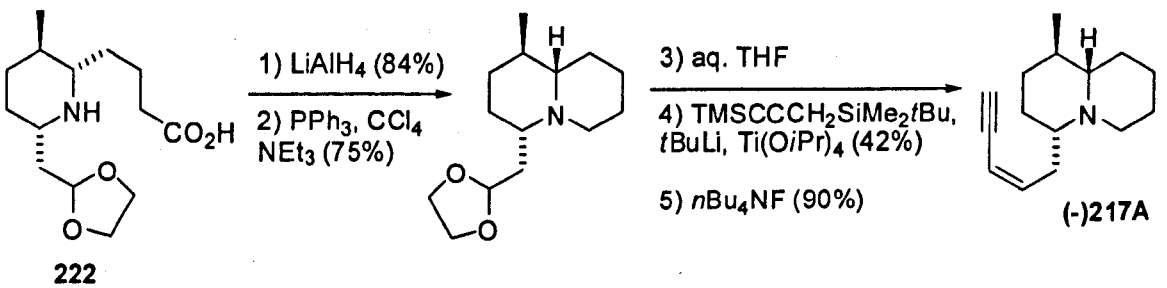
Scheme 124

The inseparable 1:1.2 mixture of diastereoisomers was heated to produce the triazoline **219** initially, which decomposed to the imine **220** as a 1:1.3 mixture of diastereoisomers. Inspired by the report of Lhommet and co-workers[94] on the stereoselective reduction of pyrrolines, Pearson and Suga managed to stereoselectively reduce the crude imine with $NaBH_4/PdCl_2$ as an inseparable 1:1.3 mixture of the two *cis*-2,6-disubstituted piperidines **221**. The two piperidines were separated after saponification of the ester group offering the precursor of quinolizidine 217A **222** in good overall yield (Scheme 125).



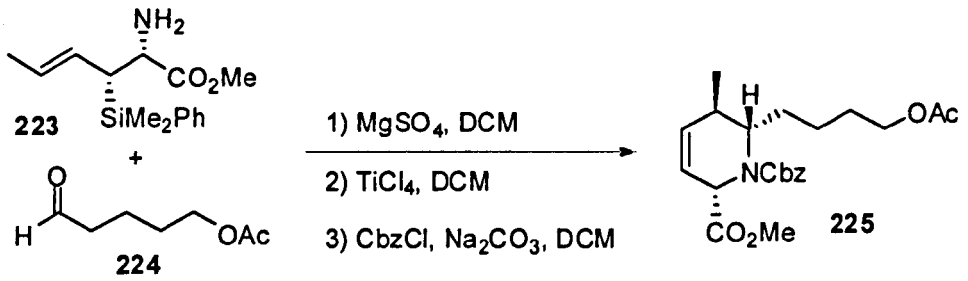
Scheme 125

After a 5-step sequence involving reduction of the acid to the alcohol, cyclisation to the quinolizidine *via* an allyl chloride, hydrolysis of the dioxolane to the aldehyde followed by olefination using Yamamoto's method[95], they managed to synthesise the corresponding silyl enyne quinolizidine, which, after treatment with TBAF, afforded the desired quinolizidine 217A (Scheme 126).



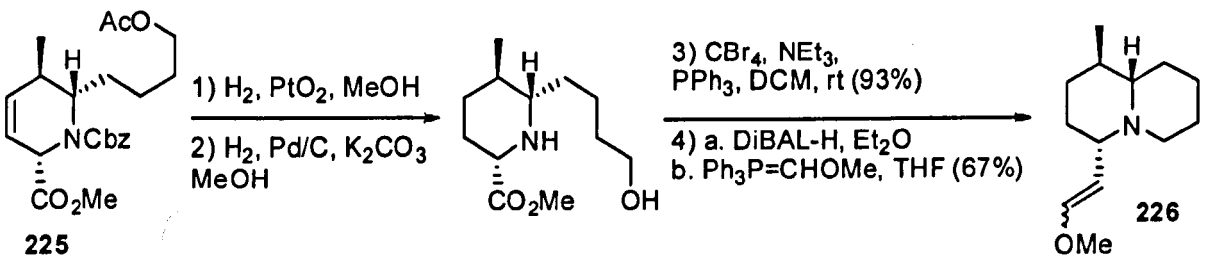
Scheme 126

In 2003, Panek and collaborators[96] described an alternative route towards quinolizidine 217A. The key step in their synthesis was the formation of the terahydropyridine core, which relied on an intramolecular imine crotylation. This chemistry was based on previous experiments towards the synthesis of dihydropyrans *via* a [4+2] annulation, which highlighted the important role of a silicon-bearing centre to control the stereoselectivity[97]. They applied this methodology to initiate the synthesis of the desired quinolizidine, using silane **223**[98, 99] and aldehyde **224** to provide Cbz-protected tetrahydropyridine **225** as a single diastereoisomer in 60% yield (Scheme 127).



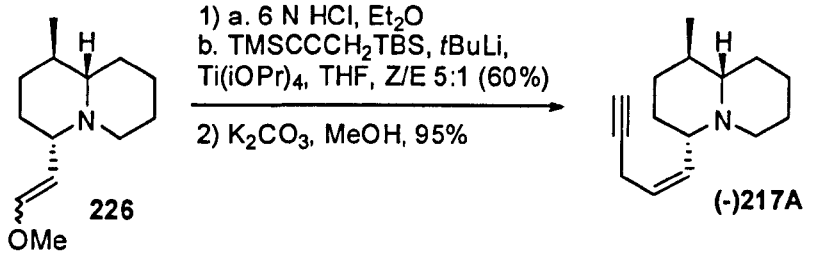
Scheme 127

A 5-step sequence of functional group interconversions afforded the enol-ether intermediate **226** (Scheme 128).



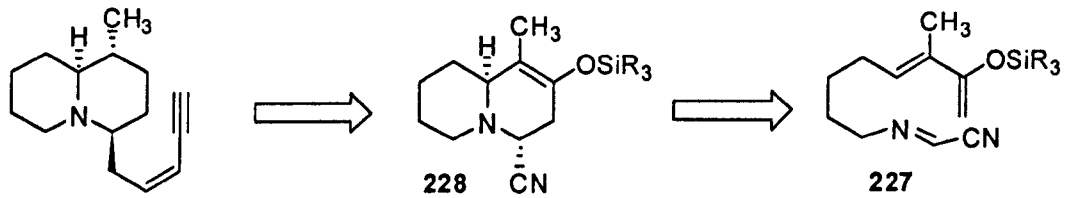
Scheme 128

Enol-ether **226** was subsequently converted to the corresponding aldehyde, which was subjected to Yamamoto's olefination and desilylation (as previously discussed) to produce quinolizidine (-)217A (Scheme 129).



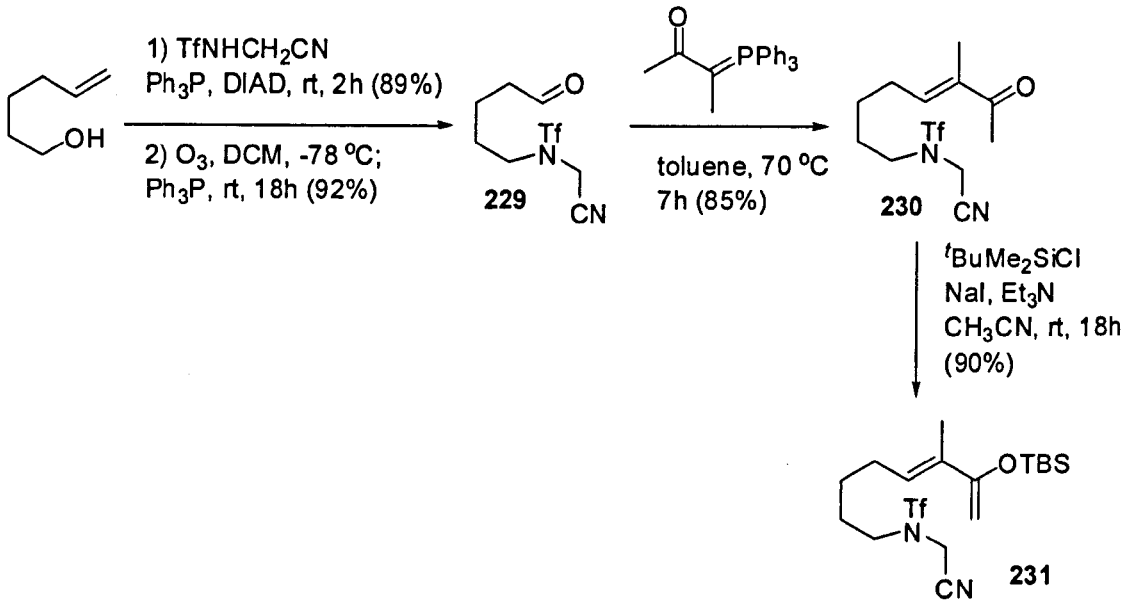
Scheme 129

The last and most recent synthesis was reported by Maloney and Danheiser in 2005[100]. Their strategy for the synthesis of the azabicyclic core of the quinolizidine involved the intramolecular [4+2] cycloaddition of iminoacetonitriles[101, 102] **227** to afford α-amino nitriles like compound **228** (Scheme 130).



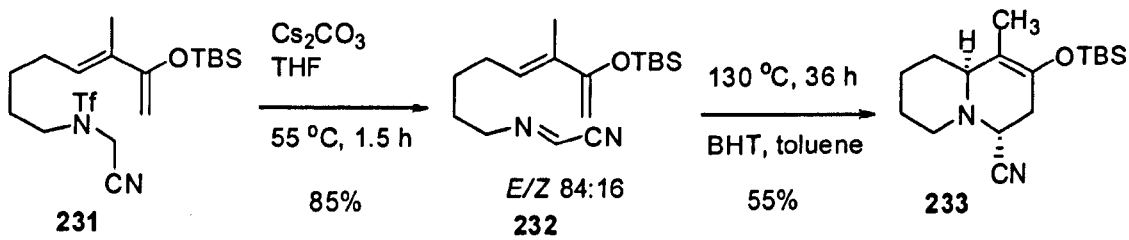
Scheme 130

Starting from commercially available 5-hexenol, Mitsunobu coupling with $TfNHCH_2CN$ yielded the corresponding sulphonamide, which underwent ozonolysis to furnish aldehyde **229**. Wittig olefination of aldehyde **229** gave the *(E)*-α,β-unsaturated ketone **230** and its conversion to the desired enol ether **231** was achieved using the general procedure of Dunogues et al[103] (Scheme 131).



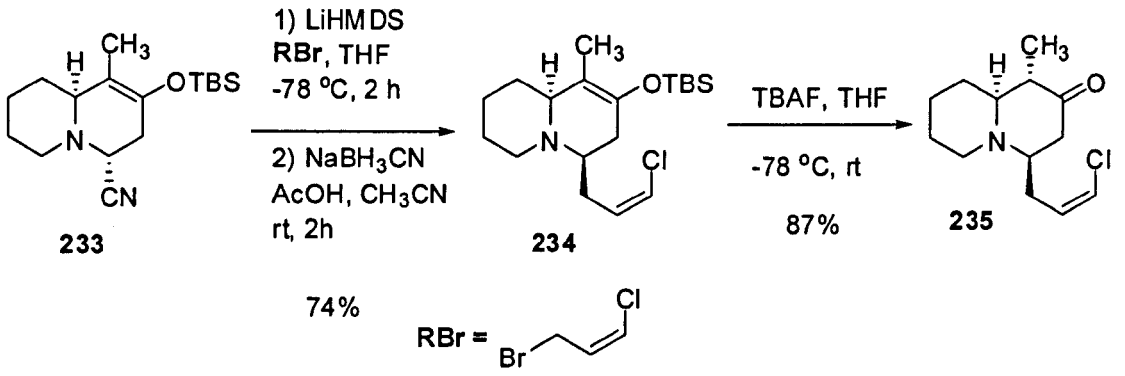
Scheme 131

The desired reagent used for the cycloaddition, iminoacetonitrile **232**, was obtained under basic conditions as a mixture of *E* and *Z* imine isomers. Azobicycle **233** was then formed as a single isomer by heating **232** at 130 °C for 36 h and the addition of BHT (butylated hydroxytoluene) was deemed necessary to avoid any decomposition or polymerisation of the product, BHT preventing radical formation which can polymerise double bonds (Scheme 132).



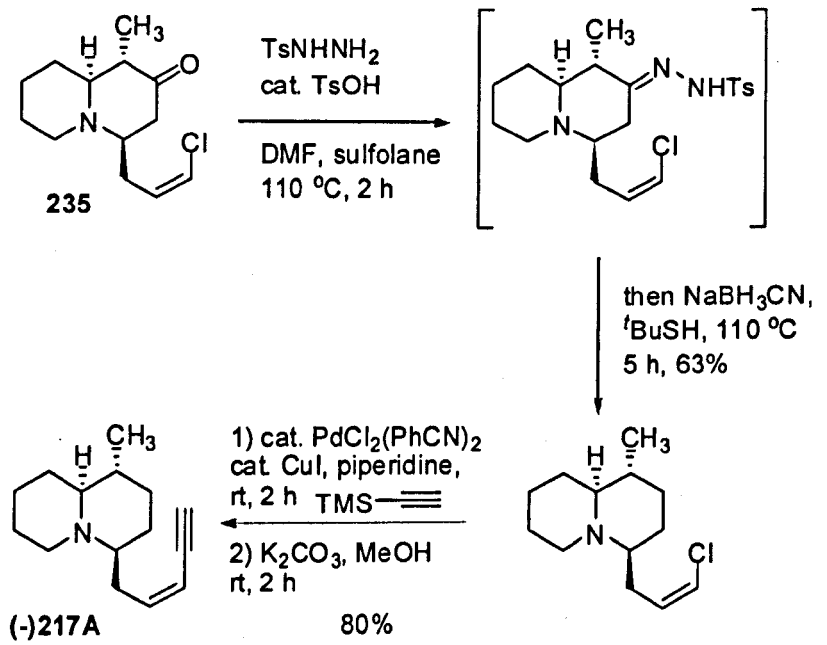
Scheme 132

Alkylation of α-amino nitrile **233** with *(Z)*-3-bromo-1-chloropropene proceeded smoothly and the desired quinolizidine **234** was then obtained by reductive decyanation (Scheme 133). Finally, cleavage of the silyl enol ether with TBAF generated ketone **235** as a single diastereoisomer with the desired stereochemistry at the methyl group.



Scheme 133

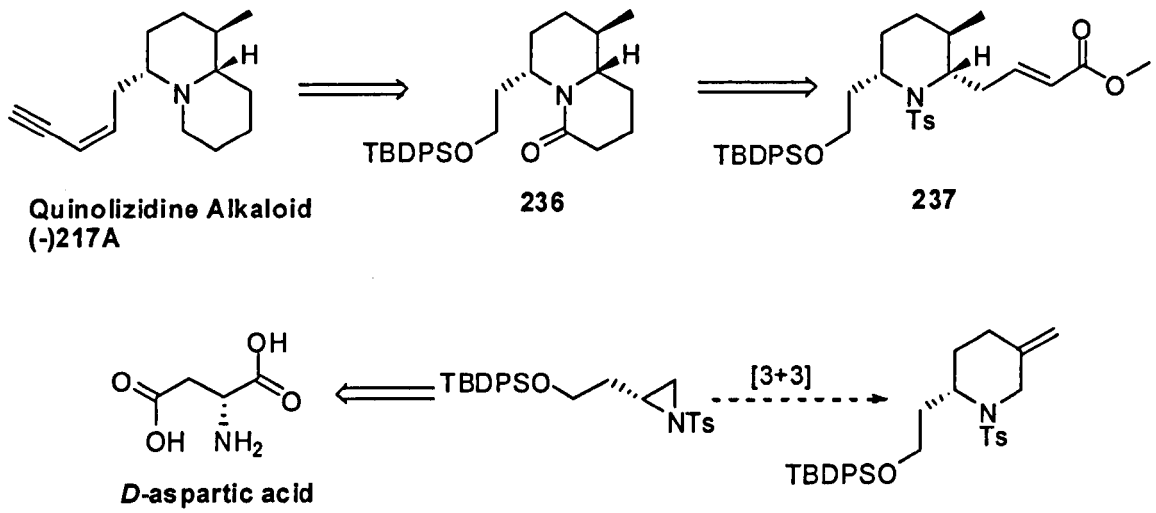
Reduction of the ketone to the corresponding alkane was performed using a Wolf-Kishner reaction, by reducing the tosylhydrazone derivative with $NaBH_3CN$ in presence of *tert*-butyl mercaptan (Scheme 134). Then a Sohogashira coupling with trimethylsilylacetylene followed by a desilylation reaction to remove the TMS group offered quinolizidine (-)217A.



Scheme 134

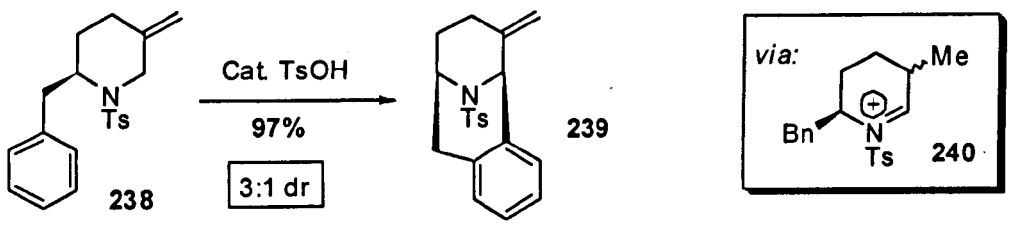
2.Retrosynthetic analysis of Quinolizidine Alkaloid (-)217A

At the beginning of our investigation, we envisaged that we could obtain quinolizidine alkaloid (-)217A from the lactame **236**, following lactam reduction and homologation of the pendant alcohol unit following the procedure outlined by Panek[96] (lactam **236** being itself obtained from the 2,5,6-trisubstituted piperidine **237**) (Scheme 135).



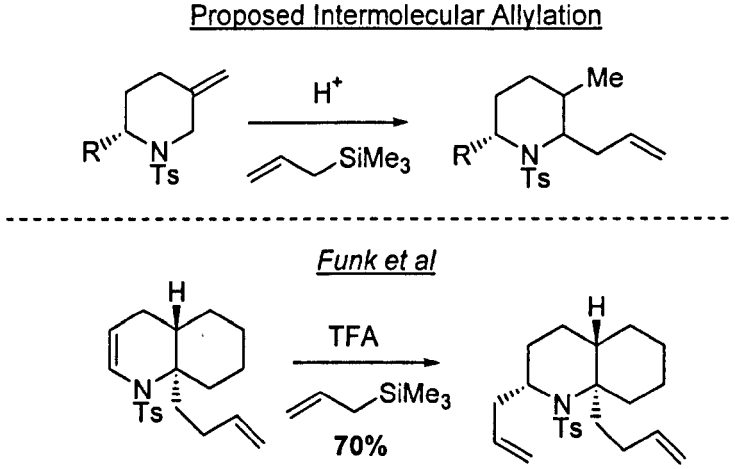
Scheme 135

The aim was to employ our cycloaddition strategy (Pd-catalysed or Mg-mediated) to access enantiopure piperidine (*S*)-**150** from aziridine (*R*)-**140**. In order to go from piperidine (*S*)-**150** to the 2,5,6-trisubstituted piperidine **237**, we wished to exploit a recent observation by our group which showed that piperidine **238** can undergo acid-catalysed cyclisation to give bicycle **239** in excellent yield, presumably through the intermediacy of iminium ion **240**[104] (Scheme 136).



Scheme 136

We anticipated that substrates which cannot undergo intramolecular addition reactions would instead be trapped by external nucleophiles and that this may provide an alternative strategy for the stereoselective synthesis of 2,6-disubstituted piperidines. As outlined in Scheme 137 and based on similar transformations by Funk, acid catalysed allylation of piperidines should furnish the corresponding allylated piperidine products[105].

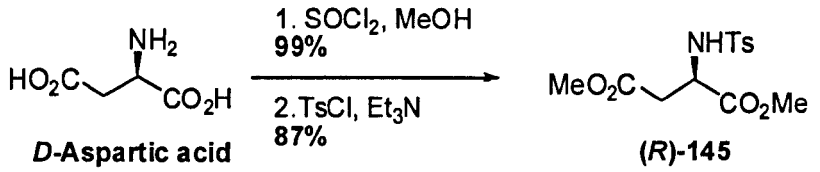


Scheme 137

3.Synthesis of the key aziridine intermediate

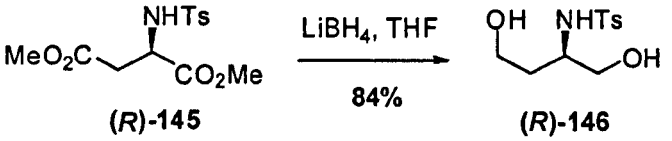
As discussed earlier, our synthetic route towards quinolizidine alkaloid 217A involves the synthesis of enantiopure aziridine **(*R*)-140**, which is the key reagent in our cycloaddition strategy (Pd-catalysed or Mg-mediated) to access enantiopure piperidine **(*S*)-150**.

D-Aspartic acid was first treated with thionyl chloride in methanol to give the diester **(*R*)-144** in excellent yield. The crude diester **(*R*)-144** was subsequently tosylated on nitrogen using tosyl chloride and triethylamine to afford product **(*R*)-145**[106-108] (Scheme 138).



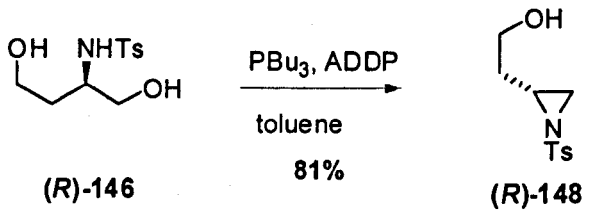
Scheme 138

The double reduction of the diester **(*R*)-145** was then carried out to form diol **(*R*)-146** in excellent yield (Scheme 139).



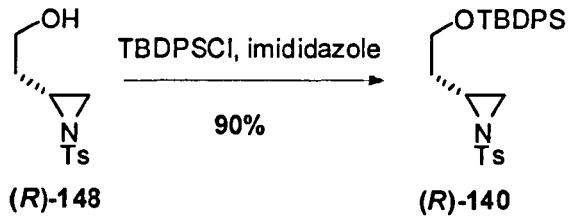
Scheme 139

We next took advantage of the preference for three-membered ring formation over four-membered ring closure to form the aziridine **(*R*)-148**[108] (Scheme 140). This was achieved *via* a Misunobu reaction, ADDP and Bu_3P offering the best yield in aziridine after difficult purification by column chromatography[109].



Scheme 140

Treatment of aziridine **(*R*)-148** with TBDPSCl and imidazole provided the silicon-protected aziridine product **(*R*)-140** (Scheme 141).



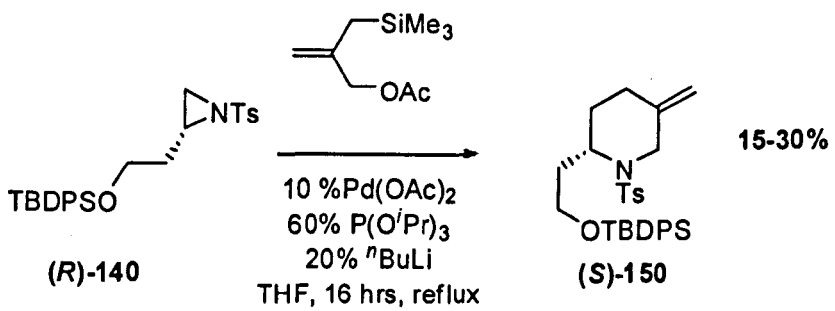
Scheme 141

Using this route, large quantities (~5g) of the desired aziridine **(*R*)-140** were synthesised.

4.Synthesis of the desired piperidine

4.1.[3+3] Cycloaddition

The desired aziridine **(*R*)-140** was subjected to our standard cycloaddition conditions (10% $Pd(OAc)_2$, 60% $P(O^iPr)_3$, 20% *n*-BuLi, THF reflux overnight), developed in the group (Scheme 142). However, this unfortunately resulted in disappointing and unreliable results (yield of piperidine ~15-30% together with by-products).



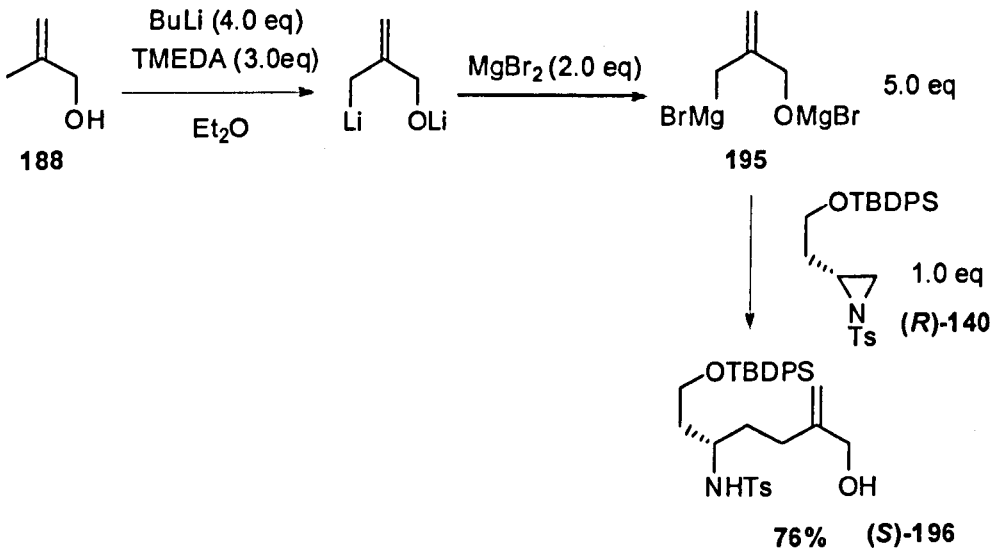
Scheme 142

As a result, we decided to turn our attention to a more promising method: the Grignard approach.

4.2.Grignard Reaction

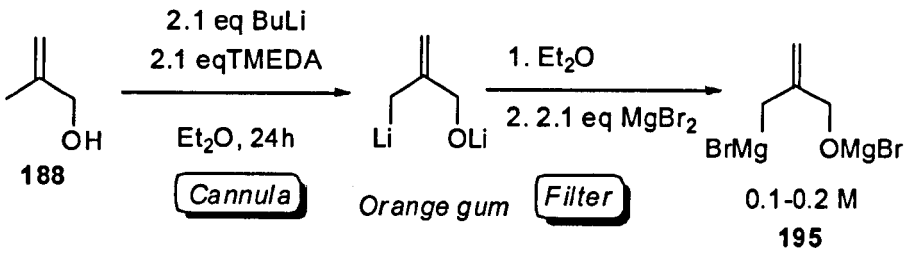
As discussed in Chapter 3, an alternative approach to the TMM equivalent was envisaged involving the use of a Grignard reagent. Encouraged by Klumpp's studies[36, 67-71], we applied the use of the Grignard chemistry for the preparation of our piperidine.

Double deprotonation of methallyl alcohol **188** followed by transmetallation with magnesium bromide and addition of this Grignard reagent **195** to our enantiopure silylether substituted aziridine (***R*)-140** led to the formation of the desired ring-opened product (***S*)-196** in high yield.

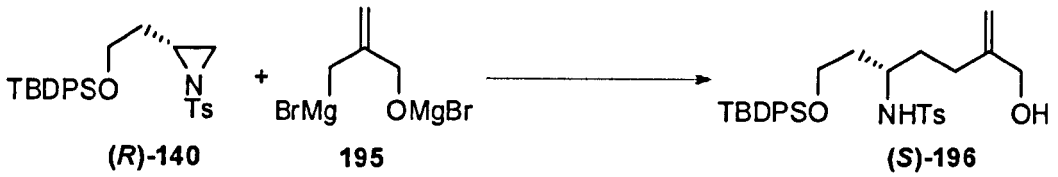


Scheme 143

Following work previously carried out by Brioche[77, 78] on epoxides, this methodology was further developed and we were able to make a solution of the Grignard reagent in THF, which, after titration, could be added to a solution of our aziridine (Scheme 144). Only 2.5 equivalents of reagent were required to achieve complete conversion (Scheme 145 and Table 24).



Scheme 144



Scheme 145

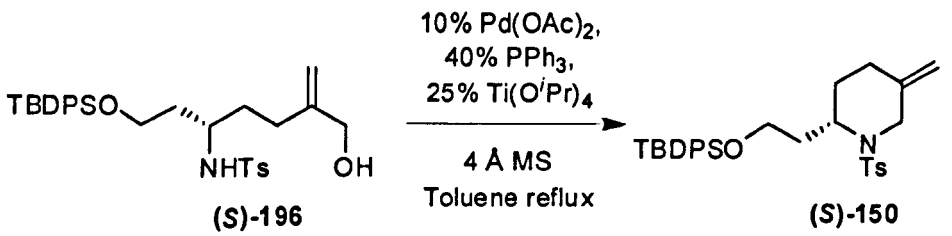
Equiv of Grignard	Product Yield
5.0[a]	76%
2.5[b]	85%

[a] Organomagnesium reagent prepared by addition of TMEDA (3.0 equiv) and *n*-BuLi (4.0 equiv) to **188** followed by $MgBr_2$ (2.0 equiv).

[b] Organomagnesium reagent prepared with by addition of TMEDA (2.1 equiv) and *n*-BuLi (2.1 equiv) to **188** followed by $MgBr_2$ (2.1 equiv).

Table 24

To complete the synthesis of the desired piperidine, we considered Yang and Hung's work[74] on Ti-mediated allylation reactions and a transition metal catalysed one-step cyclisation reaction was used (Scheme 146).



Scheme 146

We also investigated the role of $Ti(^iOPr)_4$ in the cyclisation. Originally, we thought that it behaved as a Lewis acid helping to form the Pd-allyl complex by coordinating to the O of the allyl alcohol, making it a better leaving group. However, it was discovered that it was not necessary for the reaction to occur (Table 25).

Lewis acid	Product Yield
none	84%
$Ti(^iOPr)_4$	90%

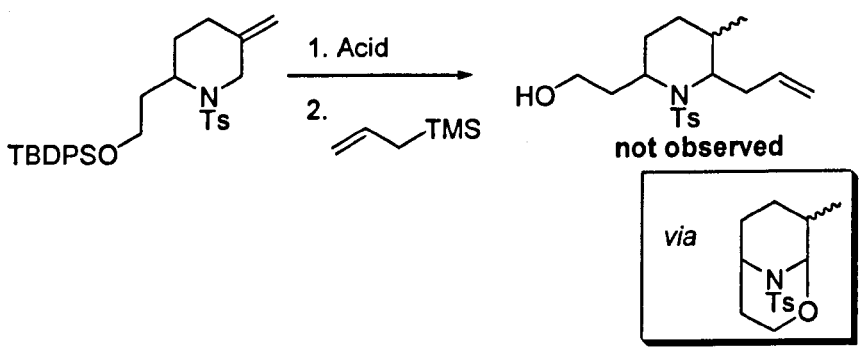
Table 25

Using this 2-step methodology, we were able to synthesise the desired piperidine on > 1 g scale.

5.Elaboration of piperidine to key quinolizidine intermediate

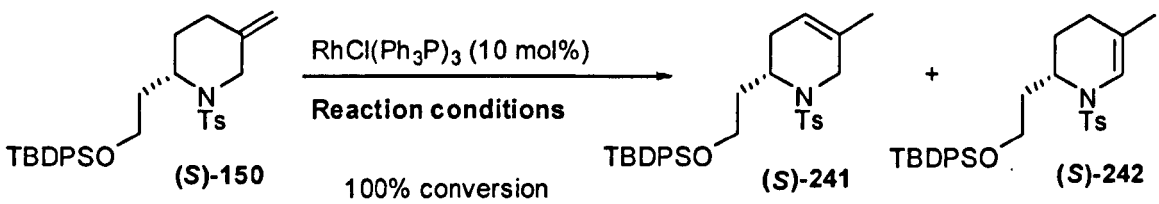
The first challenging step to overcome was the allylation of our piperidine. As mentioned earlier in this chapter, we based our reasoning on Funk's studies (see Scheme 147).

The first investigations carried out on the racemic silyloxyethyl substituted piperidine **150**, using 2 equivalents of TsOH in toluene under reflux overnight, were not conclusive, as no product was observed and only the starting material was recovered.



Scheme 147

It was decided to isomerise the *exo*-alkene to the corresponding enamide in the hope that this would promote formation of the key iminium intermediate. Work carried out by Schmidt[110] on the double bond isomerisation, catalyzed by ruthenium hydride, provided some ideas on the best conditions to use in our case (Scheme 148).



Scheme 148

SM	Reaction conditions	% 150	% 241	% 242
(±)-150	DBU (1.5 eq), EtOH reflux, o.n.	-	72	28
(±)-150	DBU (1.5 eq), EtOH reflux, 1.5 h	-	67	33
(±)-150	DBU (1.5 eq), EtOH, RT, o.n.	100	-	-
(±)-150	DBU (1.5eq), EtOH, 40 ^{0}C, 25 min	35[a]	-	11
(*S*)-150	DBU (1.5 eq), MeOH reflux, o.n.	47	23	30
(*S*)-150	DABCO (1.5 eq), EtOH reflux, 2 h	55	30	15
(*S*)-150	DBU (1.5 eq), EtOH reflux, 35 min	-	67	33

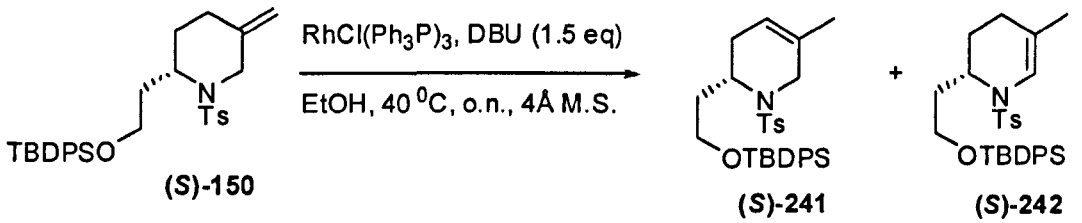
[a] No product 241 was isolated but an unidentified complex mixture was observed.

Table 26

It turned out that Wilkinson's catalyst (10 mol%), in presence of a base under reflux of ethanol (or methanol), generally afforded the two isomers, with isomer

242 being the only one potentially useful for a further allylation of the piperidine. Based on these studies, we considered the following conditions to be optimal: 10% $RhCl(Ph_3P)_3$, DBU (1.5 eq), 4Å M.S., EtOH, 40 °C overnight (Table 26).

The influence of the quantity of the catalyst on the ratio of the two isomers was then investigated (Scheme 149 and Table 27).



(S)-150 **(S)-241** **(S)-242**

Scheme 149

[Rh]	Ratio 241:242
10%	1.3 : 1
10%[a]	1 : 2
20%	1 : 2
30%	1 : 3.8
40%	1 : 3.9
100%	0 : 100

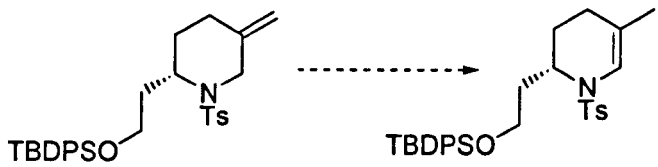
[a]Wilkinson's catalyst freshly prepared

Table 27

As can be seen in Table 27, the isomerisation provided good yields of the desired alkene isomer **(*S*)-242** but at the expense of high catalyst loadings, which is a drawback for our synthesis considering the high cost of the catalyst.

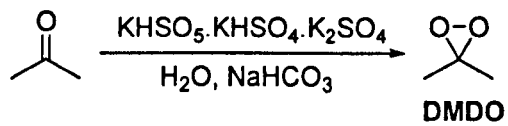
In our attempt to improve the conditions, distilled EtOH, distilled DBU and freshly prepared catalyst were used. Under these conditions, a 2:1 ratio in favour of **(*S*)-242** was obtained with only 10% Rh catalyst.

Another idea to avoid using the expensive Wilkinson's catalyst and to get the desired regioisomer **(*S*)-242** was to functionalise the *exo*-double bond on **(*S*)-150** (Scheme 150).

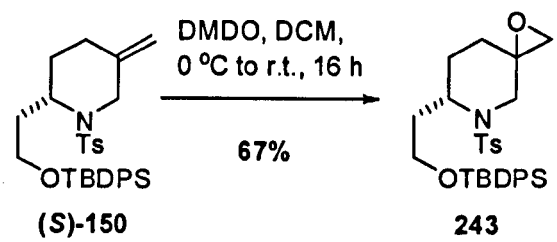


Scheme 150

The first attempt involved the synthesis of the epoxide **243**, which was deemed successful using DMDO, prepared from acetone and oxone[111], at low temperature (Schemes 151 and 152).

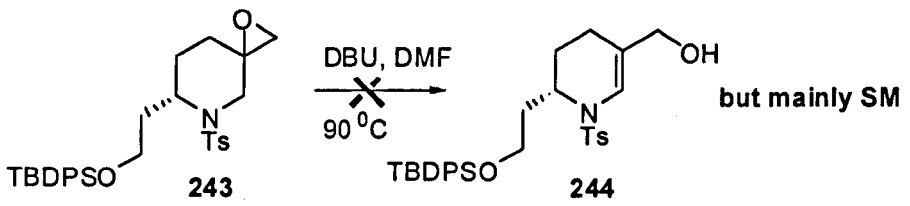


Scheme 151



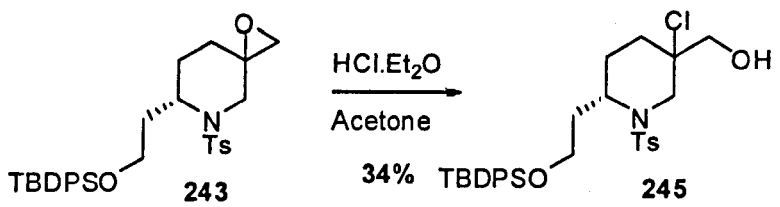
Scheme 152

It was subsequently attempted to open epoxide **243** using a base and deprotonate at C6 (Scheme 153). However, with DBU in DMF, the desired product **244** was not obtained, instead mainly starting material was isolated (60%).



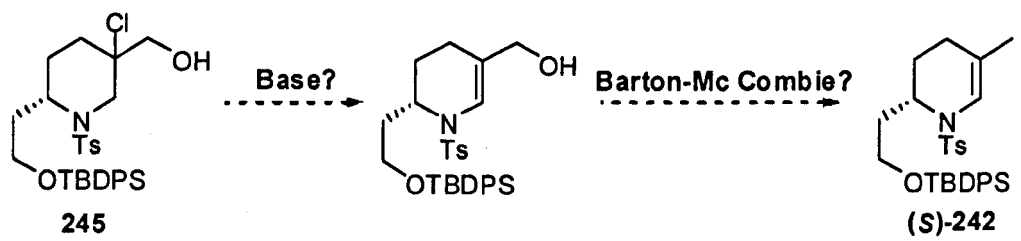
Scheme 153

Alternatively, opening epoxide **243** using a nucleophile such as a halogen was investigated. Inspired by the work done by Shiro and collaborators[112], we employed HCl as a chloride source and observed the formation of the desired product **245** (Scheme 154).



Scheme 154

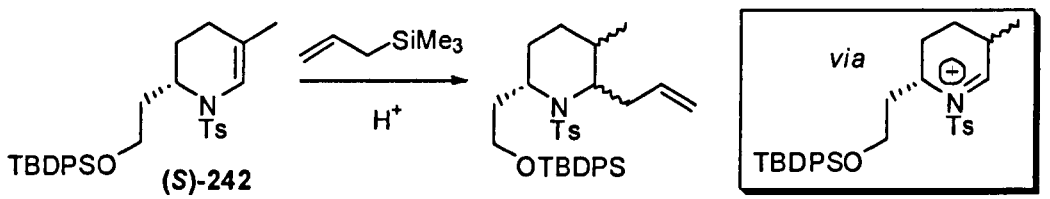
The purpose of this strategy was to synthesize product **(*S*)-242** *via* a 2-step sequence starting from compound **245** (Scheme 155).



Scheme 155

Even though this strategy looked potentially promising, we decided not to continue our investigations but to carry on the synthesis, judging this multi-step sequence too elaborate.

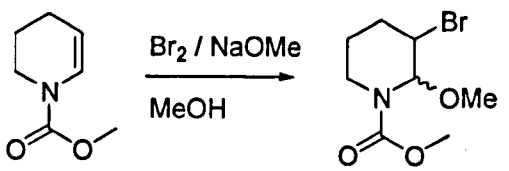
Having established good conditions for the isomerisation of the *exo* double bond into the desired *endo* double bond isomer, we could focus on the allylation step itself. This transformation was also found to be challenging. It was envisaged that addition of acid to piperidine **(*S*)-242** would form the iminium which could be trapped by an appropriate nucleophile (Scheme 156).



Scheme 156

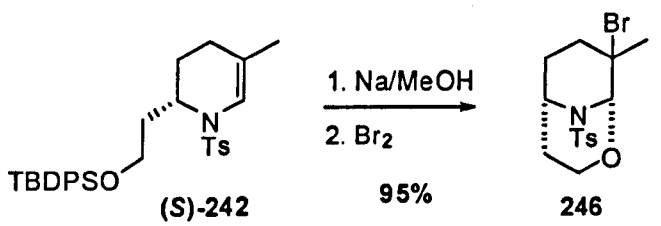
Unfortunately, after having screened a number of Brønsted acids, allylation was not observed, generally recovering starting material instead.

The next attempt involved introduction of a methoxy group in C6 position to form an aminal so that Lewis acid mediated allylation could be more easily explored. In this respect, we were encouraged by Shono and collaborators who described a similar transformation in 1987[113, 114] (Scheme 157).



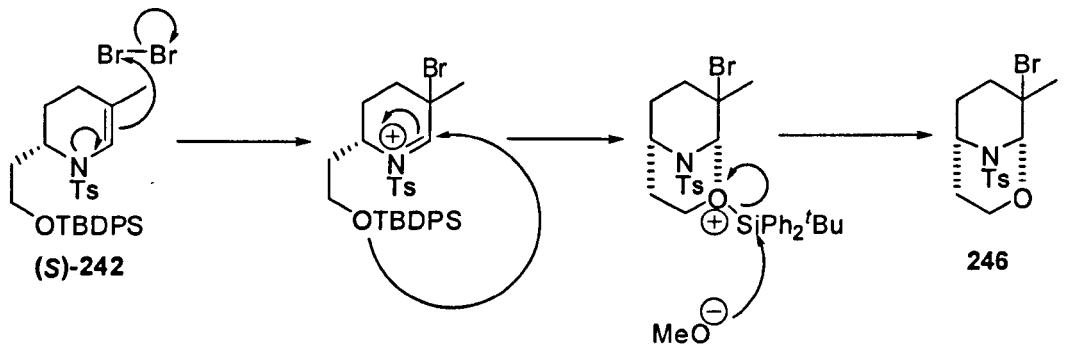
Scheme 157

When these conditions were applied to our piperidine **(*S*)-242**, the bicycle **246** was yielded, providing a suitable precursor for the allylation (Scheme 158).



Scheme 158

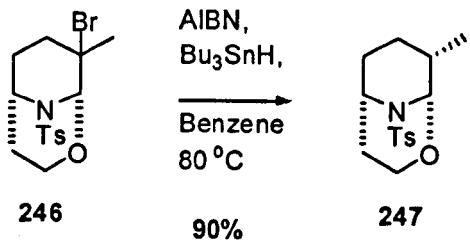
The proposed mechanism for this reaction is the following (Scheme 159)



Scheme 159

We firstly decided to remove the bromide and were encouraged to find an efficient means to reduce bromohydrins using tributyltin hydride[115].

When we applied these conditions for the debromination (AIBN, Bu_3SnH in refluxing benzene) on our substrate **246**, the formation of a single crystalline product **247** was observed in excellent yield.



Scheme 160

However, X-ray crystallography confirmed that the wrong diastereoisomer had been synthesised with regard to the natural product, as the methyl in C5 was *cis* to the group at C2 (Figure 4).

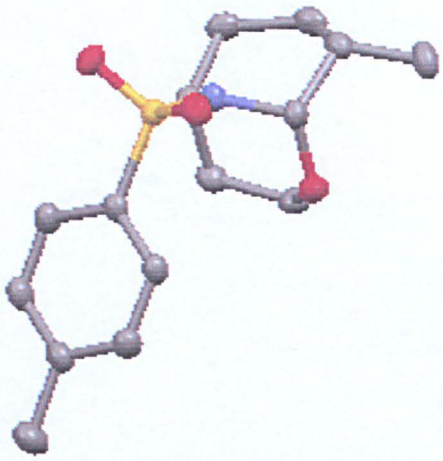
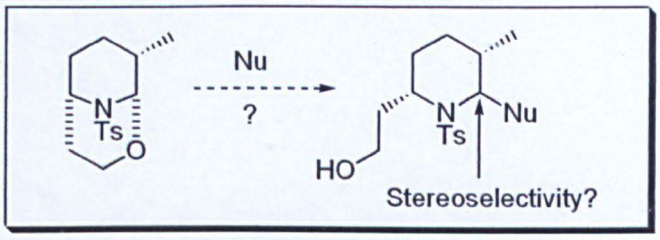


Figure 4: X-ray structure of compound 247

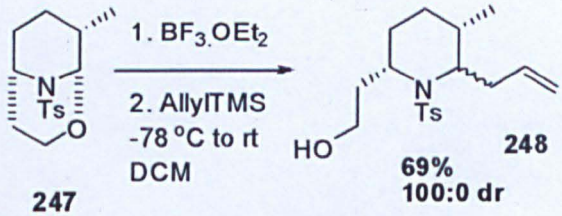
5.1.Allylation reaction

At this stage, the synthesis was continued, turning our attention to the allylation reaction (Scheme 161).



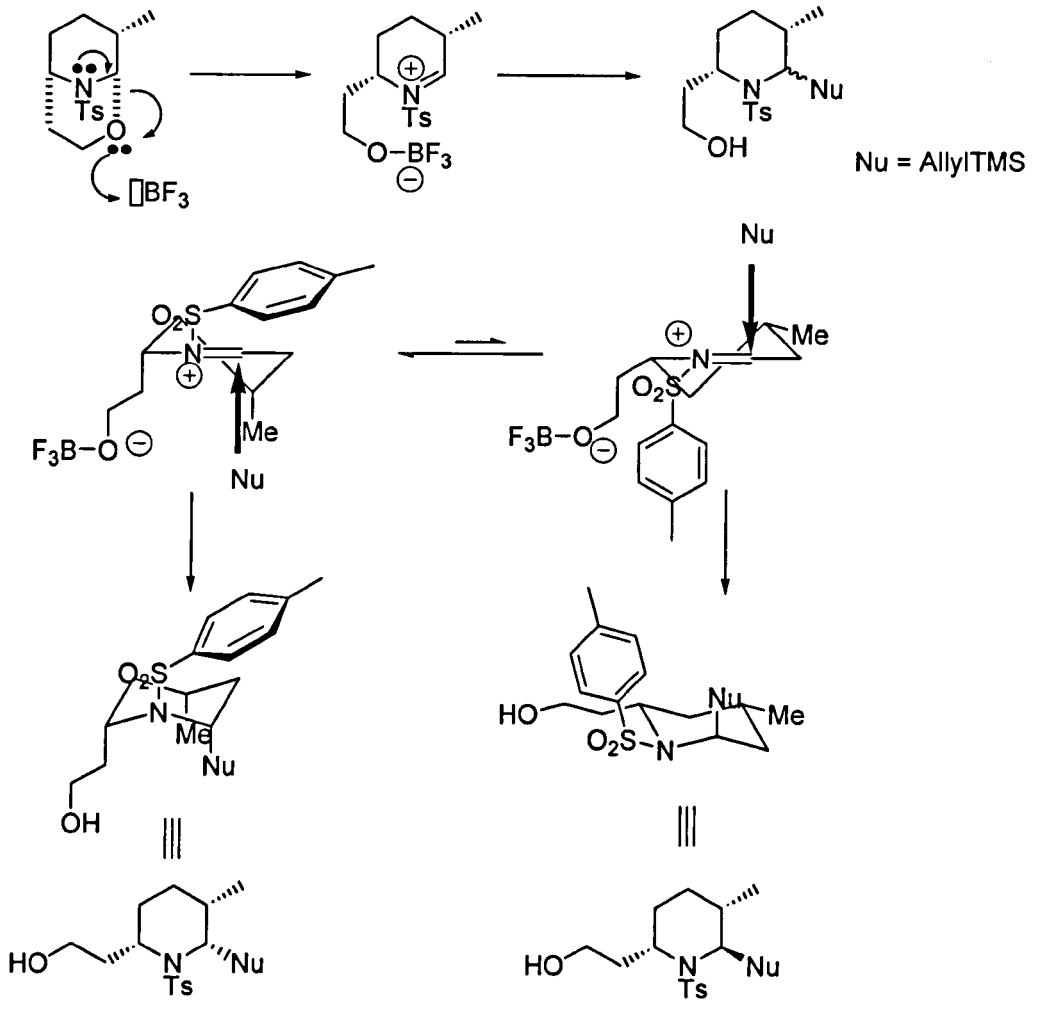
Scheme 161

Based on previous work by Ahman and Somfai[116] on the addition of carbon nucleophiles to cyclic *N*-tosyliminium ions, we screened Lewis acids such as TMSOTf, $BF_3.Et_2O$ and $TiCl_4$, but only $BF_3.Et_2O$ afforded encouraging results. Only one diastereoisomer **248** was obtained from the reaction in 69% yield (Scheme 162).



Scheme 162

The product stereochemistry at C6 was later investigated by NMR spectroscopy to confirm the presence of the all *cis*-diastereoisomer; the expected outcome is discussed in Scheme 163.

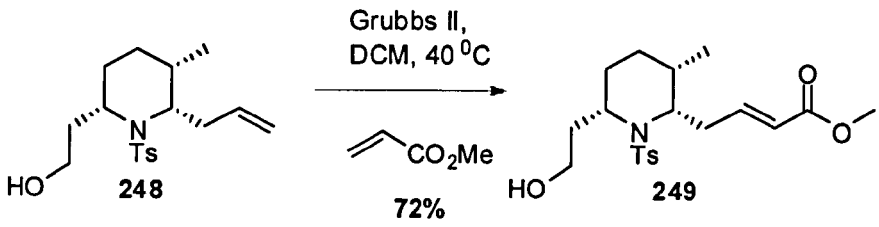


Scheme 163

N-Ts piperidines tend to place substituents at C2 in an axial geometry in order to minimise $A_{1,3}$ strain (Scheme 163)[63]. Therefore, the reaction should go via the pathway on the left hand side and lead to the *cis* product.

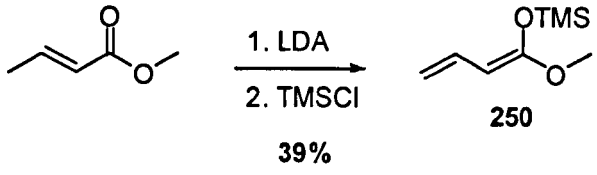
Initially, although the wrong stereochemistry in at the C5-methyl was observed, the synthesis of lactam **236** was still sought after. Therefore, the cross-metathesis onto the 2,5,6-substituted piperidine **248** was performed using methyl acrylate and

Grubbs second generation catalyst. The methyl ester **249** was obtained in good yield (Scheme 164).



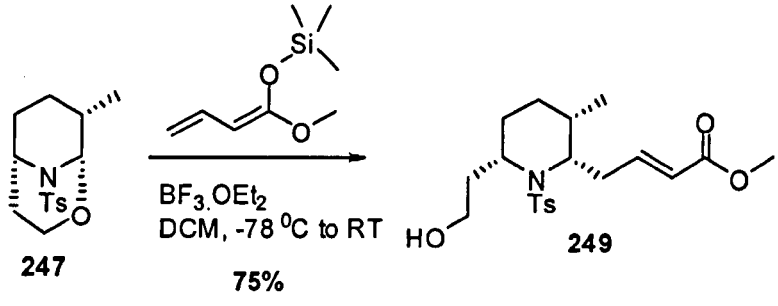
Scheme 164

Instead of using an expensive 2-step strategy to make compound **249** *via* allylation and then cross-metathesis, we proposed that we could run the allylation step directly, using diene **250** as a nucleophile. Diene **250** is readily available from methyl crotonate[117] (Scheme 165).



Scheme 165

Allylation with **247** showed the formation of only one compound **249** in good yield.



This compound was characterised and the NMR data were shown to be identical to the data obtained *via* the 2-step strategy. NOESY and COSY experiments (Figure 5) were also undertaken to confirm the stereochemistry at the C6 position: both groups in C2 and C6 were indeed *cis* (see Appendix 6.3).

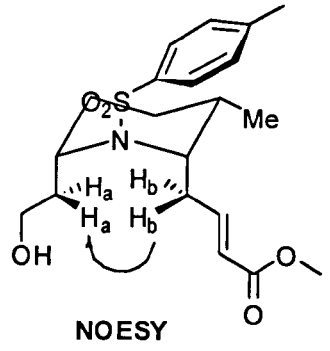
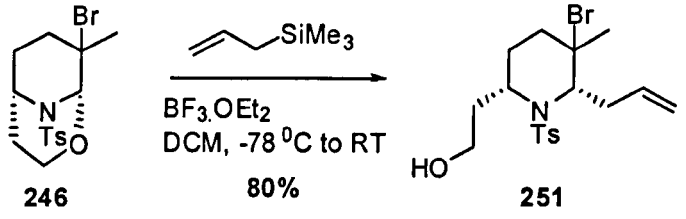
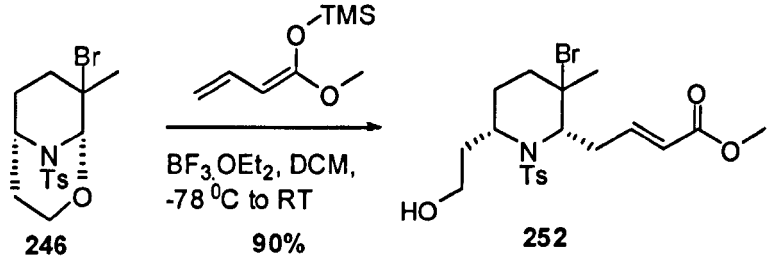


Figure 5

The allylation of the bromo-substituted bicycle **246** was also attempted. The two nucleophiles previously tested were used (namely allyltrimethylsilane and diene **250**) and we were delighted to realise that in both cases we obtained one single diastereoisomer **251** and **252** in very good yield (Schemes 166 and 167). These results confirmed earlier results concerning the stereoselectivity of the allylation: the same model can be applied to the bromo-substituted bicycle **246**.



Scheme 166

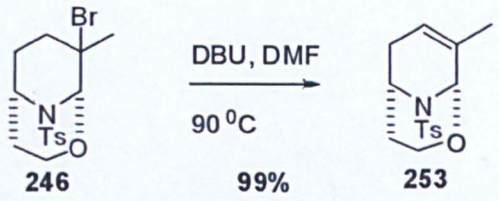


Scheme 167

Once synthesised, the substituted piperidines **251** and **252** were investigated under the conditions of dehydrobromination. In 1938, Renshaw and Conn[118] developed the dehydrobromination of bromopiperidine derivatives under basic conditions.

This method was then successfully utilised on halogenopiperidines over the past few years[114, 119, 120], with the most commonly used base being DBU heated in *N,N*-dimethylformamide.

These conditions were tested on bromopiperidine **246** and the desired product **253** was obtained in quantitative yield (Scheme 168). The crystalline compound **253** was characterised by X-ray crystallography, confirming the *cis*-stereochemistry at C2 and C6 positions (Figure 6).



246 **99%** **253**

Scheme 168

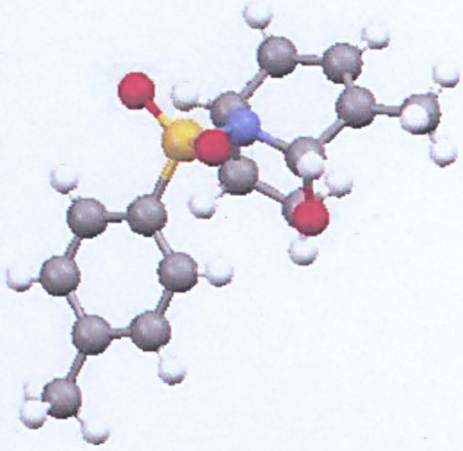
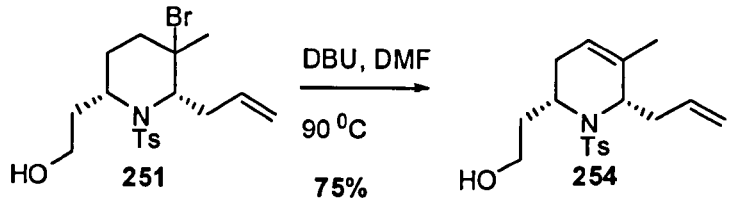


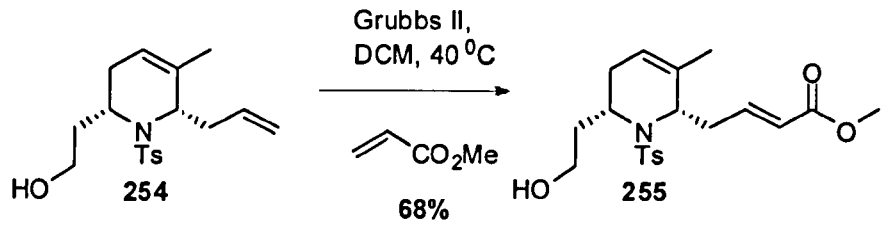
Figure 6: X-ray structure of compound 253

When the dehydrobromination reaction was carried out with piperidine **251**, the formation of compound **254** was observed as expected, in good yield (Scheme 169). The product was characterised by NOESY and COSY experiments, confirming the stereoselectivity in C2 and C6 positions.



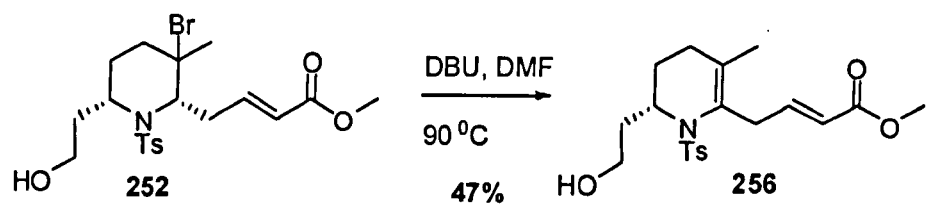
Scheme 169

Cross-metathesis on piperidine **254** was then carried out offering compound **255** in good yield (Scheme 170).



Scheme 170

Surprisingly, the dehydrobromination performed on **252** afforded the opposite regioisomer **256** to the one we expected (Scheme 171). This is attributed to the presence of the ester group in C6 position, rendering the hydrogen at C-6 more acidic.

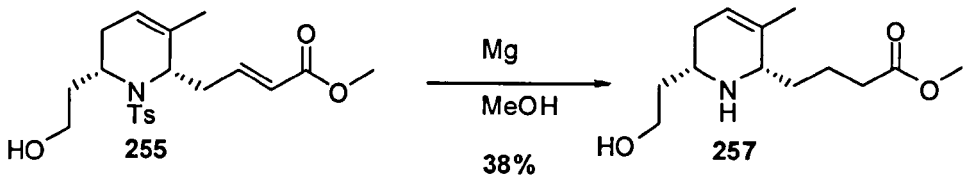


Scheme 171

5.2.*N*-Tosyl deprotection

The next challenge was to deprotect the tosyl amine of the 2,5,6-substituted piperidines **249**, **252** and **255**. Even though many methods have been previously reported[121], the removal of the tosyl group appeared to be a very difficult step in our case. Nevertheless, we first tried the most commonly used method, inspired

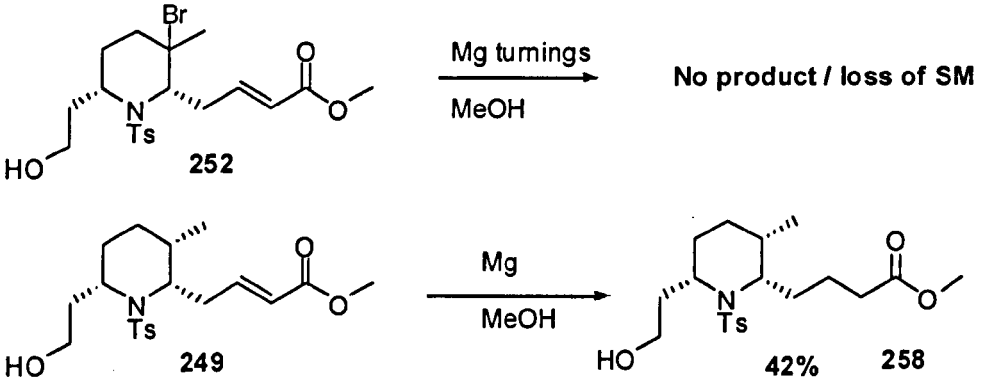
by Alonso and Andersson's works, using magnesium turnings in methanol[121] (Scheme 172).



Scheme 172

At the first glance, the results appeared encouraging, as we obtained a product, which looked like the tosyl-free piperidine **257** according to the NMR data (Scheme 172). The reaction was low yielding and no starting material was recovered. However, this result was found to be irreproducible.

Other substrates were also trialled, resulting in the loss of the starting materials and no desired product was isolated (Scheme 173).

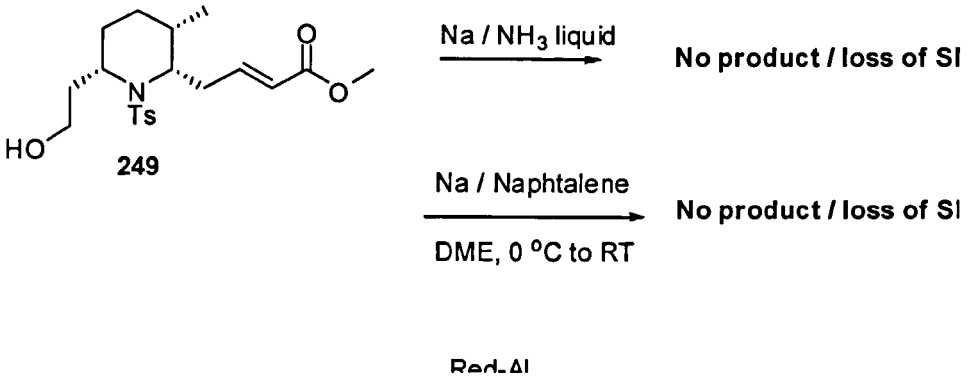


Scheme 173

Even though previous work in the group[37] using the same conditions on similar substrates gave the desired lactam, the conditions were inefficient with our piperidines. Other metal-based conditions were also screened for the deprotection, but they also revealed themselves to be unsuccessful.

Systems investigated involved sodium metal in liquid ammonia[122], sodium metal and naphthalene in DME[122] and sodium bis(2-methoxyethoxy)aluminium hydride

(Red-Al) in THF[123]; all of these methods resulted in the loss of the starting material with no evidence of any traces of product by NMR or GC/MS (Scheme 174).



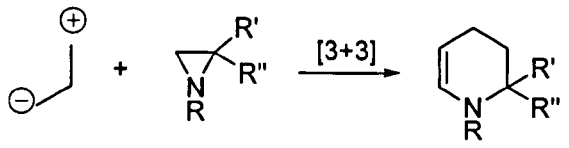
Scheme 174

We also investigated two other methods, samarium (II) iodide in THF[121] and a sodium-mercury amalgam in methanol[124]. Both conditions were revealed to be inefficient.

The difficulties observed with Ts-deprotection together with the problems encountered in controlling C-5 methyl stereochemistry prompted us to explore an alternative approach.

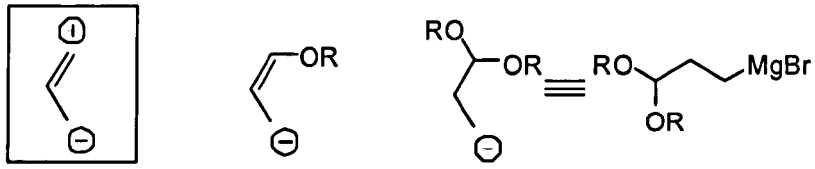
6.An alternative route towards the synthesis of quinolizidine alkaloid 217A: Büchi Grignard

We have seen two different methods developed in our group to access functionalized piperidines. A third has also been investigated: a stepwise [3+3] annelation sequence to tetrahydropyridines *via* addition of the Büchi Grignard to aziridines[125]. The key strategy that has been applied involves the formation of a six-membered ring through the reaction between two compatible three-atom containing fragments (Scheme 175).



Scheme 175

This work is based on Craig's studies, which have shown that a sulfone-based three-carbon homologating agent can be used to synthesise piperidines and deliver functionalization around the heterocycle[65, 66, 126-128]. Three carbon-homologating agents are not commonly used in organic synthesis. As synthons, these reagents bear an electrophilic motif and a nucleophilic unit in a 1,3-relationship. A specific and much studied class of three carbon-homologating reagents are propionaldehyde homoenolate equivalents. Propionaldehyde homoenolate equivalents come in various forms. Two examples of these equivalents are described below, allyl anions **259**, and an acetal masked homoenolate **260** (Scheme 176).

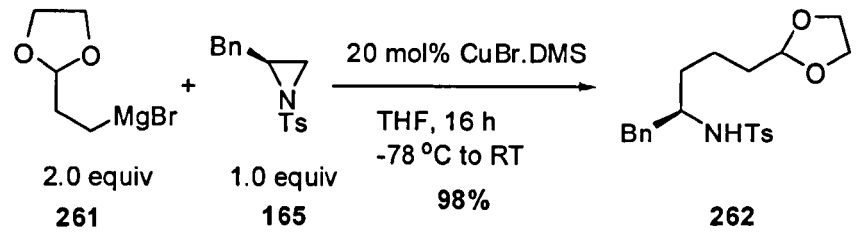


259 **260**

Scheme 176

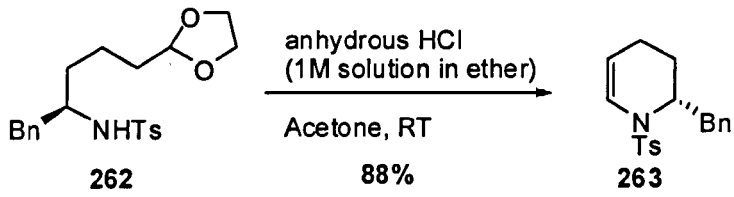
In 2006, Pattenden reported the addition of propionaldehyde homoenolate equivalent **260**[129] to aziridines and the employment of this methodology in the synthesis of a *cis* 2,6-disubstituted piperidine alkaloid.

Based on studies by Büchi[130], who showed that 1,3-dioxolane based reagent **261** represented a competent propionaldehyde homoenolate equivalent, our group investigated the efficiency of the addition of **261** to readily available Bn-substituted aziridine **165** and observed that the addition of 20 mol% CuBr.DMS improved the efficiency of the Grignard addition to the aziridine to afford the desired product **262** in high yield (Scheme 177).



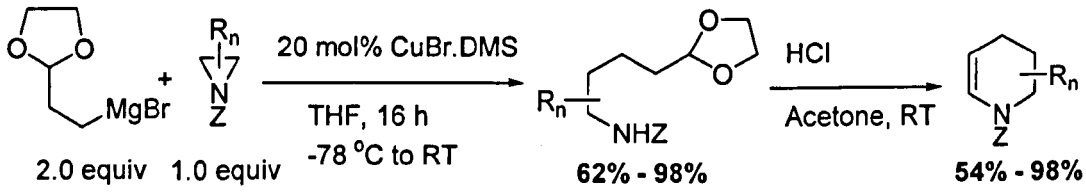
Scheme 177

They then focused on the piperidine-forming reaction and opted to perform an *in situ* acid-catalysed deprotection-cyclisation protocol. This process was found to proceed efficiently to give the corresponding tetrahydropyridine **263** (Scheme 178).



Scheme 178

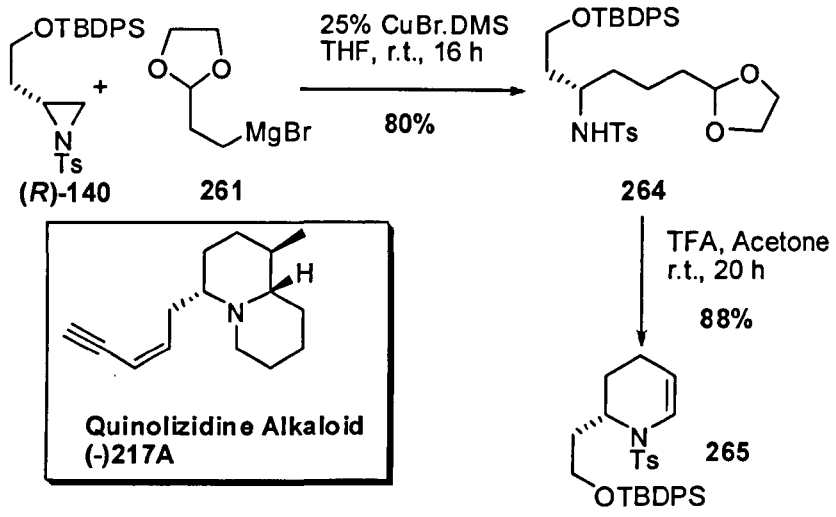
The scope of the stepwise annelation of aziridines was studied: the Grignard addition reaction was found to proceed in good to excellent yield in all cases examined, and the cyclisation reactions afforded the desired dihydropyridines in high yield, although they were generally found to be more sluggish in the formation of bicyclic and spirocyclic products (Scheme 179).



Scheme 179

We decided to apply this chemistry to aziridine **(*R*)-140**. The Grignard addition afforded the desired product **264** in excellent yield. Subsequently, the corresponding tetrahydropyridine **265** was obtained in high yield, using TFA for

the acid-promoted cyclisation; acetic acid was deemed too weak, as the reaction resulted in the recovery of the starting material (Scheme 180). From this substrate, a new strategy for the synthesis of quinolizidine alkaloid (-)217A was envisaged.



Scheme 180

The first concern was the introduction of the methyl group in C5 position. Inspired by extensive work on the functionalisation of tetrahydropyridines, the epoxidation of the endo double bond was investigated in an attempt to functionalise compound **265** at both the C5 and C6 positions in two steps.

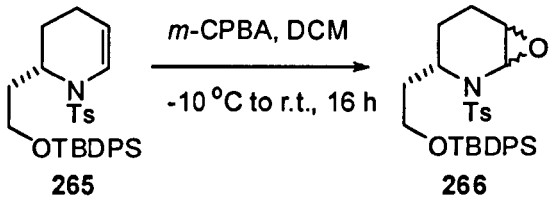
6.1.Epoxidation of tetrahydropyridines

In the past few years, much work has been done on the epoxidation of tetrahydropyridines[131-133] and has been of particular interest by two groups, Hu and collaborators[134] and Burgess and co-workers[135]. They highlighted two different and efficient methods for the epoxidation: dimethyldioxirane (DMDO) in dichloromethane and *m*-CPBA in dichloromethane. We decided to apply both methods to our tetrahydropyridine.

6.1.1.m-CPBA

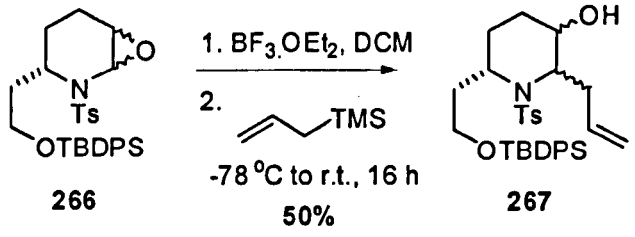
Following Hu's protocol, the addition of *m*-CPBA was carried out at -10 °C and the reaction left at room temperature overnight (Scheme 181). After work-up, the

product **266** was not further purified, as epoxides derived from tetrahydropyridines are known for their instability on silica. The crude product was used in the next step, namely the epoxide ring opening. The stereochemistry of the epoxide **266** at C5 and C6 has been established by additional experiments and is discussed later.



Scheme 181

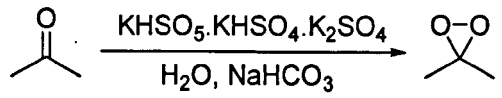
Once the epoxy-piperidine had been synthesised, we could then focus on the ring opening, using the same conditions as those used earlier with bicycle **247**. Influenced by Burgess' work[135] and the promising results obtained in earlier studies, we decided to employ $BF_3.OEt_2$ as a Lewis acid. The conditions were deemed successful as the allylated-piperidine **267** was obtained in a good yield (Scheme 182).



Scheme 182

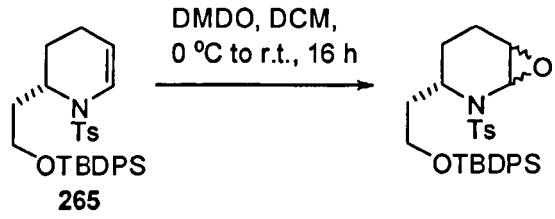
6.1.2.DMDO

Another epoxidation method was also investigated: DMDO. First, a solution of DMDO was synthesised using acetone and oxone[136] (Scheme 183).



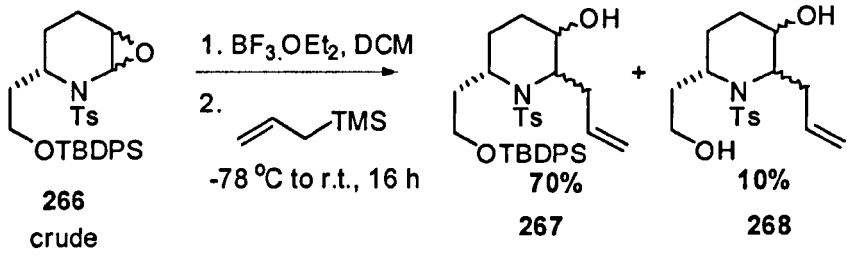
Scheme 183

This solution was added to a solution of compound **265** in dichloromethane at low temperature (Scheme 184). For the same reason as above, the crude product was used directly in the subsequent epoxide ring opening reaction.



Scheme 184

For the allylation reaction, we applied the same conditions as earlier and the corresponding allylated-piperidine was also obtained in a good yield (Scheme 185).

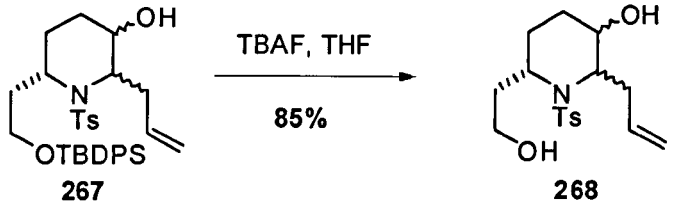


Scheme 185

Formation of the desilylated alcohol **268** was also noticed in small quantities. The amount of desilylated product was shown to increase when a large excess of Lewis acid was used. However, decreasing the amount of Lewis acid from 4 equivalents to 2 equivalents had no effect on the efficiency of the reaction. The

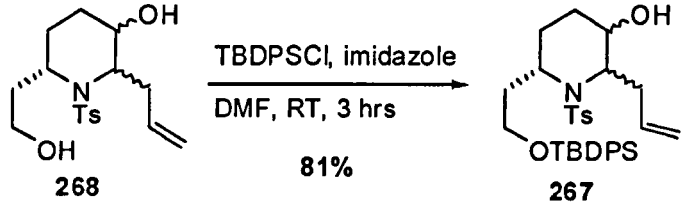
use of another Lewis acid such as $TiCl_4$ resulted in the formation of more desilylated alcohol.

To confirm that the desilylated product **268** formed during the allylation reaction came from the deprotection of compound **267**, this was submitted to standard desilylation conditions (TBAF in THF) and the product obtained was identical to that characterised during the allylation reaction (Scheme 186).



Scheme 186

The formation of this desilylated product was not a main issue since we were able to resubmit **268** to the protection conditions, following Robertson's protocol[137], and to selectively protect the primary alcohol (Scheme 187).



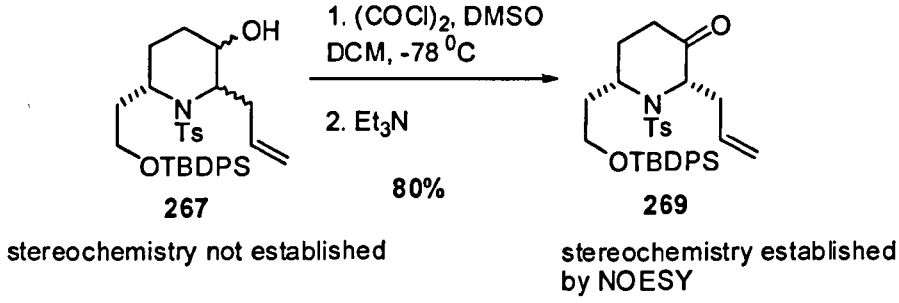
Scheme 187

The order of addition the Lewis acid and allylsilane had a slight influence on the efficiency of the reaction: the reaction was much cleaner when we first added the Lewis acid to a solution of substrate in DCM, left the reaction stir for 10-15 min at -78 °C and then added the nucleophile at the same temperature.

6.2.Investigation on the stereoselectivity of the allylation reaction

With regard to the stereoselectivity of the epoxidation and/or the allylation, we noticed that we only obtained one diastereoisomer in each case, and the same isomer was observed when we used the epoxide generated from DMDO and the one made with *m*-CPBA, suggesting that we formed only one and identical epoxide with both methods.

To clear things up, we decided to carry out additional experiments. First, we oxidised the free secondary alcohol in compound **267** resulting from the opening of the epoxide **266**, using Swern conditions (Scheme 188).



267

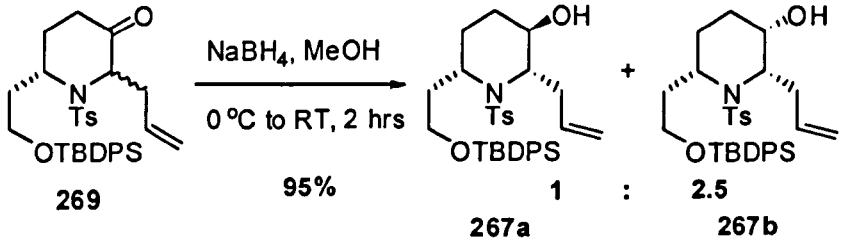
stereochemistry not established

269

stereochemistry established by NOESY

Scheme 188

With the 5-piperidinone **269** in hand, we decided to submit it to reduction conditions[138], thinking that we would get the 2 diastereoisomers in C5 position and that we would be able to separate them (Scheme 189).



269

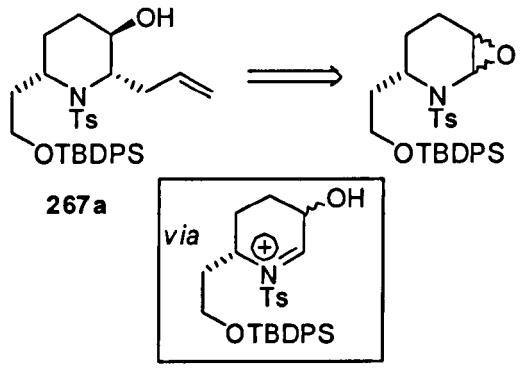
1 : 2.5

267a **267b**

Scheme 189

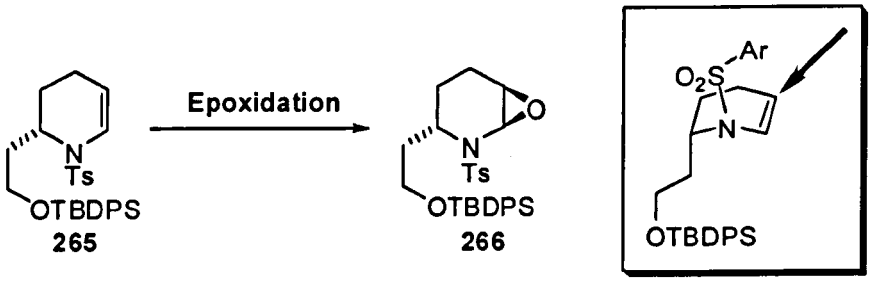
As envisaged, the 2 diastereoisomers were formed in a 2.5 to 1 ratio in favour of compound **267b**. The diastereoisomers were partially separated and subsequently characterized by NOESY experiment to identify the stereochemistry at C5 and C6 for both compounds **267a** and **267b**. The product made during the epoxidation and the allylation was revealed to be compound **267a**. This result allowed us to set a model for the epoxidation and the nucleophilic addition, which could be used to rationalise the stereoselectivity of these reactions.

As discussed, the product **267a** after allylation has an *exo*-hydroxyl group at the C5 position *trans* to the groups at C2 and C6. Since the nucleophilic addition has no effect on the stereochemistry of the group at C6, the stereochemistry of the group in C5 must have been set during the epoxidation (Scheme 190).



Scheme 190

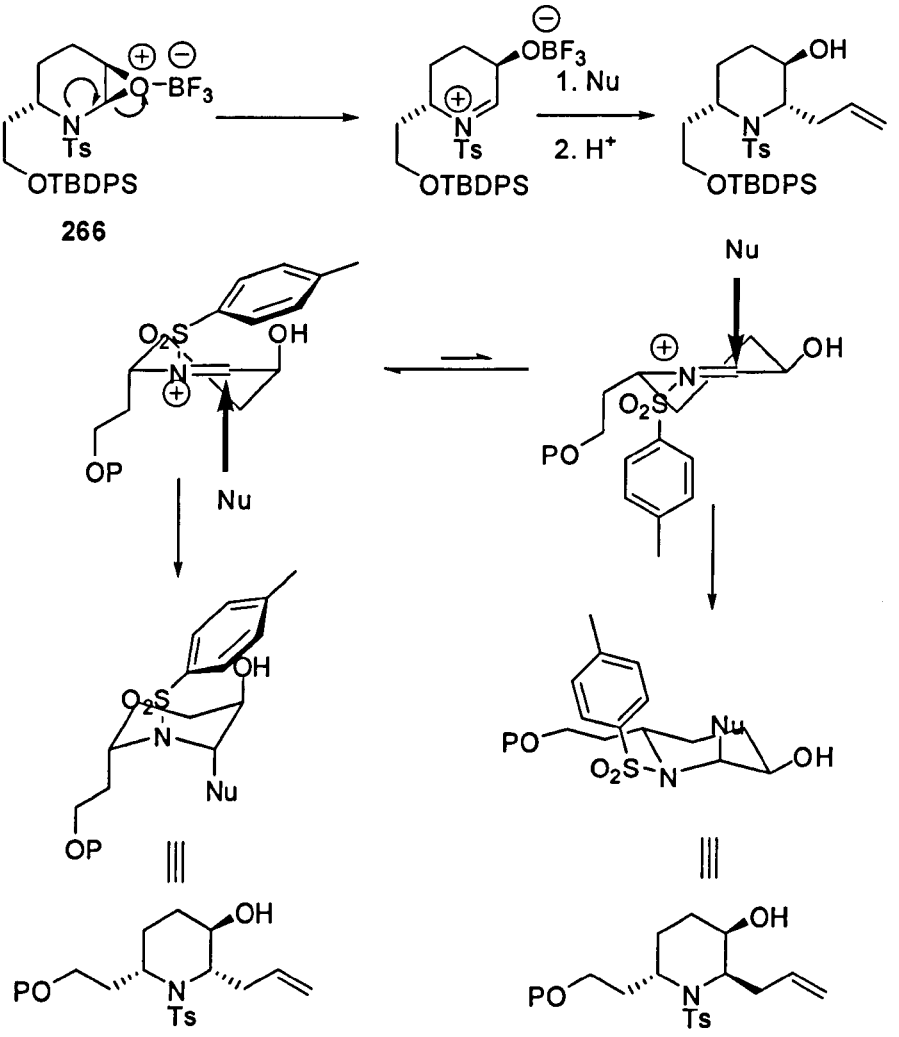
The explanation for the stereoselectivity of the reaction is highlighted in Scheme 191.



Scheme 191

The *exo*-hydroxyl group at C5 suggested epoxidation takes place at the more open face of the alkene with the C2 substituent in the more favoured axial position.

As highlighted earlier in this chapter, the allylation on piperidine **266** goes *via* an iminium intermediate and this proceed *via* a chair-like transition state (and not a twist boat-like transition state) (Scheme 192).

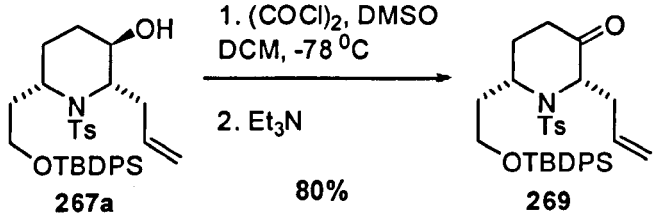


Scheme 192

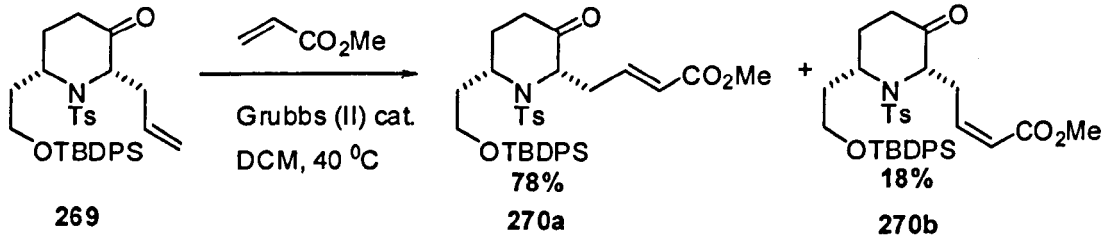
Once again, the preference for an axial group at C2 favoured the pathway on the left hand side and leads to the *cis* product, which was confirmed by the NOESY and COSY experiments.

To avoid using the expensive Grubbs'catalyst for the cross-metathesis, the allylation step was performed directly with diene **250** as a nucleophile. But, unlike the reaction carried out with bicycle **247**, we were unable to obtain the desired product, as the reaction led to an unidentified, complex mixture. The synthesis was subsequently continued on the 2,5,6-substituted piperidine **267a**.

After carrying out Swern oxidation on **267a**, leading to piperidine **269** in a good yield (Scheme 193), **269** underwent a cross-metathesis using methyl acrylate and Grubbs' second generation catalyst (Scheme 194). The reaction using the first generation catalyst afforded lower yields[139].



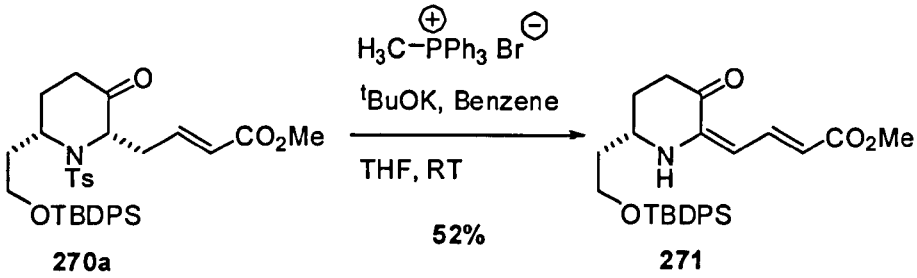
Scheme 193



Scheme 194

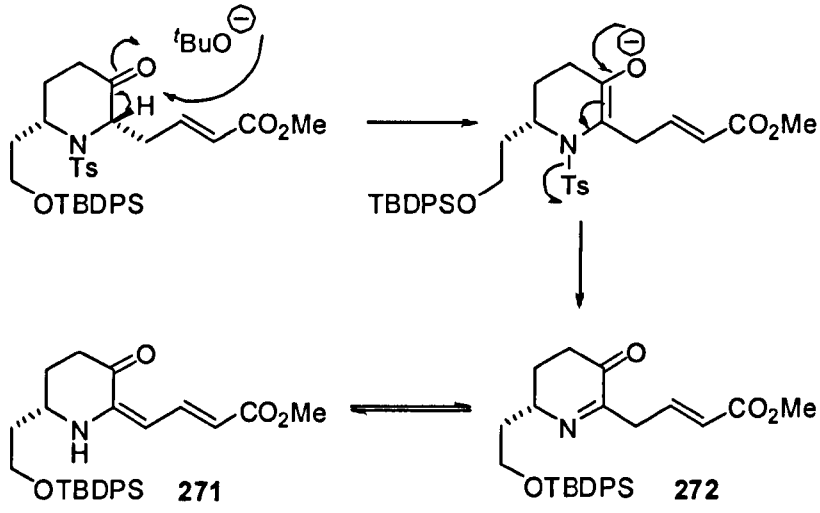
The two separable isomers *trans* and *cis*, **270b** and **270a**, were obtained in good yield, with the *trans* diastereoisomer **270a** being the major product.

We then could continue with the envisaged strategy towards the natural product. To install the *exo* double bond at the C5 position, it was initially believed that a Wittig reaction on piperidine **270a** could methylenate the carbonyl group, leading to the desired compound. However, when piperidine **270a** was submitted to the Wittig conditions[140], the main product that formed during the reaction was the free amine piperidine **271** (Scheme 195).



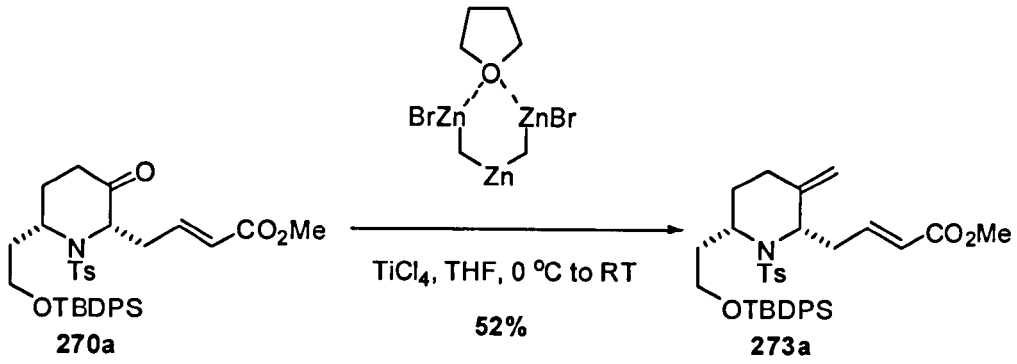
Scheme 195

The formation of this compound is attributed to a deprotonation at the α position of the nitrogen; therefore eliminating the tosyl group to give the imine **272**. Tautomerisation then yields the most stable enamine **271** (Scheme 196).



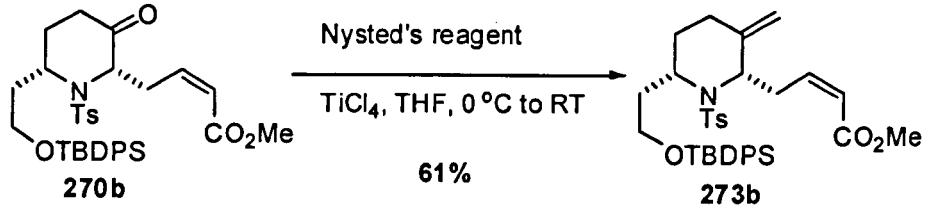
Scheme 196

Even though this method was interesting and represented an efficient way to remove the tosyl group, it led to the loss of the stereocenter in α position of the nitrogen. Therefore, another method for the methylenation of carbonyl groups was sought after. Another obvious strategy was to use Nysted's reagent[141]. The methylenation was carried out with our two isomers **270a** and **270b** to successfully obtain the desired piperidines **273a** and **273b** with the *exo* double bond (Schemes 197 and 198). The yields were moderate but some starting material was recovered in both cases.



270a 273a

Scheme 197



270b 273b

Scheme 198

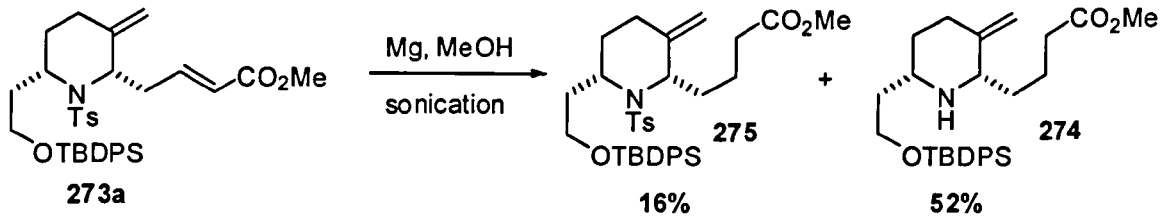
The synthesis led to the 2,5,6-substituted piperidines **273a** and **273b**, overcoming some problems along the way to allow inexpensive, yet efficient chemistry to be employed.

6.3.Tosyl deprotection

The tosyl deprotection step, which had proven to be troublesome in the previous synthesis, was the next step to be encountered. Although previously deemed to be challenging, it was decided to use the same method as employed earlier (i.e. magnesium in methanol).

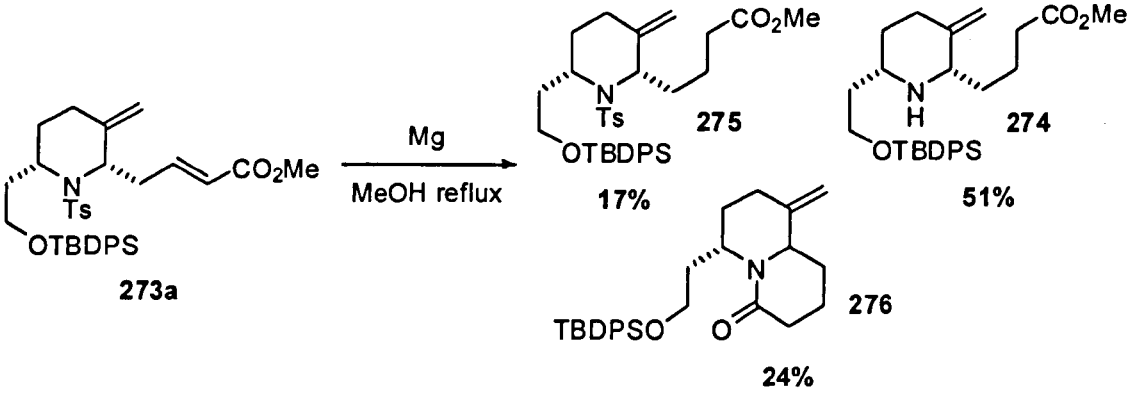
Initially, our investigations was based on the work previously done by Bäckvall on the synthesis of ferruginine[142], where magnesium was used in methanol with ultrasound to free his amine from the tosyl group. These conditions were applied to our piperidine **273a** (Scheme 199); adding powdered magnesium to a solution of **273a** in methanol and the resulting suspension was sonicated at room temperature for 40 minutes. Additional powdered magnesium was then added and sonicated for a further 30 min. Formation of the deprotected piperidine **274** was

observed in a moderately good yield. The hydrogenated ester **275** was also obtained but the corresponding lactam could not be isolated.



Scheme 199

Although successful, another method was developed to improve the synthetic protocol. Magnesium turnings were flame dried and subsequently methanol (1 mL) was added, followed by dropwise addition of a solution of the ester **273a** in methanol (Scheme 200). The solution was left stirring for 16 hours. Additional magnesium was then added and the reaction mixture was heated at reflux for 3 hours. With this modified method, the free amine **274**, the hydrogenated ester **275** and the corresponding lactam **276** were all isolated.



Scheme 200

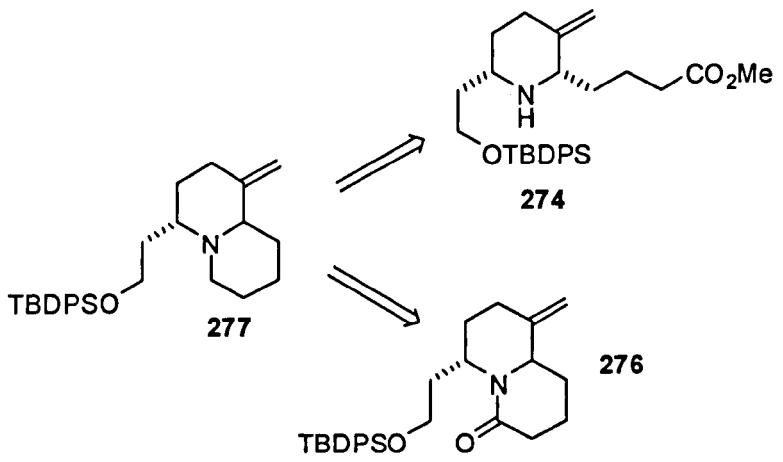
An interesting point to note was that these conditions were successful in deprotecting piperidine **273a** and affording the desired lactam **276**, whereas they were unsuccessful when applied to piperidine **249**, which has a similar structure. The only difference between the two methods is that the successful reaction was done under reflux on a larger scale. Bringing the reaction to reflux for few hours

appeared to help the reaction to occur, especially for the formation of the lactam. The reaction appeared to be more efficient and easier to run, particularly for the isolation and the purification of the different compounds when performed on a larger scale. Work done by Lisa Pattenden in the group on the desulfonylation of piperidines led to the same conclusions[143].

6.4.Quinolizidine ring formation

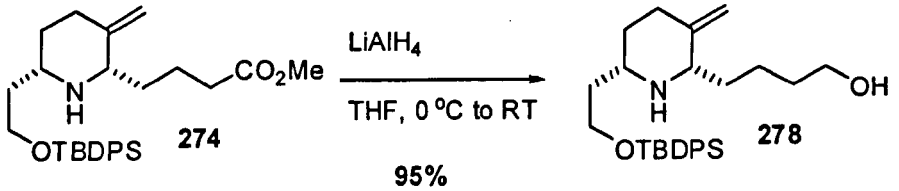
We envisaged that two routes were viable to obtain the bicycle **277** (Scheme 201):

- Starting from deprotected piperidine **274**, ester reduction and alkylation should lead us to the desired bicycle **277**;
- Starting from lactam **276**, a simple reduction should lead to **277**.



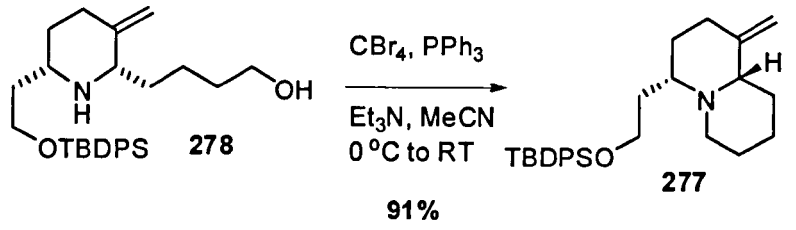
Scheme 201

Accordingly, piperidine **274** was subjected to LAH reduction to provide the corresponding alcohol **278** in excellent yield (Scheme 202).



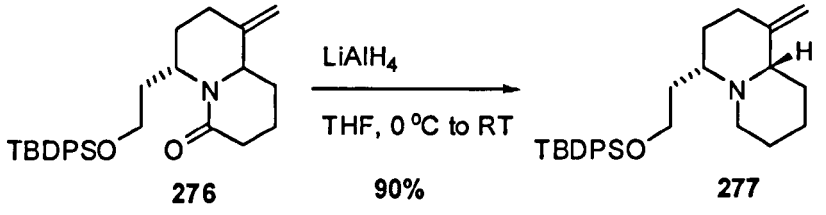
Scheme 202

Cyclisation of **278** using CBr_4-PPh_3 conditions proceeded without difficulty, offering bicycle **277** (Scheme 203).



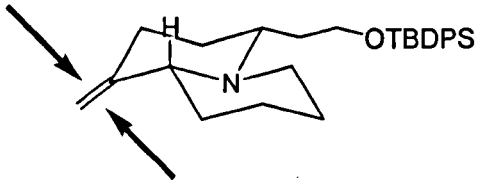
Scheme 203

Bicycle **277** was also obtained by $LiAlH_4$-reduction in a very good yield[144] (Scheme 204).



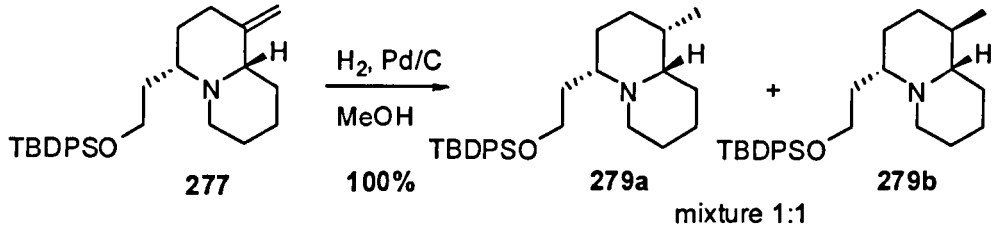
Scheme 204

The next part was the final challenging step of the total synthesis, namely the diastereoselective reduction of the *exo* double bond (Scheme 205). With only few milligrams of bicycle **277** to work with, various conditions could not be screened to optimise the hydrogenation. As a result, the most commonly used method, palladium on charcoal in methanol[145], was employed.



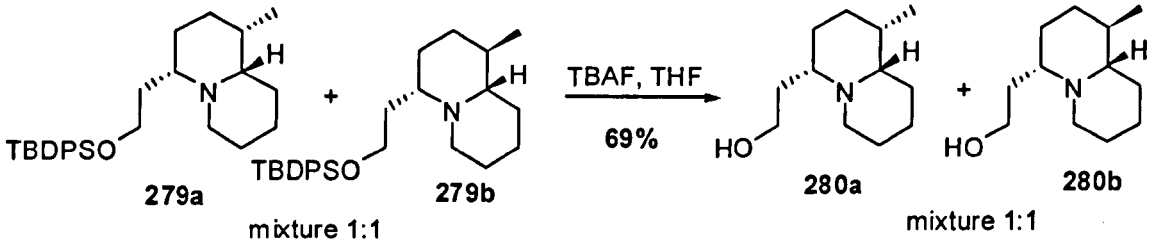
Scheme 205

Unfotunately, hydrogenation of bicycle **277** gave a 1:1 mixture of the two diastereoisomers **279a** and **279b** in quantitative yield, which were unable to be separated by column chromatography (Scheme 206).



Scheme 206

The mixture of both diastereoisomers was, however, submitted to TBAF-deprotection, offering an inseparable mixture of the two piperidines in a good yield (Scheme 207). The mass balance after column chromatography was not ideal which is attributed to the small scale of the reaction, with a very polar product, which increased the risk of loss of material.



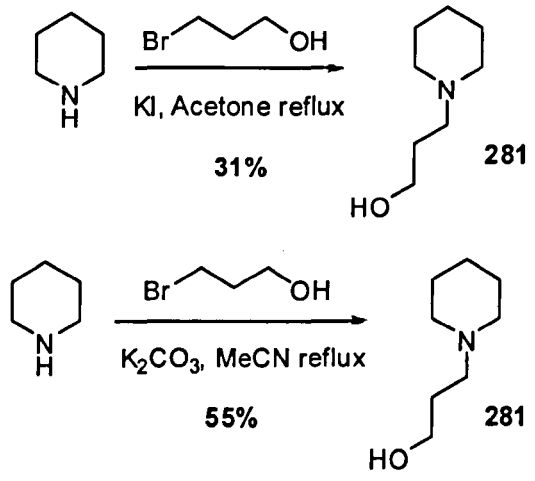
Scheme 207

6.5.Investigations on the last step towards the natural product

After this stage, only 10 mg of product had been isolated with only two steps remaining to reach the natural product quinolizidine alkaloid (-)217A and its diastereoisomer. The sequence was theoretically simple and consisted of oxidation of the alcohol followed by olefination, using either Wittig conditions or Yamamoto's method[95, 146].

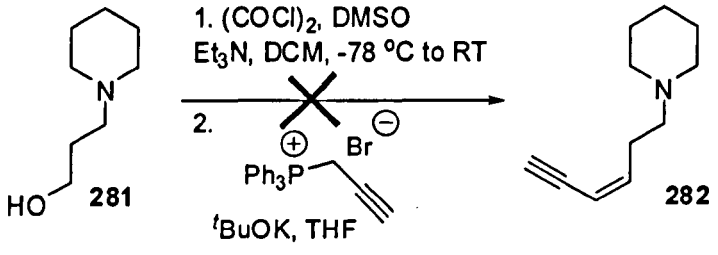
6.5.1.Model substrate

A model substrate was used for the remaining sequence in an attempt to optimise reaction conditions before using the quinolizidine intermediates **280** (**a** and **b**). The structure of the model substrate had to reflect that of our key intermediate. The first choice for the model substrate was 3-piperidin-1-yl-propan-1-ol **281**, which was readily available from piperidine and 3-propan-1-ol[147, 148] (Scheme 208).



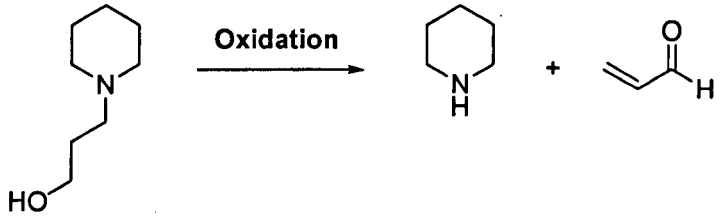
Scheme 208

Initially, the oxidation (Swern) and the olefination using Wittig conditions were trialled in a one-pot synthesis (Scheme 209). Unfortunately, this attempt appeared to be unsuccessful, as desired product **282** was not isolated.



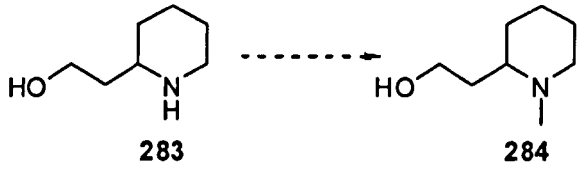
Scheme 209

As a result, both reactions were run separately and attempts to isolate the aldehyde resulting from the oxidation were made. Two methods were tested for the oxidation, Swern's conditions and Dess-Martin's reagent. Neither method was successful: a side reaction appeared to occur, preventing isolation of the aldehyde. Specifically, unusual peaks in the ^{1}H NMR spectrum were observed at around 5.5-6 ppm, potentially due to vinyl protons, but no peak appeared at 10-11 ppm, indicating that the aldehyde had not formed. A potential reason for this is that the product undergoes β-elimination (Scheme 210).



Scheme 210

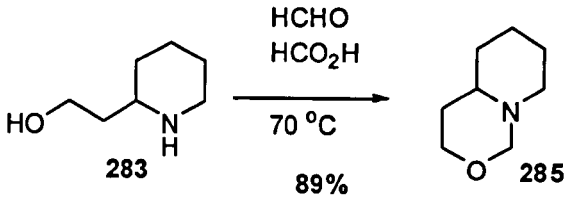
Having been unsuccessful with model substrate **281**, another alternative was envisaged, starting from commercially available 2-piperidin-2-yl-ethanol **283** (Scheme 211). Substrate **284** could be synthesised *via* a theoretically simple reductive amination, and subsequently be used as a model substrate to test the conditions for the oxidation and the olefination. Importantly, elimination of the aldehyde would be reversible in this case.



283 **284**

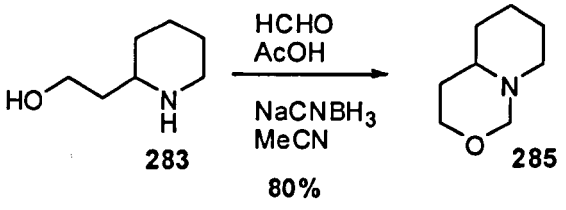
Scheme 211

Inspired by work carried out by Lin and RajanBabu[149], the reductive amination of 2-piperidin-2-yl-ethanol **283** was performed with an unexpected result: only bicycle **285** was obtained instead of the desired piperidine **284** (Scheme 212).



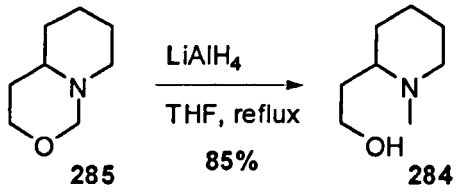
Scheme 212

A stronger reducing agent was added to speed up the reaction, but the same compound **285** was obtained[150] (Scheme 213).



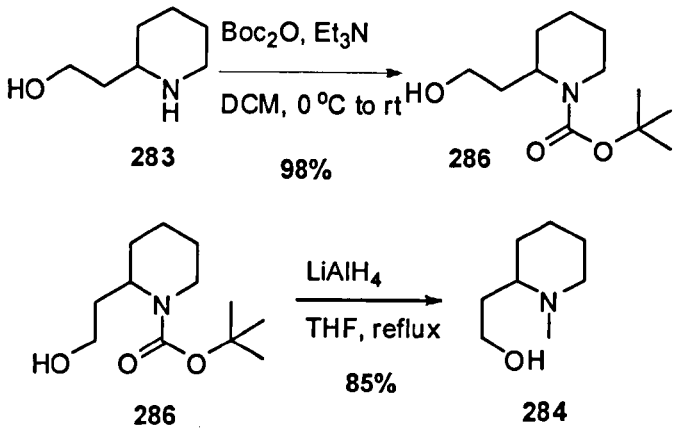
Scheme 213

This result was not a major issue, since it was overcome by submitting the bicycle to a $LiAlH_4$ reduction[151], leading to the desired piperidine **284** (Scheme 214).



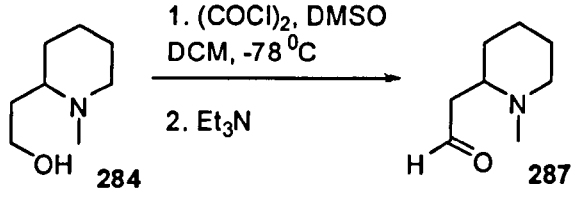
Scheme 214

Work carried out by Rouden and collaborators[152] in 2004 offered another alternative for the synthesis of the desired model substrate: protection of the free amine of compound **283** with a Boc-group following by reducing **28 6** using $LiAlH_4$ (Scheme 215). Indeed, both steps were successful and piperidine **284** was accessed very easily and in large quantities.



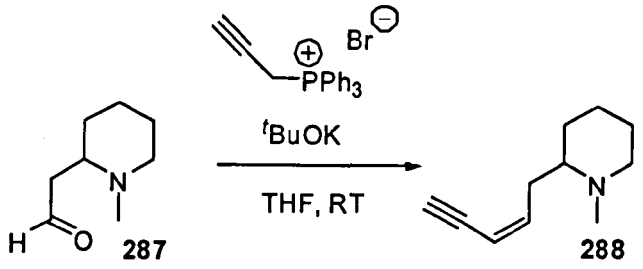
Scheme 215

The new model substrate, piperidine **284**, was subsequently oxidised, using Swern's method (Scheme 216). Following workup, the crude ^{1}H NMR spectrum displayed a broad singlet at 9.8 ppm and a signal at 201 ppm, in the crude ^{13}C NMR spectrum, both characteristic of an aldehyde. The material was not further purified to avoid any decomposition on silica.



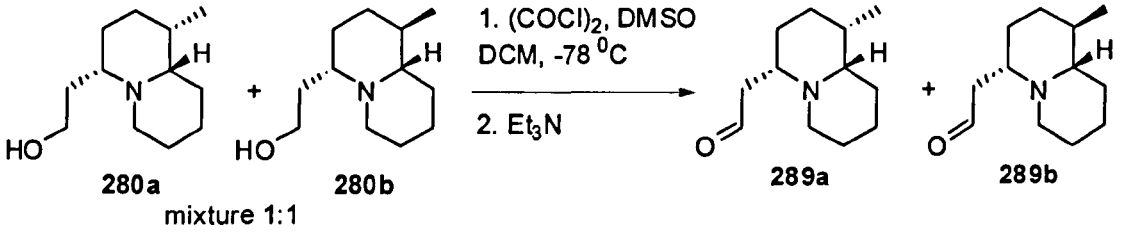
Scheme 216

The crude aldehyde was subjected to the Wittig conditions (Scheme 217). Initial crude ^{1}H NMR studies showed a doublet of triplets at 5.14 ppm, a multiplet at 5.75 ppm and a singlet at 2.23 ppm, potentially matching the 2 vinyl protons and the terminal alkyne proton, respectively. Unfortunately, a clean product could not be isolated following purification by column chromatography, as the product appeared to decompose on silica. However, the 2-step sequence was repeated on a smaller scale and the ^{1}H NMR studies led to the same conclusions: product **288** was formed using these conditions.



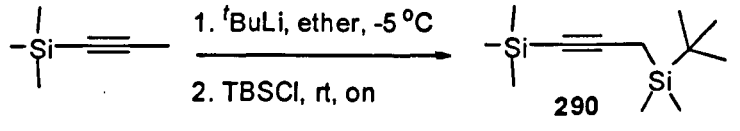
Scheme 217

With proof of concept of the final two steps, bicycles **280** (**a** and **b**) were finally employed and with only 7 mg of the mixture of the 2 diastereoisomers, there was only enough material for one attempt (Scheme 218). Unfortunately, as the reaction was performed on such a small scale, the NMR data were not very encouraging after oxidation. Potential peaks between 9 and 11 ppm, which would suggest that we formed the two aldehydes, were not clearly visible.



Scheme 218

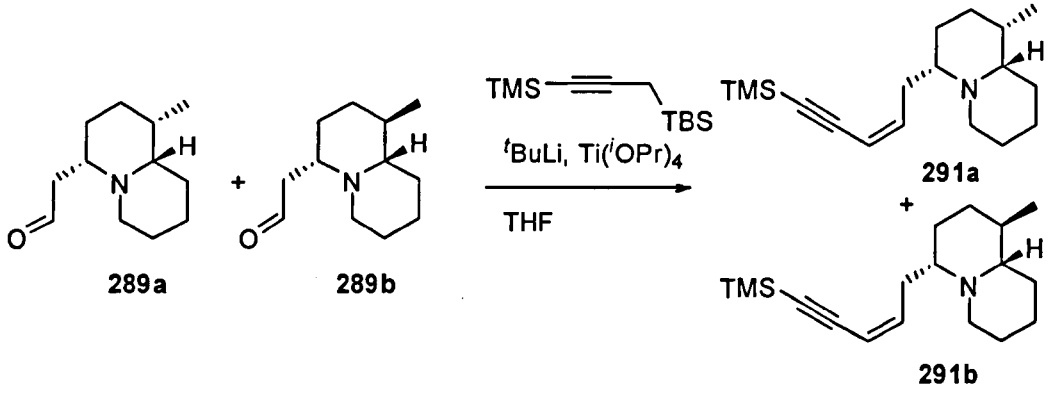
However, the crude products **289a** and **289b** from the oxidation reaction were subjected to the olefination conditions. The conditions developed by Yamamoto[95, 146] were employed, since this process was known and was previously used efficiently during previous syntheses of quinolizidine alkaloid (-)217A by Panek[96] and Pearson[89]. First, the silyl alkyne **290** had to be synthesised, which would then react with the aldehyde to form the desired enyne (Scheme 219).



50%

Scheme 219

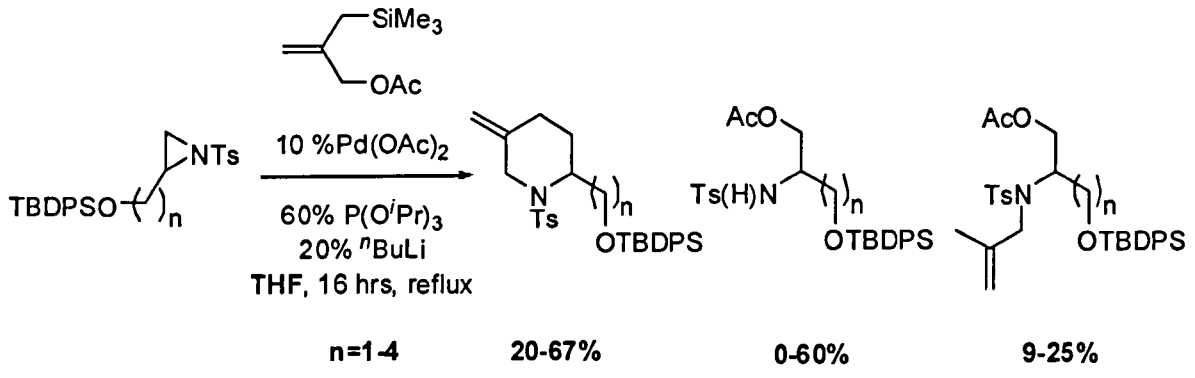
Finally, we reacted silyl alkyne **290** with the crude products from the oxidation reaction, in an attempt to obtain the silyl derivative of quinolizidine alkaloid (-)-217A and its epimer (Scheme 220). Unfortunately, after a careful column chromatography, the desired products **291a** and **291b** could not be isolated with neither the NMR data nor the GC/MS analysis being conclusive. Neither of them gave us the necessary evidence that we made the desired natural product or even its epimer.



Scheme 220

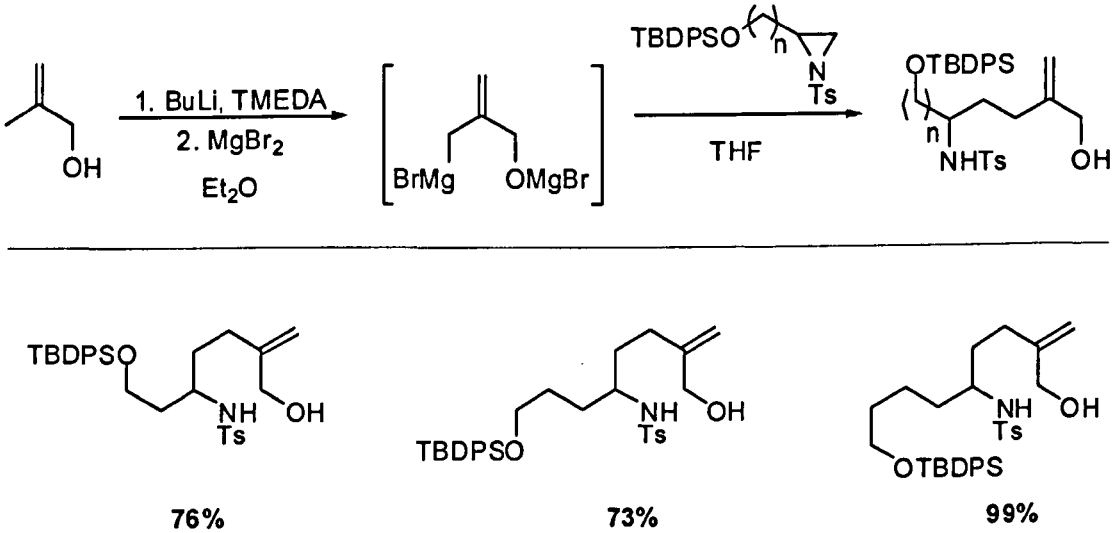
Conclusions

The very effective route towards functionalised, enantiomerically pure piperidines previously developed in the group has been investigated further. The [3+3] cycloaddition has been applied to a range of substituted aziridines, namely the silylether substituted aziridines (Scheme 221). The reaction has been proven to be a challenging and difficult to reproduce, however good results can be obtained under rigorous conditions.

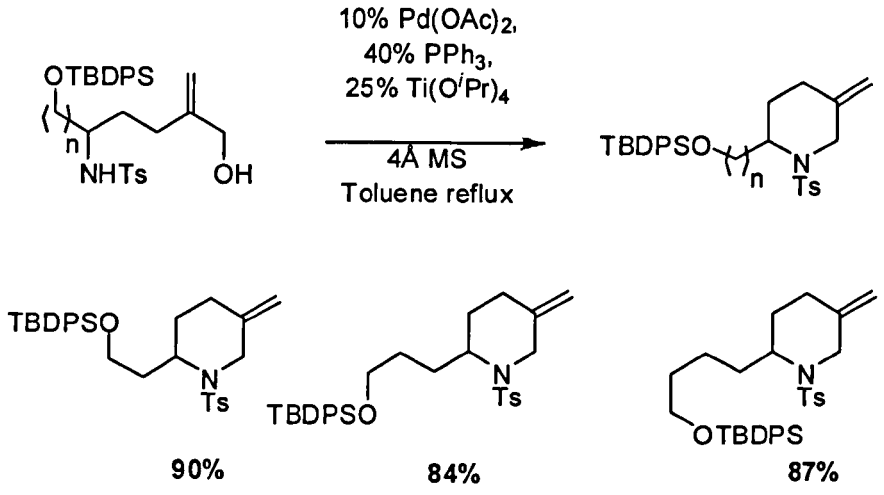


Scheme 221

The Grignard route from aziridines to piperidines, which has been developed in the group, was found to be a good alternative to the cycloaddition reaction for this particularly challenging substrate (Schemes 222 and 223).

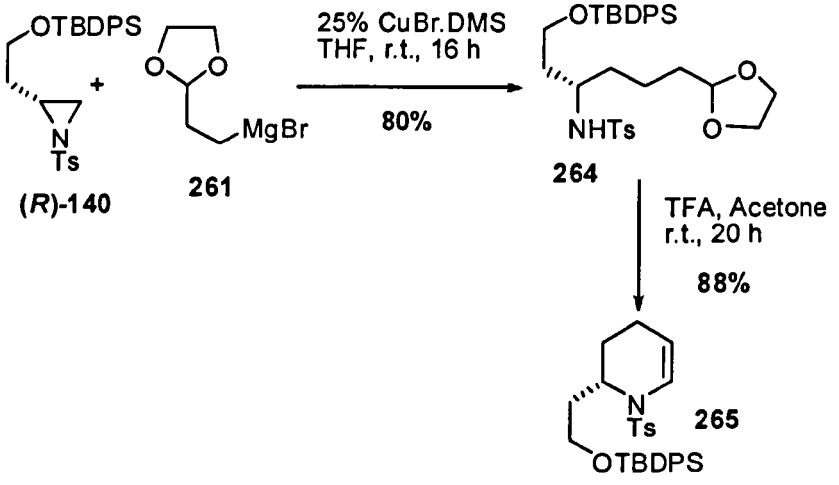


Scheme 222



Scheme 223

The addition of the Büchi Grignard reagent **261** to enantiopure silyl ether substituted aziridine **(*R*)-140** was also investigated and afforded the corresponding acetal **264** in good yield. Subsequently, the corresponding tetrahydropyridine **265** was obtained in excellent yield, using TFA for the acid-promoted cyclisation (Scheme 224).



Scheme 224

As shown before, the [3+3] cycloaddition route is an effective way to synthesise natural products with a piperidine core, therefore the applicability of the three

different [3+3] annelation strategies developed in the group was highlighted by the attempts to synthesise quinolizidine alkaloid (-)217A. Unfortunately, due to the complexity of the route and a lack of material for the last two steps, the synthesis could not be completed. However, it is envisaged that with more time and material, the desired natural product could be obtained by similar methodology described herein.

Chapter V - Experimental

1.General Considerations

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen. Flash chromatography was performed on silica gel (Davisil) according to the method of W.C. Still[153]. The solvent system used was a gradient of petroleum ether, increasing in polarity to ethyl acetate. Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) which were developed using standard visualizing agents: Ultra Violet light or potassium permanganate

^1H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or AMX-400 (400 MHz) or Av1-250 instruments or AMX-400 or AV1-400 instruments supported by an Aspect 3000 data system, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (*J*) in Hz, and assignment.

^{13}C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz) or AMX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ77.0 ppm).

Infrared (FTIR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Samples were recorded as thin films from a DCM solution using sodium chloride plates.

Low resolution mass spectra were recorded on Micromass Autospec, operating in E.I., C.I. or FAB mode; or a Perkin-Elmer Turbomass Benchtop GC-MS operating in either E.I. or C.I mode. High-resolution mass spectra (HRMS)

recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES^+) or a MicroMass Prospec operating in either FAB (FAB^+), EI (EI^+) or CI (CI^+) mode.

Elemental microanalysis performed using a Perkin-Elmer 2400 CHNS / O Series II Elemental Analyser.

Melting points, performed on recrystallised solids, were recorded on a Gallenkamp melting point apparatus and are uncorrected.

2.Purification of solvents and reagents

All solvents and reagents were purified using standard laboratory techniques according to methods published in "Purification of Laboratory Chemicals" by Perrin, Armarego, and Perrin (Pergamon Press, 1966).

Solvents and reagents were used either as received from commercial suppliers or, when necessary, purified in accordance with standard procedures as outlined below.

Grubb's Solvent System

The departmental dry solvent is a Grubbs type one manufactured by Innovative Technology. In an individual solvent line the untreated solvent is contained within a lined metal reservoir and, using nitrogen gas pressure, forced through a pair of metal columns each containing either activated alumina or molecular sieve. If oxygen removal is also required one of the cylinders contains a catalyst instead. The water and oxygen removal occurs as the solvent passes over the drying agents. The dried solvent is then dispensed to a suitable collection vessel under vacuum via a Schlenk line system. Water content of the solvents is routinely monitored by coulometric Karl Fischer titration.

Acetone was distilled from Drierite.

Acetonitrile was collected from Grubb's solvent system.

Dichloromethane was freshly distilled from calcium hydride immediately prior to use.

Diethyl ether (anhydrous grade) was distilled from sodium metal / benzophenone ketyl immediately prior to use.

Diisopropylamine was distilled from potassium hydroxide and stored over 4Å molecular sieves.

DME was distilled from calcium sulphate immediately prior to use.

DMSO was distilled from calcium hydride immediately prior to use.

Methanol was distilled from Magnesium turnings immediately prior to use.

N,N-Dimethylformamide was distilled under reduced pressure from potassium hydroxide and stored over 4 Å molecular sieves.

Petroleum ether refers to 40-60 °C petroleum distillates, which was distilled prior to use.

Tetrahydrofuran (anhydrous grade) was distilled from sodium metal / benzophenone ketyl immediately prior to use.

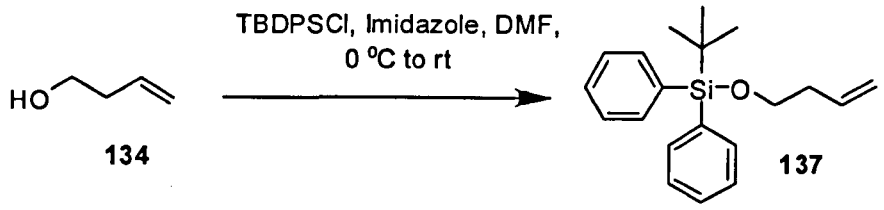
Toluene was freshly distilled from calcium hydride immediately prior to use.

Triethylamine was distilled from potassium hydroxide and stored over 4 Å molecular sieves.

Triisopropylphosphite was distilled from sodium under reduced pressure.

3.Aziridination

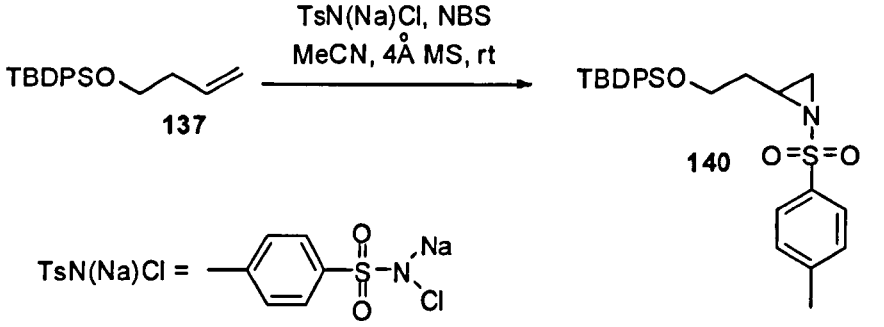
Synthesis of 4-(*tert*-butyldiphenylsiloxy)-1-butene 137[154]



134 137

3-Buten-1-ol **134** (0.5 g, 6.93 mmol, 1.0 eq), was dissolved in distilled dimethylformamide (10 mL) and the solution was cooled to 0 °C. *Tert*-butylchlorodiphenylsilane (2.25 mL, 8.66 mmol, 1.25 eq) and imidazole (1.41 g, 20.79 mmol, 3.0 eq) were added. The reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was partitioned between diethyl ether and water and the aqueous phase was extracted with Et_2O, dried over magnesium sulphate and concentrated by rotary evaporation to give a colourless liquid. Purification of the resulting liquid by silica gel chromatography (20/1, petroleum/EtOAc) provided 4-(*tert*-butyldiphenylsiloxy)-1-butene **137** (2.0 g, 93%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.06 (9H, s, C(CH_3)$_3$), 2.33 (2H, dtt, *J*=1.5, 6.5, 6.5 Hz, CH_2-C=), 3.72 (2H, t, *J*=6.5 Hz, CH_2-O), 4.98-5.06 (2H, m, H_2C=), 5.74-5.88 (1H, m, C=C-*H*), 7.31-7.47 (6H, m, Ar*H*), 7.67-7.79 (4H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.3, 26.9, 37.2, 63.5, 116.4, 127.6, 129.6, 134.0, 135.5, 135.6.

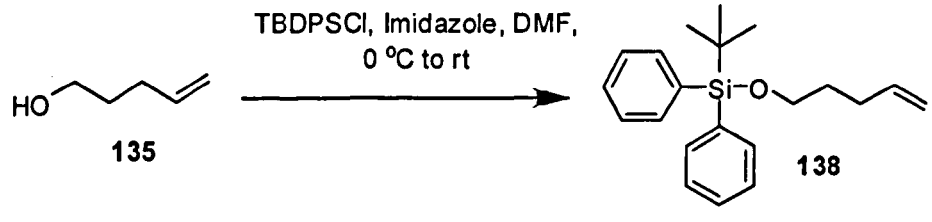
Synthesis of 3-(*tert*-butyl-diphenyl-silanyloxyethyl)-1-(toluene-4-sulfonyl)-aziridine 140



137 140

A 50 ml round-bottomed-flask was charged with 4Å molecular sieves and flame dried. A solution of 4-(*tert*-butyldiphenylsiloxy)-1-butene **137** (500 mg, 1.61 mmol, 1.0 eq) in acetonitrile (10 mL) was transferred *via* cannula. Then chloramine-T (367 mg, 1.61 mmol, 1.0 eq) and N-bromosuccinimide (57 mg, 0.32 mmol, 0.2 eq) were added. The resulting solution was stirred at room temperature for 48 h. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over magnesium sulphate, concentrated in vacuo to give a yellow oil. Purification of the resulting liquid by silica gel chromatography (10/1, petroleum/EtOAc) provided 3-(*tert*-butyl-diphenyl-silanyloxyethyl)-1-(toluene-4-sulfonyl)-aziridine **140** (100 mg, 13%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.96 (9H, s, C(CH_3)$_3$), 1.42-1.74 (2H, m, CH_2), 2.05 (1H, d, *J*=4.5 Hz, CH*H* aziridine), 2.32 (3H, s, ArCH_3), 2.60 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.76-2.88 (1H, m, C*H* aziridine), 3.49 (2H, dd, *J*=5.5, 7.0 Hz, CH_2OTBDPS), 7.18 (2H, d, *J*=8.0 Hz, Ar*H*), 7.25-7.41 (6H, m, Ar*H*), 7.48-7.57 (4H, m, Ar*H*), 7.74 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.1, 21.6, 26.8, 33.5, 34.4, 38.0, 61.2, 127.7, 128.0, 129.6, 129.7, 133.5, 135.5, 142.3, 144.4. **FTIR (thin film)**: 3071 (w), 2930 (m), 2857 (m), 1598 (w), 1472 (w), 1428 (m), 1326 (s), 1164 (s), 1093 (s) cm^{-1}. ***m/z* (TOF ES)**: 502 (MNa^+). **HRMS (TOF ES) calcd. for $C_{27}H_{33}NO_3NaSiS$ (MNa^+)**: 502.1848. Found: 502.1870.

Synthesis of 5-(*tert*-butyldiphenylsiloxy)-1-pentene 138[155]

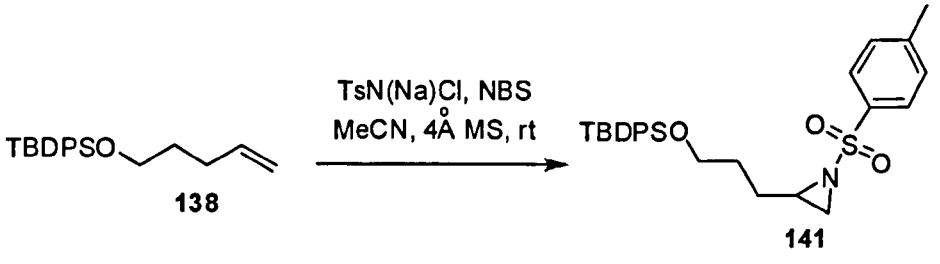


135 **138**

5-Penten-1-ol **135** (1.0 g, 11.61 mmol, 1.0 eq), was dissolved in distilled dimethylformamide (17 mL) and the solution was cooled to 0 °C. *Tert*-butylchlorodiphenylsilane (3.8 mL, 14.51 mmol, 1.25 eq) and imidazole (2.37 g, 34.83 mmol, 3.0 eq) were added. The reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was partitioned between

diethyl ether and water and the aqueous phase was extracted with Et_2O, dried over magnesium sulphate and concentrated by rotary evaporation to give a colourless liquid. Purification of the resulting liquid by silica gel chromatography (20/1, petroleum/EtOAc) provided 5-(*tert*-butyldiphenylsiloxy)-1-pentene **138** (3.83 g, 99%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.03 (s, 9H, C(CH_3)$_3$), 1.64 (tt, 2H, *J*=6.5, 7.5 Hz, CH_2), 2.13 (dt, 2H, *J*=7.0, 7.5 Hz, CH_2-C=), 3.65 (t, 2H, *J*=6.5 Hz, CH_2-O), 4.90 (dd, 1H, *J*=1.5, 10.0 Hz, CH*H*-C=), 4.98 (dd, 1H, *J*=1.5, 15.5 Hz, C*H*H-C=), 5.78 (ddt, 1H, *J*=7.0, 10.0, 15.5 Hz, C=C-*H*), 7.42-7.32 (m, 6H, Ar*H*), 7.66-7.63 (m, 4H, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 26.9, 30.0, 31.8, 63.3, 114.5, 127.6, 129.5, 134.1, 135.6, 138.6.

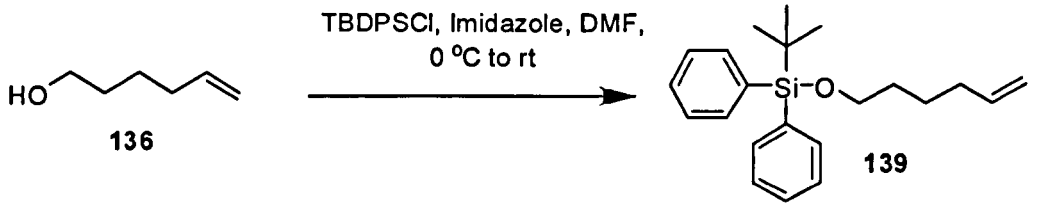
Synthesis of 4-(*tert*-butyl-diphenyl-silanyloxypropyl)-1-(toluene-4-sulfonyl)-aziridine 141



A 50 ml round-bottomed-flask was charged with 4Å molecular sieves and flame dried. A solution of 5-(*tert*-butyldiphenylsiloxy)-1-pentene **138** (1.51 g, 4.66 mmol, 1.0 eq) in acetonitrile (73 mL) were transferred *via* cannula. Then chloramine-T (1.06 g, 4.66 mmol, 1.0 eq) and N-bromosuccinimide (166 mg, 0.93 mmol, 0.2 eq) were added. The resulting solution was stirred at room temperature for 48 h. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over magnesium sulphate, concentrated in vacuo to give a yellow oil. Purification of the resulting liquid by silica gel chromatography (10/1, petroleum/EtOAc) provided 4-(*tert*-butyl-diphenyl-silanyloxypropyl)-1-(toluene-4-sulfonyl)-aziridine **141** (572 mg, 25%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.01 (9H, s, C(CH_3)$_3$), 1.33-1.58 (2H, m, CH_2), 1.63-1.78 (2H, m, CH_2), 2.06 (1H, d, *J*=4.5 Hz, CH*H* aziridine), 2.42 (3H, s, ArCH_3), 2.62 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.66-2.78 (1H, m, C*H* aziridine), 3.57 (2H, t, *J*=6.0 Hz,

C*H*$_2$OTBDPS), 7.30 (2H, d, *J*=8.0 Hz, Ar*H*), 7.35-7.43 (6H, m, Ar*H*), 7.56-7.65 (4H, m, Ar*H*), 7.80 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, CDCl$_3$)**: δ19.1, 21.6, 26.8, 27.8, 29.6, 38.0, 40.2, 62.9, 127.6, 128.0, 129.6, 129.8, 133.4, 135.5, 143.8, 144.3. **FTIR (thin film)**: 3059 (w), 2930 (m), 2856 (m), 1598 (w), 1471 (w), 1428 (m), 1325 (s), 1162 (s), 1093 (s) cm^{-1}. ***m/z* (TOF ES)**: 494 (MH$^+$). **HRMS (TOF ES) calcd. for $C_{28}H_{36}NO_3SiS$ (MH$^+$)**: 494.2185. Found: 494.2206.

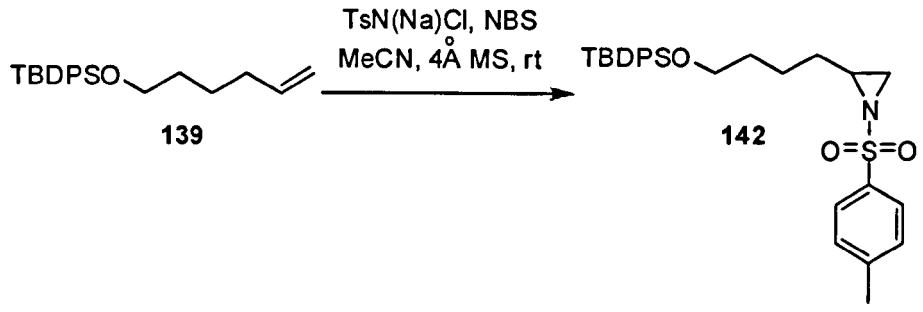
Synthesis of 6-(*tert*-butyldiphenylsiloxy)-1-hexene 139[156]



136 139

6-Hexen-1-ol **136** (2.0 g, 19.97 mmol, 1.0 eq), was dissolved in distilled dimethylformamide (29 mL) and the solution was cooled to 0 °C. *Tert*-butylchlorodiphenylsilane (6.5 mL, 24.96 mmol, 1.25 eq) and imidazole (4.08 g, 59.91 mmol, 3.0 eq) were added. The reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was partitioned between diethyl ether and water and the aqueous phase was extracted with Et_2O, dried over magnesium sulphate and concentrated by rotary evaporation to give a colourless liquid. Purification of the resulting liquid by silica gel chromatography (20/1, petroleum/EtOAc) provided 6-(*tert*-butyldiphenylsiloxy)-1-pentene **139** (6.4 g, 95%). **^{1}H NMR (250 MHz, CDCl$_3$)**: δ1.05 (9H, s, C(C*H*$_3$)$_3$), 1.40-1.63 (4H, m, C*H*$_2$), 2.04 (2H, br d, *J*=7.0 Hz, C*H*$_2$), 3.66 (2H, t, *J*=6.0 Hz, C*H*$_2$-O), 4.90-5.03 (2H, m, C*H*$_2$=C), 5.79 (1H, tdd, *J*=7.0, 10.0, 17.0 Hz, *H*-C=C), 7.33-7.46 (6H, m, Ar*H*), 7.63-7.70 (4H, m, Ar*H*). **^{13}C NMR (62.9 MHz, CDCl$_3$)**: δ19.2, 25.1, 26.9, 32.0, 33.5, 63.8, 114.3, 127.6, 129.5, 134.0, 135.6, 138.9.

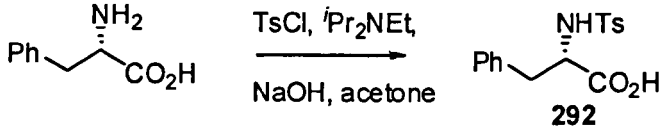
Synthesis of 5-(*tert*-butyl-diphenyl-silanyloxybutyl)-1-(toluene-4-sulfonyl)-aziridine 142



A 50 ml round-bottomed-flask is charged with molecular sieves and flame dried. A solution of 6-(*tert*-butyldiphenylsiloxy)-1-hexene **139** (1 g, 2.95 mmol, 1.0 eq) in acetonitrile (50 mL) was transferred *via* cannula. Then chloramine-T (673 mg, 2.950 mmol, 1.0 eq) and N-bromosuccinimide (105 mg, 0.59 mmol, 0.2 eq) were added. The resulting solution was stirred at room temperature for 48 h. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over magnesium sulphate, concentrated in vacuo to give a yellow oil. Purification of the resulting liquid by silica gel chromatography (10/1, petroleum/EtOAc) provided 5-(*tert*-butyl-diphenyl-silanyloxybutyl)-1-(toluene-4-sulfonyl)-aziridine **142** (420 mg, 48%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.04 (9H, s, C(CH_3)$_3$), 1.22-1.60 (6H, m, CH_2), 2.04 (1H, d, *J*=4.5 Hz, CH*H* aziridine) 2.39 (3H, s, ArCH_3), 2.62 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.66-2.78 (1H, m, C*H* aziridine), 3.57 (2H, t, *J*=6.5 Hz, CH_2OTBDPS), 7.29 (2H, d, *J*=8.0 Hz, Ar*H*), 7.33-7.49 (6H, m, Ar*H*), 7.61-7.69 (4H, m, Ar*H*), 7.81 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.6, 23.1, 26.9, 31.0, 31.9, 39.3, 40.3, 63.4, 127.6, 128.0, 129.6, 129.7, 134.0, 135.5, 143.2, 144.5. **FTIR (thin film)**: 3070 (w), 2932 (m), 2858 (m), 1598 (w), 1472 (w), 1428 (m), 1325 (s), 1163 (s), 1093 (s) cm^{-1}. ***m/z* (TOF ES)**: 508 (MH^+). **HRMS (TOF ES) calcd. for $C_{29}H_{38}NO_3SiS$ (MH^+)**: 508.2342. Found: 508.2333.

4.Amino acid route

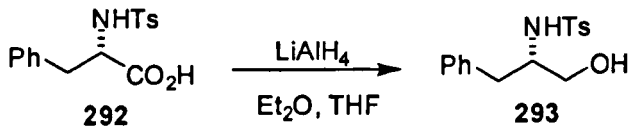
Synthesis of (*S*)-3-phenyl-2-(toluene-4-sulfonylamino)-propionic acid 292[157]



292

To a solution of (*S*)-phenylalanine (5.0 g, 30 mmol, 1.0 eq.) in aqueous 2 M NaOH (15 ml, 30 mmol, 1.0 eq.) at 0 °C, was added 4-toluenesulfonyl chloride (6.0 g, 31 mmol, 1.04 eq.), followed by *N*-ethyldiisopropylamine (5.8 ml, 33 mmol, 1.1 eq.) and acetone (15 ml). The homogeneous yellow mixture obtained was stirred for 6 hours at room temperature. The reaction mixture was washed with 2 portions of Et_2O and the combined organic washings extracted with $NaOH_{aq}$. The combined basic aqueous layers were cooled to 0 °C and acidified (pH 1) by the addition of concentrated hydrochloric acid. The mixture was extracted with ethyl acetate and the combined extracts washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give **292** as a white solid, 8.0 g (86%). **m.p.**=150-151 °C (lit. **m.p.**=158-159 °C)[158] $[\alpha]_D$=-2.1 (c=1.4, acetone), (lit. $[\alpha]_D$=-1.34 (c=10.0, acetone)[158]). **^{1}H NMR (250 MHz $CDCl_3$)**: δ2.38 (3H, s, ArC*H*$_3$), 2.97 (1H, dd, *J*=6.5, 14.0 Hz, C*H*H), 3.09 (1H, dd, *J*=5.0, 14.0 Hz, CH*H*), 4.20 (1H, m, C*H*), 5.15 (1H, d, *J*=8.0 Hz, NH), 5.28 (1H, br s, CO_2*H*), 7.01-7.13 (2H, m, Ar*H*), 7.15-7.34 (5H, m, Ph*H*), 7.57 (2H, d, *J*=8.0 Hz, Ar*H*).

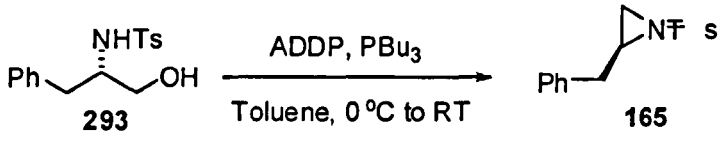
Synthesis of (*S*)-*N*-(1-benzyl-2-hydroxy-ethyl)-4-methyl-benzenesulfonamide 293[159]



292 293

To a stirred suspension of lithium aluminium hydride (1.07 g, 28.30 mmol, 3 eq.) in diethyl ether (70 ml) at room temperature was added a solution of **292** (4.0 g, 14.70 mmol, 1.0 eq.) in 1:1 diethyl ether-tetrahydrofuran (70 ml) dropwise. Upon completion of addition the mixture was heated under reflux for 30 min. The reaction mixture was cooled to 0 °C and water added cautiously, followed by aqueous 1 M NaOH and then water. The resulting colourless suspension was filtered through Celite®, and the filtrate was concentrated under reduced pressure to give **293** as a colourless oil, 2.63 g (92%). The material was carried through to the next step without further purification (see below). **^{1}H NMR (250 MHz $CDCl_3$)**: δ2.06 (1H, br s, OH), 2.41 (3H, s, ArC*H*$_3$), 2.62 (1H, dd, *J*=7.0, 14.0 Hz, C*H*H), 2.78 (1H, dd, *J*=7.0, 14.0 Hz, CH*H*), 3.36-3.70 (3H, m, C*H* + C*H*$_2$O), 4.41 (1H, br s, NH), 6.91-7.02 (2H, m, Ar*H*), 7.10-7.31 (5H, m, Ph*H*), 7.57 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.5, 37.8, 56.6, 63.9, 126.7, 127.0, 128.6, 129.2, 129.7, 136.8, 137.0, 143.3.

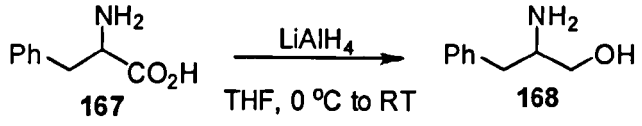
Synthesis of (*S*)-2-benzyl-1-(toluene-4-sulfonyl)-aziridine 165[159]



ADDP (2.66 g, 10.53 mmol, 1.5 eq) was added to a solution of **293** (2.14 g, 7.02 mmol, 1.0 eq) and tributylphosphine (2.80 mL, 11.23 mmol, 1.6 eq) in toluene (66 mL) at 0 °C and the reaction was stirred for 2 h at this temperature, before warming to room temperature overnight. The reaction mixture was then partitioned between Et_2O and water, and the layers were separated. The aqueous layer was extracted with a further 2 portions of Et_2O. The combined organic fractions were dried over $MgSO_4$, concentrated and then purified by flash chromatography (10:1, 40-60 petroleum ether/ethyl acetate) gave **165** as a colourless solid 1.44 g (71%). **m.p.**=91-92 °C (lit. **m.p.**=91-92 °C) **$[\alpha]_D$**=+9.1 (c=1.0, DCM), (lit. **$[\alpha]_D$**=+10.1 (c=1.0, DCM))[59]. **^{1}H NMR (250 MHz $CDCl_3$)**: δ2.16 (1H, d, *J*=4.5 Hz, CH*H*-N), 2.42 (3H, s, ArC*H*$_3$), 2.67 (1H, dd, *J*=7.0, 15.0 Hz, CH*H*Ph), 2.72 (1H, d, *J*=7.0 Hz, C*H*H-N), 2.80 (1H, dd, *J*=5.0, 15.0 Hz,

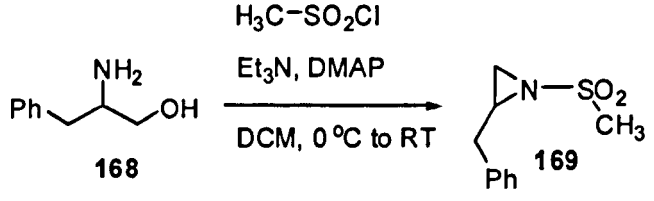
C*H*HPh), 2.89-3.00 (1H, m, C*H*N), 6.99-7.17 (5H, m, Ph*H*), 7.21 (2H, d, *J*=8.5 Hz, Ar*H*), 7.67 (2H, d, *J*=8.5 Hz, Ar*H*).

Synthesis of *N*-(1-benzyl-2-hydroxy-ethyl)-4-methyl-benzenesulfonamide 168



To a stirred suspension of lithium aluminium hydride (1.03 g, 27.0 mmol, 2.2 eq.) in THF (70 ml) at 0 °C, was added **167** (2.03 g, 12.3 mmol, 1.0 eq.).The mixture was heated under reflux overnight. The reaction mixture was cooled to 0 °C and potassium carbonate was added cautiously. The resulting colourless suspension was filtered through Celite®, and the filtrate was concentrated under reduced pressure to give **168** as a yellow oil, 1.23 g (66%). The material was carried through to the next step without further purification. **^{1}H NMR (250 MHz $CDCl_3$)**: δ2.06 (1H, br s, OH), 2.62 (1H, dd, *J*=7.0, 14.0 Hz, C*H*HPh), 2.78 (1H, dd, *J*=7.0, 14.0 Hz, CH*H*Ph), 3.36-3.70 (3H, m, C*H* + CH_2O), 4.41 (2H, br s, NH_2), 7.10-7.31 (5H, m, Ph*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ37.8, 56.6, 63.9, 127.0, 128.6, 137.0, 143.3.

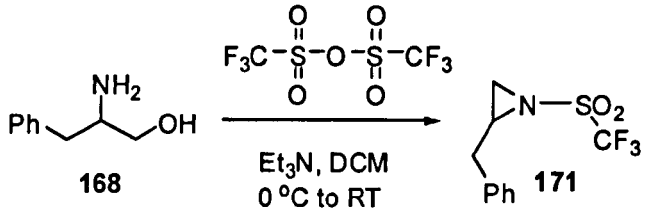
Synthesis of 2-benzyl-1-methanesulfonyl-aziridine 169



To a solution of racemic **168** mixed with triethylamine (1.9 mL, 13.40 mmol, 3.5 eq) in dry DCM (6 mL), were slowly added methanesulfonylchloride (650 µL, 8.43 mmol, 2.2 eq) and DMAP (94 mg, 0.77 mmol, 0.2 eq) at 0 °C and the resulting solution was stirred for 30 min. The solution was left at room temperature overnight. The solvent was removed under reduced pressure and

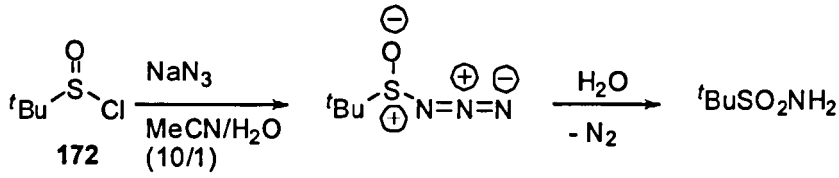
diluted with EtOAc. The organic layer was washed twice with brine and was dried over $MgSO_4$. The solution was then filtered, concentrated under reduce pressure and purified by flash chromatography (3:1, petroleum ether/ethyl acetate) to provide the product **169** as an oil (350 mg, 43%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ2.19 (1H, d, *J*=4.5 Hz, C*H*HN), 2.63-2.78 (2H, m, C*H*N + CH*H*N), 2.72 (3H, m, C*H*$_3$), 2.87-3.03 (2H, m, C*H*$_2$Ph), 7.22-7.39 (5H, m Ph*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ36.5, 37.9, 39.6, 41.7, 127.5, 129.1, 130.0, 137.7. **FTIR (thin film)**: 3063 (w), 3029 (m), 2933 (m), 2854 (w), 1604 (m), 1497 (m), 1455 (m), 1393 (w), 1315 (s), 1235 (m), 1151 (s), 969 (s), 948 (s), 857 (s), 796 (s), 745 (s), 673 (s) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{10}H_{14}NO_2S$ (MH^+)**: 212.0745. Found: 212.0748.

Synthesis of 2-benzyl-1-trifluoromethanesulfonyl-aziridine 171[160]



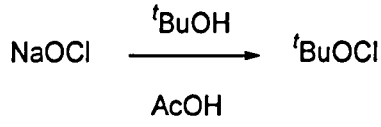
Triflic anhydride (630 μL, 3.75 mmol, 2.2 eq) was added dropwise to a solution of racemic **168** (260 mg, 1.71 mmol, 1.0 eq) and triethylamine (760 μL, 5.46 mmol, 3.2 eq) in dry DCM (7 mL) at -78 °C, where after the mixture was kept at -30 °C overnight. The reaction mixture was diluted with DCM and washed twice with 0.1 M HCl and twice with $Na_2CO_{3(aq)}$. The organic layer was dried over $MgSO_4$. The solution was then filtered, concentrated under reduce pressure and purified by flash chromatography (6:1, petroleum ether/ethyl acetate) to provide the product **171** as an oil (310 mg, 68%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ2.39 (1H, d, *J*=5.0 Hz, CH*H*), 2.78-3.03 (3H, m, C*H*$_2$Ph + C*H*HN), 3.03-3.18 (1H, m, C*H*N), 7.10-7.33 (5H, m, Ph*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ38.4, 39.0, 39.1, 118.2 (q, *J*=280 Hz), 127.7, 129.2, 129.8, 136.4. **FTIR (thin film)**: 3029 (m), 2926 (m), 2864 (w), 1606 (m), 1483 (m), 1425 (m), 1393 (w), 1315 (s), 1235 (m), 1151 (s), 969 (s), 948 (s), 857 (s) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{10}H_{11}F_3NO_2S$ (MH^+)**: 266.2432. Found: 266.2463.

Synthesis of *tert*-butylsulfonamide[161]



Sodium azide (1.4 g, 21.15 mmol, 1.75 eq) was suspended in acetonitrile (8.5 mL) and water (850 μL). The mixture was heated to just below the boiling point of acetonitrile, the source of heat was removed, and *tert*-butylsulfinyl chloride **172** (1.5 mL, 12.09 mmol, 1.0 eq) was added slowly to the vigorously stirred mixture. The reaction is highly exothermic, and the addition rate was adjusted to maintain gentle reflux of acetonitrile. After the addition was complete, the reaction mixture was allowed to cool to room temperature. Ethyl acetate and water were added, and the layers were separated. The aqueous layer was extracted once with ethyl acetate, and the combined organic layers were washed with water and dried with $MgSO_4$. After the solvents were evaporated in vacuo, the residue was mixed with ether and the crystals were filtered and washed with ether. The product was recrystallized from acetone to afford 1.0 g (60%) of *tert*-butylsulfonamide as colourless crystals (**m.p.**=162-163 °C, lit. **m.p.**=162-165 °C)[162]. The compound was used directly without further characterisation.

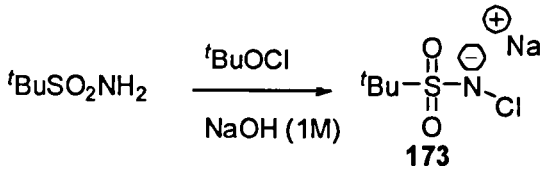
Synthesis of *tert*-butyl hypochlorite[163, 164]



Reaction conducted in the dark. A 5% aqueous solution of sodium hypochlorite (75 mL, 5% available chlorine) was cooled to 0 °C. To this was added a solution of glacial acetic acid (7.5 mL) and *tert*-butanol (11.25 mL) in one portion and the resulting mixture was stirred for 3 mins. The organic layer was separated and washed successively with sodium carbonate (10% solution) and water. The product was dried over calcium chloride and filtered to yield the title compound

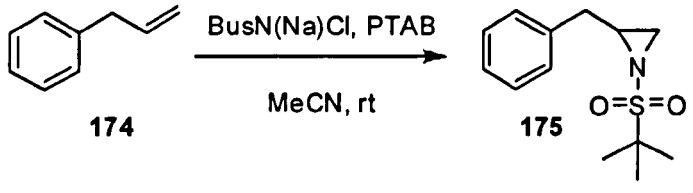
as a yellow liquid. The product was stored below 4 °C in the dark over calcium chloride.

Synthesis of the *N*-chloramine salt of *tert*-butylsulfonamide 173[161]



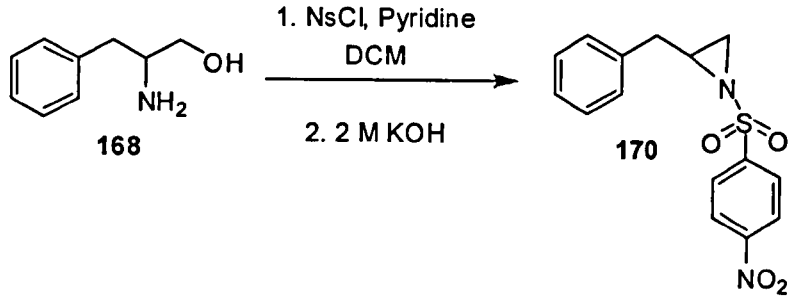
^{t}BuOCl (267 mg, 2.47 mmol, 1.0 eq) was added slowly to a stirred solution of *tert*-butylsulfonamide (338 mg, 2.47 mmol, 1.0 eq) in an aqueous solution of NaOH (1 M, 2.5 mL, 2.47 mmol, 1.0 eq) at room temperature. The resulting solution was stirred for 1 h. The solution was then concentrated to dryness in vacuum. The solid was triturated with ether, filtered and dried in drying pistol (80 °C) overnight to afford the product **173** as a white powder (430 mg, 90%).

Synthesis of 2-benzyl-1-(2-methyl-propane-2-sulfonyl)-aziridine 175[165]



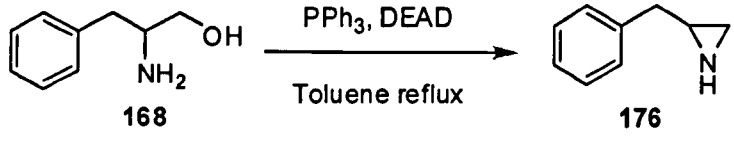
To a mixture of **174** (125 mg, 1.06 mmol, 1.0 eq) and the *N*-chloramine salt of *tert*-butylsulfonamide **173** (246 mg, 1.27 mmol, 1.2 eq) in 17 mL of CH_3CN were added phenyltrimethylammonium tribromide (40 mg, 0.11 mmol, 0.1 eq) at 25 °C. After 12h of vigorous stirring, the reaction mixture was concentrated and purified by flash chromatography (5:1, petroleum ether/ethyl acetate) to provide the product **175** as an oil (100 mg, 37%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.43 (9H, s, $C(CH_3)_3$), 2.09 (1H, d, *J*=4.5 Hz, CH*H* aziridine), 2.58-2.61 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.72-2.85 (1H, m, C*H* aziridine), 2.92-3.07 (2H, m, CH_2Ph), 7.18-7.36 (5H, m Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ24.1, 32.9, 37.4, 39.3, 59.3, 126.9, 128.6, 129.1, 136.5.

Synthesis of 2-benzyl-1-(4-nitro-benzenesulfonyl)-aziridine 170[166, 167]



4-nitrobenzenesulfonyl chloride (3.34 g, 15.06 mmol, 3.0 eq) was added in one portion to a suspension of **168** (759 mg, 5.02 mmol, 1.0 eq) in DCM (4.2 mL) and pyridine (2.1 mL) and stirred at rt for 4 hours. This was then diluted with DCM and washed with 2 portions aqueous 1 M HCl, and the aqueous washings extracted with DCM. The combined organic extracts were then carefully shaken with 6 successive portions of aqueous 2 M KOH. The aqueous washings were further extracted with DCM and the combined organics were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and the resulting residue purified by flash chromatography (2:1, petroleum ether/ethyl acetate) to give aziridine **170** (810 mg, 51%) as a colorless oil. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ2.30 (1H, d, *J*=4.5 Hz, C*H*HN), 2.48 (1H, m, CH*H*N), 2.91 (3H, m, C*H*N + CH_2Ph), 6.90-7.12 (5H, m, Ph*H*), 7.87 (2H, d, *J*=9.0 Hz, Ar*H*), 8.15 (2H, d, *J*=9.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ33.1, 37.2, 42.4, 124.3, 127.0, 128.3, 128.6, 129.0, 136.5, 143.8, 150.4.

Synthesis of 2-benzyl-aziridine 176[106, 168]



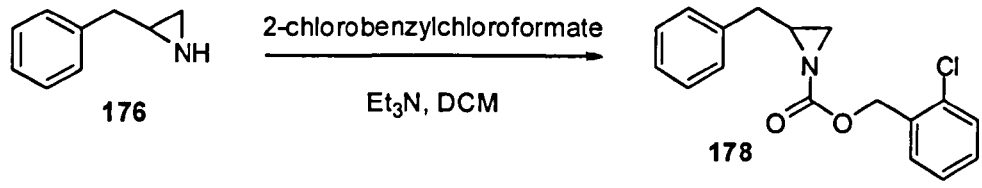
The amino alcohol **168** (1.48 g, 9.76 mmol, 1.0 eq) was dissolved in toluene (15 mL) and was added to a solution of triphenylphosphine (2.69 g, 10.25 mmol, 1.05 eq) and diethylazodicarboxylate (1.6 mL, 10.25 mmol, 1.05 eq) in toluene (22 mL). After refluxing overnight, the mixture was poured into water and diluted

with diethyl ether. Drying over $MgSO_4$, filtration, and concentration gave a residue, which was diluted with diethyl ether and left in the freezer overnight. Precipitated triphenylphosphine oxide was filtered off, and the filtrate was concentrated and subjected to column chromatography (10:1, DCM/MeOH) to give aziridine **176** (850 mg, 65%) as a colorless oil. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.45 (1H, d, *J*=3.5 Hz, C*H*HN), 1.82 (1H, d, *J*=5.5 Hz, CH*H*N), 2.16-2.25 (1H, m, C*H*N), 2.65 (1H, dd, *J*=6.0 Hz, *J*=14.5 Hz, C*H*HPh), 2.80 (1H, dd, *J*=6.0 Hz, *J*=14.5 Hz, CH*H*Ph), 7.20-7.35 (5H, m, Ph*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ25.0, 31.0, 40.2, 126.4, 128.5, 128.8, 139.4.

Synthesis of 2-benzyl-aziridine-1-carboxylic acid 4-nitro-benzyl ester 177

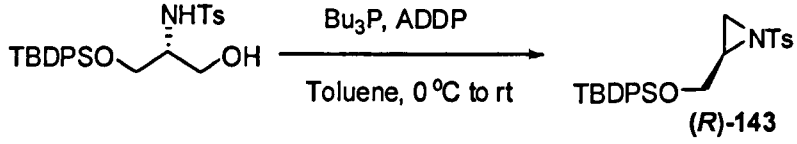
To a solution of amino alcohol **176** (80 mg, 0.60 mmol, 1.0 eq) dissolved in DCM (3 mL) at 0 °C were added triethylamine (126 μL, 0.90 mmol, 1.5 eq) and 4-nitrobenzylchloroformate (155 mg, 0.72 mmol, 1.2 eq). After stirring overnight at rt, the mixture was concentrated and subjected to column chromatography (2:1, petroleum ether/ethyl acetate) to give aziridine **177** (120 mg, 64%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ2.15 (1H, d, *J*=4.5 Hz, C*H*HN), 2.48 (1H, d, *J*=6.0 Hz, CH*H*N), 2.70-2.97 (3H, m, CH_2Ph + C*H*N), 5.20 (2H, s, CH_2O), 7.25-7.33 (5H, m, Ph*H*), 7.45 (2H, d, *J*=9.0 Hz, Ar*H*), 8.20 (2H, d, *J*=9.0 Hz, Ar*H*). **^{13}C NMR (400 MHz, $CDCl_3$)**: δ31.8, 38.4, 39.0, 66.4, 123.8, 126.8, 128.0, 128.6, 128.9, 137.6, 143.0, 147.7, 162.8. ***m/z* (TOF ES)**: 312 (M^+).

Synthesis of 2-benzyl-aziridine-1-carboxylic acid 2-chloro-benzyl ester 178



To a solution of amino alcohol **176** (80 mg, 0.60 mmol, 1.0 eq) dissolved in DCM (3 mL) at 0 °C were added triethylamine (130 μL, 0.90 mmol, 1.5 eq) and 2-chlorobenzylchloroformate (110 μL, 0.72 mmol, 1.2 eq). After stirring overnight at rt, the mixture was concentrated and subjected to column chromatography (2:1, petroleum ether/ethyl acetate) to give aziridine **178** (180 mg, 99%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ2.12 (1H, d, *J*=4.5 Hz, C*H*HN), 2.42 (1H, d, *J*=6.0 Hz, CH*H*N), 2.67-2.80 (2H, m, CH_2Ph), 2.88-3.02 (1H, m, C*H*N), 5.20 (2H, s, CH_2O), 7.20-7.33 (5H, m, Ph*H*), 7.37-7.40 (3H, m, Ar*H*), 7.42-7.50 (1H, m, Ar*H*). **^{13}C NMR (400 MHz, $CDCl_3$)**: δ31.7, 38.3, 38.7, 43.6, 65.4, 126.6, 126.9, 127.2, 128.5, 129.5, 129.9, 130.9, 133.5, 137.7, 163.0. ***m/z* (TOF ES)**: 301 (M^+).

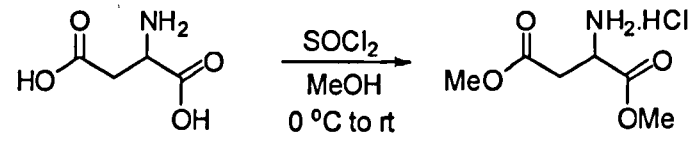
Synthesis of (*R*)-2-(*tert*-butyl-diphenyl-silanoxymethyl)-1-(toluene-4-sulfonyl)-aziridine 143



ADDP (877 mg, 3.47 mmol, 1.2 eq) was added to a solution of starting material (1.40 g, 2.89 mmol, 1.0 eq) and tributylphosphine (1.07 mL, 4.34 mmol, 1.5 eq) in toluene (20 mL) at 0 °C and stirred for 2 h at this temperature, and then warmed to room temperature overnight. The reaction mixture was then partitioned between Et_2O and water, and the layers were separated. The aqueous layer was extracted with a further 2 portions of Et_2O. The combined organic fractions were dried over $MgSO_4$, concentrated and then purified by flash chromatography to provide (*R*)-

143 as a colourless oil (1.07 g, 80%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.96 (9H, s, C(CH_3)$_3$), 2.15 (1H, d, *J*=5.0 Hz, C*H*H aziridine), 2.40 (3H, s, ArCH_3), 2.65 (1H, d, *J*=11.0 Hz, CH*H* aziridine), 2.94-3.04 (1H, m, C*H* aziridine), 3.60 (1H, dd, *J*=11.5, 5.5 Hz, C*H*HOTBDPS), 3.70 (1H, dd, *J*=11.5, 4.0 Hz, CH*H*OTBDPS), 7.25-7.47 (8H, m, Ar*H*), 7.54-7.62 (4H, m, Ar*H*), 7.85 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.1, 21.6, 26.6, 30.4, 40.9, 63.1, 127.7, 128.0, 129.7, 129.8, 135.1, 135.5, 143.2, 144.4. **FTIR (thin film)**: 3071 (w), 2931 (m), 2858 (m), 1598 (w), 1472 (w), 1428 (m), 1327 (s), 1164 (s), 1093 (s) cm^{-1}. ***m/z* (TOF ES)**: 466 (MH^+). **HRMS (TOF ES) calcd. for $C_{26}H_{32}NO_3SiS$ (MH^+)**: 466.1872. Found: 466.1851.

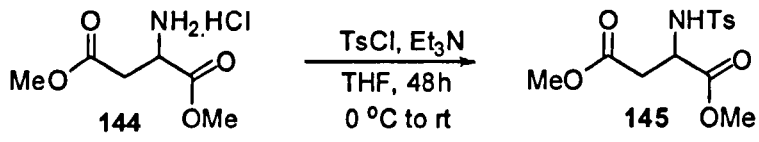
Synthesis of 2-Amino-succinic acid dimethyl ester 144[107, 108, 169]



(*D,L*) - aspartic acid **144**

Thionyl chloride (3.1 ml, 42.07 mmol, 1.4 eq) was added dropwise to a solution of (*D,L*)-aspartic acid (4.0 g, 30.05 mmol, 1.0 eq) in dry methanol (40 mL) at 0 °C, the reaction was allowed to warm to room temperature and stirred for 48 h. The reaction was evaporated under reduced pressure to give a light yellow oil and then triturated with diethylether and filtered to give **144** as a white solid (5.90 g, 99% crude). **m.p.**=113-114 °C (lit. **m.p.**=116-117 °C)[107, 108]. **^{1}HNMR (250 MHz, $CDCl_3$)**: δ2.73 (1H, dd, *J*=7.5, 16.5 Hz, CH*H*), 2.82 (1H, dd, *J*=4.5, 16.5 Hz, C*H*H), 3.71 (3H, s, CH_3), 3.75 (3H, s, CH_3), 3.85 (1H, dd, *J*=4.5, 7.5 Hz, C*H*-N).

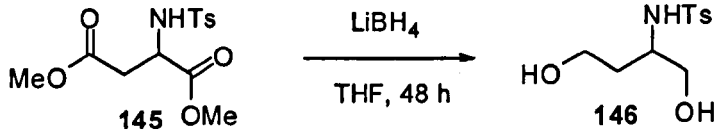
Synthesis of 2-(toluene-4-sulfonylamino)-succinic acid dimethyl ester 145[37, 170]



144 **145**

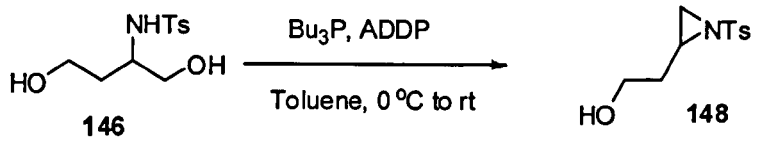
A flask was charged with diester **144** (5.80 g, 29.36 mmol, 1.0 eq) and THF (22 mL) and cooled to 0 °C. Distilled triethylamine (18 mL, 129.18 mmol, 4.4 eq) and then p-toluenesulfonylchloride (6.1 g, 32.23 mmol, 1.1 eq) were added and the mixture stirred at room temperature for 72 h. The reaction mixture was acidified with HCl (32%) to pH 3 and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution then dried over $MgSO_4$ and evaporated under reduce pressure to give **145** as an oily yellow residue (8.05 g, 87% crude). **^{1}HNMR (250 MHz, $CDCl_3$)**: δ2.41 (3H, m, C*H*$_3$), 2.84 (1H, dd, *J*=5.0, 17.0, *H*CH-C=O), 2.97 (1H, dd, *J*=5.0, 17.0, HC*H*-C=O), 3.59 (3H, s, C*H*$_3$), 3.66 (3H, s, C*H*$_3$), 4.06-4.18 (1H, m, C*H*-N), 5.60 (1H, d, *J*=8.0 Hz, NH), 7.30 (2H, d, *J*=8.0 Hz, Ar*H*), 7.73 (2H, d, *J*=8.0 Hz, Ar*H*). **FTIR (thin film)**: 3849 (br), 3061 (m), 2956 (m), 1748 (s), 1599 (m), 1440 (s), 1346 (s).

Synthesis of *N*-(3-hydroxy-1-hydroxymethyl-propyl)-4-methyl-benzenesulfonamide 146[171]



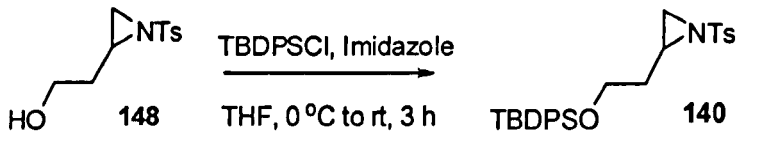
A solution of the diester **145** (1 g, 3.17 mmol, 1.0 eq) in THF (15 ml) was added dropwise *via* cannula to a solution of lithium borohydride (152 mg, 6.80 mmol, 2.2 eq) in THF (23 mL) at 0 °C and stirred for 48 h. Aqueous potassium carbonate solution and water were added to quench the reaction and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure and then purified by flash chromatography to provide **146** as a white powder (1.37 g, 84%). **m.p.**=88 °C. **^{1}HNMR (250 MHz, $CDCl_3$)**: δ1.59-1.77 (2H, m, C*H*$_2$), 1.91 (1H, br s, OH), 2.43 (3H, s, C*H*$_3$), 3.37-3.87 (5H, m, C*H*$_2$ + C*H*-N), 7.36 (2H, d, *J*=8.5 Hz, Ar*H*), 7.66 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.6, 34.4, 53.0, 58.7, 64.6, 127.1, 129.8, 140.5, 143.7.

Synthesis of 2-hydroxyethyl-1-(toluene-4-sulfonyl)-aziridine 148 *via* Mitsunobu reaction



A 50 mL round-bottomed-flask was charged with **146** (548 mg, 2.11 mmol, 1.0 eq), distilled tributylphosphine (840 μL, 3.38 mmol, 1.6 eq) and toluene (20 mL) at room temperature. The reaction mixture was cooled to 0 °C. Then, 1,1'-azodicarbonyldipiperidine (ADDP) (800 mg, 3.17 mmol, 1.5 eq) was added in small portions. The reaction mixture was stirred 2 h at 0 °C, then it was allowed to reach rt and stirred overnight. The reaction mixture was evaporated under reduced pressure, dissolved in a mixture DCM/MeOH (10:1), dried on silica and purified by flash column chromatography (1:1 petroleum ether/EtOAc) to provide a colourless oil, **148** (411 mg, 81%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.36-1.53 (1H, m, *H*CH), 1.89-2.10 (1H, m, HC*H*), 2.14 (1H, d, *J*=4.5 Hz, CH*H* aziridine) 2.44 (3H, s, ArCH_3), 2.64 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.83-2.97 (1H, m, C*H* aziridine), 3.55-3.74 (2H, CH_2OH), 7.34 (2H, d, *J*=8.0 Hz, Ar*H*), 7.82 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ25.8, 29.6, 42.1, 55.3, 68.2, 128.3, 131.8, 132.0, 133.3. **FTIR (thin film)**: 3527 (br), 2925 (w), 1597 (w), 1320 (m), 1232 (w), 1160 (s), 1092 (w) cm^{-1}. ***m/z* (TOF ES)**: 264 (MNa^+). **HRMS (TOF ES) calcd. for $C_{11}H_{15}NO_3NaS$ (MNa^+)**: 264.0670. Found: 264.0666.

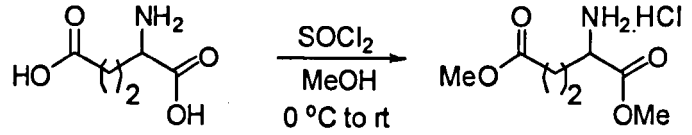
Synthesis of (*R*)-2-(*tert*-butyl-diphenyl-silanoxyethyl)-1-(toluene-4-sulfonyl)-aziridine 140



Substrate **148** was dissolved in THF (2.5 mL) and the solution was cooled to 0 °C. TBDPSCl (552 mL, 2.12 mmol, 1.25 eq) and imidazole (347 mg, 5.10 mmol, 3.0 eq) were added. The reaction mixture was allowed to reach rt and stirred for 3 h.

The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over magnesium sulphate, concentrated in vacuum. Purification of the resulting liquid by silica gel chromatography (10/1, petroleum/EtOAc) provided **140** as a yellow oil (734 mg, 90%). Characterisation data for this compound has been described earlier.

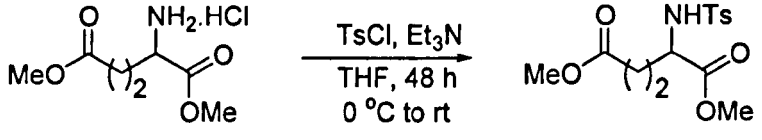
Synthesis of 2-amino-pentanedioic acid dimethyl ester[107, 108, 169]



(*D,L*) - glutamic acid

Thionyl chloride (1.24 mL, 16.95 mmol, 1.4 eq) was added dropwise to a solution of (*D,L*)-glutamic acid (2.0 g, 12.11 mmol, 1.0 eq) in dry methanol (16 mL) at 0 °C, the reaction was allowed to warm to room temperature and stirred for 48 h. The reaction was evaporated under reduced pressure to give a light yellow oil and then triturated with diethyl ether and filtered to give 2-amino-pentanedioic acid dimethyl ester as a white solid (2.53 g, 99% crude). **^{1}HNMR (250 MHz, DMSO)**: δ1.94-2.11 (2H, m, C*H*$_2$), 2.39-2.62 (2H, m, C*H*$_2$-C=O), 3.62 (1H, s, C*H*$_3$), 3.75 (1H, s, C*H*$_3$), 4.08 (1H, t, *J*=6.5 Hz, C*H*-N). **FTIR (thin film)**: 3852 (br), 3058 (m), 2957 (m), 1750 (s), 1595 (m), 1442 (s), 1343 (s).

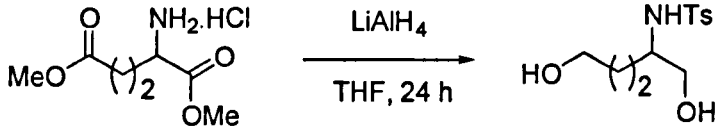
Synthesis of 2-(toluene-4-sulfonylamino)-pentanedioic acid dimethyl ester [172]



A flask was charged with the dimethyl ester (2.53 g, 11.96 mmol, 1.0 eq) and THF (10 ml) and cooled to 0 °C. Distilled triethylamine (7.3 ml, 52.62 mmol, 4.4 eq) and then *p*-toluenesulfonylchloride (2.51 g, 13.16 mmol, 1.1 eq) were added and the mixture was stirred at room temperature for 72 h. The reaction mixture

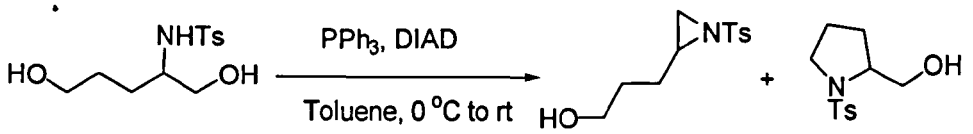
was acidified with HCl (32%) to pH 3 and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogenocarbonate solution then dried over $MgSO_4$ and evaporated under reduce pressure to give 2-(toluene-4-sulfonylamino)-pentanedioic acid dimethyl as an oily yellow residue (3.85 g, 98% crude). **^{1}HNMR (250 MHz, $CDCl_3$)**: δ1.82 (1H, m, C*H*H), 2.00 (1H, m, CH*H*), 2.37 (3H, m, CH_3), 2.41 (2H, m, CH_2-C=O), 3.41 (3H, s, CH_3), 3.56 (3H, s, CH_3), 3.90 (1H, m, C*H*-N), 5.60 (1H, d, *J*=9.5 Hz, NH), 7.20 (2H, d, *J*=8.0 Hz, Ar*H*), 7.63 (2H, d, *J*=8.0 Hz, Ar*H*). **FTIR (thin film)**: 3852 (br), 3050 (m), 2963 (m), 1749 (s), 1612 (m), 1440 (s), 1342 (s).

Synthesis of *N*-(4-hydroxy-1-hydroxymethyl-butyl)-4-methyl-benzenesulfonamide



A solution of the diester (3.85 g, 11.69 mmol, 1.0 eq) in THF (56 mL) was added dropwise *via* cannula to a solution of lithium borohydride (976 mg, 25.72 mmol, 2.2 eq) in THF (85 mL) at 0 °C and stirred for 24 h. Aqueous potassium carbonate solution and water were added to quench the reaction and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and the solvent removed in vacuo. The solid residue was recrystallised in DCM/Petrol, providing the diol as a white powder, 1.62 g (51%). **m.p.**=83-85 °C. **^{1}HNMR (250 MHz, $CDCl_3$)**: δ1.35-1.63 (4H, m, CH_2), 1.90 (2H, br s, OH), 2.42 (3H, s, CH_3), 3.18-3.31 (1H, m, C*H*-N), 3.41-3.63 (4H, m, CH_2-O), 7.30 (2H, d, *J*=8.0 Hz, Ar*H*), 7.77 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.5, 28.0, 28.4, 42.1, 55.3, 62.3, 64.6, 127.1, 129.7, 135.6, 138.4. **FTIR (thin film)**: 3476 (br), 3294 (s), 2946 (m), 2875 (m), 1718 (w), 1436 (w), 1321 (m), 1157 (s), 1093 (m), 1047 (m) cm^{-1}. ***m/z* (TOF ES)**: 274 (MH^+). **HRMS (TOF ES) calcd. for C12H20N4S**: 274.1113. Found: 274.1113.

Synthesis of 2-hydroxypropyl-1-(toluene-4-sulfonyl)-aziridine[173]



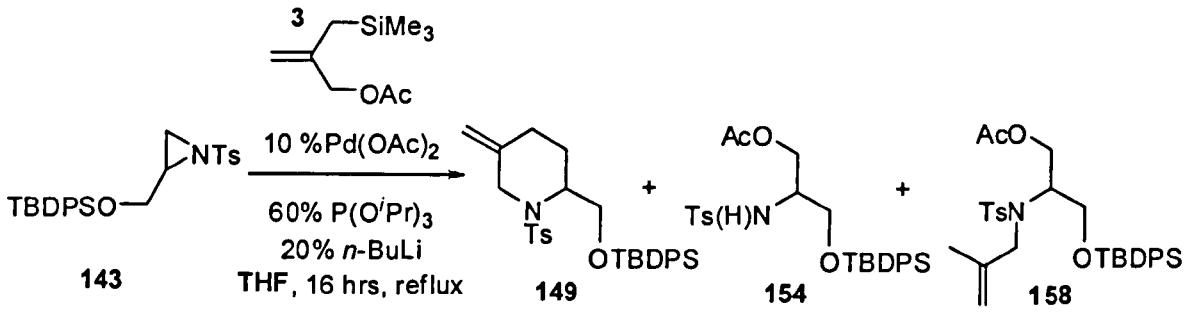
A 50 mL round-bottomed-flask was charged with the diol (300 mg, 1.10 mmol, 1.0 eq), triphenylphosphine (460 mg, 1.76 mmol, 1.6 eq) and toluene (10 mL) at room temperature. The reaction mixture was cooled to 0 °C. Then, diisopropyl azodicarboxylate (DIAD) (324 μL, 1.65 mmol, 1.5 eq) was added. The reaction mixture was stirred 2 h at 0 °C, then it was allowed to reach rt and stirred overnight. Water was added and the reaction mixture was extracted with diethylether, dried over $MgSO_4$ and purified by flash column chromatography (1:2 petroleumether/EtOAc) to provide the hydroxy-aziridine as a white solid (30 mg, 11%), and the pyrrolidine as a yellow oil (250 mg, 89%).

Hydroxy-aziridine: **m.p.**=120-121 °C. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.31-1.45 (1H, m, *H*CH), 1.47-1.60 (2H, m, C*H*$_2$), 1.65-1.82 (1H, m, HC*H*), 2.05 (1H, d, *J*=4.50 Hz, CH*H* aziridine) 2.43 (3H, s, ArC*H*$_3$), 2.60 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.72-2.84 (1H, m, C*H* aziridine), 3.60 (2H, t, *J*=6.0 Hz, C*H*$_2$OH), 7.32 (2H, d, *J*=8.0 Hz, Ar*H*), 7.81 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ25.8, 28.3, 29.6, 55.3, 68.2, 128.3, 131.8, 132.0, 133.3. **FTIR (thin film)**: 3430 (br), 3056 (w), 2923 (w), 2359 (m), 1437 (m), 1327 (w), 1182 (m), 1119 (s) cm^{-1}.

Pirrolidine[10]: **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.29-1.46 (1H, m, C*H*$_2$), 1.52-1.81 (3H, m, *H*CH + C*H*$_2$), 2.37 (3H, s, ArC*H*$_3$), 3.11-3.24 (1H, m, CH*H*-N), 3.31-3.45 (1H, m, *H*CH-N) 3.50-3.68 (3H, m, C*H*N + C*H*$_2$-O), 7.27 (2H, d, *J*=8.0 Hz, Ar*H*), 7.67 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.5, 21.9, 24.3, 28.9, 50.1, 61.8, 65.9, 127.6, 129.8, 143.8.

5.[3+3] Cycloaddition

Synthesis of (*R*)-2-(*tert*-butyl-diphenyl-silanoxymethyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 149



A solution of **143** (88 mg, 0.19 mmol, 1.5 eq) in THF (1.2 mL) was treated with freshly prepared 0.14 M palladium catalyst solution[d] (90 μL, 0.012 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (27 μL, 0.126 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (12:1 petroleum ether/EtOAc) to give mainly the desired piperidine **149** (45mg, 67%).

149: **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.06 (9H, s, C(CH_3)$_3$), 1.34-1.52 (1H, m, CH_2), 1.79-1.98 (2H, m, CH_2), 2.02-2.23 (1H, m, CH_2), 2.40 (3H, s, ArCH_3), 3.62 (1H, d, *J*=15.5 Hz, C6-*H*), 3.72-3.86 (2H, m, CH_2OTBDPS), 3.96-4.08 (1H, m, C2-*H*), 4.20 (1H, d, *J*=15.5 Hz, C6-*H'*), 4.66 (1H, br s, C=C*H*H), 4.75 (1H, br s, C=CH*H*), 7.20 (2H, d, *J*=8.0 Hz, Ar*H*), 7.35-7.48 (6H, m, Ar*H*), 7.60-7.69 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 24.6, 26.9, 27.1, 47.7, 53.6, 62.9, 110.3, 127.2, 127.8, 129.4, 129.8, 133.3, 135.6, 137.7, 141.2, 142.9. **FTIR (CH_2Cl_2)**: 3072 (w), 2931 (m), 2858 (m), 1598 (w), 1428 (m), 1342 (s), 1162 (s), 1113 (s) cm^{-1}. ***m/z* (TOF ES)**: 542 (MNa^+). **HRMS (TOF ES) calcd. for $C_{30}H_{37}NO_3NaSiS$** (MNa^+): 542.2161. Found: 542.2138.

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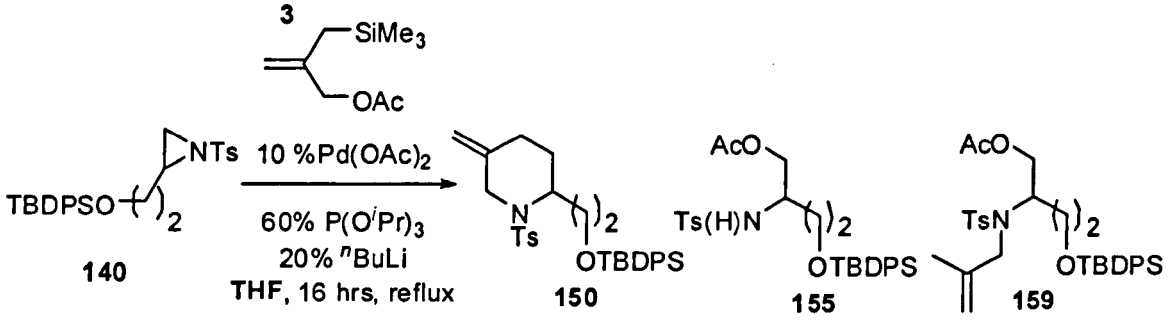
[d] **Representative procedure for 0.14 M Pd catalyst used in cycloaddition reactions:**
To a suspension of $Pd(OAc)_2$ (50 mg, 0.22 mmol, 1.0 eq.) in THF (1.61 mL) was added $P(O^iPr)_3$ (0.33 mL, 1.34 mmol, 6.0 eq.), and then *n*-butyllithium (2.5 M in hexane, 0.18 mL, 0.44 mmol, 2.0 eq) was added and the resultant solution was stirred for 15 min before use.

154: **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.98 (9H, s, C(CH_3)$_3$), 1.81 (3H, s, CH_3-C=O), 2.34 (3H, s, ArCH_3), 3.28-3.59 (3H, m, C*H*-N + CH_2O), 3.89-4.17 (2H, m, CH_2-O), 4.89 (1H, d, *J*=8.0 Hz, NH), 7.16 (2H, d, *J*=8.0 Hz, Ar*H*), 7.26-7.43 (6H, m, Ar*H*), 7.46-7.56 (4H, m, Ar*H*), 7.66 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.0, 20.7, 21.5, 26.8, 53.3, 61.5, 63.0, 127.0, 127.8, 129.7, 130.0, 132.9, 135.5, 137.8, 143.4, 170.7. **FTIR (CH_2Cl_2)**: 3282 (br), 2931 (m), 2857 (m), 1744 (s), 1428 (m), 1337 (m), 1238 (m), 1163 (s), 1111 (s) cm^{-1}. ***m/z*** **(TOF ES)**: 548 (MNa^+). **HRMS (TOF ES) calcd. for $C_{28}H_{35}NO_5NaSiS$ (MNa^+)** 548.1903. Found: 548.1884.

158: ***m/z*** **(TOF ES)**: 602 (MNa^+). **HRMS (TOF ES) calcd. for $C_{32}H_{41}NO_5NaSiS$ (MNa^+)**: 602.2372. Found: 602.2347.

Synthesis of 2-(*tert*-butyl-diphenyl-silanoxyethyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 150 *via* [3+3] Cycloaddition



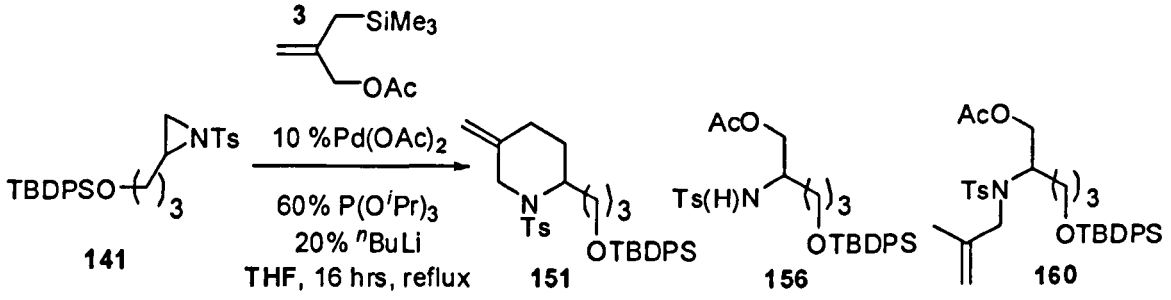
A solution of **140** (208 mg, 0.43 mmol, 1.5 eq) in THF (2.8 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (206 μL, 0.029 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (61 μL, 0.29 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (12:1 petroleum ether/EtOAc).

150: (65%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.05 (9H, s, C(CH_3)$_3$), 1.30-1.49 (2H, m, CH_2), 1.65-1.82 (2H, m, CH_2), 1.83-2.04 (2H, m, CH_2), 2.37 (3H, s, ArCH_3), 3.52 (1H, d, *J*=15.0 Hz, C6-*H*), 3.57-3.77 (2H, m, CH_2OTBDPS), 4.05-4.15 (1H, m, C2-*H*), 4.21 (1H, d, *J*=15.0 Hz, C6-*H'*), 4.67 (1H, br, C=C*H*H), 4.76 (1H, br, C=CH*H*), 7.18 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.47 (6H, m, Ar*H*), 7.59-7.70 (6H,

m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 26.9, 27.3, 28.0, 32.9, 46.5, 50.0, 61.1, 110.3, 127.4, 127.7, 129.4, 129.6, 133.6, 135.6, 136.8, 142.3, 144.4. **FTIR (CH_2Cl_2)**: 3060 (w), 2931 (m), 2847 (m), 1466 (w), 1428 (m), 1341 (s), 1160 (s), 1111 (s) cm^{-1}. ***m/z* (TOF ES)**: 556 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{39}NO_3NaSiS$** (MNa^+): 556.2318. Found: 556.2330.

<u>155:</u> (17%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.98 (9H, s, C(C*H*$_3$)$_3$), 1.54-1.62 (2H, m, C*H*$_2$), 1.89 (3H, s, C*H*$_3$-C=O), 2.33 (3H, s, ArC*H*$_3$), 3.38-3.71 (3H, m, C*H*-N + C*H*$_2$O), 4.0 (2H, app ddd, *J*=5.5, 11.5, 17.5, C*H*$_2$-O), 5.30 (1H, d, *J*=7.5 Hz, NH), 7.16 (2H, d, *J*=8.0 Hz, Ar*H*), 7.26-7.43 (6H, m, Ar*H*), 7.46-7.56 (4H, m, Ar*H*), 7.66 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.0, 20.7, 21.5, 26.8, 33.9, 51.0, 60.7, 65.5, 127.1, 127.8, 129.7, 129.9, 132.9, 135.5, 137.8, 143.3, 170.7. **FTIR (CH_2Cl_2)**: 3282 (br), 2931 (m), 2860 (m), 1744 (s), 1428 (m), 1235 (m), 1162 (s), 1111 (s) cm^{-1}. ***m/z* (TOF ES)**: 562 (MNa^+). **HRMS (TOF ES) calcd. for $C_{29}H_{37}NO_5NaSiS$** (MNa^+): 562.2059. Found: 562.2059.

Synthesis of 2-(*tert*-butyl-diphenyl-silanoxypropyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 151 *via* [3+3] Cycloaddition



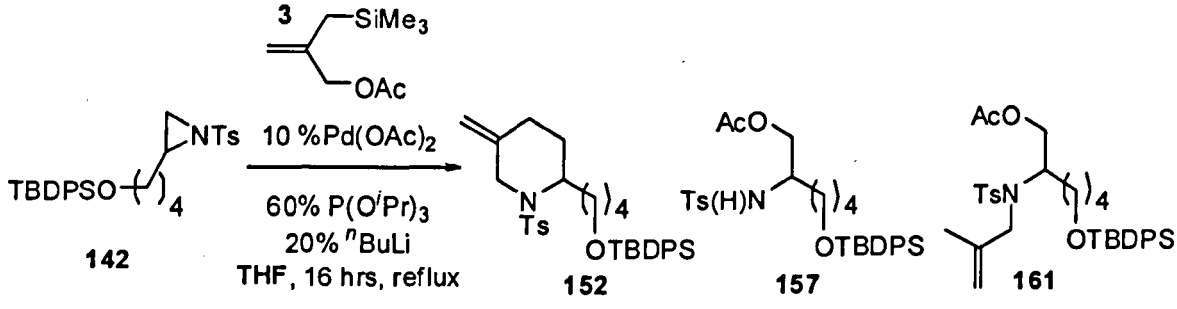
A solution of **141** (249 mg, 0.51 mmol, 1.5 eq) in THF (3.3 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (240 μL, 0.034 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (71.5 μL, 0.34 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (12:1 petroleum ether/EtOAc).

<u>151:</u> (20%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.03 (9H, s, C(C*H*$_3$)$_3$), 1.27-1.43 (2H, m, C*H*$_2$), 1.49-1.67 (2H, m, C*H*$_2$), 1.73-1.86 (2H, m, C*H*$_2$), 1.89-2.02 (2H, m,

CH_2), 2.38 (3H, s, ArCH_3), 3.60 (1H, br, C6-*H*), 3.63-3.71 (2H, m, CH_2OTBDPS), 3.84-3.95 (1H, m, C2-*H*), 4.23 (1H, d, *J*=15.0 Hz, C6-*H*), 4.64 (1H, br, C=C*H*H), 4.75 (1H, br, C=CH*H*), 7.20 (2H, d, *J*=8.0 Hz, Ar*H*), 7.33-7.44 (6H, m, Ar*H*), 7.61-7.69 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.4, 26.2, 26.9, 27.3, 28.4, 31.4, 48.2, 52.5, 63.6, 110.4, 127.3, 127.6, 129.4, 129.6, 133.4, 135.6, 137.8, 142.4, 143.5. **FTIR (CH_2Cl_2)**: 3071 (w), 2932 (m), 2857 (m), 1472 (w), 1428 (m), 1340 (s), 1159 (s), 1111 (s) cm^{-1}. ***m/z* (TOF ES)**: 548 (MH^+). **HRMS (TOF ES) calcd. for $C_{32}H_{42}NO_3SiS$** (MH^+): 548.2655. Found: 548.2634.

156: (25%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.02 (9H, s, $C(CH_3)_3$), 1.35-1.58 (4H, m, CH_2), 1.93 (3H, s, CH_3-C=O), 2.38 (3H, s, ArCH_3), 3.38-3.65 (4H, m, CH_2O), 3.90 (1H, ddd, *J*=4.5, 11.5, 12.5, C*H*-N), 4.71 (1H, d, *J*=8.5 Hz, NH), 7.24 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.47 (6H, m, Ar*H*), 7.57-7.65 (4H, m, Ar*H*), 7.71 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 20.6, 21.5, 26.8, 28.2, 28.8, 52.6, 63.1, 65.8, 127.0, 127.7, 129.7, 132.9, 133.7, 135.5, 138.1, 143.4, 170.8. **FTIR (CH_2Cl_2)**: 3275 (br), 2931 (m), 2858 (m), 1744 (s), 1428 (m), 1237 (m), 1161 (s), 1093 (s) cm^{-1}. ***m/z* (TOF ES)**: 576 (MNa^+). **HRMS (TOF ES) calcd. for $C_{30}H_{39}NO_5NaSiS$** (MNa^+): 576.2216. Found: 576.2202.

Synthesis of 2-(*tert*-butyl-diphenyl-silanoxypropyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 152 *via* [3+3] Cycloaddition



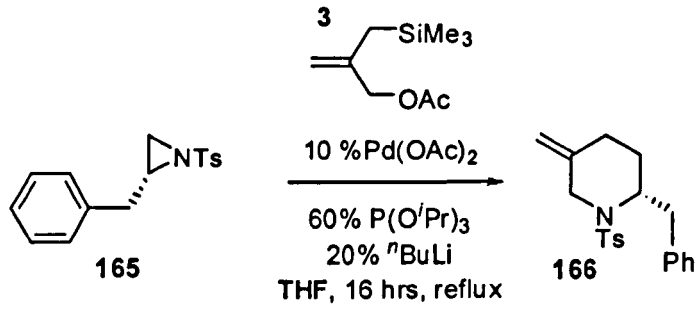
A solution of **142** (100 mg, 0.20 mmol, 1.5 eq) in THF (1.3 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (95 μL, 0.013 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (28 μL, 0.13 mmol, 1.0 eq)

and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (12:1 petroleum ether/EtOAc).

152: (20%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.04 (9H, s, C(CH_3)$_3$), 1.30-1.48 (4H, m, CH_2), 1.49-1.61 (2H, m, CH_2), 1.63-1.78 (2H, m, CH_2), 1.88-2.0 (2H, m, CH_2), 2.37 (3H, s, ArCH_3), 3.64 (3H, m, CH_2OTBDPS + C6-*H*), 3.83-3.95 (1H, m, C2-*H*), 4.22 (1H, d, *J*=15 Hz, C6-*H'*), 4.64 (1H, br s, C=C*H*H), 4.74 (1H, br s, C=CH*H*), 7.21 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.43 (6H, m, Ar*H*), 7.61-7.70 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.3, 21.5, 22.6, 26.9, 27.2, 27.9, 29.8, 32.3, 46.5, 52.7, 63.7, 110.3, 127.3, 127.6, 129.4, 129.5, 133.4, 135.6, 137.6, 141.1, 142.6. **FTIR (CH_2Cl_2)**: 3071 (w), 2930 (m), 2856 (m), 1467 (w), 1428 (m), 1340 (s), 1159 (s), 1111 (s), 900 (m), 822 (m), 703 (s) cm^{-1}. ***m/z* (TOF ES)**: 562 (MH^+). **HRMS (TOF ES) calcd. for $C_{33}H_{44}NO_3SiS$** (MH^+): 562.2811. Found: 562.2833.

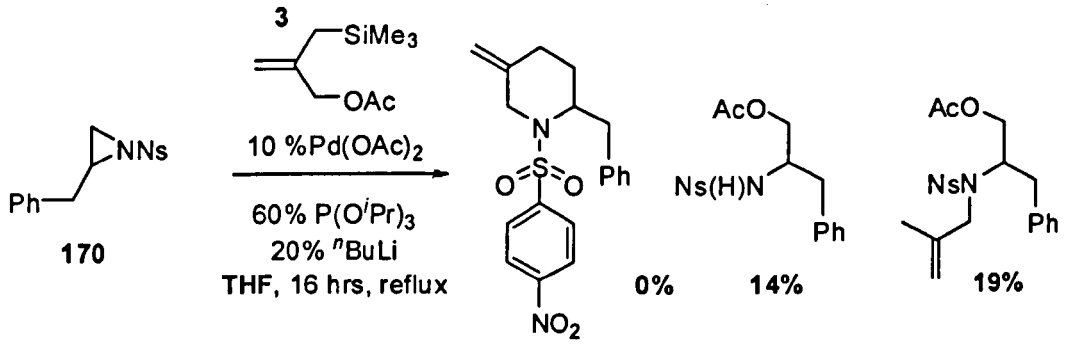
157: (60%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.02 (9H, s, C(CH_3)$_3$), 1.33-1.52 (6H, m, CH_2), 1.93 (3H, s, CH_3-C=O), 2.38 (3H, s, ArCH_3), 3.38-3.61 (4H, m, CH_2O), 3.90 (1H, ddd, *J*=5.0, 11.5, 12.5, C*H*-N), 4.71 (1H, d, *J*=8.5 Hz, NH), 7.24 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.47 (6H, m, Ar*H*), 7.57-7.65 (4H, m, Ar*H*), 7.71 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 22.8, 26.9, 28.2, 30.9, 32.1, 52.8, 63.4, 65.8, 127.0, 127.7, 129.6, 133.9, 135.5, 137.5, 143.3, 143.6, 170.8. **FTIR (CH_2Cl_2)**: 3283 (br), 2931 (m), 2858 (m), 1743 (s), 1428 (s), 1331.4 (s), 1234(s), 1161 (s), 1092 (s) cm^{-1}. ***m/z* (TOF ES)**: 590 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{41}NO_5NaSiS$** (MNa^+): 590.2372. Found: 590.2389.

Synthesis of 2-benzyl-5-methylene-1-(toluene-4-sulfonyl)-piperidine 166 *via* [3+3] Cycloaddition



A solution of **165** (79 mg, 0.28 mmol, 1.5 eq) in THF (1.8 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (130 μL, 0.018 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (39 μL, 0.18 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (5:1 petroleum ether/EtOAc) to give piperidine **166** (55 mg, 59%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.21-1.54 (2H, m, C*H*$_2$), 1.98 (1H, dt, *J*=4.0, 14.5 Hz, CH*H*), 2.26-2.45 (1H, m, C*H*H), 2.38 (3H, s ArC*H*$_3$), 2.94 (2H, d, *J*=7.5 Hz, C*H*$_2$Ph), 3.74 (1H, d, *J*=15.0 Hz, C6-*H*), 4.08-4.20 (1H, m, C2-*H*), 4.25 (1H, d, *J*=15.0 Hz, C6-*H*), 4.71 (1H, s, C=C*H*H), 4.81 (1H, s, C=CH*H*), 7.12-7.37 (7H, m, Ph*H* + Ar*H*), 7.63 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.5, 26.4, 27.1, 36.9, 46.8, 54.3, 110.6, 126.5, 127.3, 128.6, 129.2, 129.5, 137.7, 138.2, 141.0, 143.0.

Synthesis of 2-benzyl-5-methylene-1-(4-nitro-benzenesulfonyl)-piperidine *via* [3+3] Cycloaddition



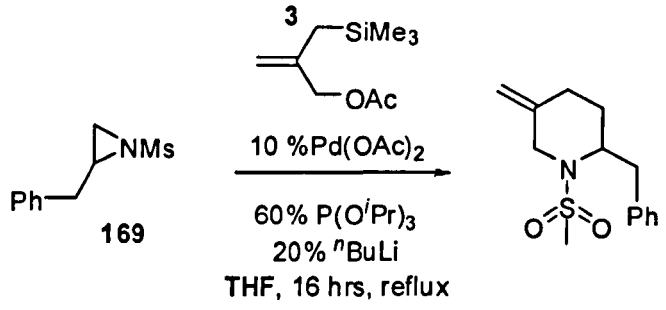
A solution of **170** (202 mg, 0.64 mmol, 1.5 eq) in THF (4.2 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (302 μL, 0.042 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (88 μL, 0.42 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (3:1 petroleum ether/EtOAc) to give mainly the starting material back (79 mg, 39%) and what could be the two by-products (**179** 34 mg, 19% and **180** 23 mg, 14%; structures confirmed by ^{1}H NMR and LC/MS) but no trace of the desired piperidine.

<u>180:</u> 14% ^{1}H NMR (500 MHz, DMSO): δ1.88 (3H, s, C*H*$_3$), 2.50-2.78 (2H, m, C*H*$_2$), 3.60-3.68 (1H, m, C*H*-N), 3.85-3.98 (2H, m, C*H*$_2$OCO), 7.03-7.12 (5H, m,

PhH), 7.80 (2H, d, *J*=9.0 Hz, ArH), 8.20 (2H, d, *J*=9.0 Hz, ArH). ***m/z* (TOF ES)**: 379 (MH^+).

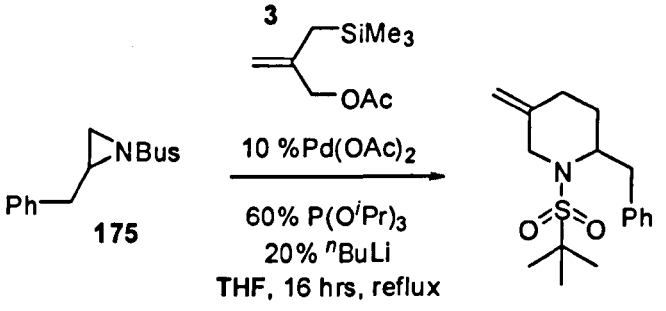
<u>179:</u> 19% ^{1}H NMR (500 MHz, DMSO): δ1.67 (3H, s, CH_3), 1.78 (3H, s, CH_3), 2.70-2.80 (2H, m, CH_2), 3.88-4.06 (4H, m, $CH_2C{=}C + CH_2OCO$), 4.19-4.29 (1H, m, CHN), 5.0 (2H, br s, $CH_2{=}C$), 7.10-7.27 (5H, m, PhH), 8.03 (2H, d, *J* = 9.0 Hz, ArH), 8.33 (2H, d, *J* = 9.0 Hz, ArH). ***m/z* (TOF ES)**: 433 (MH^+).

Synthesis of 2-benzyl-1-methanesulfonyl-5-methylene-piperidine *via* [3+3] Cycloaddition



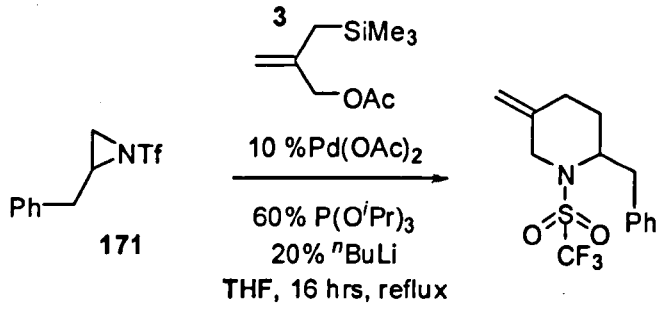
A solution of **169** (235 mg, 1.11 mmol, 1.5 eq) in THF (7.4 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (530 μL, 0.074 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (154 μL, 0.74 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (2:1 petroleum ether/EtOAc) to give mainly the starting material back (210 mg, 89%) but no trace of the desired piperidine.

Synthesis of 2-benzyl-5-methylene-1-(propane-2-sulfonyl)-piperidine *via* [3+3] Cycloaddition



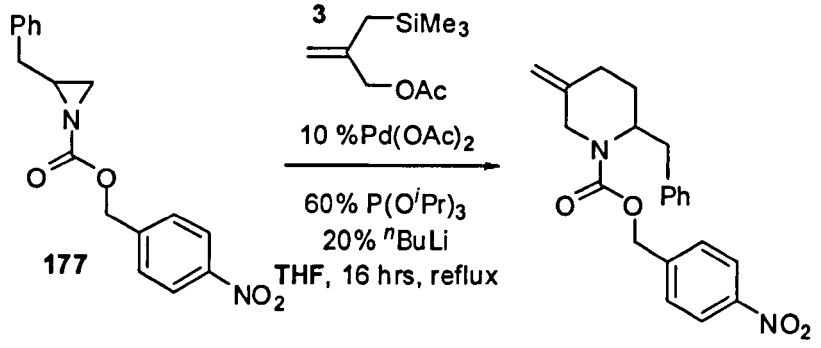
A solution of **175** (63 mg, 0.25 mmol, 1.5 eq) in THF (1.6 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (119 μL, 0.017 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (35 μL, 0.17 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo and the residue purified by flash chromatography (5:1 petroleum ether/EtOAc) to give only the starting material back but no trace of the desired piperidine.

Synthesis of 2-benzyl-5-methylene-1-trifluoromethanesulfonyl-piperidine *via* [3+3] Cycloaddition



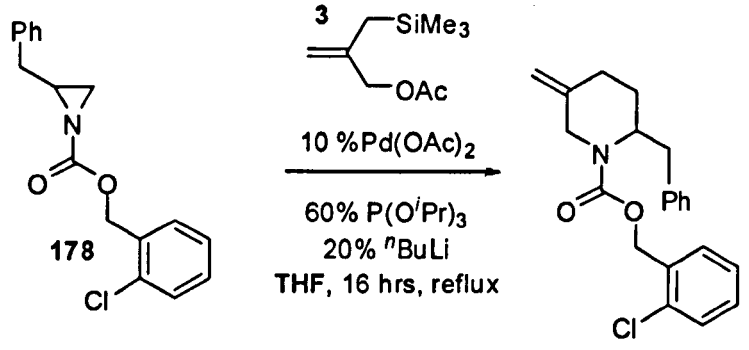
A solution of **171** (96 mg, 0.36 mmol, 1.5 eq) in THF (1.6 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (172 μL, 0.024 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (50 μL, 0.24 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo. The purification of the residue by flash chromatography resulted to a big mess since we were not able to characterize any compounds but no trace of the desired piperidine.

Synthesis of 2-benzyl-5-methylene-piperidine-1-carboxylic acid 4-nitro-benzyl ester *via* [3+3] Cycloaddition



A solution of **177** (123 mg, 0.39 mmol, 1.5 eq) in THF (2.6 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (188 μL, 0.026 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (55 μL, 0.26 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16h. Solvent was removed in vacuo and the residue purified by flash chromatography (5:1 petroleum ether/EtOAc) to give only the starting material back (105 mg, 85%) but no trace of the desired piperidine.

Synthesis of 2-benzyl-5-methylene-piperidine-1-carboxylic acid 2-chloro-benzyl ester *via* [3+3] Cycloaddition

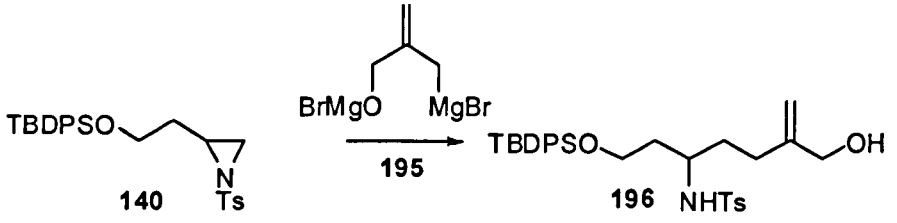


A solution of **178** (102 mg, 0.34 mmol, 1.5 eq) in THF (2.3 mL) was treated with freshly prepared 0.14 M palladium catalyst solution (161 μL, 0.023 mmol, 0.1 eq), and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **3** (47 μL, 0.23 mmol, 1.0 eq) and the reaction mixture heated at reflux for 16 h. Solvent was removed in vacuo

and the residue purified by flash chromatography (3:1 petroleum ether/EtOAc) to give only the starting material back (51 mg, 42%) but no trace of the desired piperidine.

6.Grignard route

Synthesis of *N*-(1-[2-(*t*-butyl-diphenyl-silanyloxy)-1-ethyl]-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide 196



Preparation of Grignard Reagent:

A 100 mL two-necked flask was charged with 2.0 M *n*-butyllithium (5.96 mL, 11.93 mmol, 4.0 eq.). Diethyl ether (8.5 mL) was added and the pale yellow reaction mixture was cooled to 0 °C. This was followed by addition of TMEDA (1.44 mL, 8.95 mmol, 3.0 eq.) and 2-methyl-2-propen-1-ol (0.25 mL, 2.98 mmol, 1.0 eq.) was added dropwise resulting in a bright yellow homogenous solution. The reaction mixture was stirred at 0 °C for 2 h then allowed to warm to room temperature generating a bright orange solution. The solution was cooled to 0 °C and dried magnesium bromide (1.11 g, 5.96 mmol, 2.0 eq.) was added generating a cloudy solution. The resulting suspension was stirred at room temperature for 1 hour.

Titration of the Grignard Reagent solution:

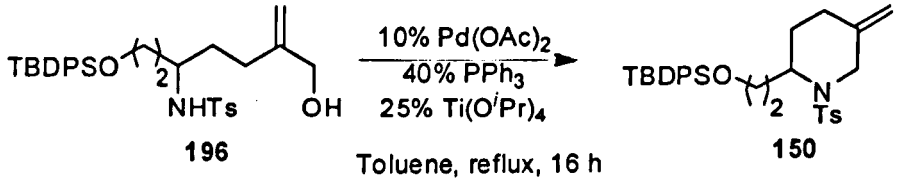
The titrateion was carried out using (*D,L*)-menthol (20 mg) and 1,10-phenanthroline in THF (1.0 mL). The Grgnard Reganet solution was added to the menthol solution until a red-purple colour persisted. The molarity of the solution was then calculated by dividing the number of mmol of menthol used by the

volume in mL of Grignard solution used to achieve the colour change. This gave a concentration between 0.1 and 0.2M.

Reaction with aziridine:

3-(*Tert*-butyl-diphenyl-silanyloxyethyl)-1-(toluene-4-sulfonyl)-aziridine **140** (270 g, 0.56 mmol, 1.0 eq) in THF (8.5 mL) was added to the solution of Grignard reagent **195** prepared above *via* cannula. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride then extracted with ethyl acetate and the combined organic extracts were washed with brine. The solution was dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 2:1 petroleum ether/ethyl acetate to give **196** as a clear oil, 235 mg (76%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.05 (9H, s, C(CH_3)$_3$), 1.41-1.72 (4H, m, CH_2), 2.0-2.11 (2H, m, =C-CH_2), 2.40 (3H, s, ArCH_3), 3.38-3.55 (2H, m, TBDPSOCH_2), 3.60-3.72 (1H, m, C*H*-N), 4.02 (2H, s, CH_2-O), 4.80 (1H, br s, C=C*H*), 5.01 (1H, br s, C=C*H*), 5.42 (1H, d, *J*=7.5 Hz, NH), 7.22 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.50 (6H, m, Ar*H*), 7.54-7.62 (4H, m, Ar*H*), 7.70 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (125 MHz, $CDCl_3$)**: δ19.0, 21.5, 26.9, 28.6, 29.3, 30.9, 52.4, 61.2, 66.0, 105.9, 109.8, 127.1, 129.9, 132.9, 133.0, 135.5, 135.6, 143.1, 148.2. **FTIR (CH_2Cl_2)**: 3475 (br), 3276 (br), 2929 (s), 2851 (m), 1657 (w), 1423.1 (m), 1323 (m), 1157 (s), 1112 (s). ***m/z* (TOF ES)**: 574 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{41}NO_4NaSiS$** (MNa^+): 574.2423. Found: 574.2396.

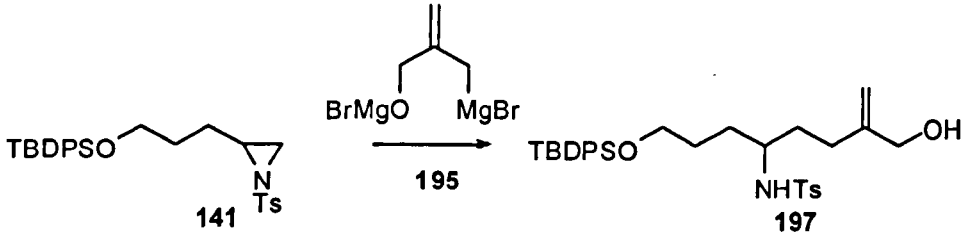
Synthesis of 2-(*tert*-butyl-diphenyl-silanoxyethyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 150 *via* Grignard



A flask containing 4Å molecular sieves (115 mg) was flame dried in vacuo. After cooling, palladium acetate (14 mg, 0.065 mmol, 0.1 eq) and triphenylphosphine

(68 mg, 0.26 mmol, 0.4 eq) were added together with toluene (2.9 mL). To the resulting yellow reaction mixture was added a solution of **196** (356 mg, 0.65 mmol, 1.0 eq) in toluene (3.9 mL) *via* cannula followed by titanium isopropoxide (48 μL, 0.16 mmol, 0.25 eq). The reaction mixture was placed under reflux for 16 h. The reaction was quenched with 1 M HCl from pH~6 to pH~2 and extracted with EtOAc. The aqueous layer were basified with 1 M NaOH from pH~2 to pH~6-7 and further extracted with EtOAc. The combined organic fractions were washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 20:1 petroleum ether/ethyl acetate to give **150** as a clear oil, 289 mg (84%). Characterisation data for this compound has been described earlier.

Synthesis of *N*-(1-[2-(*t*-butyl-diphenyl-silanyloxy)-1-propyl]-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide 197



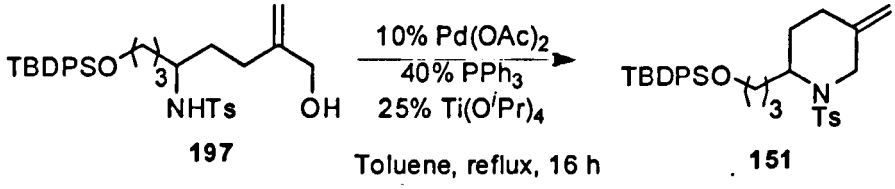
Preparation of Grignard Reagent:

A 100 mL two-necked flask was charged with 1.7M *n*-butyllithium (14 mL, 23.84 mmol, 4.0 eq.). Diethyl ether (17 mL) was added and the pale yellow reaction mixture was cooled to 0 °C. This was followed by addition of TMEDA (2.88 mL, 17.88 mmol, 3.0 eq.) and 2-methyl-2-propen-1-ol (0.5 mL, 5.96 mmol, 1.0 eq.) was added dropwise resulting in a bright yellow homogenous solution. The reaction mixture was stirred at 0 °C for 2 h then allowed to warm to room temperature generating a bright orange solution. The solution was cooled to 0 °C and dried magnesium bromide (2.22 g, 11.92 mmol, 2.0 eq.) was added generating a cloudy solution. The resulting suspension was stirred at room temperature for 1 hour.

Reaction with aziridine:

3-(*Tert*-butyl-diphenyl-silanyloxypropyl)-1-(toluene-4-sulfonyl)-aziridine **141** (270 g, 0.56 mmol, 1.0 eq) in THF (17 mL) was added to the solution of Grignard reagent **195** prepared above *via* cannula. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride then extracted with ethyl acetate and the combined organic extracts were washed with brine. The solution was dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 2:1 petroleum ether/ethyl acetate to give **197** as a clear oil, 410 mg (73%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.01 (9H, s, C(C*H*$_3$)$_3$), 1.29-1.76 (6H, m, CH_2), 1.98 (2H, t, *J*=7 Hz, =C-C*H*$_2$), 2.36 (3H, s, ArC*H*$_3$), 3.17-3.30 (1H, m, C*H*-N), 3.44-3.53 (2H, m, TBDPSOC*H*$_2$), 3.97 (2H, s, C*H*$_2$-O), 4.56 (1H, d, *J*=8.0 Hz, NH), 4.76 (1H, br s, C=C*H*), 4.99 (1H, br s, C=C*H*), 7.22 (2H, d, *J*=8.0 Hz, Ar*H*), 7.33-7.44 (6H, m, Ar*H*), 7.57-7.65 (4H, m, Ar*H*), 7.70 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 26.8, 28.2, 28.5, 30.9, 33.1, 53.6, 63.4, 65.8, 105.9, 109.8, 127.0, 127.7, 129.6, 129.7, 133.7, 135.5, 143.2, 148.1. **FTIR (CH_2Cl_2)**: 3479 (br), 3277 (br), 2930 (s), 2857 (m), 1654 (w), 1598 (w), 1428 (m), 1323 (m), 1157 (s), 1111 (s). ***m/z* (TOF ES)**: 566 (MH^+). **HRMS (TOF ES) calcd. for $C_{32}H_{44}NO_4SiS$** (MH^+): 566.2760. Found: 566.2769.

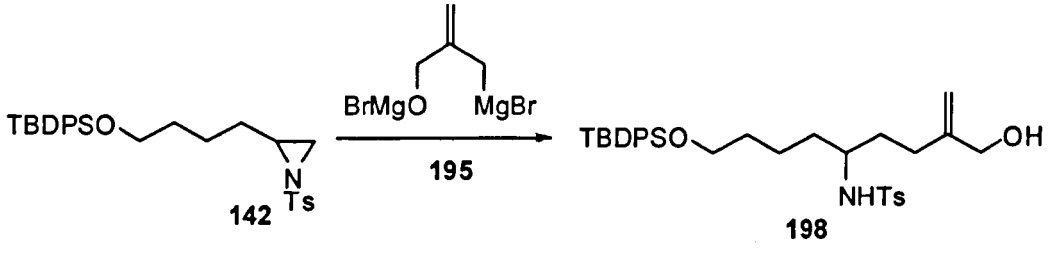
Synthesis of 2-(*tert*-butyl-diphenyl-silanoxypropyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 151 *via* Grignard



A flask containing 4Å molecular sieves (77 mg) was flame dried in vacuo. After cooling, palladium acetate (10 mg, 0.04 mmol, 0.1 eq) and triphenylphosphine (45 mg, 0.17 mmol, 0.4 eq) were added together with toluene (2 mL). To the resulting yellow reaction mixture was added a solution of **197** (245 mg, 0.43 mmol, 1.0 eq) in toluene (2.6 mL) *via* cannula followed by titanium isopropoxide (32 μL, 0.11

mmol, 0.25 eq). The reaction mixture was placed under reflux for 16 h. The reaction was quenched with 1 M HCl from pH~6 to pH~2 and extracted with EtOAc. The aqueous layer were basified with 1 M NaOH from pH~2 to pH~6-7 and further extracted with EtOAc. The combined organic fractions were washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 20:1 petroleum ether/ethyl acetate to give **151** as a clear oil, 200 mg (84%). Characterisation data for this compound has been described earlier.

Synthesis of *N*-(1-[2-(*t*-butyl-diphenyl-silanyloxy)-1-butyl]-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide 198



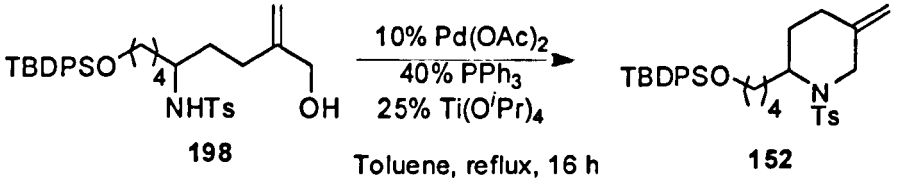
Preparation of Grignard Reagent:

A 100 mL two-necked flask was charged with 2.5 M *n*-butyllithium (9.54 mL, 23.84 mmol, 4.0 eq.). Diethyl ether (17 mL) was added and the pale yellow reaction mixture was cooled to 0 °C. This was followed by addition of TMEDA (2.88 mL, 17.88 mmol, 3.0 eq.) and 2-methyl-2-propen-1-ol (0.5 mL, 5.96 mmol, 1.0 eq.) was added dropwise resulting in a bright yellow homogenous solution. The reaction mixture was stirred at 0 °C for 2 h then allowed to warm to room temperature generating a bright orange solution. The solution was cooled to 0 °C and dried magnesium bromide (2.22 g, 11.92 mmol, 2 eq.) was added generating a cloudy solution. The resulting suspension was stirred at room temperature for 1 hour.

Reaction with aziridine:

3-(*Tert*-butyl-diphenyl-silanyloxybutyl)-1-(toluene-4-sulfonyl)-aziridine **142** (147 g, 0.29 mmol, 1.0 eq) in THF (17 mL) was added to the solution of Grignard reagent **195** prepared above *via* cannula. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride then extracted with ethyl acetate and the combined organic extracts were washed with brine. The solution was dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 2:1 petroleum ether/ethyl acetate to give **198** as a clear oil, 180 mg (99%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.03 (9H, s, C(C*H*$_3$)$_3$), 1.10-1.67 (8H, m, C*H*$_2$), 1.93-2.12 (3H, m, OH + =C-C*H*$_2$), 2.34 (3H, s, ArC*H*$_3$), 3.12-3.28 (1H, m, C*H*-N), 3.46-3.58 (2H, m, TBDPSOC*H*$_2$), 3.97 (2H, s, C*H*$_2$-O), 4.74 (1H, br s, C=C*H*), 4.88 (1H, d, *J*=8.5, NH), 4.98 (1H, br s, C=C*H*), 7.22 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.47 (6H, m, Ar*H*), 7.59-7.68 (4H, m, Ar*H*), 7.73 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 21.6, 26.9, 28.4, 30.9, 32.2, 33.0, 53.8, 63.4, 65.8, 105.9, 109.7, 127.0, 127.6, 129.6, 133.4, 135.5, 138.4, 143.2, 148.2. **FTIR (CH_2Cl_2)**: 3484 (br), 3279 (br), 2932 (s), 2859 (m), 1654 (w), 1598 (w), 1467 (m), 1428 (s), 1323 (m), 1157 (s), 1111 (s). ***m/z* (TOF ES)**: 580 (MH^+). **HRMS (TOF ES) calcd. for $C_{33}H_{46}NO_4SiS$** (MH^+): 580.2917. Found: 580.2924.

Synthesis of 2-(*tert*-butyl-diphenyl-silanoxybutyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine 152 *via* Grignard

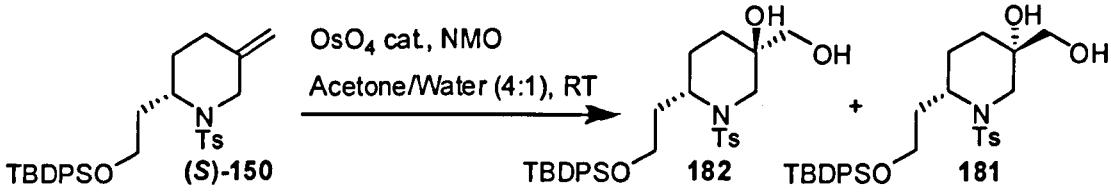


A flask containing 4Å molecular sieves (85 mg) was flame dried in vacuo. After cooling, palladium acetate (11 mg, 0.05 mmol, 0.1 eq) and triphenylphosphine (49.6 mg, 0.19 mmol, 0.4 eq) were added together with toluene (2.1 mL). To the resulting yellow reaction mixture was added a solution of **198** (274 mg, 0.47 mmol, 1.0 eq) in toluene (2.8 mL) *via* cannula followed by titanium isopropoxide

(35 μL, 0.12 mmol, 0.25 eq). The reaction mixture was placed under reflux for 16 h. The reaction was quenched with 1 M HCl from pH~6 to pH~2 and extracted with EtOAc. The aqueous layer were basified with 1M NaOH from pH~2 to pH~6-7 and further extracted with EtOAc. The combined organic fractions were washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 20:1 petroleum ether/ethyl acetate to give **152** as a clear oil, 240 mg (90%). Characterisation data for this compound has been described earlier.

7.Functionalisation

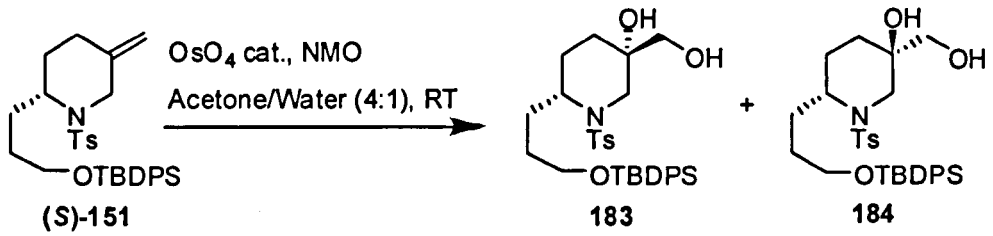
Synthesis of 6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-hydroxymethyl-1-(toluene-4-sulfonyl)-piperidin-3-ol 181 and 182



A solution of **(*S*)-150** (145 mg, 0.27 mmol, 1.0 eq) in a 4:1 mixture of acetone:water (30 mL), was treated with NMO (96 mg, 0.82 mmol, 3.0 eq) and a crystal of osmium tetroxide. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of a saturated aqueous solution of Na_2SO_3. The reaction was then evaporated to dryness *in vacuo* and the residue was extracted with DCM/MeOH (10:1). The organic phase was dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 10:1 DCM/MeOH to give a mixture of two inseparable diastreoisomers **181** and **182** in a ratio 5:1, 110 mg (71%). The chemical shifts of the major diastereoisomer only are reported, since many of the peaks of the minor diastereoisomer were masked. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.96 (9H, s, $C(C_{H3})_3$), 1.35-1.77 (6H, m, CH_2), 2.26 (3H, s, ArCH_3), 3.17-3.50 (4H, m, CH_2-O), 3.70 (1H, d, *J*=13.5 Hz, C6*H*), 4.02 (1H, d, *J*=13.5 Hz, C6*H'*), 4.12-4.30 (1H, m, C2*H*), 7.05 (2H, d, *J*=8.0 Hz, Ar*H*), 7.24-7.41 (6H, m, Ar*H*), 7.45-7.58 (6H, m,

Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.1, 21.5, 25.7, 26.8, 28.2, 29.3, 45.1, 49.3, 60.9, 64.3, 70.2, 126.6, 127.2, 127.7, 129.8, 133.5, 135.5, 138.1, 143.1. **FTIR (CH_2Cl_2)**: 3440 (br), 2932 (m), 1428 (w), 1333 (m), 1159 (s), 1109 (s). ***m/z* (TOF ES)**: 590 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{41}NO_5NaSiS$** (MNa^+): 590.2372. Found: 590.2366.

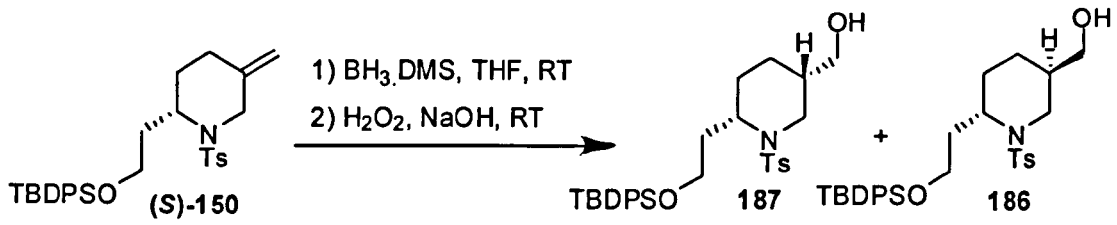
Synthesis of 6-[2-(*tert*-butyl-diphenyl-silanyloxy)-propyl]-3-hydroxymethyl-1-(toluene-4-sulfonyl)-piperidin-3-ol 183 and 184



A solution of **(*S*)-151** (177 mg, 0.32 mmol, 1.0 eq) in a 4:1 mixture of acetone:water (36 mL), was treated with NMO (114 mg, 0.97 mmol, 3.0 eq) and a crystal of osmium tetroxide. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of a saturated aqueous solution of Na_2SO_3. The reaction was then evaporated to dryness *in vacuo* and the residue was extracted with DCM/MeOH (10:1). The organic phase was dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 10:1 DCM/MeOH to give a mixture of two inseparable diastreoisomers **183** and **184** in a ratio 6:1, 156 mg (83%). The chemical shifts of the major diastereoisomer only are reported, since many of the peaks of the minor diastereoisomer were masked. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.94 (9H, s, C(CH_3)$_3$), 1.05-1.20 (2H, m, CH_2), 1.23-1.69 (6H, m, CH_2), 2.24 (3H, s, ArCH_3), 3.32-3.43 (2H, m, CH_2-O), 3.61-3.72 (2H, m, CH_2-O), 3.73 (1H, d, *J*=13.5 Hz, C6*H*-N), 3.80-3.92 (1H, m, C2*H*), 3.92 (1H, d, *J*=13.5 Hz, C6*H'*-N), 7.10 (2H, d, *J*=8.0 Hz, Ar*H*), 7.23-7.40 (6H, m, Ar*H*), 7.46-7.59 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz in $CDCl_3$)**: δ19.1, 21.5, 23.2, 24.9, 25.6, 28.2, 29.6, 45.1, 47.0, 60.4, 63.3, 70.1, 126.7, 127.2, 127.7, 129.6, 133.8, 135.5, 138.3, 143.2. **FTIR (CH_2Cl_2)**: 3418 (br), 2932 (m), 2858 (m), 1428 (w), 1332 (m), 1155 (s), 1111 (s).

***m/z* (TOF ES)**: 590 (MNa^+). **HRMS (TOF ES) calcd. for $C_{32}H_{43}NO_5NaSiS$** (MNa^+): 604.2529. Found: 604.2525.

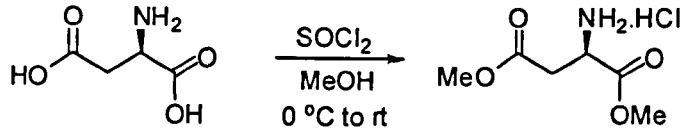
Synthesis of 2-(*tert*-butyl-diphenyl-silanoxyethyl)-5-hydroxymethyl-1-(toluene-4-sulfonyl)-piperidine 186 and 187



To a solution of **(*S*)-150** (80 mg, 0.15 mmol, 1.0 eq) in THF (3.4 mL) at 0 °C was added borane-dimethylsulfide (42 μL, 0.45 mmol, 3.0 eq) and the temperature was raised to rt over 2.5 h. After 2.5 h, an aqueous solution of NaOH (1 M, 450 μL, 0.45 mmol, 3.0 eq) and hydrogen peroxide (30% in water, 49 mL, 0.45 mmol, 3.0 eq) were slowly added to the reaction mixture and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 3:1 petroleum ether/ethyl acetate to give a mixture of two inseparable diastreoisomers **186** and **187** in a ratio 6:1, 121 mg (76%). The chemical shifts of the major diastereoisomer only are reported, since many of the peaks of the minor diastereoisomer were masked. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.02 (9H, s, C(CH_3)$_3$), 1.31-1.89 (6H, m, CH_2), 2.33 (3H, s, ArCH_3), 2.85 (1H, dd, *J*=2.5, 14.0 Hz, C6*H*), 3.26-3.65 (4H, m, CH_2-O), 3.79 (1H, d, *J*=14.0 Hz, C6*H'*), 4.17-4.30 (1H, m, C2*H*), 7.12 (2H, d, *J*=8.0 Hz, Ar*H*), 7.30-7.49 (6H, m, Ar*H*), 7.52-7.70 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.1, 19.8, 21.5, 23.7, 26.8, 31.5, 34.9, 40.0, 50.0, 61.1, 61.2, 127.0, 127.7, 129.6, 129.7, 133.5, 135.5, 138.3, 142.8. **FTIR (CH_2Cl_2)**: 3508 (br), 2931 (m), 1428 (w), 1329 (m), 1162 (s), 1093 (s). ***m/z* (TOF ES)**: 574 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{41}NO_4NaSiS$** (MNa^+): 574.2423. Found: 574.2408.

8.Natural product

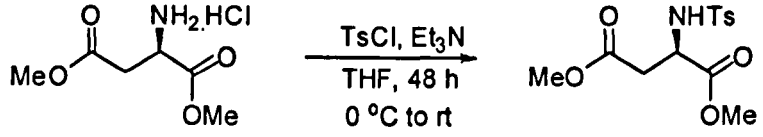
Synthesis of (2*R*)-amino-succinic acid dimethyl ester (*R*)-144[107, 108, 169]



(*D*)-aspartic acid (*R*)-144

Thionyl chloride (3.1 ml, 42.07 mmol, 1.4 eq) was added dropwise to a solution of *(D)*-(-)-aspartic acid (4 g, 30.05 mmol, 1.0 eq) in dry methanol (40 mL) at 0 °C, the reaction was allowed to warm to room temperature and stirred for 48 h. The reaction was evaporated under reduced pressure to give a light yellow oil and then triturated with diethyl ether and filtered to give **(*R*)-144** as a white solid (5.90 g, 99%). $[\alpha]_D^{22}$=-15 (c=1). **m.p.**=113-114 °C (lit. **m.p.**=116-117 °C)[107]. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ2.73 (1H, dd, *J*=7.5, 16.5 Hz, CH-*H*), 2.82 (1H, dd, *J*=4.5, 16.5 Hz, CH-*H*), 3.71 (3H, s, CH_3), 3.75 (3H, s, CH_3), 3.85 (1H, dd, *J*=4.5, 7.5 Hz, C*H*-N).

Synthesis of (2*R*)-(toluene-4-sulfonylamino)-succinic acid dimethyl ester (*R*)-145

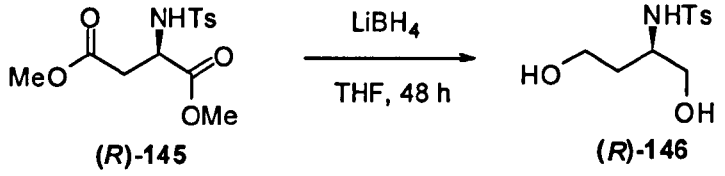


(*R*)-144 (*R*)-145

A flask was charged with diester **(*R*)-144** (5.80 g, 29.36 mmol, 1.0 eq) and THF (22 mL) and cooled to 0 °C. Distilled triethylamine (18 mL, 129.18 mmol, 4.4 eq) and then p-toluenesulfonylchloride (6.1 g, 32.23 mmol, 1.1 eq) were added and the mixture stirred at room temperature for 48 h. The reaction mixture was acidified with HCl (32%) to pH 3 and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution then

dried over $MgSO_4$ and evaporated under reduce pressure to give **(*R*)-145** as an oily yellow residue (8.1 g, 87%). $[\alpha]_D^{22}$= +4 (c=1.0). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ2.41 (3H, m, C*H*$_3$), 2.84 (1H, dd, *J*=5.0, 17.0, *H*-CH-C=O), 2.97 (1H, dd, *J*=5.0, 17.0, *H*-CH-C=O), 3.59 (3H, s, C*H*$_3$), 3.66 (3H, s, C*H*$_3$), 4.06-4.18 (1H, m, C*H*-N), 5.60 (1H, d, *J*=8.0 Hz, N*H*), 7.30 (2H, d, *J*=8.0 Hz, Ar*H*), 7.73 (2H, d, *J*=8.0 Hz, Ar*H*). **FTIR (thin film)**: 3849 (br), 3061 (m), 2956 (m), 1748 (s), 1599 (m), 1440 (s), 1346 (s).

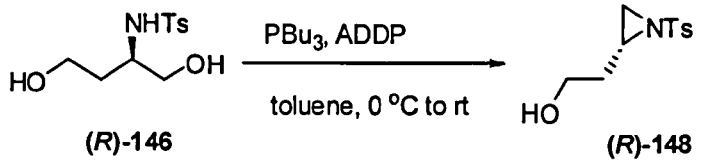
Synthesis of *N*-(3-hydroxy-1-hydroxymethyl-propyl)-4-methyl-benzenesulfonamide (*R*)-146[171]



(*R*)-145 (*R*)-146

A solution of the diester **(*R*)-145** (1 g, 3.17 mmol, 1.0 eq) in THF (15 ml) was added dropwise *via* cannula to a solution of lithium borohydride (152 mg, 6.80 mmol, 2.2 eq) in THF (23 mL) at 0 °C and stirred for 48 h. Aqueous potassium carbonate solution and water were added to quench the reaction and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure and then purified by flash chromatography to provide **(*R*)-146** as a white powder, 1.37 g (84%). **m.p.**=88 °C, **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.59-1.77 (2H, m, C*H*$_2$), 1.91 (1H, br, OH), 2.43 (3H, s, ArC*H*$_3$), 3.37-3.87 (5H, m, 2 x C*H*$_2$ + C*H*-N), 7.36 (2H, d, *J*=8.5 Hz, Ar*H*), 7.66 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.6, 34.4, 53.0, 58.7, 64.6, 127.1, 129.8, 140.5, 143.7.

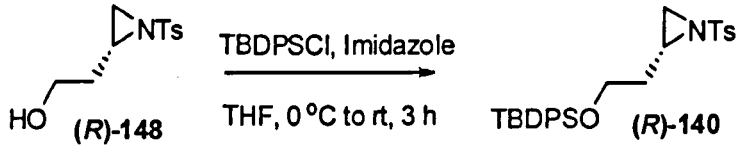
Synthesis of 2-hydroxyethyl-1-(toluene-4-sulfonyl)-aziridine (*R*)-148 *via* Mitsunobu reaction



(*R*)-146 (*R*)-148

A 50 mL round-bottomed-flask was charged with **(*R*)-146** (548 mg, 2.11 mmol, 1.0 eq), distilled tributylphosphine (840 µL, 3.38 mmol, 1.6 eq) and toluene (20 mL) at room temperature. The reaction mixture was cooled to 0 °C and 1,1'-azodicarbonyldipiperidine (ADDP) (800 mg, 3.17 mmol, 1.5 eq) was added in small portions. The reaction mixture was stirred 2 h at 0 °C, then it was allowed to reach rt and stirred overnight. The reaction mixture was evaporated under reduced pressure, dissolved in a mixture DCM/MeOH (10:1), dried on silica and purified by flash column chromatography (1:1 petroleum ether/EtOAc) to provide a colourless oil, **(*R*)-148** 411 mg (81%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.36-1.53 (1H, m, *H*-CH), 1.89-2.10 (1H, m, *H*-CH), 2.14 (1H, d, *J*=4.5 Hz, CH*H* aziridine) 2.44 (3H, s, ArCH_3), 2.64 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.83-2.97 (1H, m, C*H* aziridine), 3.55-3.74 (2H, m, CH_2OH), 7.34 (2H, d, *J*=8.0 Hz, Ar*H*), 7.82 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ25.8, 29.6, 42.1, 55.3, 68.2, 128.3, 131.8, 132.0, 133.3. **FTIR (thin film)**: 3527 (br), 2925 (w), 1597 (w), 1320 (m), 1232 (w), 1160 (s), 1092 (w) cm^{-1}. ***m/z* (TOF ES)**: 264 (MNa^+). **HRMS (TOF ES) calcd. for $C_{11}H_{15}NO_3NaS$ (MNa^+)**: 264.0670. Found: 264.0666.

Synthesis of (*R*)-2-(*tert*-butyl-diphenyl-silanoxyethyl)-1-(toluene-4-sulfonyl)-aziridine (*R*)-140



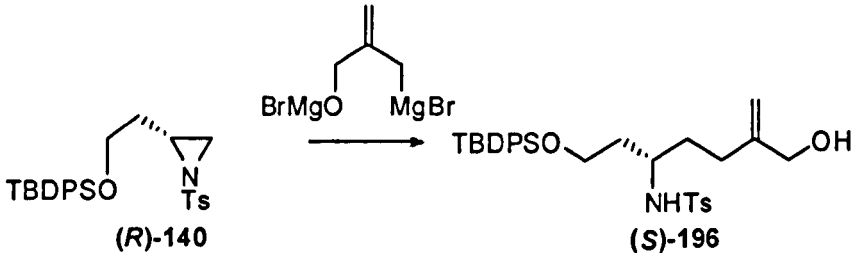
(*R*)-148 (*R*)-140

Substrate **(*R*)-148** was dissolved in THF (2.5 mL) and the solution was cooled to 0 °C. TBDPSCl (552 µL, 2.12 mmol, 1.25 eq) and imidazole (347 mg, 5.10 mmol,

3.0 eq) were added. The reaction mixture was allowed to reach rt and stirred for 3 h. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over magnesium sulphate and concentrated under vacuum. Purification of the resulting oil by silica gel chromatography (10/1, petroleum/EtOAc) provided **(*R*)-140** as a yellow oil (734 mg, 90%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.96 (9H, s, C(CH_3)$_3$), 1.42-1.74 (2H, m, CH_2), 2.05 (1H, d, *J*=4.5 Hz, CH*H* aziridine) 2.32 (3H, s, ArCH_3), 2.60 (1H, d, *J*=7.0 Hz, CH*H* aziridine), 2.76-2.88 (1H, m, C*H* aziridine), 3.49 (2H, dd, *J*=5.5, 7.0 Hz, CH_2OTBDPS), 7.18 (2H, d, *J*=8.0 Hz, Ar*H*), 7.25-7.41 (6H, m, Ar*H*), 7.48-7.57 (4H, m, Ar*H*), 7.74 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.1, 21.6, 26.8, 33.5, 34.4, 38.0, 61.2, 127.7, 128.0, 129.6, 129.7, 133.5, 135.5, 142.3, 144.4. **FTIR (thin film)**: 3071 (w), 2930 (m), 2857 (m), 1598 (w), 1472 (w), 1428 (m), 1326 (s), 1164 (s), 1093 (s) cm^{-1}. ***m/z* (TOF ES)**: 502 (MNa^+). **HRMS (TOF ES) calcd. for $C_{27}H_{33}NO_3NaSiS$ (MNa^+)**: 502.1848. Found: 502.1870.

8.1.Grignard route

Synthesis of *N*-(1-[2-(*t*-butyl-diphenyl-silanyloxy)-1-ethyl]-4-hydroxymethyl-pent-4-enyl)-4-methyl-benzenesulfonamide (*S*)-196

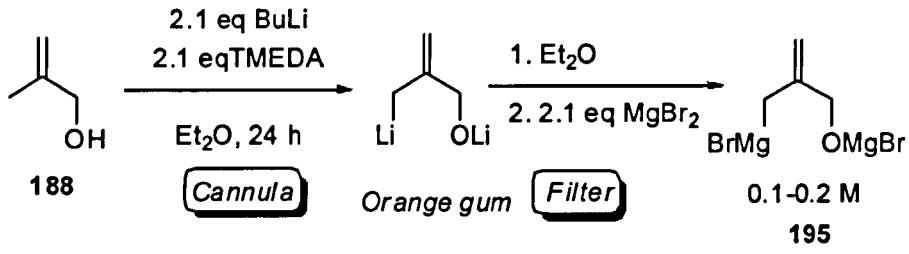


Preparation of Grignard Reagent

A 100 mL two-necked flask was charged with 2.0 M *n*-butyllithium (5.96 mL, 11.93 mmol, 4.0 eq.). Diethyl ether (8.5 mL) was added and the pale yellow reaction mixture was cooled to 0 °C. This was followed by addition of TMEDA (1.44 mL, 8.95 mmol, 3.0 eq.) and 2-methyl-2-propen-1-ol (0.25 mL, 2.98 mmol,

1.0 eq.) was added dropwise resulting in a bright yellow homogenous solution. The reaction mixture was stirred at 0 °C for 2 h then allowed to warm to room temperature generating a bright orange solution. The solution was cooled to 0 °C and dried magnesium bromide (1.11 g, 5.96 mmol, 2.0 eq.) was added generating a cloudy solution. The resulting suspension was stirred at room temperature for 1 hour.

Improved preparation of Grignard Reagent



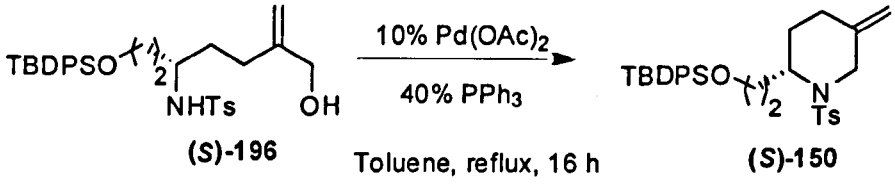
To *n*-BuLi (15 mL, 10 M, 2.1 eq) at 0 °C were added anhydrous ether (114 mL) and TMEDA (22.6 mL, 2.1 eq). After the solution was cooled at -78 °C, methallyl alcohol **188** was added dropwise (6.4 mL, 1.0 eq) and the reaction was stirred at -78 °C for 1 h. The bath was then removed and the resulting mixture was vigorously stirred for 24 h. After this time, stirring was stopped for 30 min and the solvent was removed *via* cannula filtration. Anhydrous ether (100 mL) was added to the remaining orange solid and the suspension was cooled to 0 °C. At this point, a solution of freshly prepared $MgBr_2$ [prepared from magnesium (3.9 g, 2.1 equiv) and dibromoethane (13.8 mL, 2.1 eq) in ether (58 mL)] was transferred quickly *via* cannula to the suspension. After addition, the bath was removed and the suspension was vigorously stirred for 30-45 min. At this stage, the stirring was stopped and the Grignard solution was separated from colorless solid via cannula. The Grignard solution was stored at 0 °C under argon.

Reaction with aziridine

A solution of Grignard reagent prepared above (0.14 M, 10 mL, 1.40 mmol, 2.5 eq) was added to 3-(*tert*-butyl-diphenyl-silanyloxyethyl)-1-(toluene-4-sulfonyl)-

aziridine **(*R*)-140** (270 mg, 0.56 mmol, 1.0 eq) in THF (6 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride then extracted with ethyl acetate and the combined organic extracts were washed with brine. The solution was dried over $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by column chromatography in 2:1 petroleum ether/ethyl acetate to give **(*S*)-196** as a clear oil, 260 mg (85%). **^{1}H NMR (250 MHz in $CDCl_3$)**: δ1.05 (9H, s, C(CH_3)$_3$), 1.41-1.72 (4H, m, CH_2), 2.0-2.11 (2H, m, =C-CH_2), 2.40 (3H, s, ArCH_3), 3.38-3.55 (2H, m, TBDPSOCH_2), 3.60-3.72 (1H, m, C*H*-N), 4.02 (2H, s, CH_2-O), 4.80 (1H, br, C=C*H*), 5.01 (1H, br, C=C*H*), 5.42 (1H, d, *J*=7.5 Hz, N*H*), 7.22 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.50 (6H, m, Ar*H*), 7.54-7.62 (4H, m, Ar*H*), 7.70 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (125 MHz in $CDCl_3$)**: δ19.0, 21.5, 26.9, 28.6, 29.3, 30.9, 52.4, 61.2, 66.0, 105.9, 109.8, 127.1, 129.9, 132.9, 133.0, 135.5, 135.6, 143.1, 148.2. **FTIR (CH_2Cl_2)**: 3475 (br), 3276 (br), 2929 (s), 2851 (m), 1657 (w), 1423 (m), 1323 (m), 1157 (s), 1112 (s). ***m/z* (TOF ES)**: 574 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{41}NO_4NaSiS$ (MNa^+)**: 574.2423. Found: 574.2396.

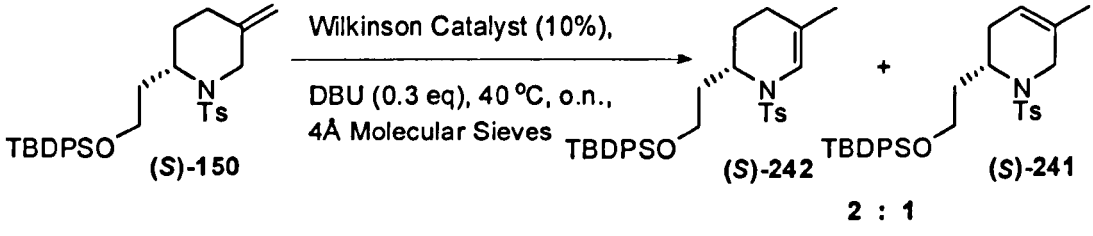
Synthesis of 2-(*tert*-butyl-diphenyl-silanoxyethyl)-5-methylene-1-(toluene-4-sulfonyl)-piperidine (*S*)-150 *via* Grignard



A flask containing 4Å molecular sieves (115 mg) was flame dried in vacuo. After cooling, palladium acetate (15 mg, 0.065 mmol, 0.1 eq) and triphenylphosphine (68 mg, 0.26 mmol, 0.4 eq) were added together with toluene (2.9 mL). To the resulting yellow reaction mixture was added a solution of **(*S*)-196** (356 mg, 0.65 mmol, 1.0 eq) in toluene (3.9 mL) *via* cannula. The reaction mixture was placed under reflux for 16 h. The reaction was quenched with 1 M HCl from pH~6 to pH~2 and extracted with EtOAc. The aqueous layer were basified with 1 M NaOH from pH~2 to pH~6-7 and further extracted with EtOAc. The combined organic fractions were washed with brine, dried over $MgSO_4$ and solvent was

removed *in vacuo*. The residue was purified by column chromatography in 20:1 petroleum ether/ethyl acetate to give **(*S*)-150** as a clear oil, 289 mg (84%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.05 (9H, s, C(CH_3)$_3$), 1.30-1.49 (2H, m, CH_2), 1.65-1.82 (2H, m, CH_2), 1.83-2.04 (2H, m, CH_2), 2.37 (3H, s, ArCH_3), 3.52 (1H, d, *J*=15.0 Hz, C6-*H*), 3.57-3.77 (2H, m, CH_2OTBDPS), 4.05-4.15 (1H, m, C2-*H*), 4.21 (1H, d, *J*=15.0 Hz, C6-*H'*), 4.67 (1H, br s, C=C*H*H), 4.76 (1H, br s, C=CH*H*), 7.18 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.47 (6H, m, Ar*H*), 7.59-7.70 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 26.9, 27.3, 28.0, 32.9, 46.5, 50.0, 61.1, 110.3, 127.4, 127.7, 129.4, 129.6, 133.6, 135.6, 136.8, 142.3, 144.4. **FTIR (CH_2Cl_2)**: 3060 (w), 2931 (m), 2847 (m), 1466 (w), 1428 (m), 1341 (s), 1160 (s), 1111 (s) cm^{-1}. ***m/z* (TOF ES)**: 556 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{39}NO_3NaSiS$ (MNa^+)**: 556.2318. Found: 556.2330.

Synthesis of 2-(*tert*-butyl-diphenyl-silanyloxyethyl)-5-methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (*S*)-242 and 2-(*tert*-butyl-diphenyl-silanyloxyethyl)-5-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine (*S*)-241

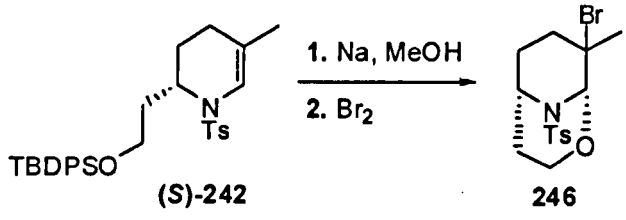


The catalyst solution was freshly prepared as follows: a flask containing 4Å molecular sieves (190 mg) was flame dried in vacuo. Wilkinson's catalyst (17 mg, 0.019 mmol, 0.1 eq), DBU (9 μL, 0.06 mmol, 0.3 eq) and ethanol (6 mL) were added and this solution was added to the substrate **(*S*)-150** *via* cannula. The reaction mixture was stirred at 40 ^{0}C for 16 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (30:1 petroleum ether/EtOAc) to give the product as a mixture 2:1 in favour of piperidine **(*S*)-242** (126 mg, 66%). **(*S*)-242:** **$[\alpha]_D^{22}$=-13.0** (c=0.012). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.05 (9H, s, C(CH_3)$_3$), 1.17-1.34 (4H, m, CH_2), 1.54 (3H, s, CH_3), 1.87-1.99 (2H, m, CH_2), 2.40 (3H, s, CH_3Ar), 3.73 (2H, m, CH_2-O), 3.93-4.05 (1H, m, C*H*-N), 6.29 (1H, s,

H-C=C), 7.24 (2H, d, *J*=7.5 Hz, Ar*H*), 7.32-7.49 (6H, m, Ar*H*), 7.56-7.69 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 20.9, 21.6, 22.7, 22.8, 26.9, 34.4, 49.3, 60.7, 118.0, 118.2, 127.1, 127.7, 129.6, 135.5, 135.6, 142.0, 143.2, 144.5. ***m/z* (TOF ES)**: 556 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{39}NO_3NaSiS$ (MNa^+)**: 556.2161. Found: 556.2138.

(*S*)-241: ^{1}H NMR (250 MHz, $CDCl_3$): δ1.01 (9H, s, C(C*H*$_3$)$_3$), 1.46-1.66 (5H, m, C*H*$_2$), 1.69 (1H, dd, *J*=5.0 Hz, *J*=17.0 Hz, HC*H*), 2.02-2.20 (1H, m, *H*CH), 2.36 (3H, s, C*H*$_3$Ar), 3.16 (1H, d, *J*=18.0 Hz, CH*H*-N), 3.48-3.71 (2H, m, C*H*$_2$-O) 3.86 (1H, d, *J*=18.0 Hz, C*H*H-N), 4.13-4.25 (1H, m, C*H*-N), 5.19-5.31 (1H, m, *H*-C=C), 7.15 (2H, d, *J*=8.0 Hz, Ar*H*), 7.33-7.46 (6H, m, Ar*H*), 7.54-7.66 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz in $CDCl_3$)**: δ19.3, 19.7, 20.5, 21.4, 21.9, 22.3, 44.6, 51.5, 62.3, 118.3, 120.3, 121.2, 126.9, 127.7, 129.5, 129.7, 133.4, 135.6, 143.9. ***m/z* (TOF ES)**: 556 (MNa^+). **HRMS (TOF ES) calcd. for $C_{31}H_{39}NO_3NaSiS$ (MNa^+)**: 556.2161. Found: 556.2138.

Synthesis of 8-bromo-8-methyl-9-(toluene-4-sulfonyl)-2-oxa-9-aza-bicyclo [3.3.1] nonane 246

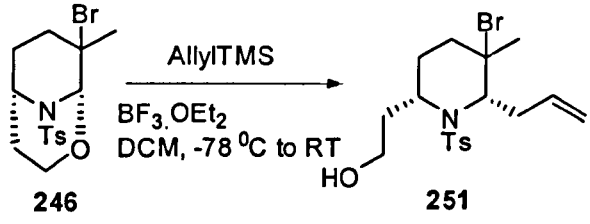


(*S*)-242 **246**

Sodium metal (3 mg, 0.12 mmol, 1.2 eq) was dissolved in MeOH (1 mL). To this solution, piperidine **(*S*)-242** (36 mg, 0.09 mmol, 1.0 eq) dissolved in MeOH (1 mL) was added *via* cannula followed by bromine (7 μL, 0.12 mmol, 1.2 eq). After concentration of the solution in vacuo by one half, diethyl ether was added. This mixture was washed with water. The aqueous wash was extracted with ether. Combined organic fractions were washed with brine, dried over sodium sulphate and concentrated in vacuo. The residue was purified by flash chromatography (5:1 petroleum ether/EtOAc) to give **246** as a yellow oil (95%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.41-1.63 (3H, m, C*H*$_2$), 1.85 (3H, s, C*H*$_3$), 1.95-2.15 (3H, m, C*H*$_2$), 2.42 (3H, s, ArC*H*$_3$), 3.62-3.90 (2H, m, C*H*$_2$O), 4.01-4.12 (1H, m, C*H*-N), 5.43

(1H, br, O-C*H*-N), 7.28 (2H, d, *J*=8.5 Hz, Ar*H*), 7.84 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.6, 28.2, 30.9, 33.4, 30.8, 38.2, 45.9, 59.9, 84.7, 127.7, 129.4, 142.3, 144.4. **FTIR (CH_2Cl_2)**: 2928 (m), 1598 (w), 1449 (w), 1342 (m), 1164 (s), 1141 (m), 1093 (m), 1048 (m), 1018 (m), 998 (m) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{15}H_{20}NO_3NaS^{79}Br$ (MNa^+)**: 396.0245. Found: 396.0245.

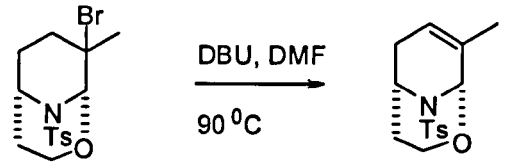
Synthesis of 2-[6-allyl-5-bromo-5-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-ethanol 251



246 **251**

At -78 °C, bicycle **246** (80 mg, 0.21 mmol, 1.0 eq) was dissolved in DCM (8 mL). To this solution was added freshly distilled $BF_3.OEt_2$ (105 μL, 0.85 mmol, 4.0 eq) followed by allyltrimethylsilane (203 μL, 1.28 mmol, 6.0 eq). The resulting solution was stirred at -78 °C for 2 hours and then left at room temperature for 14 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (1:1 petroleum ether/EtOAc) to give piperidine **251** as a colourless oil and as a single diastereoisomer (71 mg, 80%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.45-1.79 (6H, m, CH_2), 1.82 (3H, s, CH_3), 1.89-2.18 (2H, m, CH_2), 2.41 (3H, s, ArCH_3), 2.64 (1H, br, OH), 3.53-3.70 (1H, m, *H*-CH-O), 3.80-3.97 (1H, m, C*H*-N), 4.12-4.29 (1H, m, H-C*H*-O), 4.38 (1H, app t, *J*=7.0 Hz, C*H*-N), 4.99-5.22 (2H, m, =CH_2), 5.89-6.11 (1H, m, -C*H*=C), 7.28 (2H, d, *J*=8.5 Hz, Ar*H*), 7.84 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.6, 26.1, 31.5, 34.3, 38.0, 39.0, 48.2, 59.4, 64.8, 67.7, 114.9, 117.6, 128.1, 129.1, 142.3, 144.4. **FTIR (CH_2Cl_2)**: 3518 (s), 2930 (m), 2852 (m), 1728 (w), 1599 (w), 1445 (w), 1329 (s), 1159 (s), 1093 (m), 1048 (m), 1020 (m), 996 (m) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{18}H_{27}NO_3S^{79}Br$ (MH^+)**: 416.0895. Found: 416.0894.

Synthesis of 8-methyl-9-(toluene-4-sulfonyl)-2-oxa-9-aza-bicyclo[3.3.1]non-7-ene 253

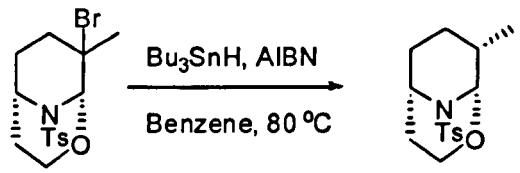


246 253

DBU (25 μL, 0.15 mmol, 1.1 eq) was added to a solution of piperidine **246** (52 mg, 0.14 mmol, 1.0 eq) dissolved in DMF (3 mL). The resulting solution was stirred at 90 ^{0}C for 16 hours. The reaction mixture was then diluted with ether and washed with water. The aqueous was extracted twice with ether, the combined organic fractions were then washed with brine and dried over magnesium sulphate. The residue was purified by flash chromatography (1:1 petroleum ether/EtOAc) to give **253** as a colourless oil (40 mg, 99%). **^{1}H NMR (250 MHz, $CDCl_3$):** δ1.38-1.64 (3H, m, C*H*$_2$), 1.68 (3H, s, C*H*$_3$), 1.81-2.14 (3H, m, C*H*$_2$), 2.36 (3H, s, ArC*H*$_3$), 3.38-3.53 (1H, m, C*H*HO), 3.75-3.91 (1H, m, C*H*-N), 3.96-4.15 (1H, m, C*H*HO), 5.47 (1H, br, O-C*H*-N), 5.70-5.77 (1H, m, *H*-C=C-CH$_3$), 7.22 (2H, d, *J*=8.5 Hz, Ar*H*), 7.75 (2H, d, *J*=8.5 Hz, Ar*H*) **^{13}C NMR (100.0 MHz, $CDCl_3$):** δ20.6, 22.0, 29.3, 32.0, 46.2, 57.8, 80.4, 114.7, 125.5, 128.0, 130.0, 138.6, 143.7. **FTIR (CH_2Cl_2):** 2932 (m), 1450 (w), 1381 (w), 1344 (s), 1252 (w), 1234 (w), 1186 (w), 1161 (s), 1106 (m), 1010 (s), 953 (m), 890 (w), 861 (w), 815 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{15}H_{20}NO_3S$ (MH^+):** 294.1164. Found: 294.1175.

See Appendix 6.1

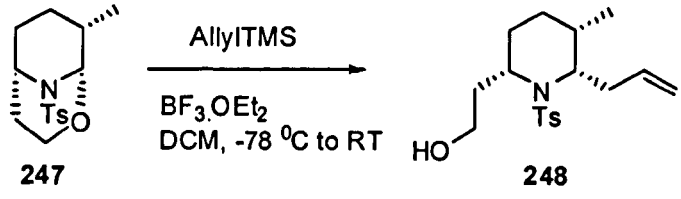
Synthesis of 8-Methyl-9-(toluene-4-sulfonyl)-2-oxa-9-aza-bicyclo[3.3.1]nonane 247



246 247

AIBN (20 mg, 0.13 mmol, 1.0 eq) was added to a solution of **246** (47 mg, 0.13 mmol, 1.0 eq) in benzene (2.3 mL). The solution was purged with nitrogen for 15 min then tributyltin hydride (100 μL, 0.38 mmol, 3.0 eq) was added and the resulting mixture was stirred under reflux for 16 hrs. The reaction mixture was cooled to room temperature and the benzene was removed in vacuo to give an oil. Purification by flash chromatography (5:1 petroleum ether/EtOAc) afforded the product **247** as white crystals (36 mg, 92%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.96 (3H, d, *J*=6.5 Hz, C*H*$_3$-CH), 1.22-1.35 (1H, m, CH$_3$-C*H*), 1.58-1.97 (6H, m, C*H*$_2$), 2.35 (3H, s, C*H*$_3$), 3.33-3.45 (1H, m, CH$_2$-C*H*-N), 3.84-3.97 (1H, m, CH*H*O), 3.97-4.06 (1H, m, C*H*HO), 5.22 (1H, d, *J*=2.5 Hz, N-C*H*-O), 7.22 (2H, d, *J*=8.5 Hz, Ar*H*), 7.72 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ17.8, 21.6, 26.8, 26.9, 30.9, 36.6, 46.0, 60.6, 81.6, 127.4, 129.6, 140.1, 144.3. **HRMS (TOF ES) calcd. for $C_{15}H_{22}NO_3S$ (MH^+)**: 296.1320. Found: 296.1326.
See Appendix 6.2

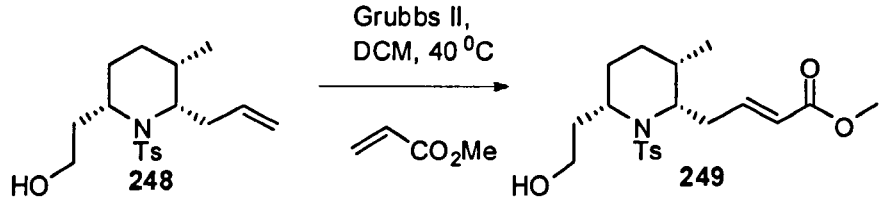
Synthesis of 2-[6-allyl-5-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-ethanol 248



Bicycle **247** (43 mg, 0.15 mmol, 1.0 eq) was dissolved in DCM (5.5 mL) and cooled to -78 ^{0}C. To this solution was added freshly distilled $BF_3.OEt_2$ (72 μL, 0.58 mmol, 4.0 eq) followed by allyltrimethylsilane (140 μL, 0.87 mmol, 6.0 eq). The resulting solution was stirred at -78 ^{0}C for 2 hours and then left at room temperature for 14 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (2:1 petroleum ether/EtOAc) to give piperidine **248** as a colourless oil and as a single diastereoisomer (35 mg, 69%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.45 (3H, d, *J*=13.5 Hz, CH-C*H*$_3$), 1.82 (3H, m, C*H*$_2$ + C*H*-CH$_3$), 1.89-2.18 (4H, m, C*H*$_2$), 2.26-2.46 (4H, m, CH*H*-CH=CH$_2$ + ArC*H*$_3$), 2.50-2.64 (1H, m, C*H*H-CH=CH$_2$), 3.48-3.65 (1H, m, C*H*-N), 3.74-3.90 (1H, m, *H*-CH-O), 4.15

(1H, q, *J*=7.0 Hz, C*H*-N), 4.32 (1H, t, *J*=6.5 Hz, C*H*-O), 4.99-5.13 (2H, m, =CH_2), 5.84-6.05 (1H, m, -C*H*=C), 7.19 (2H, d, *J*=8.5 Hz, Ar*H*), 7.73 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.3, 21.6, 26.1, 31.5, 33.2, 38.0, 39.0, 48.2, 59.4, 64.8, 117.6, 128.1, 129.1, 135.8, 142.3, 144.4. **FTIR (CH_2Cl_2)**: 3533 (s), 2935 (m), 1445 (m), 1329 (s), 1159 (s), 1093 (m), 1053 (w), 1020 (w), 996 (w), 875 (w), 814 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{18}H_{28}NO_3S$ (MH^+)**: 338.1790 Found: 338.1777.

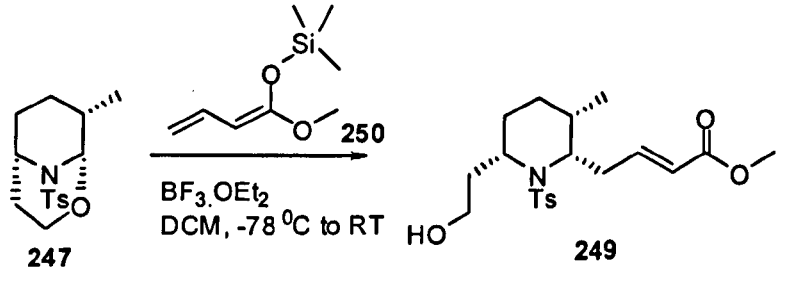
Synthesis of 4-[6-(2-hydroxy-ethyl)-3-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-but-2-enoic acid methyl ester 249



Methyl acrylate (40 μL, 0.45 mmol, 3.0 eq) was added to a solution of substrate **248** (50 mg, 0.15 mmol, 1.0 eq) dissolved in DCM (3.1 mL) followed by addition of Grubbs' second generation catalyst (13 mg, 0.015 mmol, 0.1 eq). The resulting solution was stirred at 40 °C for 16 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (1:1 petroleum ether/EtOAc) to give piperidine **249** as a colourless oil (43 mg, 72%).

See below for characterisation

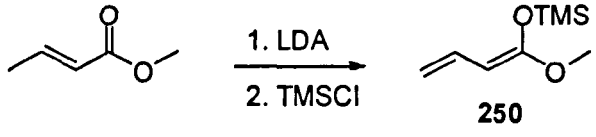
Synthesis of 4-[6-(2-hydroxy-ethyl)-3-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-but-2-enoic acid methyl ester 249



Bicycle **247** (36 mg, 0.12 mmol, 1.0 eq) was dissolved in DCM (4 mL) and cooled to -78 ^{0}C. To this solution was added freshly distilled $BF_3.OEt_2$ (70 μL, 0.49 mmol, 4.0 eq) followed by diene **250** (130 mg, 0.73 mmol, 6.0 eq). The resulting solution was stirred at -78 ^{0}C for 2 hours and then left at room temperature for 14 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (1:1 petroleum ether/EtOAc) to give piperidine **249** as a colourless oil and as a single diastereoisomer (35 mg, 75%). **^{1}H NMR (500 MHz, $CDCl_3$)**: δ0.82 (3H, d, *J*=6.0 Hz, CH-C*H*$_3$), 1.21-1.37 (2H, m, C*H*$_2$), 1.41-1.47 (1H, m, C*H*H), 1.54-1.65 (2H, m, C*H*$_2$), 1.79-1.88 (2H, m, C*H*$_2$), 2.36-2.53 (5H, m, C*H*$_2$-CH= + ArC*H*$_3$), 3.55-3.68 (1H, dt, *J*=4.0, 12.0 Hz, C*H*-O), 3.75 (3H, s, OC*H*$_3$), 3.83 (1H, td, *J*=3.0, 12.0 Hz, C*H*-O), 4.14-4.21 (2H, m, C*H*-N), 5.83 (1H, td, *J*=1.5, 15.5 Hz, CH=C*H*-CO_2Me), 7.07-7.15 (1H, m, C*H*=CH-CO_2Me), 7.29 (2H, d, *J*=8.5 Hz, Ar*H*), 7.71 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 22.4, 28.9, 32.7, 33.6, 37.4, 48.3, 51.6, 57.0, 58.9, 122.9, 126.7, 129.9, 138.1, 143.3, 146.9, 166.5. **FTIR (CH_2Cl_2)**: 3528 (s), 2953 (m), 1722 (s), 1656 (w), 1437 (m), 1324 (m), 1160 (s), 1087 (m), 1067 (w), 999 (w), 816 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{20}H_{30}NO_5S$ (MH^+)**: 396.1845 Found: 396.1849.

NOESY spectrum: See Appendix 6.3

Synthesis of (1-methoxy-buta-1,3-dienyloxy)-trimethyl-silane 250[117]

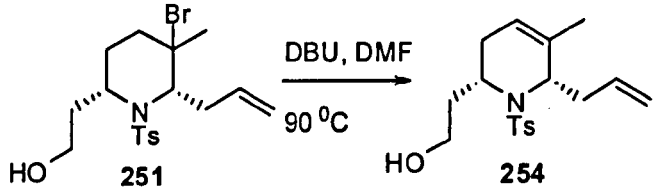


250

In a 250 mL 3-necked round-bottom flask were placed THF (75 mL) and diisopropylamine (14 mL, 100 mmol, 1.0 eq) under nitrogen. The solution was cooled to -78 °C and maintained at that temperature throughout the reaction. *n*-Butyllithium (50 mL, 100 mmol, 1.0 eq) was added dropwise to this solution. The reaction mixture was allowed to stir for 15 min. HMPA (21 mL, 120 mmol, 1.2 eq) was added to the solution, which was allowed to stir for 10 min. Methyl crotonate (10.6 mL, 100 mmol, 1.0 eq) was added *via* syringe dropwise. The resulting solution was stirred for 30 min. Trimethylsilyl chloride (20 mL, 157

mmol, 1.6 eq) was added to the reaction mixture with additional stirring for 20 min. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The solvent was removed under reduced pressure, and the residue was diluted with pentane and filtered to remove LiCl salts. The filtrate was washed with water and dried over $MgSO_4$. Pentane was removed under reduced pressure, and the residue was distilled at 24 mm and collected between 50 and 60 °C to give product **250** as a clear liquid (6.8 g, 39%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ0.25 (9H, s, C*H*$_3$ (TMS)), 3.60 (3H, s, C*H*$_3$-O), 4.51 (1H, d, *J*=10.5 Hz), 4.63 (1H, dd, *J*=2.0, 10.5 Hz), 4.87 (1H, dd, *J*=2.0, 17.0 Hz), 6.51 (1H, dt, *J*=10.5, 17.0 Hz). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ20.3, 54.8, 80.7, 106.9, 132.5, 158.7.

Synthesis of 2-[6-allyl-5-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-2-yl]-ethanol 254



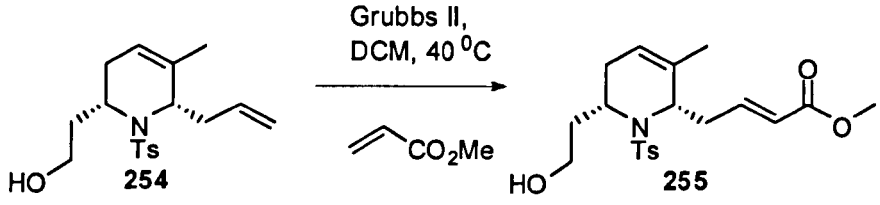
DBU (30 μL, 0.201 mmol, 1.1 eq) was added to a solution of piperidine **251** (76 mg, 0.183 mmol, 1.0 eq) dissolved in DMF (5 mL). The resulting solution was stirred at 90 °C for 14 hours. The reaction mixture was then diluted with ether and washed with water. The aqueous layer was extracted twice with ether, the combined organic fractions were then washed with brine and dried over magnesium sulphate. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to give **254** as a colourless oil (46 mg, 75%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.45-1.74 (6H, m, C*H*$_2$ + C*H*$_3$), 1.75-1.93 (1H, m, *H*-CH), 2.26-2.48 (4H, m, *H*-CH + ArC*H*$_3$), 2.52-2.68 (1H, m, *H*-CH), 2.79 (1H, br s, OH), 3.49-3.74 (1H, m, *H*-CH-O), 3.90-3.99 (1H, m, *H*-CH-O), 4.02-4.12 (1H, m, C*H*-N), 4.28-4.38 (1H, m, C*H*-N), 4.99-5.19 (2H, m, =C*H*$_2$), 5.20-5.31 (1H, m, *H*-C=C-CH$_3$), 5.95-6.17 (1H, m, *H*-C=CH$_2$), 7.26 (2H, d, *J*=8.0 Hz, Ar*H*), 7.63 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ23.6, 25.2, 34.3, 37.6, 39.6, 47.6, 58.9, 67.7, 113.9, 116.6, 118.3, 120.3, 128.7, 129.0, 140.3, 145.4. **FTIR**

(CH_2Cl_2): 3620 (s), 2962 (m), 2856 (m), 1744 (w), 1522 (w), 1413 (w), 1289 (s), 1169 (s), 1073 (m), 1047 (m), 1020 (m), 990 (m) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{18}H_{26}NO_3S$ (MH^+)**: 336.1633. Found: 336.1650.

COSY spectrum: See Appendix 6.4

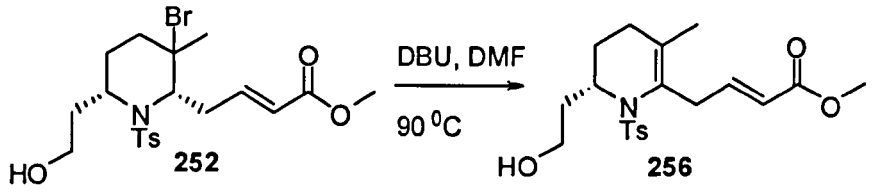
NOESY spectrum: See Appendix 6.5

Synthesis of 4-[6-(2-hydroxy-ethyl)-3-methyl-1-(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-pyridin-2-yl]-but-2-enoic acid methyl ester 255



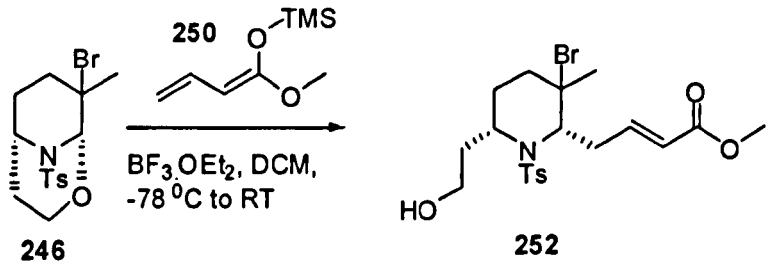
Methyl acrylate (43 μL, 0.474 mmol, 3.0 eq) was added to a solution of substrate **254** (53 mg, 0.16 mmol, 1.0 eq) dissolved in DCM (3 mL) followed by addition of Grubbs' second generation catalyst (13 mg, 0.016 mmol, 0.1 eq). The resulting solution was stirred at 40 °C for 14 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (1:1 petroleum ether/EtOAc) to give piperidine **255** as a colourless oil (42 mg, 68%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.47-1.85 (4H, m, C*H*$_2$), 2.39 (3H, s, C*H*$_3$), 2.55-2.82 (2H, m, C*H*$_2$), 3.52-3.67 (1H, m, *H*-CH-O), 3.73 (3H, s, O-C*H*$_3$), 3.77-3.92 (1H, m, H-C*H*-O), 4.02-4.16 (1H, m, C*H*-N), 4.30-4.40 (1H, m, C*H*-N), 5.28-5.36 (1H, m, *H*-C=C-CH$_3$), 5.91 (1H, td, *J*=1.5 Hz, *J*=15.5 Hz, HC=C*H*-CO), 7.02-7.17 (1H, m, *H*C=CH-CO), 7.25 (2H, d, *J*=8.0 Hz, Ar*H*), 7.63 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.5, 22.3, 32.0, 33.7, 36.5, 51.6, 55.2, 57.5, 63.1, 114.9, 121.7, 123.0, 126.5, 129.8, 138.3, 143.5, 146.5, 166.8. **FTIR (CH_2Cl_2)**: 3532 (s), 2948 (m), 1725 (s), 1645 (w), 1437 (m), 1324 (m), 1162 (s), 1088 (m), 1067 (w), 999 (w), 816 (w) **HRMS (TOF ES) calcd. for $C_{20}H_{28}NO_5S$ (MH^+)**: 394.1688. Found: 394.1700.

Synthesis of 4-[6-(2-hydroxy-ethyl)-3-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-but-2-enoic acid methyl ester 256



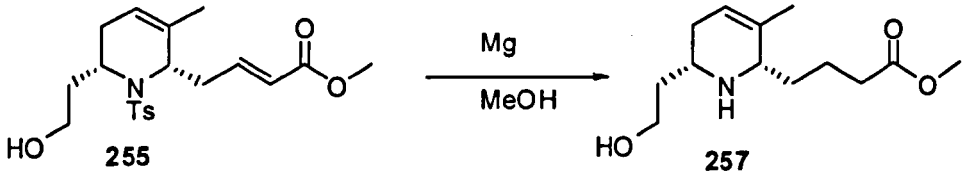
DBU (30 μL, 0.20 mmol, 1.1 eq) was added to a solution of piperidine **252** (85 mg, 0.18 mmol, 1.0 eq) dissolved in DMF (7 mL). The resulting solution was stirred at 90 ^{0}C for 14 hours. The reaction mixture was then diluted with ether and washed with water. The aqueous was extracted twice with ether, the combined organic fractions were then washed with brine and dried over magnesium sulphate. The residue was purified by flash chromatography (1:1 petroleum ether/EtOAc) to give **256** as a colourless oil (33 mg, 47%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.07 (3H, s, C*H*$_3$), 1.35-1.85 (8H, m, C*H*$_2$), 2.43 (3H, s, C*H*$_3$), 3.16 (1H, d, *J*=3.5 Hz, OH), 3.55-4.0 (3H, m, C*H*N + C*H*$_2$O), 3.72 (3H, s, OC*H*$_3$), 5.81 (1H, d, *J*=15.5 Hz, CH=C*H*-CO_2Me), 6.55 (1H, dd, *J*=10.5 Hz, 15.5 Hz, C*H*=CH-CO_2Me), 7.30 (2H, d, *J*=8.0 Hz, Ar*H*), 7.70 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (100.0 MHz, $CDCl_3$)**: δ21.6, 22.0, 24.1, 25.2, 26.1, 32.3, 38.7, 46.1, 49.3, 51.9, 59.4, 121.6, 127.8, 130.2, 137.2, 144.2, 147.4, 166.8. **FTIR (CH_2Cl_2)**: 3458 (s), 2942 (m), 1710 (s), 1638 (m), 1439 (w), 1330 (m), 1271 (m), 1158 (s), 1094 (w), 1017 (w), 913 (w), 814 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{20}H_{28}NO_5S$ (MH^+)**: 394.1688. Found: 394.1700.

Synthesis of 2-[6-allyl-5-bromo-5-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-ethanol 252



Bicycle **246** (47 mg, 0.13 mmol, 1.0 eq) was dissolved in DCM (5 mL) and cooled to -78 °C. To this solution was added freshly distilled $BF_3.OEt_2$ (65 µL, 0.50 mmol, 4.0 eq) followed by diene **250** (130 mg, 0.75 mmol, 6.0 eq). The resulting solution was stirred at -78 °C for 2 hours and then left at room temperature for 14 hours. Solvent was removed in vacuo and the residue purified by flash chromatography (1:1 petroleum ether/EtOAc) to give piperidine **252** as a colourless oil and as a single diastereoisomer (90%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.49-1.98 (9H, m, CH_2 + CH_3), 2.00-2.21 (1H, m, *H*-CH), 2.40 (3H, s, ArCH_3), 2.51 (1H, br s, OH), 2.59 (2H, dt, *J*=1.5 Hz, *J*=7.0 Hz, CH_2-C=), 3.56-3.89 (5H, m, O-CH_3 + CH_2-O), 4.24 (1H, q, *J*=6.5 Hz, C*H*-N), 4.39 (1H, t, *J*=6.5 Hz , C*H*-N), 5.90 (1H, d, *J*=16.0 Hz, HC=C*H*-CO), 7.00-7.16 (1H, m, *H*C=CH-CO), 7.26 (2H, d, *J*=8.5 Hz, Ar*H*), 7.77 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.6, 25.9, 31.4, 33.0, 37.6, 38.0, 48.4, 51.7, 59.3, 64.1, 67.7, 107.6, 123.4, 128.0, 129.2, 137.1, 143.4, 166.7. **FTIR (CH_2Cl_2)**: 3572 (s), 2950 (m), 1722 (s), 1657 (m), 1437 (m), 1324 (m), 1159 (s), 1093 (w), 1020 (w), 915 (m). **HRMS (TOF ES) calcd. for $C_{20}H_{29}NO_5S^{79}Br$** (MH^+): 474.0950. Found: 474.0962.

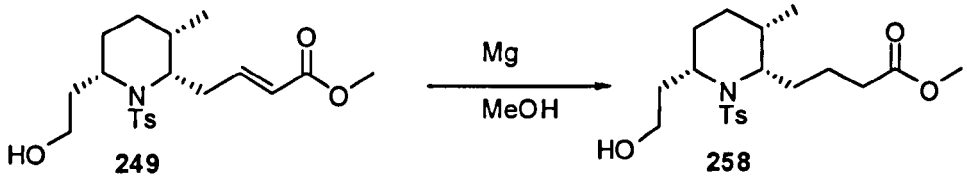
Synthesis of 4-[6-(2-hydroxy-ethyl)-3-methyl-1,2,5,6-tetrahydro-pyridin-2-yl]-butyric acid methyl ester 257



To a solution of Mg turnings (223 mg, 9.14 mmol, 60.0 eq) suspended in MeOH (1.8 mL) was added piperidine **255** (59 mg, 0.15 mmol, 1.0 eq) dissolved in MeOH (1.8 mL). The resulting solution was stirred for 16 hours. The reaction was quenched with HCl (1 M) and extracted with ethyl acetate. The aqueous phase was then basified with NaOH (1 M) and extracted with a mixture DCM / MeOH (10/1). The combined organic fractions were dried over magnesium sulphate. The residue was purified by flash chromatography (1:1 petroleum ether/EtOAc) to give **257** as a colourless oil (14 mg, 38%).This compound was tentatively

characterised by ^{1}H, ^{13}C NMR spectroscopy. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.49-2.09 (11H, m, CH_2 + CH_3), 2.27 (2H, td, *J*=2.5, 7.0 Hz, CH_2-CO), 2.88-3.04 (1H, m, C*H*-N), 3.29-3.43 (1H, m, C*H*-N), 3.66 (3H, s, O-CH_3), 3.77-3.91 (2H, m, CH_2-O), 5.47-5.55 (1H, m, C*H*=C-CH_3). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ20.0, 20.4, 22.3, 32.0, 33.7, 36.5, 51.6, 55.2, 57.5, 63.1, 114.9, 121.7, 166.8.

Synthesis of 4-[6-(2-Hydroxy-ethyl)-3-methyl-1,2,5,6-tetrahydro-pyridin-2-yl]-butyric acid methyl ester 258



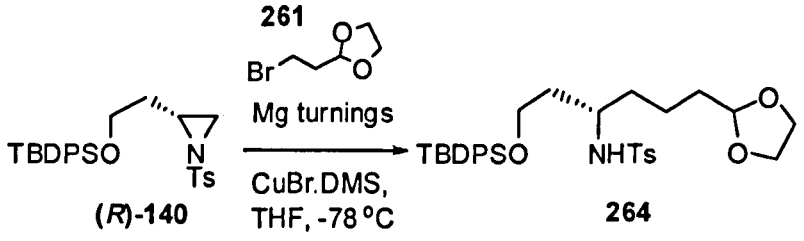
To a solution of Mg turnings (190 mg, 7.80 mmol, 60.0 eq) suspended in MeOH (1.5 mL) was added piperidine **249** (50 mg, 0.13 mmol, 1.0 eq) dissolved in MeOH (1.5 mL). The resulting solution was stirred for 16 hours. The reaction was quenched with HCl (1 M) and extracted with ethyl acetate. The aqueous phase was then basified with NaOH (1 M) and extracted with a mixture DCM / MeOH (10/1). The combined organic fractions were dried over magnesium sulphate. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to give **258** as a colourless oil (21 mg, 42%) **^{1}H NMR (250 MHz, $CDCl_3$)**: δ0.81 (3H, d, *J*=6.0 Hz, CH_3-CH), 1.03-2.04 (11H, m, CH_2), 2.26-2.51 (2H, m, CH_2CO_2), 2.41 (3H, s, CH_3), 3.58-3.77 (1H, m, C*H*N), 3.66 (3H, s, CH_3O), 3.84-3.99 (2H, m, CH_2-OH), 4.06-4.19 (1H, m, C*H*N), 7.28 (2H, d, *J*=8.0 Hz, Ar*H*), 7.69 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.6, 21.9, 22.9, 23.0, 28.1, 29.6, 34.0, 34.1, 38.3, 48.9, 52.0, 58.4, 59.6, 127.1, 130.2, 138.8, 143.5, 173.2. **FTIR (CH_2Cl_2)**: 3528 (s), 2955 (s), 2876 (m), 1735 (s), 1438 (w), 1335 (m), 1161 (s), 1116 (w), 1088 (w), 999 (w), 866 (w), 816 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{20}H_{32}NO_5S$** (MH^+): 398.2001. Found: 398.2000.

8.2.Büchi Grignard Route

Preparation of the Büchi Grignard Reagent

To a 50 mL two-necked flask fitted with a reflux condenser was added magnesium turnings (484 mg, 17.25 mmol, 1.7 eq) and THF (10 mL), then 2-(2-bromo-ethyl)-[1,3]dioxolane (1.2 mL, 10.2 mmol, 1.0 eq) was added. The solution was allowed to cool to room temperature and the concentration of the Büchi Grignard solution assessed by titration[e]. An aliquot was removed and placed into a separate flask[174].

Synthesis of (*R*)-*N*-(1-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-4-[1,3]dioxolan-2-yl-butyl)-4-methyl-benzenesulfonamide 264

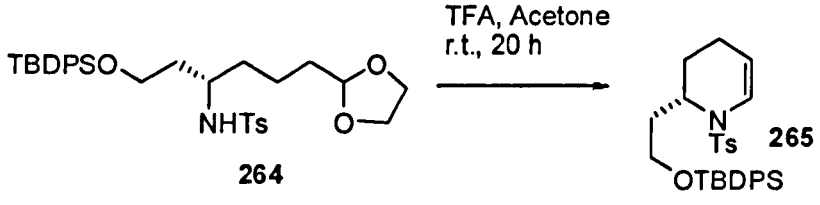


A solution of CuBr.DMS (157 mg, 0.76 mmol, 0.4 eq) in DMS (2.3 mL) was added to the Büchi Grignard **261** solution (3 mL, 0.64 M, 1.91 mmol, 2.0 eq) at -78 °C and stirred for 1 hour. Then a solution of **(*R*)-140** (458 mg, 0.96 mmol, 1 eq) in THF (2 mL) was added at -78 °C and stirred for 10 minutes. The solution was left stirring and allowed to warm to room temperature overnight. The reaction was quenched with water and the organic layer was separated. The aqueous layer was re-extracted with ethyl acetate (2 portions), the organic layers were combined and washed with brine. The solution was dried over $MgSO_4$ and concentrated

[e] Titration carried out with 31 mg (*D,L*)-menthol, 5mg 1,10-phenanthroline and 1.5 mL THF creating a 2.0 mmol solution. The Grignard solution was added to the solution until a red-purple colour persisted. The molarity was calculated by dividing 0.2 by the amount in mL used to achieve the colour change.

under reduced pressure. The residue was purified by column chromatography (4:1 petroleum ether/ethyl acetate) to give **264** as a white solid, 478 mg (86%). **m.p.**=79 °C. $[\alpha]^{23}_D$=+30 (*c* 0.01 g/mL, CH_2Cl_2). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.02 (9H, s, SiC(CH_3)$_3$), 1.20-1.69 (8H, m, CH_2), 2.39 (3H, s, ArCH_3), 3.31-3.55 (2H, m, *CH*NH + OC*H*O), 3.59-3.72 (1H, m, OCH_2), 3.76-3.99 (4H, m, OCH_2CH_2O), 4.76 (1H, t, *J*=4.5 Hz, OCH_2), 5.30 (1H, d, *J*=8.0 Hz, N*H*), 7.21 (2H, d, *J*=8.0 Hz, Ar*H*), 7.32-7.49 (6H, m, Ar*H*), 7.54-7.63 (4H, d, *J*=8.0 Hz, Ar*H*), 7.70 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.0, 19.9, 21.5, 26.8, 33.5, 34.5, 35.4, 52.6, 61.2, 64.8, 104.3, 127.1, 127.8, 129.6, 129.9, 133.1, 135.5, 138.2, 142.9. **FTIR (thin film)**: 3253 (br), 2929 (m), 2856 (m), 1472 (m), 1429 (m), 1319 (m), 1152 (s), 1113 (s), 1086 (s), 816 (m) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{32}H_{43}NO_5NaSiS$** (MNa^+): 604.2529. Found: 604.2504.

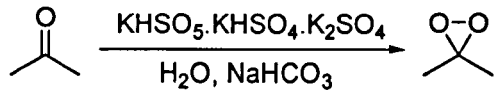
Synthesis of 2-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine 265



Trifluoroacetic acid (100 μL, 1.31 mmol, 5 eq) was added to a solution of **264** (152 mg, 0.26 mmol, 1 eq) in anhydrous acetone (3 mL) at room temperature and left stirring overnight. Another 5 equivalents of TFA were added and the resulting solution was left stirring for a further 3 hours. The reaction was quenched with $NaHCO_3$, extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (15:1 petroleum ether/ethyl acetate) to give **265** as a clear oil, 120 mg, (88%). $[\alpha]^{23}_D$ = -120 (*c* 0.01 g/mL, CH_2Cl_2). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.00 (9H, s, SiC(CH_3)$_3$), 1.37-1.89 (6H, m, CH_2), 2.34 (3H, s, ArCH_3), 3.58-3.80 (2H, m, OCH_2), 4.03-4.16 (1H, m, NC*H*), 4.87-4.98 (1H, m, NCH=C*H*), 6.48-6.56 (1H, m, NC*H*=CH), 7.20 (2H, d, *J*=8.0 Hz, *Ar-H*), 7.26-7.40 (6H, m, Ar*H*), 7.55-7.66 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**:

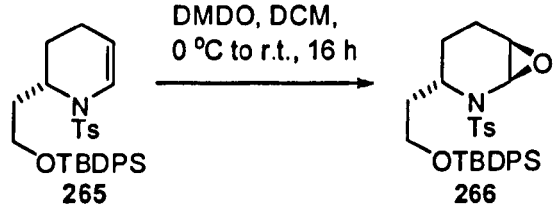
δ17.2, 21.6, 22.6, 26.9, 29.0, 34.3, 50.0, 60.6, 109.0, 123.7, 127.1, 127.7, 129.6, 129.9, 135.5, 135.6, 138.2, 147.8. **FTIR (thin film):** 3070 (w), 2929 (m), 2857 (m), 1645 (w), 1428 (m), 1344 (s), 1167 (s), 1111 (s), 823 (w), 705 (s) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{30}H_{38}NO_3SiS$** (MH^+): 520.2342. Found: 520.2351.

Dimethyldioxirane in acetone[111]



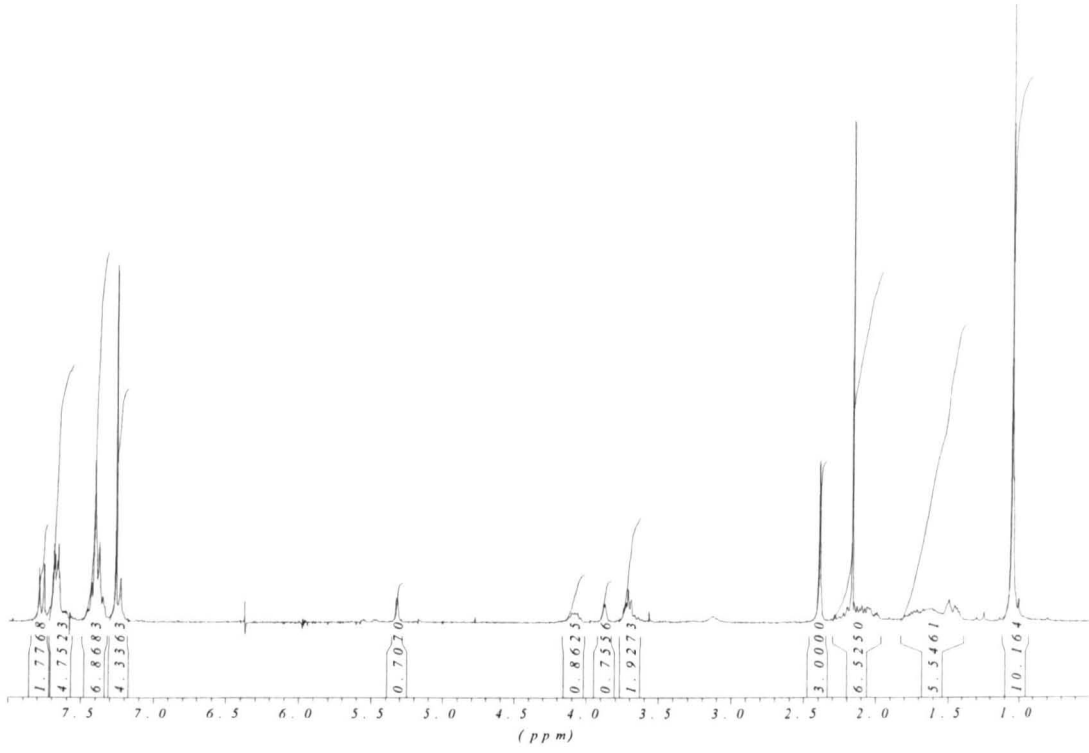
A 2-necked flask equipped with an air condenser packed with glass wool and a solid addition funnel was charged with H_2O (20 mL), acetone (13 mL) and $NaHCO_3$ (12.0 g). Oxone® was placed into the solid addition funnel. The top of the condenser was fitted with a distillation receiving bend and a receiving flask, which was cooled to –78 °C with a CO_2/acetone bath. A slight vacuum was applied and oxone® added in one portion. A yellow liquid was collected in the receiving flask, and this was stirred with $MgSO_4$ for 15 min, and then filtered. The concentration of dimethyldioxirane in acetone was determined by iodometric titration: 1.00 mL of a solution of dimethyldioxirane in acetone was added to a 3:2 mix of acetic acid and acetone (2 mL). A saturated solution of KI (2 mL) was added and stored in the dark for 10 min. Addition of a 0.001 M solution of $Na_2S_2O_3$ determined the concentration to be 0.06 M.

Epoxidation of 265 with dimethyldioxirane

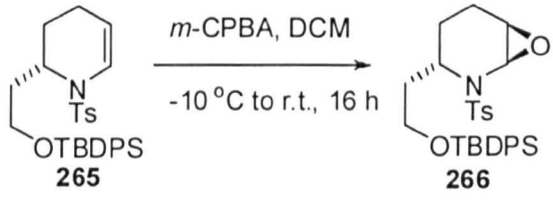


A 0.06 M solution of dimethyldioxirane in acetone (5 mL, 0.30 mmol, 2.5 eq.) was added to a solution of **265** (63 mg, 0.12 mmol, 1 eq.) in CH_2Cl_2 (12 mL) at 0 °C *via* syringe. The reaction was stirred at 0 °C for 1 h and then allowed to warm

to room temperature overnight. The reaction mixture was then concentrated in vacuo to provide the crude epoxide **266** as colourless oil. No further purification was carried out.



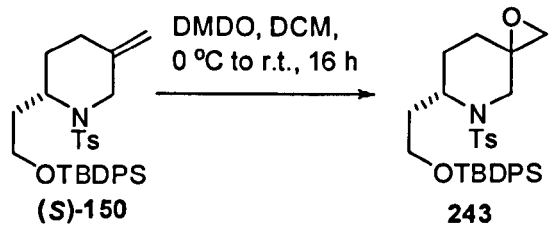
Epoxidation of 265 with *m*-CPBA



265 **266**

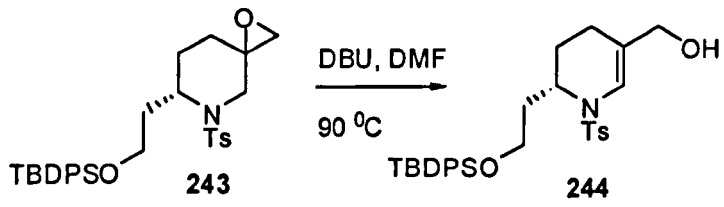
To a solution of **265** (180 mg, 0.35 mmol, 1.0 eq.) in CH_2Cl_2 (12 mL) was added 77% *m*-CPBA (117 mg, 0.52 mmol, 1.5 eq.) in CH_2Cl_2 (6 mL) *via* cannula at -10 °C. The reaction was stirred at -10 °C for an hour and then allowed to warm to room temperature overnight. The reaction mixture was then washed with 10% Na_2SO_3, saturated $NaHCO_3$ and brine, and then dried ($MgSO_4$) and concentrated. No further purification was carried out.

Epoxidation of (*S*)-150 with dimethyldioxirane



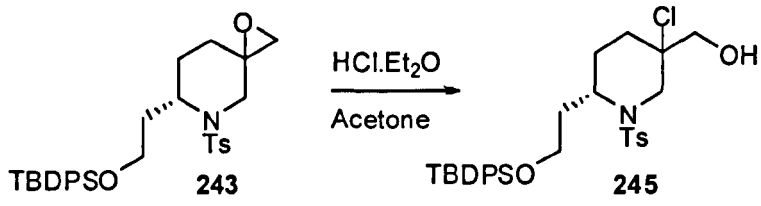
A 0.06 M solution of dimethyldioxirane in acetone (5 mL, 0.30 mmol, 2.5 eq.) was added to a solution of **(*S*)-150** (65 mg, 0.12 mmol, 1.0 eq.) in CH_2Cl_2 (12 mL) at 0 °C via syringe. The reaction was stirred at 0 °C for 1 h and then allowed to warm to room temperature overnight. The reaction mixture was then concentrated in vacuo to provide the crude epoxide **243** as colourless oil. The residue was purified by flash chromatography (5:1 petroleum ether/ethyl acetate) to give product **243** as a major diastereoisomer (43 mg, 67%). **^{1}H NMR (250 MHz, $CDCl_3$):** δ0.99 (9H, s, SiC(CH_3)$_3$), 1.38-1.53 (1H, m, CH_2), 1.63-2.06 (5H, m, CH_2), 2.33 (3H, s, CH_3), 2.53 (1H, d, *J*=4.5 Hz, CH*H*N), 2.62 (1H, d , *J*=4.5 Hz, C*H*HN), 3.38 (2H, s, CH_2OC), 3.56-3.76 (2H, m, CH_2OTBDPS), 3.99-4.01 (1H, m, C*H*N), 7.18 (2H, d, *J*=8.0 Hz, Ar*H*), 7.26-7.42 (6H, m, Ar*H*), 7.54-7.65 (4H, m, Ar*H*), 7.72 (2H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (100.0 MHz, $CDCl_3$):** δ19.6, 22.0, 26.0, 27.3, 32.6, 47.2, 49.7, 51.9, 61.5, 128.0, 128.1, 129.7, 130.1, 135.2, 136.0, 138.4, 144.3. **FTIR (thin film):** 2931 (m), 2858 (m), 1472 (w), 1428 (m), 1389 (w), 1337 (s), 1160 (s), 1111 (s), 1008 (w), 965 (w), 931 (w), 821 (m) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{31}H_{40}NO_4SiS$** (MH^+): 550.2447. Found: 550.2437.

Synthesis of [6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-3-yl]-methanol 244



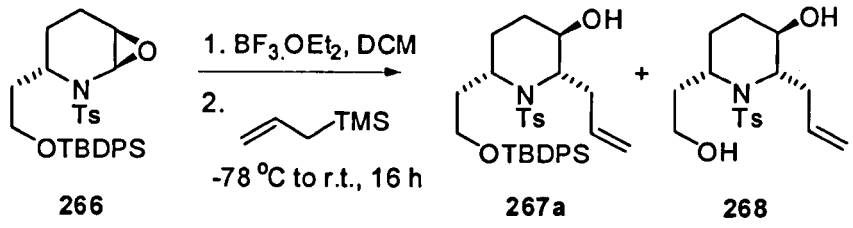
DBU (9 μL, 0.06 mmol, 1.2 eq) was added to a solution of piperidine **243** (25 mg, 0.05 mmol, 1.0 eq) dissolved in DMF (1 mL). The resulting solution was stirred at 90 ^{0}C for 14 hours. The reaction mixture was then diluted with ether and washed with water. The aqueous was extracted twice with ether, the combined organic fractions were then washed with brine and dried over magnesium sulphate. The residue was purified by flash chromatography (1:1 petroleum ether/EtOAc) to give starting material **243** (15 mg, 60%) but none of the desired product.

Synthesis of [6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-chloro-1-(toluene-4-sulfonyl)-piperidin-3-yl]-methanol 245



HCl in ether (1.0 M, 100 μL, 0.1 mmol, 2.5 eq) was added to a solution of **243** (21 mg, 0.04 mmol, 1.0 eq) in anhydrous acetone (1 mL) at room temperature and left stirring for 16 hrs. The mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (5:1 petroleum ether/ethyl acetate) to give **245** (8 mg, 34%). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.03 (9H, s, SiC(CH_3)$_3$), 1.60-1.89 (6H, m, CH_2), 2.31-2.44 (2H, m, CH_2N), 2.36 (3H, s, CH_3), 2.77 (1H, m, OH), 3.40-3.54 (2H, m, CH_2OTBDPS), 3.72 (2H, s, CH_2OH), 4.19-4.30 (1H, m, C*H*N), 7.18 (2H, d, *J*=8.0 Hz, *ArH*), 7.32-7.49 (6H, m, Ar*H*), 7.54-7.70 (6H, m, Ar*H*). **^{13}C NMR (100.0 MHz, $CDCl_3$)**: δ19.2, 21.9, 25.4, 27.2, 29.2, 31.0, 47.2, 50.0, 51.0, 61.4, 69.7, 127.4, 128.1, 128.2, 130.1, 133.2, 135.9, 138.4, 144.3. **FTIR (thin film)**: 3503 (w), 2930 (m), 2860 (m), 2360 (s), 1457 (w), 1428 (m), 1339 (m), 1162 (s), 1099 (s), 949 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{31}H_{41}NO_4SiS^{35}Cl$** ($MH^+$): 586.2214. Found: 586.2233.

Synthesis of 2-allyl-6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-piperidin-3-ol 267a



266 **267a** **268**

To a solution of **266** (made using DMDO) (88 mg, 0.16 mmol, 1.0 eq.) in DCM (6 mL) at -78 ^{0}C, $BF_3.OEt_2$ (85 μL, 0.66 mmol, 4.0 eq.) was added slowly. The resulting solution was left stirring for 15 min, then allyltrimethylsilane (155 μL, 0.96 mmol, 6.0 eq) was added slowly at the same temperature. The reaction mixture was stirred at room temperature overnight and quenched with ammonium chloride. The products were extracted with EtOAc and the organic phase was washed with sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$, concentrated under vacuum and purified by silica gel chromatography (4:1 petroleum ether/EtOAc) to give **267a** (65 mg, 70%) and **268** (7 mg, 10%) as two oils.

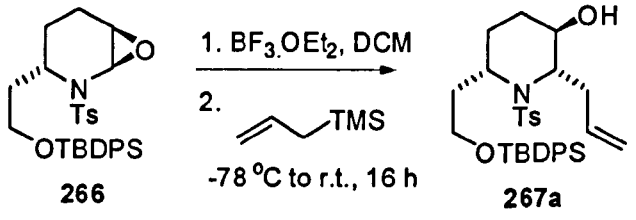
267a: $[\alpha]^{21}_D$= -6.4 (*c* 0.011 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.08 (9H, s, $SiC(CH_3)_3$), 1.35-1.40 (1H, m, C*H*H), 1.48-1.52 (1H, m, C*H*H), 1.75-1.87 (3H, m, C*H*H + CH_2), 1.95-2.03 (1H, m, CH*H*), 2.21-2.36 (2H, m, CH_2-CH=CH), 2.41 (3H, s, ArCH_3), 3.65-3.74 (2H, m, OCH_2), 3.80 (1H, br s, C*H*OH), 3.97-4.02 (1H, m, N-C*H*-CHOH), 4.14-4.19 (1H, m, N-C*H*), 4.99-5.07 (2H, m, CH=CH_2), 5.68-5.78 (1H, m, C*H*=CH_2), 7.20 (2H, d, *J*=8.0 Hz, Ar*H*), 7.26-7.40 (6H, m, Ar*H*), 7.55-7.66 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 20.1, 21.2, 21.5, 26.9, 37.3, 39.3, 49.4, 58.9, 61.7, 65.5, 117.8, 127.4, 127.7, 129.5, 133.2, 133.6, 135.5, 135.6, 136.3, 143.7. **FTIR (thin film):** 3530 (s), 3080 (m), 2960 (s), 2860 (s), 1670 (w), 1470 (w), 1430 (m), 1330 (m), 1260 (s), 1160 (s), 1110 (s), 939 (m), 816 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{33}H_{44}NO_4SiS$** (MH^+): 578.2760. Found: 578.2756.

COSY spectrum: See Appendix 6.6

NOESY spectrum: See Appendix 6.7

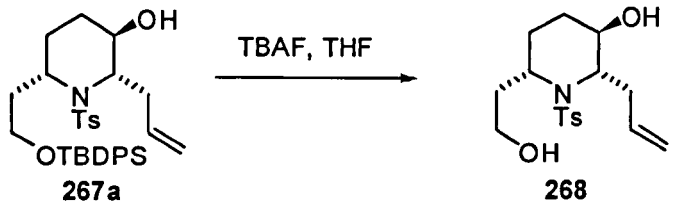
268: $[\alpha]^{21}_D$=+50 (*c* 0.01 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.11-1.34 (2H, m, C*H*$_2$), 1.42-1.53 (1H, m, CH*H*), 1.57-2.0 (3H, m, C*H*$_2$), 2.21-2.54 (5H, m, C*H*$_2$ + Ar-C*H*$_3$), 3.09 (1H, br s, C*H*OH), 3.57-3.72 (1H, m, N-C*H*-CHOH), 3.73-3.81 (2H, m, OC*H*$_2$), 4.14-4.27 (1H, m, N-C*H*), 4.98-5.16 (2H, m, CH=C*H*$_2$), 5.72-5.91 (1H, m, C*H*=CH$_2$), 7.29 (2H, d, *J*=8.5 Hz, Ar*H*), 7.79 (2H, d, *J*=8.5 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ21.3, 21.6, 29.7, 37.7, 39.7, 48.5, 58.7, 59.4, 65.3, 118.0, 127.3, 129.6, 134.8, 137.6, 143.5. **FTIR (thin film)**: 3407 (s), 2938 (m), 1721 (w), 1638 (w), 1441 (w), 1400 (w), 1319 (m), 1157 (s), 1098 (m), 924 (m), 816 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{17}H_{26}NO_4S$** (MH^+): 340.1583. Found: 340.1589.

Synthesis of 2-allyl-6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-piperidin-3-ol 267a



To a solution of **266** (made using *m*-CPBA) (50 mg, 0.09 mmol, 1.0 eq.) in DCM (1 mL) at -78 ^{0}C, $BF_3.OEt_2$ (23 μL, 0.19 mmol, 2.0 eq.) was added slowly. The resulting solution was left stirring for 15 min, then allyltrimethylsilane (45 μL, 0.28 mmol, 3.0 eq) was added slowly at the same temperature. The reaction mixture was stirred at room temperature overnight and quenched with ammonium chloride. The products were extracted with EtOAc and the organic phase was washed with sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$, concentrated under vacuum and purified by silica gel chromatography (4:1 petroleum ether/EtOAc) to give **267a** (27 mg, 50%). See above for characterisation.

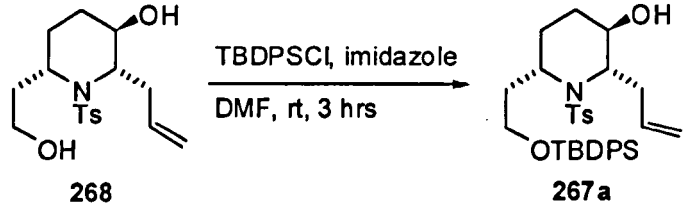
Synthesis of 2-allyl-6-(2-hydroxy-ethyl)-1-(toluene-4-sulfonyl)-piperidin-3-ol 268



267a **268**

To a solution of **267a** (65 mg, 0.11 mmol, 1.0 eq.) in THF (2 mL), TBAF (1.0 M in THF, 250 μL, 0.25 mmol, 2.2 eq.) was added slowly. The reaction mixture was stirred at room temperature overnight and quenched with water. The product was extracted with EtOAc and the organic phase was washed with brine. The organic layer was dried over $MgSO_4$, concentrated under vacuum and purified by silica gel chromatography (1:1 petroleum ether/EtOAc) to give **268** (32 mg, 85%) an oil. See above for characterisation.

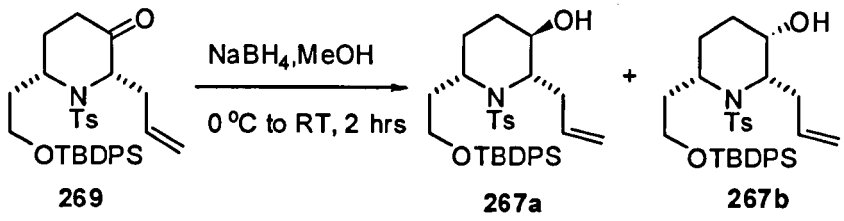
Synthesis of 2-allyl-6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-piperidin-3-ol 267a



268 **267a**

Substrate **268** (207 mg, 0.61 mmol, 1.0 eq) was dissolved in DMF (15 mL) and TBDPSCl (190 μL, 0.73 mmol, 1.20 eq) and imidazole (50 mg, 0.73 mmol, 1.20 eq) were added to this solution. The reaction mixture was stirred for 3 h. The reaction mixture was quenched with NH_4Cl, extracted 4 times with Et_2O and washed with brine. The organic layer was dried over sodium sulphate and concentrated under vacuum. Purification of the resulting oil by silica gel chromatography (10/1, petroleum/EtOAc) provided **267a** as a colourless oil (286 mg, 81%). See above for characterisation.

Synthesis of 2-allyl-6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-piperidin-3-ol 267a



269 **267a** **267b**

Substrate **269** (37 mg, 0.06 mmol, 1.0 eq) was dissolved in MeOH (15 mL) and sodium borohydride (2.4 mg, 0.06 mmol, 1.0 eq) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into aqueous 10% HCl solution, extracted with EtOAc. The organic layer was washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and solvent was removed to give a 2.5:1 mixture of the 2 diastereoisomers (35 mg, 95 %) in favour of **267b**. Purification of the resulting oil by silica gel chromatography (4/1, petroleum/EtOAc) provided pure samples of **267a** (5 mg, 14 %) and **267b** (5 mg, 14 %) as colourless oils.

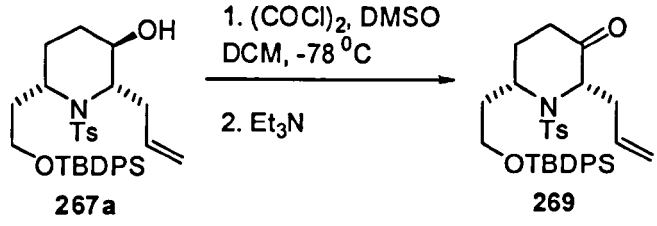
<u>267a :</u> see above for characterisation.

<u>267b:</u> **^{1}H NMR (500 MHz, $CDCl_3$)**: δ1.05 (9H, s, SiC(CH_3)$_3$), 1.21-1.36 (2H, m, CH_2), 1.45-1.62 (2H, m, CH_2), 1.76-1.85 (1H, m, C*H*H), 1.92-2.00 (1H, m, CH*H*), 2.20-2.30 (1H, m, C*H*H), 2.38 (3H, s, ArCH_3), 2.53-2.61 (1H, m, C*H*H), 3.54 (1H, br s, C*H*OH), 3.60-3.69 (2H, m, OCH_2), 4.06-4.13 (1H, m, N-C*H*-CHOH), 4.27-4.33 (1H, m, N-C*H*), 4.01-5.08 (2H, m, CH=CH_2), 5.84-5.95 (1H, m, C*H*=CH_2), 7.20 (2H, d, *J*=8.0 Hz, Ar*H*), 7.34-7.45 (6H, m, Ar*H*), 7.61-7.70 (6H, m, Ar*H*). **^{13}C NMR (100.0 MHz, $CDCl_3$)**: δ19.4, 20.3, 21.0, 22.5, 26.5, 37.6, 39.1, 49.4, 59.0, 61.5, 65.5, 117.2, 127.3, 127.1, 129.3, 133.9, 134.6, 135.4, 135.6, 136.3, 144.7. **FTIR (thin film):** 3533 (s), 3076 (m), 2952 (s), 2864 (s), 1674 (w), 1470 (w), 1419 (m), 1332 (m), 1260 (s), 1157 (s), 1112 (s), 939 (m) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{33}H_{44}NO_4SiS$** (MH^+): 578.2850. Found: 578.2843.

COSY spectrum: See Appendix 6.8

NOESY spectrum: See Appendix 6.9

Synthesis of 2-allyl-6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-(toluene-4-sulfonyl)-piperidin-3-one 269



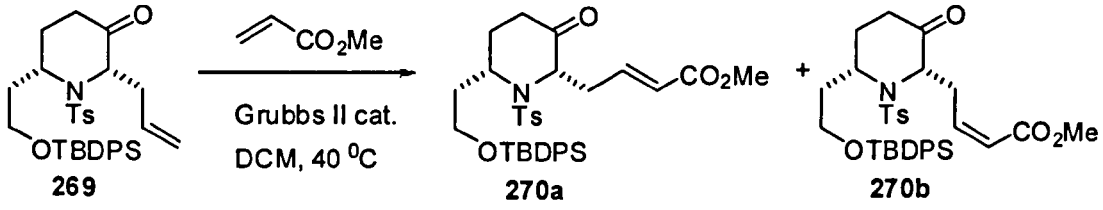
267a **269**

Oxalyl chloride (60 μL, 0.66 mmol, 2.25 eq) was added to DCM (5 mL) at -78 °C then DMSO (95 μL, 1.32 mmol, 4.5 eq) was added and the reaction stirred for 5 minutes. A solution of alcohol **267a** (170 mg, 0.29 mmol, 1.0 eq) in DCM (2.5 mL) was added to the mixture. After 1 hour, Et_3N (280 μL, 1.99 mmol, 6.75 eq) was added and the mixture was allowed to warm to room temperature. The reaction was quenched with water and the product was extracted with DCM. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oily residue was purified by by silica gel chromatography (10:1 petroleum ether/EtOAc) to give **269** (135 mg, 80%). $[\alpha]^{21}_D$=+42 (*c* 0.005 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.08 (9H, s, $SiC(CH_3)_3$), 1.20-1.29 (1H, m, C*H*H-C=O), 1.46-1.56 (1H, m, C*H*H), 1.68-1.77 (1H, m, C*H*H), 1.97-2.04 (1H, m, C*H*H), 2.04-2.10 (1H, m, C*H*H), 2.30-2.46 (2H, m, C*H*H + C*H*H), 2.40 (3H, s, ArCH_3), 2.52-2.59 (1H, m, C*H*H), 3.67-3.74 (1H, m, CH*H*-OSi), 3.77-3.83 (1H, m, C*H*H-OSi), 3.98-4.06 (1H, m, N-C*H*), 4.37-4.42 (1H, m, N-C*H*), 5.05-5.15 (2H, m, CH=CH_2), 5.78-5.88 (1H, m, C*H*=CH_2), 7.24 (2H, d, *J*=8.0 Hz, Ar*H*), 7.36-7.46 (6H, m, Ar*H*), 7.61 (2H, d, *J*=8.0 Hz, Ar*H*), 7.64-7.69 (4H, d, *J*=8.0 Hz, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.3, 21.5, 25.0, 26.9, 35.5, 39.2, 40.9, 51.2, 60.9, 63.7, 118.4, 127.0, 127.8, 129.8, 129.9, 133.3, 133.5, 135.6, 136.0, 143.7, 208.5. **FTIR (thin film)**: 2939 (m), 2858 (m), 1730 (s), 1428 (w), 1360 (w), 1327 (w), 1167 (s), 1111 (s), 980 (w), 949 (w), 821 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{33}H_{42}NO_4SiS$** (MH^+): 576.2604. Found: 576.2589.

COSY spectrum: See Appendix 6.10

NOESY spectrum: See Appendix 6.11

Synthesis of 4-[6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-oxo-1-(toluene-4-sulfonyl)-piperidin-2-yl]-but-2-enoic acid methyl ester 270a



269 270a 270b

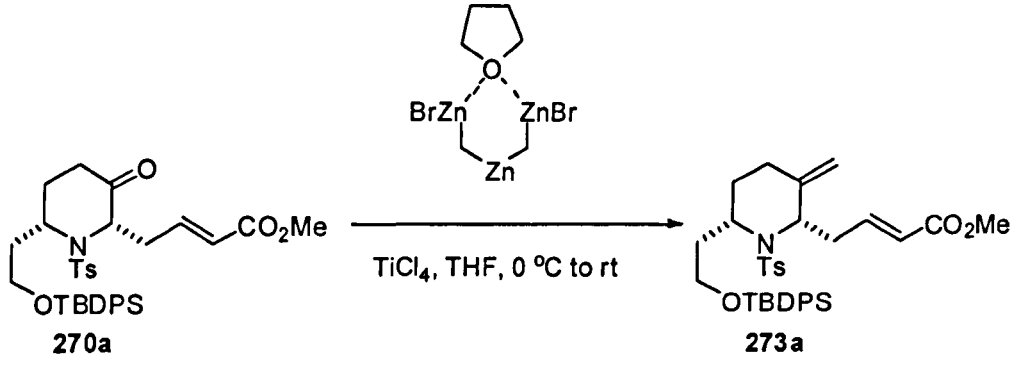
To s aolution of **269** (134 mg, 023 mmol, 1.0 eq) in DCM (4 mL), was added methyl acrylate (65 μL, 0.70 mmol, 3.0 eq) followed by Grubbs' second generation catalyst (20 mg, 0.02 mmol, 0.1 eq). The reaction mixture was stirred at reflux for 16 hours and then concentrated by rotary evaporation. The resulting oily residue was purified by silica gel chromatography (6:1 petroleum ether/EtOAc) to give **270a** (115 mg, 78%) and **270b** (26 mg, 18%).

<u>270a:</u> $[\alpha]^{21}_D$=+34 (*c* 0.011 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.11 (9H, s, $SiC(CH_3)_3$), 1.24-1.75 (4H, m, CH_2), 2.03-2.18 (1H, m, C*H*H), 2.29-2.40 (1H, m, C*H*H), 2.44 (3H, s, $ArCH_3$), 2.46-2.56 (1H, m, C*H*H), 2.65-2.76 (1H, m, C*H*H), 3.66-3.74(1H, m, CH*H*-OSi), 3.77 (3H, s, OCH_3), 3.78-3.86 (1H, m, C*H*H-OSi), 4.06 -4.17 (1H, m, N-C*H*), 4.44-4.53 (1H, m, N-C*H*-CO), 5.89 (1H, d, *J*=15.5 Hz, CH=C*H*-CO_2CH_3), 6.94 (1H, td, *J*=7.5 Hz, *J*=15.5 Hz, C*H*=CH-CO_2CH_3), 7.28 (2H, d, *J*=8.0 Hz, Ar*H*), 7.38-7.50 (6H, m, Ar*H*), 7.66 (2H, d, *J*=8.0 Hz, Ar*H*), 7.67-7.72 (4H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.6, 25.0, 26.9, 29.7, 35.5, 37.6, 51.2, 51.6, 60.7, 62.6, 124.2, 127.1, 127.8, 129.8, 130.0, 133.5, 135.6, 136.0, 143.1, 144.0, 166.0, 207.8. **FTIR (thin film)**: 2928 (m), 2845 (m), 1727 (s), 1426 (w), 1343 (w), 1164 (s), 1111 (s), 980 (w), 819 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{35}H_{44}NO_6SiS$** (MH^+): 634.2659. Found: 634.2667.

<u>270b:</u> $[\alpha]^{21}_D$=+42 (*c* 0.014 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.11 (9H, s, $SiC(CH_3)_3$), 1.23-1.37 (1H, m, C*H*H), 1.54-1.82 (2H, m, C*H*H), 1.93-2.05 (1H, m, C*H*H), 2.08-2.19 (1H, m, C*H*H), 2.37-2.51 (4H, m, C*H*H + $ArCH_3$), 3.02-3.15 (1H, m, C*H*H), 3.17-3.30 (1H, m, C*H*H), 3.62-3.74 (4H, m, CH*H* + OCH_3),

3.78-3.89 (1H, m, CH*H*-OSi), 4.06-4.17 (1H, m, N-C*H*), 4.44-4.53 (1H, m, N-C*H*-CO), 5.96 (1H, d, *J*=11.5 Hz, CH=C*H*-CO_2CH_3), 6.44 (1H, td, *J*=7.0 Hz, *J*=11.5 Hz, C*H*=CH-CO_2CH_3), 7.28 (2H, d, *J*=8.0 Hz, Ar*H*), 7.37-7.51 (6H, m, Ar*H*), 7.64 (2H, d, *J*=8.0 Hz, Ar*H*), 7.67-7.77 (4H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.7, 22.0, 23.1, 27.3, 30.1, 34.2, 35.8, 51.2, 51.6, 61.2, 63.3, 122.1, 127.4, 128.2, 130.2, 130.4, 134.1, 136.0, 136.5 144.3, 145.0, 166.3, 208.1. **FTIR (thin film)**: 2924 (m), 2853 (m), 1721 (s), 1462 (w), 1431 (w), 1361 (w), 1166 (s), 1112 (s), 821 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{35}H_{44}NO_6SiS$** (MH^+): 634.2659. Found: 634.2644.

Synthesis of 4-[6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-oxo-1-(toluene-4-sulfonyl)-piperidin-2-yl]-but-2-enoic acid methyl ester 273a

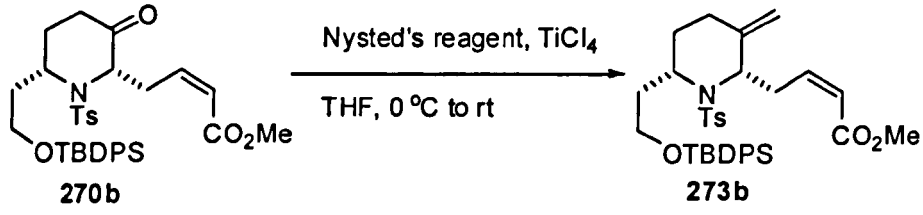


270a **273a**

To a solution of Nysted reagent (570 μL, 0.29 mmol, 3.0 eq) in THF (1 mL) at 0 °C, was added titanium tetrachloride (32 μL, 0.29 mmol, 3.0 eq) dropwise. The resulting dark brown solution was stirred at 0 °C for 20 min. To this mixture was then added a solution of substrate **270a** (62 mg, 0.10 mmol, 1.0 eq) at rt for 16 hrs. The solution was quenched by addition of HCl (1 M) and the product was extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$. The resulting oily residue was purified by silica gel chromatography (5:1 petroleum ether/EtOAc) to give **273a** (32 mg, 52%) and starting material **270a** (28 mg, 45%). $[\alpha]^{21}_D$=+30 (*c* 0.01 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.08 (9H, s, $SiC(CH_3)_3$), 1.18-1.31 (2H, m, CH_2), 1.80-1.93 (2H, m, CH_2), 2.08-2.27 (2H, m, CH_2), 2.41 (3H, s, $ArCH_3$), 2.45-2.67 (2H, m, CH_2), 3.68-3.83 (5H, m, OCH_3 + CH_2-OSi), 4.02-4.10 (1H, m, N-C*H*), 4.55-4.61 (1H, m, N-C*H*), 4.65

(1H, br s, C=C*H*H), 4.76 (1H, br s, C=CH*H*), 5.84 (1H, d, *J*=15.5 Hz, CH=C*H*-CO_2CH_3), 6.86 (1H, td, *J*=7.5 Hz, *J*=15.5 Hz, C*H*=CH-CO_2CH_3), 7.23 (2H, d, *J*=8.0 Hz, Ar*H*), 7.36-7.49 (6H, m, Ar*H*), 7.62-7.73 (6H, m, Ar*H*). **^{13}C NMR (62.9 MHz, $CDCl_3$)**: δ19.2, 21.5, 24.5, 26.9, 27.8, 37.9, 39.8, 50.0, 51.5, 58.9, 61.6, 111.5, 120.2, 123.4, 127.0, 127.7, 129.6, 133.6, 135.6, 137.8, 142.5, 142.9, 144.9, 166.6. **FTIR (thin film)**: 3050 (w), 2937 (m), 2854 (m), 1721 (s), 1659 (w), 1426 (w), 1332 (w), 1161 (s), 1104 (s), 922 (w), 813 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{36}H_{45}NO_5NaSiS$** (MNa^+): 654.2685. Found: 654.2706.

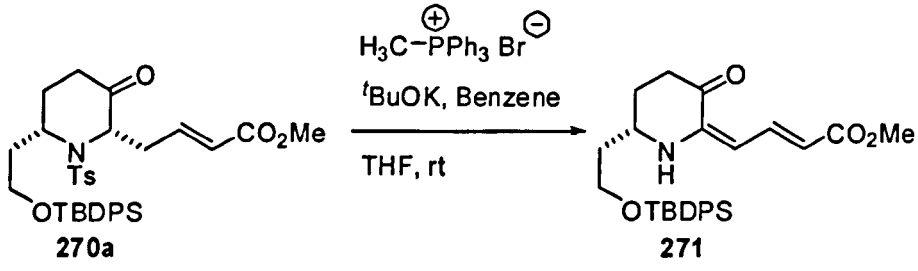
Synthesis of 4-[6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-methylene-1-(toluene-4-sulfonyl)-piperidin-2-yl]-but-2-enoic acid methyl ester 273b



To a solution of Nysted reagent (610 μL, 0.32 mmol, 3.0 eq) in THF (1 mL) at 0 °C, was added titanium tetrachloride (35 μL, 0.32 mmol, 3.0 eq) dropwise. The resulting dark brown solution was stirred at 0 °C for 20 min. To this mixture was then added a solution of substrate **270b** (67 mg, 0.11 mmol, 1.0 eq) at rt for 16 hrs. The solution was quenched by addition of HCl (1 M) and the product was extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$. The resulting oily residue was purified by silica gel chromatography (5:1 petroleum ether/EtOAc) to give **273b** (41 mg, 61%). $[\alpha]^{21}_D$=-60 (*c* 0.01 g/mL, CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$):** δ1.09 (9H, s, $SiC(CH_3)_3$), 1.15-1.26 (1H, m, C*H*H), 1.47-1.56 (2H, m, CH_2), 1.72 (1H, dt, *J*=4.5, 15.0 Hz, *CH*H), 1.87-1.97 (1H, m, CH*H*), 2.11-2.21 (1H, m, CH*H*-CH_2-OSi), 2.26-2.36 (1H, m, C*H*H-CH_2-OSi), 2.42 (3H, s, ArCH_3), 3.00-3.22 (2H, m, CH_2), 3.64-3.81 (2H, m, CH_2-OSi), 3.69 (3H, s, CH_3O), 4.03-4.10 (1H, m, N-C*H*), 4.66 (1H, br s, C=C*H*H), 4.78 (1H, br s, C=CH*H*), 5.91 (1H, td, *J*=1.5, *J*=11.5 Hz, CH=C*H*-CO_2CH_3), 6.41-6.50 (1H, m, C*H*=CH-CO_2CH_3), 7.24 (2H, d, *J*=8.0 Hz, Ar*H*), 7.37-7.48 (6H, m, Ar*H*),

7.65-7.74 (6H, m, Ar*H*). **^{13}C NMR (400 MHz, $CDCl_3$):** δ19.2, 21.5, 24.8, 26.9, 27.2, 36.3, 37.8, 50.1, 51.1, 59.0, 61.3, 110.6, 120.7, 123.0, 127.2, 127.7, 129.6, 133.8, 135.6, 137.6, 142.9, 143.9, 146.6, 166.6. **FTIR (thin film):** 3050 (w), 2937 (m), 2854 (m), 1721 (s), 1659 (w), 1426 (w), 1332 (w), 1161 (s), 1104 (s), 922 (w), 813 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{36}H_{45}NO_5NaSiS$** (MNa^+): 654.2699. Found: 654.2708.

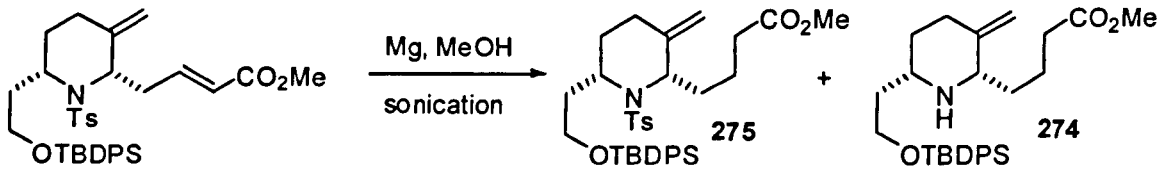
Synthesis of 4-(6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-oxo-piperidin-2-ylidene)-but-2-enoic acid methylester 271



A mixture of anhydrous potassium *tert*-butoxide (30 mg, 0.27 mmol, 5.6 eq) and methyltriphenylphosphonium bromide (84 mg, 0.24 mmol, 5.0 eq) in anhydrous benzene (12 mL) was allowed to stir at room temperature for 75 min. The substrate **270a** (30 mg, 0.05 mmol, 1.0 eq) in THF (5 mL) was then added into the resulting yellowish solution dropwise at rt. The mixture was stirred at rt overnight. The solution was quenched with water, diluted with EtOAc and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The resulting oily residue was purified by silica gel chromatography (5:1 petroleum ether/EtOAc) to give **271** (14 mg, 52%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ1.11 (9H, s, $SiC(CH_3)_3$), 1.67-1.91 (4H, m, CH_2), 1.99-2.09 (1H, m, CH*H*), 2.43-2.54 (1H, m, CH*H*), 2.66 (1H, td, *J*=4.5 Hz, *J*=17.5 Hz, N-C*H*), 3.69 (3H, s, OCH_3), 3.82-3.87 (2H, m, CH_2-OSi), 5.08 (1H, br s, NH), 5.94 (1H, d, *J*=14.5 Hz, C=C*H*-CH=CH-CO_2CH_3), 6.02 (1H, d, *J*=13.0 Hz, C=CH-C*H*=CH-CO_2CH_3), 7.32 (1H, dd, *J*=13.0 Hz, *J*=14.5 Hz, C=CH-CH=C*H*-CO_2CH_3), 7.39-7.51 (6H, m, Ar*H*), 7.66-7.72 (4H, m, Ar*H*). **FTIR (thin film):** 3364 (w), 2949 (m), 2854 (m), 1691 (s), 1588 (s), 1426 (m), 1337 (w), 1306 (w), 1249 (w), 1135

(s), 1112 (s), 818 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{28}H_{36}NO_4Si$** (MH^+): 478.2414. Found: 478.2411.

Synthesis of 4-(6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-methylene-piperidin-2-yl)-butyric acid methyl ester 274



273a

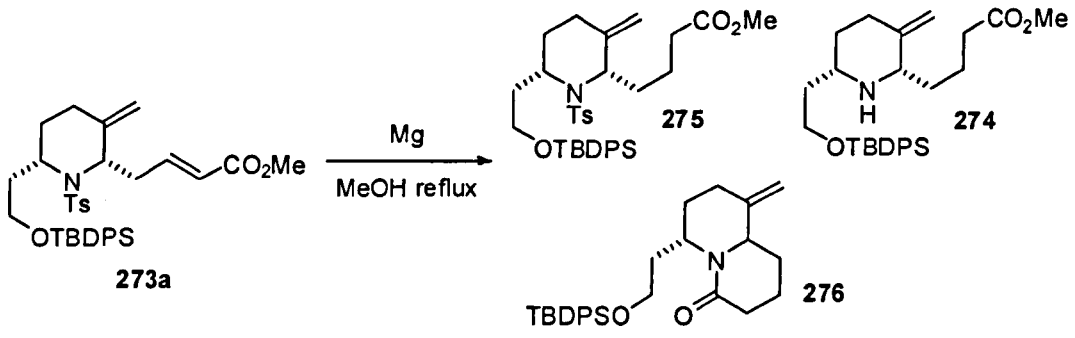
To a solution of **273a** (37 mg, 0.06 mmol, 1.0 eq) in methanol (2 mL) was added powdered magnesium (42 mg, 1.75 mmol, 30.0 eq) and the resulting suspension sonicated at room temperature for 40 minutes. Additional powdered magnesium (42 mg, 1.75 mmol, 30.0 eq) was then added and the reaction mixture sonicated for a further 30 min. The solution was quenched by addition of HCl (1 M) and the product was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oily residue was purified by silica gel chromatography (gradient from 5:1 petroleum ether/EtOAc to 10:1 DCM/MeOH) to give **274** (15 mg, 52%) and **275** (6 mg, 16%).

<u>274:</u> **^{1}H NMR (400 MHz, $CDCl_3$):** δ1.08 (9H, s, $SiC(CH_3)_3$), 1.57-1.84 (8H, m, CH_2), 2.08-2.18 (2H, m, CH_2), 2.32-2.42 (1H, m, NC*H*), 2.35 (2H, t, *J*=7.5 Hz, CH_2CO_2Me), 2.89-3.02 (1H, m, NC*H*), 3.68 (3H, s, OCH_3), 3.74-3.84 (2H, m, CH_2-OSi), 4.72 (1H, br s, C=CH*H*), 4.77 (1H, br s, C=C*H*H), 7.37-7.46 (6H, m, Ar*H*), 7.65-7.72 (4H, m, Ar*H*). **^{13}C NMR (400 MHz, $CDCl_3$):** δ19.6, 22.0, 22.6, 26.9, 27.3, 32.1, 34.2, 35.1, 51.5, 55.0, 59.0, 61.8, 110.9, 127.7, 129.6, 135.6, 143.1, 144.8, 174.0. **FTIR (thin film)**: 2928 (s), 2854 (m), 1734 (s), 1456 (w), 1428 (m), 1385 (w), 1257 (w), 1194 (w), 1169 (w), 1111 (s), cm^{-1}. **HRMS (TOF ES) calcd. for $C_{29}H_{42}NO_3Si$** (MH^+): 480.2922. Found: 480.2934.

<u>275:</u> **^{1}H NMR (400 MHz, $CDCl_3$):** δ1.09 (9H, s, $SiC(CH_3)_3$), 1.45-1.55 (2H, m, CH_2), 1.67-1.80 (4H, m, CH_2), 1.83-1.94 (2H, m, CH_2), 2.13-2.28 (2H, m, CH_2),

2.34-2.44 (5H, m, ArC*H*$_3$ + C*H*$_2$-CO_2Me), 3.63-3.82 (5H, m, OC*H*$_3$ + C*H*$_2$-OSi), 3.97-4.05 (1H, m, N-C*H*), 4.48 (1H, t, *J*=7.5 Hz, N-C*H*), 4.65 (1H, br s, C=C*H*H), 4.76 (1H, br s, C=CH*H*), 7.23 (2H, d, *J*=8.0 Hz, Ar*H*), 7.36-7.49 (6H, m, Ar*H*), 7.63-7.74 (6H, m, Ar*H*). **^{13}C NMR (400 MHz, $CDCl_3$)**: δ19.6, 21.9, 22.6, 25.2, 27.3, 27.9, 33.9, 36.9, 38.5, 50.5, 51.9, 60.1, 61.9, 110.9, 127.1, 127.5, 128.1, 129.8, 134.1, 136.0, 138.3, 143.1, 144.8, 174.0. **FTIR (thin film)**: 3071 (w), 296 (s), 2855 (s), 1737 (s), 1462 (m), 1428(m), 1334 (m), 1162 (s), 1111 (s), 999 (w), 916 (w), 822 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{36}H_{47}NO_5NaSiS$** (MNa^+): 656.2842. Found: 656.2840.

Synthesis of 4-(6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-methylene-piperidin-2-yl)-butyric acid methyl ester 274



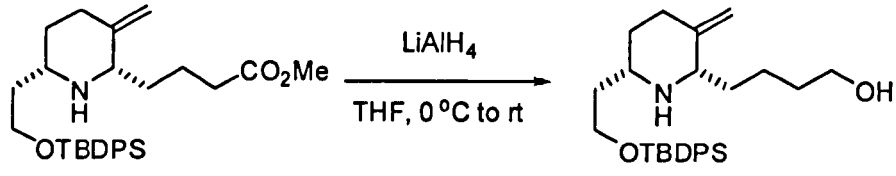
Magnesium turnings (93 mg, 3.84 mmol, 30.0 eq) were flame dried in a 2 neck flask fitted with a condenser. The flask was cooled under nitrogen then methanol (1 mL) was added followed by dropwise addition of a solution of the ester **273a** (81 mg, 0.13 mmol, 1.0 eq) in methanol (1.5 mL). The solution was left stirring for 16 hours and another 30 equivalents of magnesium turnings were added and the reaction mixture was heated at reflux for 3 hours. The solution was quenched by addition of HCl (1 M) and the product was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oily residue was purified by silica gel chromatography (gradient from 5:1 petroleum ether/EtOAc to 10:1 DCM/MeOH) to give **274** (32 mg, 51%), **275** (14 mg, 17%) and **276** (14 mg, 24%).

274: see above for characterisation.

<u>275:</u> see above for characterisation.

<u>276:</u> **^{1}H NMR (400 MHz, $CDCl_3$):** δ1.03 (9H, s, SiC(CH_3)$_3$), 1.53-1.76 (8H, m, CH_2), 1.87-1.95 (2H, m, CH_2), 2.39-2.48 (2H, m, CH_2), 3.63-3.73 (2H, m, CH_2-OSi), 3.88-3.93 (1H, m, N-C*H*), 4.40-4.45 (1H, m, N-C*H*), 4.94 (1H, br s, C=C*H*H), 4.97 (1H, br s, C=CH*H*), 7.33-7.44 (6H, m, Ar*H*), 7.60-7.68 (4H, m, Ar*H*). **^{13}C NMR (400 MHz, $CDCl_3$):** δ19.1, 20.0, 22.7, 26.0, 26.8, 27.0, 32.3, 34.9, 49.1, 55.7, 62.1, 110.2, 123.4, 127.6, 129.5, 135.5, 144.8, 169.5. **FTIR (thin film):** 3062 (w), 2937 (s), 2856 (s), 1726 (s), 1630 (s), 1605 (s), 1427 (w), 1332 (w), 1161 (m), 1106 (s), 823 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{28}H_{38}NO_2Si$** (MH^+): 448.2672. Found: 448.2678.

Synthesis of 4-(6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-methylene-piperidin-2-yl)-butan-1-ol 278

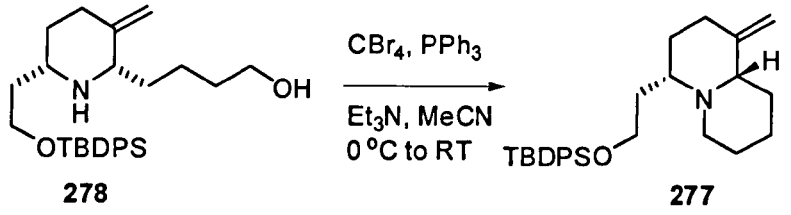


274 **278**

$LiAlH_4$ (7 mg, 0.18 mmol, 5.0 eq) was added to a solution of **274** (17 mg, 0.04 mmol, 1.0 eq) in THF (2 mL) at 0 °C. The solution was left stirring for 16 hours at room temperature. The solution was quenched by addition of potassium carbonate and the product was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The desired product **278** was obtained without further purification (15 mg crude, 95%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ1.08 (9H, s, SiC(CH_3)$_3$), 1.32-1.69 (6H, m, CH_2), 1.75-1.89 (4H, m, CH_2), 2.11-2.22 (2H, m, CH_2), 2.41-2.48 (1H, m, NC*H*), 3.06-3.20 (1H, m, NC*H*-C=CH_2), 3.64 (2H, t, *J*=6.0 Hz, CH_2-OH), 3.75-3.88 (2H, m, CH_2-OSi), 4.78 (1H, br s, C=CH*H*), 4.84 (1H, br s, C=C*H*H), 7.38-7.48 (6H, m, Ar*H*), 7.65-7.71 (4H, m, Ar*H*). **^{13}C NMR (250 MHz, $CDCl_3$):** δ19.4, 22.2, 23.6, 26.9, 27.4, 32.3, 34.2, 35.8, 51.7, 55.2, 59.4, 61.8, 111.3, 128.2, 130.3, 136.0, 143.4, 145.8. **FTIR (thin film):** 3336 (br), 2930 (s), 2846 (s), 1464 (w),

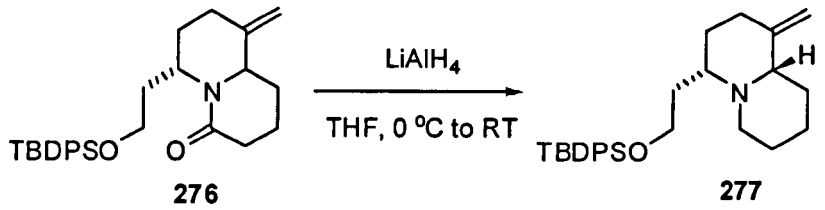
1423 (m), 1388 (w), 1103 (s) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{28}H_{42}NO_2Si$** (MH^+): 452.2985. Found: 452.2983.

Synthesis of 4-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-methylene-octahydro-quinolizine 277



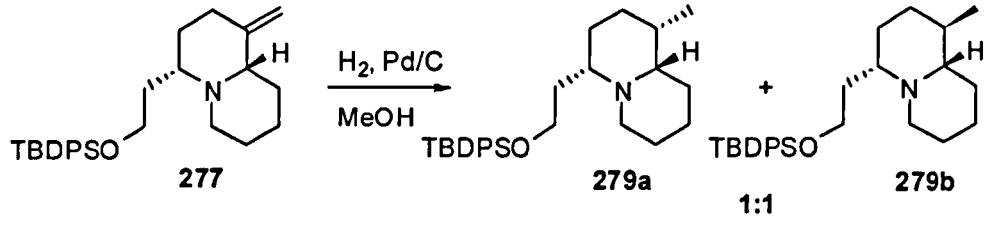
Carbon tetrabromide (28 mg, 0.08 mmol, 1.25 eq) was added to a solution of substrate **278** (30mg, 0.07 mmol, 1.0 eq) in DCM (1 mL) at 0 °C. When all the CBr_4 had dissolved, triphenylphosphine (26 mg, 0.1 mmol, 1.5 eq) was added to the reaction mixture at 0 °C. The solution was left stirring for 1 hour at 0 °C then triethylamine (152 μL, 1.09 mmol, 16.5 eq) was added. The solution was concentrated under reduced pressure and the resulting white solid was purified by silica gel chromatography (200:1 $CHCl_3$/MeOH) to give the desired bicycle **277** (26 mg, 91%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.07 (9H, s, $SiC(CH_3)_3$), 1.20-2.45 (15H, m, CH_2), 3.03-3.19 (1H, m, N-C*H*), 3.75 (2H, t, *J*=7.5 Hz, CH_2-OSi), 4.77 (2H, br s, C=CH_2), 7.37-7.49 (6H, m, Ar*H*), 7.65-7.72 (4H, m, Ar*H*). **^{13}C NMR (250 MHz, $CDCl_3$)**: δ19.2, 20.0, 22.7, 26.9, 28.9, 29.7, 35.0, 36.8, 49.1, 50.2, 55.7, 61.6, 110.2, 123.4, 127.6, 129.5, 135.5, 144.8 **FTIR (thin film):** 2928 (s), 2855 (s), 1472 (m), 1428 (m), 1388 (w), 1257 (w), 1186 (w), 1112 (s), 898 (w) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{28}H_{40}NOSi$** (MH^+): 434.2879. Found: 434.2885.

Synthesis of 4-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-methylene-octahydro-quinolizine 277



$LiAlH_4$ (6 mg, 0.14 mmol, 5.0 eq) was added to a solution of **276** (25 mg, 0.06 mmol, 1.0 eq) in THF (3 mL) at 0 °C. The solution was left stirring for 16 hours at room temperature. The solution was quenched by addition of potassium carbonate and the product was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product **277** (23 mg, 90%). No further purification was carried out. The spectroscopic data matches that described earlier.

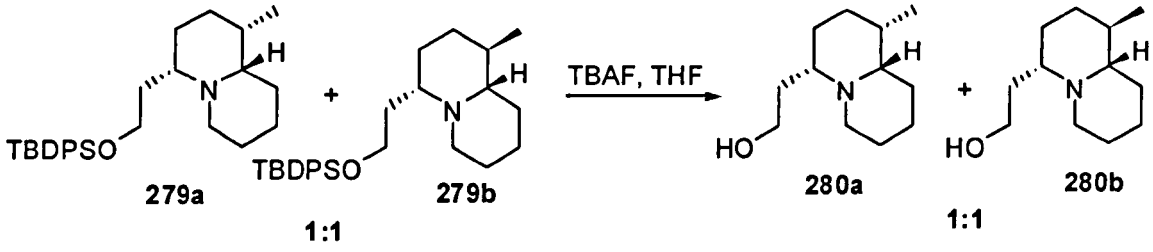
Synthesis of 4-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-1-methyl-octahydro-quinolizine 279a and 279b



To a solution of **277** (67 mg, 0.23 mmol) in methanol (2.3 mL) was added palladium on 10% carbon (16 mg) and the mixture was stirred under an atmosphere of hydrogen overnight. The reaction mixture was filtered over Hyflo Super Cel and washed with methanol. The solvent was removed under reduced pressure to give an inseparable mixture of the two diastereoisomers **279a** and **279b**. No further purification was carried out. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ0.85 (3H, d, *J*=6.0 Hz, C-C*H*$_3$), 0.95 (3H, d, *J*=7.0 Hz, C-C*H*$_3$), 1.06 (18H, s, SiC(C*H*$_3$)$_3$), 1.12-2.11 (32H, m, C*H*$_2$), 3.06-3.21 (2H, m, N-C*H*), 3.73 (4H, m, C*H*$_2$-OSi), 4.77 (2H, br s, C=C*H*$_2$), 7.32-7.50 (12H, m, Ar*H*), 7.60-7.77 (8H, m,

Ar*H*). **^{13}C NMR (250 MHz, $CDCl_3$)**: δ13.4, 19.2, 19.3, 22.1, 25.0, 26.3, 26.0, 26.6, 26.9, 28.9, 31.6, 31.8, 32.0, 33.3, 33.8, 36.8, 45.0, 46.9, 51.5, 51.6, 52.9, 61.6, 62.0, 62.1, 66.2, 127.6, 129.6, 134.0, 134.1, 134.8, 135.6. **FTIR (thin film):** 2930 (s), 2856 (s), 1459 (w), 1428 (m), 1388 (w), 1112 (s), 1083 (s), 823 (m), 737 (m), 701 (s) cm^{-1}. **HRMS (TOF ES) calcd. for $C_{28}H_{42}NOSi$** (MH^+): 436.3036. Found: 436.3026.

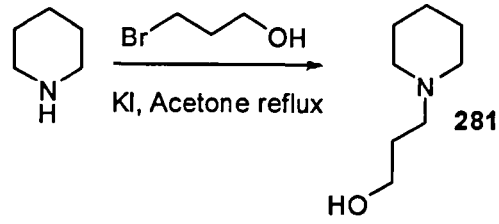
Synthesis of 2-(1-methyl-octahydro-quinolizin-4-yl)-ethanol 280a and 280b



To a solution of **279a** and **279b** (25 mg, 0.06 mmol) in THF (2 mL) was added TBAF (1.0M in THF, 90 μL, 0.09 mmol, 1.5 eq) and the resulting mixture was stirred at rt overnight. The reaction was quenched with water and the product extracted with ethyl acetate. The organic phase was then dried over Na_2SO_4 and concentrated under reduce pressure. Purification of the oily residue by silica gel chromatography (20:1, $CHCl_3$/MeOH) provided an inseparable mixture of the two diastereoisomers **280a** and **280b** (7 mg, 69%). A clean sample that was free from contamination by Et_3N could not be obtained. So the sample was used directly in the subsequent step. **HRMS (TOF ES) calcd. for $C_{12}H_{24}NO$** (MH^+): 198.1858. Found: 198.1854.

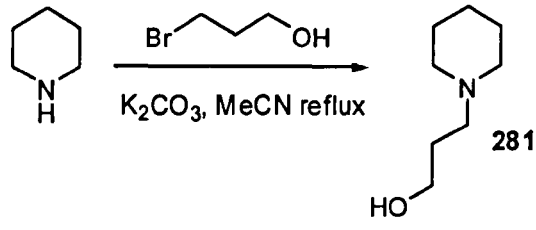
8.3.Model Substrate

Synthesis of 3-piperidin-1-yl-propan-1-ol 281[147, 148]



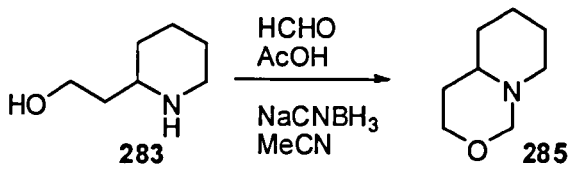
3-Bromopropan-1-ol (1.3 mL, 14.39 mmol, 1.0 eq) was added to a solution of piperidine (2.84 mL, 28.78 mmol, 2.0 eq) and potassium iodide (< 5 mg) in acetone (30 mL) and the resulting mixture was stirred under reflux for 16 hours. The solution was concentrated by rotary evaporation and the product **281** was obtained by distillation under reduced pressure b.p.: 110°C, 10-15 mmHg (646 mg, 31%) (lit[147, 148]: b.p. 94-95°C, 0.5 mmHg). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.36-1.49 (2H, m, C*H*$_2$), 1.56 (4H, q, *J*=5.5 Hz, CH_2), 1.66-1.73 (2H, m, C*H*$_2$), 2.33-2.52 (4H, m, C*H*$_2$-N), 2.55 (2H, t, *J*=5.5 Hz, N-C*H*$_2$), 3.79 (2H, t, *J*=5.5 Hz, C*H*$_2$-OH), 5.87 (1H, br s, OH).

Synthesis of 3-piperidin-1-yl-propan-1-ol 281[147, 148]



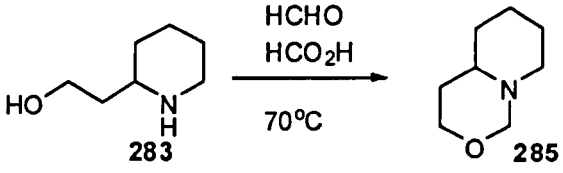
3-Bromopropan-1-ol (3 mL, 34.32 mmol, 1.0 eq) was added to a solution of piperidine (3.60 mL, 36.03 mmol), 1.05 eq) and potassium carbonate (4.08 g, 29.52 mmol, 0.86 eq) in acetonitrile (70 mL) and the resulting mixture was stirred under reflux for 16 hours. The solution was filtered, concentrated by rotary evaporation and the product **281** was obtained by distillation under reduced pressure.

Synthesis of hexahydro-pyrido[1,2-c][1,3]oxazine 285[150]



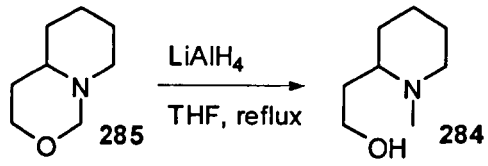
To a solution of **283** (504 mg, 3.90 mmol, 1.0 eq) in acetonitrile (58 mL) was added formaldehyde (37% aq, 18.2 mL, 223.0 mmol, 57.0 eq), AcOH (1.3 mL) and $NaCNBH_3$ (1.35 g, 21.5 mmol, 5.5 eq) and the resulting solution was left stirring overnight. The dark solids were removed by filtration, washed with dichloromethane and acetonitrile and the solution was concentrated under reduced pressure. The resulting oily residue was distilled under vacuum to give **285** (440 mg, 80%) as a clear oil (b.p.: 90°C, ~10 mmHg). (lit.[150] b.p.: 114-115°C, 15 mmHg). **^{13}C NMR (250 MHz, $CDCl_3$)**: δ23.6, 25.2, 31.6, 32.0, 48.8, 60.4, 67.9, 86.8.

Synthesis of hexahydro-pyrido[1,2-c][1,3]oxazine 285[149]



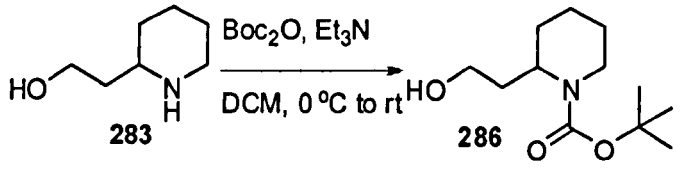
Substrate **283** (504 mg, 3.90 mmol, 1.0 eq) was mixed with formaldehyde (37% aq, 1.6 mL) and formic acid (2 mL) cautiously. The mixture was kept at 70 °C in an oil bath for 24 h. Water was added and then 50% aq. NaOH was used to adjust the pH to 14. The solution was saturated with NaCl and extracted with DCM. The combined organic extracts were dried over Na_2SO_4. Filtration and concentration afforded a crude oil which was subjected to distillation to give **285** (254 mg, 89%) as a liquid (b.p.: 90°C, 10 mmHg).

Synthesis of 2-(1-methyl-piperidin-2-yl)-ethanol 284[151]



To a solution of substrate **285** (254 mg, 1.80 mmol, 1.0 eq) in THF (110 mL) was added $LiAlH_4$ (683 mg, 18.0 mmol, 10.0 eq) and the resulting mixture was heated under reflux for 16 hrs. The reaction was quenched with NaOH (20%) and then with water at 0 °C. The lithium salts were removed by filtration, washed with DCM and the aqueous phase was extracted with DCM. The combined organic extracts were dried over Na_2SO_4. The crude product **284** (220 mg, 85%) was pure enough to be carried through directly the next step. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.20-1.34 (1H, m, CH*H*), 1.43-1.62 (5H, m, C*H*$_2$), 1.68-1.77 (1H, m, CH*H*N), 1.92-2.08 (2H, m, C*H*$_2$), 2.15-2.23 (1H, m, C*H*HN), 2.32 (3H, s, C*H*$_3$), 2.86 (1H, ddt, *J*=1.5, 3.5, 11.5 Hz, C*H*N), 3.63-3.70 (1H, m, CH*H*OH), 3.86-3.94 (1H, m, C*H*HOH). **^{13}C NMR (250 MHz, $CDCl_3$)**: δ24.1, 25.0, 28.9, 32.4, 43.2, 56.6, 60.7, 62.6.

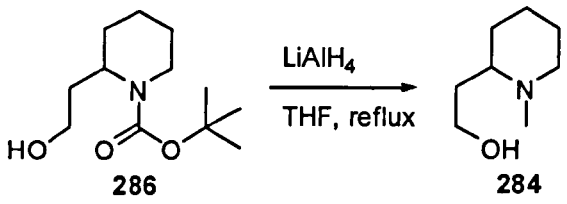
Synthesis of 2-(2-oxoethyl)-1-piperidinecarboxylic acid tert-butyl ester 286[152]



To a solution of substrate **283** (229 mg, 1.60 mmol, 1.0 eq) in DCM (2.6 mL) at 0 °C was added Et_3N (270 μL, 1.92 mmol, 1.2 eq) followed by a solution of Boc-anhydride (352 mg, 1.61 mmol, 1.01 eq) *via* cannula and the resulting mixture was left stirring at rt for 16 hrs. The reaction was quenched with $NaHCO_3$ and the product was extracted with DCM. The combined organic extracts were dried over $MgSO_4$. The crude product **286** (360 mg, 98%) was pure enough to be carried through directly the next step. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ1.36-1.67 (6H, m,

CH_2), 1.48 (9H, s, CH_3), 1.70-1.82 (1H, m, CH*H*), 1.89-2.05 (1H, m, C*H*H), 2.69 (1H, td, *J*=2.70 Hz, 13.0 Hz, C*H*HN), 3.28-3.47 (1H, br s, OH), 3.57-3.68 (1H, m, CH*H*N), 3.80-4.10 (2H, m, CH_2OH), 4.36-4.54 (1H, m, C*H*N). **^{13}C NMR (250 MHz, $CDCl_3$)**: δ19.2, 25.5, 28.4, 29.2, 32.4, 40.0, 48.2, 59.4, 80.0, 155.3.

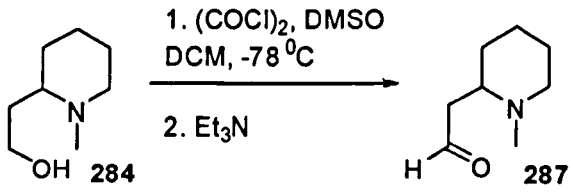
Synthesis of hexahydro-pyrido[1,2-c][1,3]oxazine 284



286 **284**

A solution of substrate **286** (360 mg, 1.57 mmol, 1.0 eq) in THF (25 mL) was added dropwise to a solution of $LiAlH_4$ (365 mg, 9.60 mmol, 5.9 eq) in THF (25 mL), the resulting solution was stirred at rt for 30 min and then was heated under reflux for 16 hrs. The reaction was quenched with NaOH (20%) and then with water at 0 °C. The lithium salts were removed by filtration, washed with DCM and the aqueous phase was extracted with DCM. The combined organic extracts were dried over Na_2SO_4. The crude product **284** (192 mg, 85%) was pure enough to be carried through directly the next step.

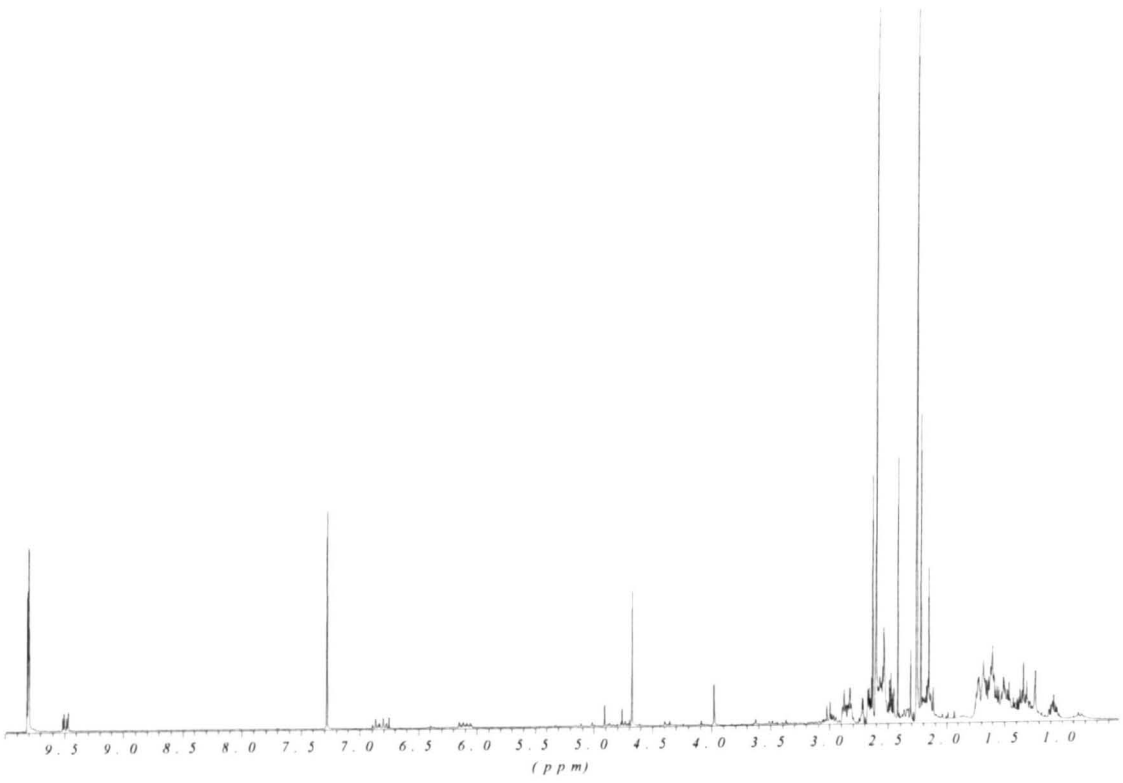
Synthesis of (1-methyl-piperidin-2-yl)-acetaldehyde 287

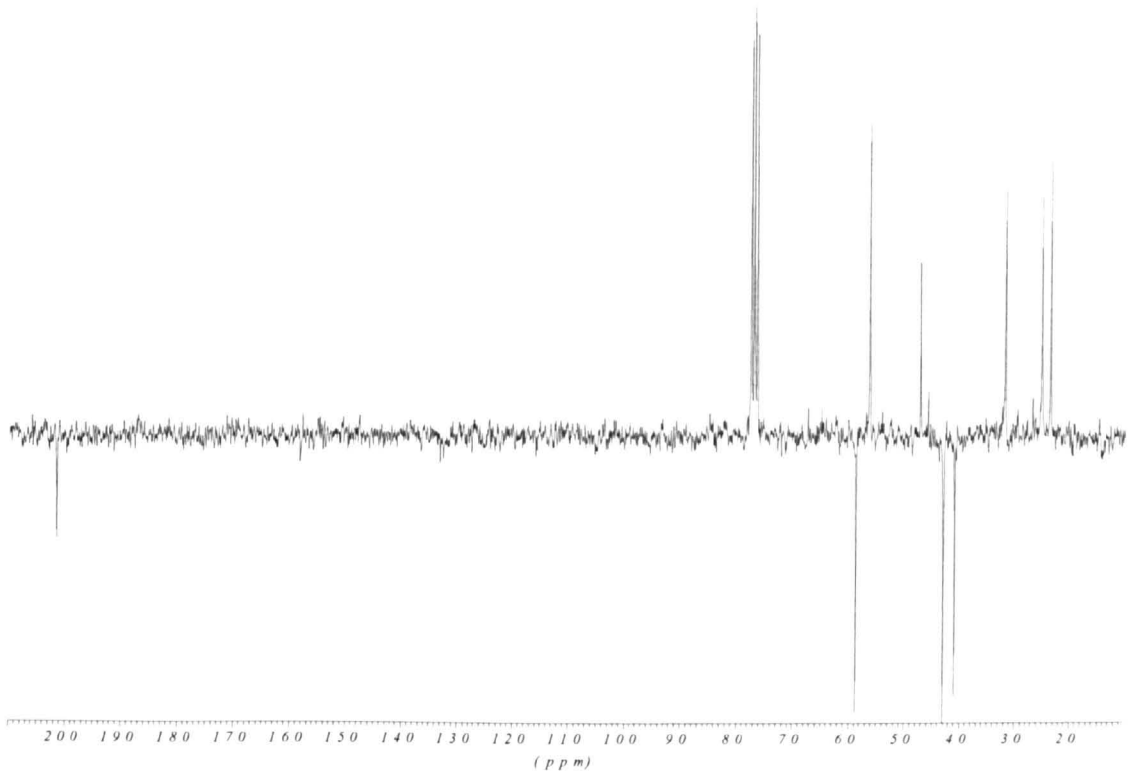


284 **287**

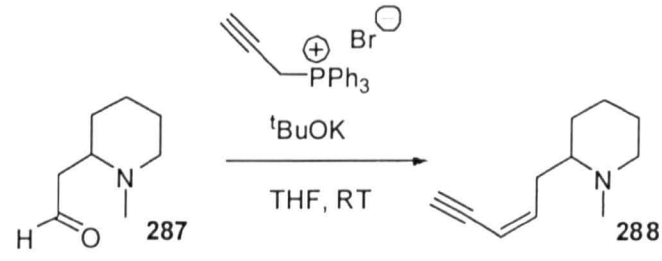
Oxalyl chloride (175 μL, 1.99 mmol, 2.25 eq) was added to DCM (14.5 mL) at -78 °C then DMSO (285 μL, 4.01 mmol, 4.5 eq) was added and the reaction stirred for 5 minutes. A solution of alcohol **284** (127 mg, 0.89 mmol, 1.0 eq) in DCM (2.5 mL) was added to the mixture. After 2 hours, Et_3N (840 μL, 6.01 mmol, 6.75 eq) was added and the mixture was allowed to warm to room temperature. The

reaction was quenched with water and the product was extracted with DCM. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oily residue **287** (92 mg) was not purified further.



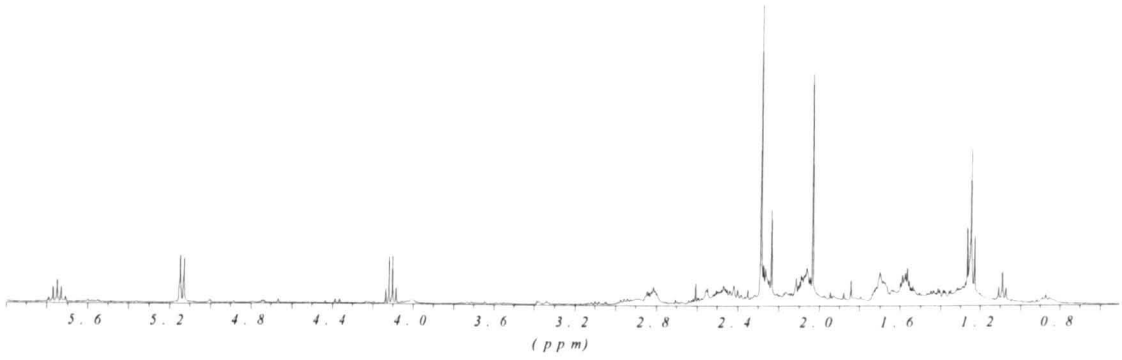


Synthesis of 4-(6-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-3-oxo-piperidin-2-ylidene)-but-2-enoic acid methylester 288

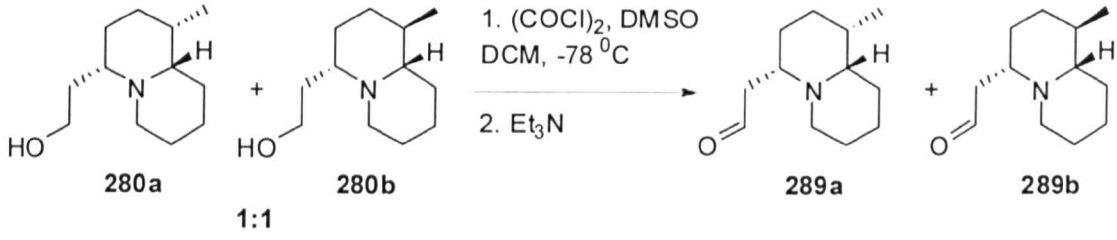


A mixture of anhydrous potassium *tert*-butoxide (90 mg, 0.79 mmol, 1.5 eq) and propargyltriphenylphosphonium bromide (360 mg, 0.79 mmol, 1.5 eq) in dry THF (8 mL) was allowed to stir at room temperature for 75 min. The substrate **287** (74 mg, 0.52 mmol, 1.0 eq) in THF (7 mL) was then added into the resulting yellow solution dropwise at rt. The mixture was stirred at rt overnight. The solution was quenched with water, diluted with EtOAc and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4.

The compound appeared to decompose after attempted purification by silica gel chromatography (A crude ^{1}H NMR spectrum is given below).



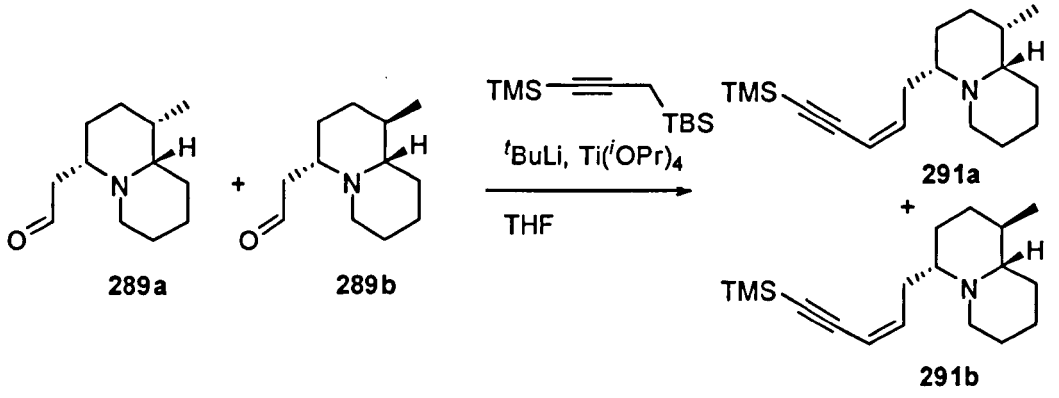
Synthesis of (1-methyl-octahydro-quinolizin-4-yl)-acetaldehyde



Oxalyl chloride (7 μL, 0.08 mmol, 2.25 eq) was added to DCM (1 mL) at -78 °C then DMSO (12 μL, 0.16 mmol, 4.5 eq) was added and the reaction stirred for 5 minutes. A solution of alcohols **280a** and **280b** (7 mg, 0.04 mmol, 1.0 eq) in DCM (2 mL) was added to the mixture. After 2 hours, Et_3N (33 μL, 0.24 mmol, 6.75 eq) was added and the mixture was allowed to warm to room temperature. The reaction was quenched with water and the product was extracted with DCM. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered

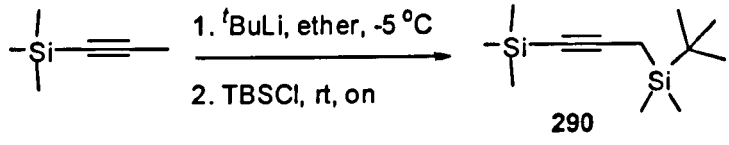
and concentrated under reduced pressure. The resulting oily residue was used directly in the next step.

Synthesis of 1-methyl-4-pent-2-en-4-ynyl-octahydro-quinolizine 291a and 291b



A solution of *tert*-butyllithium (27 µL, 0.046 mmol, 1.7 M solution in pentane, 1.3 eq) was added to a solution of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-1-propyne (7.6 mg, 0.0.034 mmol, 0.96 eq) in dry THF (1.0 mL) at -78 °C. After 1 h, titanium tetraisopropoxide (14 µL, 0.046 mmol, 1.3 eq) was added to the mixture. After 10 min, a solution of the crude aldehydes **289a** and **289b** (0.035 mmol, 1.0 eq) in dry THF (1.0 mL) was added to the organotitanium reagent and the resulting mixture was held at -78 °C for 1 h, -40 °C for 2 h, -20 °C for 1 h, and room temperature for 2.5 h, after which saturated NH_4Cl was added and the mixture was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated. Purification of the crude reaction mixture by column chromatography did not provide the desired products.

Synthesis of 3-(*tert*-butyl-dimethyl-silanyl)-1-trimethylsilanyl-propyne 290[95, 146]

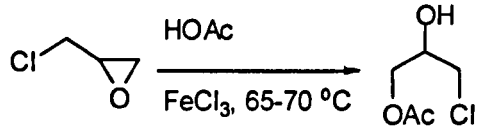


To a solution of 1-(trimethylsilyl)propyne (1.2 mL, 13.54 mmol, 1.0 eq) in ether (20 mL) was added *t*-butyllithium (1.7 M in pentane, 8 mL, 13.54 mmol, 1.0 eq) at -5 °C. After stirring for 30 min, *t*-butyldimethylsilyl chloride (2.04 g, 13.54 mmol, 1.0 eq) was added and the mixture was stirred for 12 hrs. The resulting mixture was poured into ice-cooled water and the product was extracted with ether. The combined extracts were dried and concentrated. The residue was distilled under reduced pressure to give 3-(*tert*-butyl-dimethyl-silyl)-1-trimethylsilyl-propyne **290** (1.53 g, 50%), b.p.=80 °C, 15 mmHg (lit[95, 146]: b.p.=106-107 °C, 31 mmHg). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ0.08 (6H, s, C*H*$_3$), 0.14 (9H, s, C*H*$_3$), 0.93 (9H, s, C*H*$_3$), 1.58 (2H, s, C*H*$_2$).

Synthesis of tris(triphenylphosphine)chlororhodium (I)[175, 176]

To a solution of freshly recrystallised PPh_3, (870 mg, 3.32 mmol, 4.8 eq) in ethanol (25.5 ml) at 78 °C, was added a solution of rhodium trichloride trihydrate (145 mg, 0.69 mmol, 1.0 eq) in boiling ethanol (9.3 ml.) and the solution was heated under reflux for 30 min. The hot solution was filtered and the burgundy-red crystals of the complex were washed with degassed ether (2 x 15 ml) and dried *in vacuo.* Yield (375 mg, 59%), m. p. 155°C (lit.[175] **m.p.**=157-158 °C).

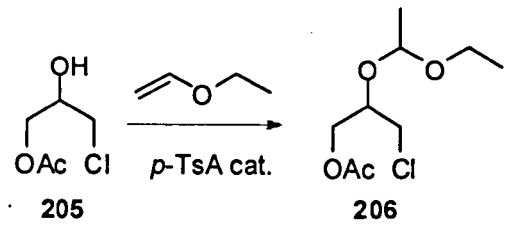
Synthesis of acetic acid 3-chloro-2-hydroxy-propyl ester 205[83, 84]



203 **205**

Epichlorohydrin **203** (8.5 mL, 108.7 mmol, 1.0 eq) was slowly added to a solution of iron trichloride (18 mg, 0.11 mmol, 0.001 eq) in glacial acetic acid (6.55 g, 108.9 mmol, 1.0 eq). The mixture was heated at reflux for 24 hours. The solvent was removed under reduced pressure and the product **205** was not further purified but used directly in the next step. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ2.02 (3H, s, C*H*$_3$C=O), 3.49-3.57 (2H, m, C*H*$_2$Cl), 4.01 (1H, q, *J*=5.5 Hz, C*H*-OH), 4.12 (1H, d, *J*=5.5 Hz, C*H*$_2$-O).

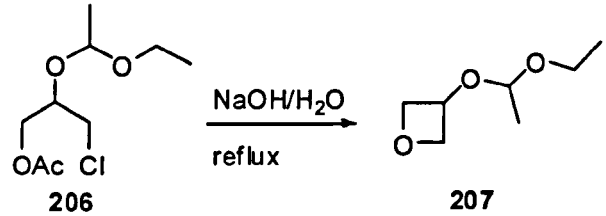
Synthesis of cetic acid 3-chloro-2-(1-ethoxy-ethoxy)-propyl ester 206[83, 84]



205 206

p-Toluenesulfonic acid monohydrate (105 mg, 0.54 mmol, 0.005 eq) was added to crude **205** (1.66 g, 108.7 mmol, 1.0 eq) and ethyl vinyl ether (11.8 mL, 122.9 mmol, 1.13 eq) was added dropwise with stirring. The mixture was cooled to maintain a reaction temperature of 35-37 °C. After the addition was completed, the mixture was heated at reflux for 16 hrs. The excess of ethyl vinyl ether was removed under reduced pressure and the product **206** was not further purified but used directly in the next step. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.14 (3H, t, *J*=7.0 Hz, CH_3), 1.33 (3H, d, *J*=5.5 Hz, CH_3CH), 2.02 (3H, s, $CH_3C{=}O$), 3.37-3.76 (5H, m, CH_2Cl + CH_2-O + CHO), 3.88-4.25 (3H, m, O-CH-O + CH_2-OAc).

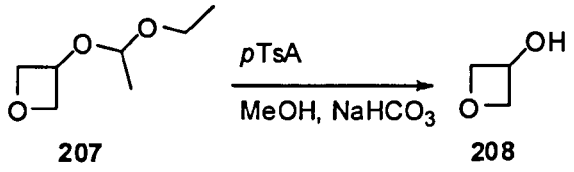
Synthesis of 3-(1-ethoxy-ethoxy)-oxetane 207[83, 84]



206 207

Crude **206** (2.44 g, 108.7 mmol, 1.0 eq) was added dropwise with stirring to a solution of aqueous sodium hydroxide (12 g, 298.9 mmol, 2.75 eq) in water (12 mL) at 105 °C, and the reaction mixture was heated under reflux for an additional 4 hour period. The mixture was cooled and was washed with water. The aqueous layer was washed with DCM and the combined organic phases were stripped of solvent to give crude **207** (10 g, 63%). The product was not further purified but used directly in the next step. **^{1}H NMR (250 MHz, $CDCl_3$)**: δ1.05-1.45 (6H, m, CH_3), 3.31-3.76 (6H, m, CH_2O), 3.79-4.04 (1H, m, OCH), 4.59-4.91 (1H, m, OCH).

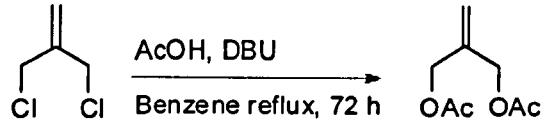
Synthesis of oxetan-3-ol 208[83, 84]



207 208

Methanol (6 mL) was added to compound **207** (10 g, 68.4 mmol, 1.0 eq) and the mixture was cooled to 15 °C. *p*-Toluenesulfonic acid monohydrate (80 mg, 0.41 mmol, 0.006 eq) was added with stirring. The reaction temperature increased slightly and then decreased to room temperature. The mixture was stirred for another 45 min and then solid sodium bicarbonate (40 mg, 0.48 mmol, 0.007 eq) was added. The reaction mixture was then distilled between 120-150 °C (20 mm Hg) but no desired oxetane **208** was isolated, the product appeared to polymerise.

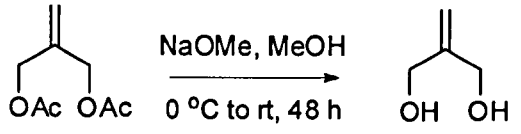
Synthesis of acetic acid 2-acetoxymethyl-allyl ester 212[85]



211 212

A stirred solution of acetic acid (6.9 g, 115 mmol, 2.8 eq) in benzene (25 mL) was treated at rt with a solution of DBU (16.4 g, 108 mmol, 2.6 eq) in benzene (25 mL). The yellow mixture was then added slowly to a solution of 3-chloro-2-(chloromethyl)-1-propene **211** (5.1 g, 40.8 mmol, 1.0 eq) in benzene (50 mL) and the mixture was warmed at 60 °C for 72 h. A white precipitate was then removed by filtration and washed with benzene and the combined benzene phases were washed with water and dried. Evaporation of solvent under reduced pressure left a yellow oil. Distillation of this residue under vacuum (85-90 °C, 15 mmHg) gave pure product **212** (6.73 g, 96%). (lit.[85] b.p.=148 °C (70 mmHg)). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ2.02 (6H, s, CH_3-C=O), 4.58 (4H, s, CH_2O), 5.32 (2H, s, CH_2=C).

Synthesis of 2-methylene-propane-1,3-diol 209[85]

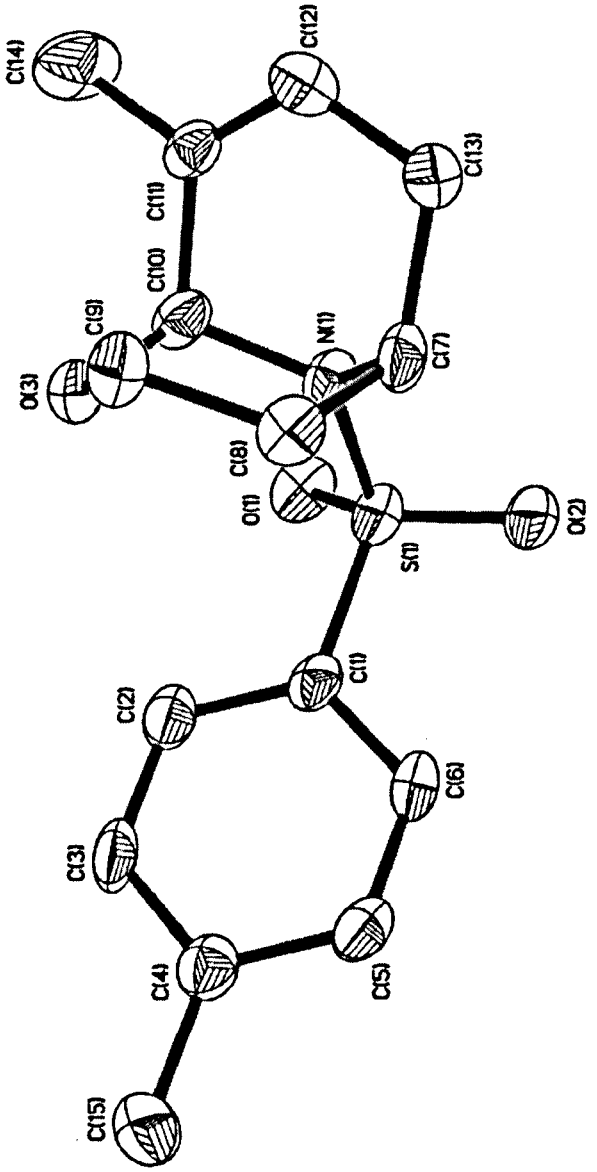


212 **209**

A stirred solution of substrate **212** (6.73 g, 39.1, mmol, 1.0 eq) in methanol (24 mL) was treated at 0°C with a solution of sodium methoxide (660 mg, 11.73 mmol, 0.3 eq) in methanol (10 mL). The mixture was kept at 0 °C for 2 h and then at rt for 48 h. Solvent was removed by evaporation under reduced pressure, and distillation (110 °C, ~15 mmHg) of the residue offered product **209** as a colourless liquid (2.75 g, 80%) (lit.[85] b.p.=156 °C (63 mmHg). **^{1}H NMR (250 MHz, $CDCl_3$)**: δ4.25 (4H, s, CH_2O), 5.21 (2H, s, CH_2=C).

Appendices

6.1.X-Ray data for 253



Crystal data for C15H19NO3S; M = 293.37. Crystallises from petroleum ether as colourless needles; crystal dimensions 0.14 x 0.12 x 0.03 mm^3. Orthorhombic, a = 7.404(2) Å, b = 11.268(3) Å, c = 17.150(5) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, U = 1430.8(7) $Å^3$, Z = 4, Dc = 1.362 Mg/m^3, space group $P2_12_12_1$, Mo-Ka radiation (λ = 0.71073 Å), μ(Mo-Ka) = 0.233 mm^{-1}, F(000) = 624.

Data collected were measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Cell parameters were refined from the setting angles of 2506 reflections (θ range 2.16 < 24.98°).
Reflections were measured from a hemisphere of data collected of frames each covering 0.3 degrees in omega. Of the 10920 reflections measured, all of which were corrected for Lorentz and polarisation effects and for absorption by semi empirical methods based on symmetry-equivalent and repeated reflections (minimum and maximum transmission coefficients 0.9681 and 0.9930), 3259 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. The structure was solved by direct methods and refined by full matrix least squares methods on F^2. Hydrogen atoms were placed geometrically and refined with a riding model (including torsional freedom for methyl groups) and with Uiso constrained to be 1.2 (1.5 for methyl groups) times Ueq of the carrier atom. Refinement converged at a final R = 0.0585 (wR2 = 0.1531, for all 2506 data, 184 parameters, mean and maximum δ/σ 0.000, 0.000) with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.372 and 0.810 $e.Å^{-3}$. A weighting scheme $w = 1/[s^2(Fo^2) + (0.0590*P)^2 + 2.3795*P]$ where $P=(Fo^2 + 2 * Fc^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXTL[Y] as implemented on the Pentium computer.

Reference Y SHELXTL version, An integrated system for solving and refining crystal structures from diffraction data (Revision 5.1), Bruker AXS LTD

Supplementary material

anisotropic thermal vibrational parameters with e.s.d.s

hydrogen atom position parameters

observed structure amplitudes and calculated structure factors.

Table 1. Crystal data and structure refinement for sandon1_0m.

Identification code	sandon1_0m	
Empirical formula	C15 H19 N O3 S	
Formula weight	293.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.404(2) Å	α= 90°.
	b = 11.268(3) Å	β= 90°.
	c = 17.150(5) Å	γ = 90°.
Volume	1430.8(7) Å^3	
Z	4	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.233 mm^{-1}	
F(000)	624	
Crystal size	0.14 x 0.12 x 0.03 mm^3	
Theta range for data collection	2.16 to 24.98°.	
Index ranges	-7<=h<=8, -8<=k<=13, -20<=l<=20	
Reflections collected	10920	
Independent reflections	2506 [R(int) = 0.0816]	
Completeness to theta = 24.98°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9930 and 0.9681	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2506 / 0 / 184	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0585, wR2 = 0.1304	
R indices (all data)	R1 = 0.1074, wR2 = 0.1531	
Absolute structure parameter	-0.06(18)	
Extinction coefficient	0.0063(18)	
Largest diff. peak and hole	0.810 and -0.372 e.Å^{-3}	

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103) for sandon1_0m. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	4006(2)	1661(1)	8196(1)	30(1)
N(1)	2012(5)	2107(3)	8455(2)	29(1)
O(1)	5235(5)	2555(3)	8476(2)	35(1)
O(2)	4186(5)	460(3)	8455(2)	35(1)
O(3)	787(5)	3740(3)	7752(2)	33(1)
C(1)	4144(7)	1650(4)	7176(3)	28(1)
C(2)	4278(7)	2707(4)	6768(3)	34(1)
C(3)	4337(8)	2699(4)	5962(3)	36(2)
C(4)	4248(7)	1647(5)	5537(3)	33(1)
C(5)	4120(8)	579(4)	5954(3)	34(1)
C(6)	4077(7)	577(4)	6759(3)	29(1)
C(7)	393(6)	1365(4)	8321(3)	30(1)
C(8)	-532(7)	1778(4)	7573(3)	32(1)
C(9)	-870(7)	3104(4)	7573(3)	32(1)
C(10)	1554(7)	3358(4)	8479(3)	30(1)
C(11)	314(7)	3556(4)	9165(3)	27(1)
C(12)	-783(9)	2681(5)	9402(3)	37(1)
C(13)	-758(7)	1467(4)	9065(3)	32(1)
C(14)	355(10)	4772(5)	9510(3)	52(2)
C(15)	4264(9)	1639(5)	4655(3)	46(2)

Table 3. Bond lengths [Å] and angles [°] for sandon1_0m.

S(1)-O(2)	1.431(3)
S(1)-O(1)	1.440(3)
S(1)-N(1)	1.621(4)
S(1)-C(1)	1.753(5)
N(1)-C(10)	1.450(6)
N(1)-C(7)	1.480(6)
O(3)-C(10)	1.435(6)
O(3)-C(9)	1.453(6)
C(1)-C(2)	1.385(6)
C(1)-C(6)	1.406(6)
C(2)-C(3)	1.384(7)
C(2)-H(2)	0.9500
C(3)-C(4)	1.394(7)
C(3)-H(3)	0.9500
C(4)-C(5)	1.403(7)
C(4)-C(15)	1.513(7)
C(5)-C(6)	1.380(7)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-C(8)	1.527(7)
C(7)-C(13)	1.538(7)
C(7)-H(7)	1.0000
C(8)-C(9)	1.516(7)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.509(7)
C(10)-H(10)	1.0000
C(11)-C(12)	1.341(7)
C(11)-C(14)	1.493(7)
C(12)-C(13)	1.485(7)

C(12)-H(12)	0.9500
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800

O(2)-S(1)-O(1)	120.0(2)
O(2)-S(1)-N(1)	107.0(2)
O(1)-S(1)-N(1)	105.5(2)
O(2)-S(1)-C(1)	107.3(2)
O(1)-S(1)-C(1)	107.5(2)
N(1)-S(1)-C(1)	109.2(2)
C(10)-N(1)-C(7)	111.3(4)
C(10)-N(1)-S(1)	121.4(3)
C(7)-N(1)-S(1)	121.4(3)
C(10)-O(3)-C(9)	111.7(4)
C(2)-C(1)-C(6)	119.1(4)
C(2)-C(1)-S(1)	120.1(4)
C(6)-C(1)-S(1)	120.8(4)
C(3)-C(2)-C(1)	120.1(5)
C(3)-C(2)-H(2)	120.0
C(1)-C(2)-H(2)	120.0
C(2)-C(3)-C(4)	121.8(4)
C(2)-C(3)-H(3)	119.1
C(4)-C(3)-H(3)	119.1
C(3)-C(4)-C(5)	117.7(4)
C(3)-C(4)-C(15)	121.8(5)
C(5)-C(4)-C(15)	120.4(5)
C(6)-C(5)-C(4)	120.9(4)
C(6)-C(5)-H(5)	119.5

C(4)-C(5)-H(5)	119.5
C(5)-C(6)-C(1)	120.4(4)
C(5)-C(6)-H(6)	119.8
C(1)-C(6)-H(6)	119.8
N(1)-C(7)-C(8)	108.8(4)
N(1)-C(7)-C(13)	106.2(4)
C(8)-C(7)-C(13)	115.2(4)
N(1)-C(7)-H(7)	108.8
C(8)-C(7)-H(7)	108.8
C(13)-C(7)-H(7)	108.8
C(9)-C(8)-C(7)	112.0(4)
C(9)-C(8)-H(8A)	109.2
C(7)-C(8)-H(8A)	109.2
C(9)-C(8)-H(8B)	109.2
C(7)-C(8)-H(8B)	109.2
H(8A)-C(8)-H(8B)	107.9
O(3)-C(9)-C(8)	110.3(4)
O(3)-C(9)-H(9A)	109.6
C(8)-C(9)-H(9A)	109.6
O(3)-C(9)-H(9B)	109.6
C(8)-C(9)-H(9B)	109.6
H(9A)-C(9)-H(9B)	108.1
O(3)-C(10)-N(1)	111.1(4)
O(3)-C(10)-C(11)	113.1(4)
N(1)-C(10)-C(11)	107.9(4)
O(3)-C(10)-H(10)	108.2
N(1)-C(10)-H(10)	108.2
C(11)-C(10)-H(10)	108.2
C(12)-C(11)-C(14)	124.6(5)
C(12)-C(11)-C(10)	119.8(4)
C(14)-C(11)-C(10)	115.6(5)
C(11)-C(12)-C(13)	123.5(5)
C(11)-C(12)-H(12)	118.3
C(13)-C(12)-H(12)	118.3

C(12)-C(13)-C(7)	113.5(4)
C(12)-C(13)-H(13A)	108.9
C(7)-C(13)-H(13A)	108.9
C(12)-C(13)-H(13B)	108.9
C(7)-C(13)-H(13B)	108.9
H(13A)-C(13)-H(13B)	107.7
C(11)-C(14)-H(14A)	109.5
C(11)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(11)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(4)-C(15)-H(15A)	109.5
C(4)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(4)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

Symmetry transformations used to generate equivalent atoms:

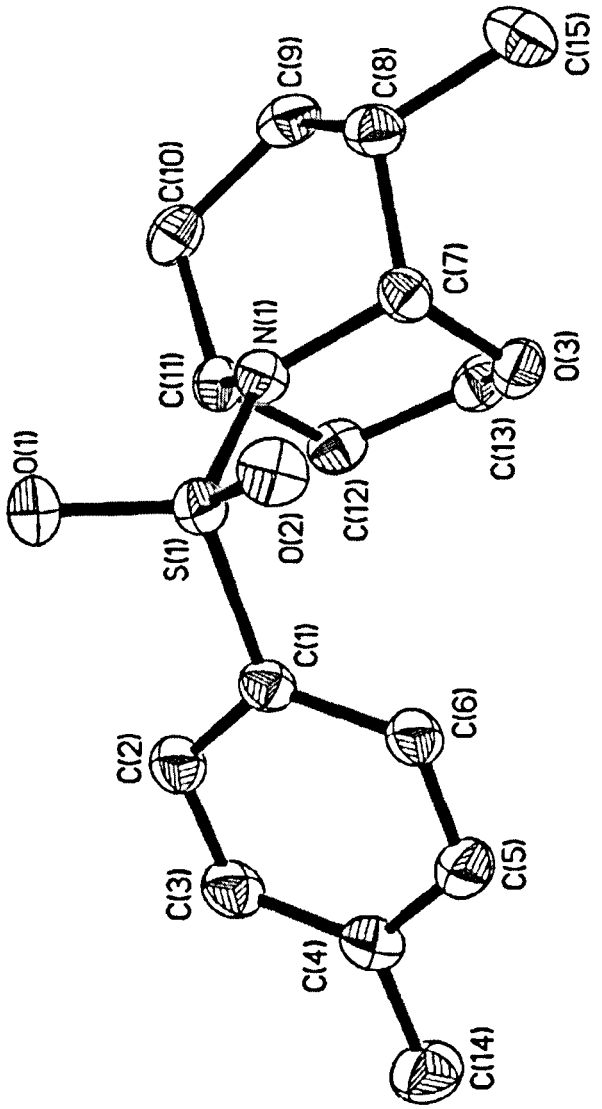
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for sandon1_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	29(1)	23(1)	37(1)	0(1)	-2(1)	4(1)
N(1)	24(2)	22(2)	39(3)	-1(2)	-1(2)	-1(2)
O(1)	22(2)	38(2)	45(2)	-7(2)	-8(2)	1(2)
O(2)	40(2)	28(2)	37(2)	4(2)	-1(2)	11(2)
O(3)	41(2)	22(2)	36(2)	2(1)	7(2)	0(2)
C(1)	21(3)	25(2)	38(3)	0(2)	3(2)	8(3)
C(2)	36(3)	23(3)	41(3)	1(2)	1(3)	3(3)
C(3)	41(4)	16(3)	50(4)	7(2)	6(3)	3(3)
C(4)	30(3)	29(3)	40(3)	0(2)	6(3)	1(3)
C(5)	41(3)	24(3)	39(3)	-6(2)	1(3)	4(3)
C(6)	28(3)	18(2)	40(3)	2(2)	-3(3)	0(2)
C(7)	32(3)	16(2)	41(3)	2(2)	1(2)	-2(2)
C(8)	31(3)	31(3)	34(3)	-3(2)	-2(2)	2(3)
C(9)	34(3)	26(3)	36(3)	1(2)	-7(3)	2(3)
C(10)	35(3)	26(3)	30(3)	-7(3)	-3(2)	5(2)
C(11)	29(3)	28(3)	25(3)	-3(2)	-5(2)	9(3)
C(12)	40(4)	41(3)	31(3)	4(2)	6(3)	-1(3)
C(13)	35(3)	27(3)	32(3)	5(2)	3(3)	3(3)
C(14)	65(5)	46(4)	45(4)	-23(3)	9(3)	-11(4)
C(15)	64(4)	36(3)	38(3)	6(3)	6(3)	-6(4)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 103) for sandon1_0m.

	x	y	z	U(eq)
H(2)	4329	3439	7042	40
H(3)	4442	3431	5691	43
H(5)	4061	-152	5679	41
H(6)	4001	-155	7032	35
H(7)	779	521	8256	35
H(8A)	235	1568	7121	39
H(8B)	-1698	1356	7515	39
H(9A)	-1321	3353	7055	38
H(9B)	-1804	3301	7965	38
H(10)	2689	3819	8570	36
H(12)	-1621	2846	9808	45
H(13A)	-2012	1226	8942	38
H(13B)	-282	908	9460	38
H(14A)	-263	5327	9160	79
H(14B)	1612	5024	9579	79
H(14C)	-256	4764	10017	79
H(15A)	3739	2380	4460	69
H(15B)	3554	965	4464	69
H(15C)	5511	1568	4469	69

6.2.X-Ray data for 247



Crystal data for C15 H21 N O3 S; M = 295.39. Crystallises from petroleum ether as colourless needles; crystal dimensions 0.14 x 0.12 x 0.03 mm^3. Orthorhombic, a = 7.7722(4) Å, b = 11.0799(6) Å, c = 17.1162(9) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, U = 1473.96(13) $Å^3$, Z = 4, Dc = 1.331 Mg/m^3, space group $P2_12_12_1$, Mo-Ka radiation (λ = 0.71073 Å), μ(Mo-Ka) = 0.227 mm^{-1}, F(000) = 632.

Data collected were measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Cell parameters were refined from the setting angles of 3890 reflections (θ range 2.19 < 28.97°).

Reflections were measured from a hemisphere of data collected of frames each covering 0.3 degrees in omega. Of the 28817 reflections measured, all of which were corrected for Lorentz and polarisation effects and for absorption by semi empirical methods based on symmetry-equivalent and repeated reflections (minimum and maximum transmission coefficients 0.9540 and 0.9777), 3890 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. The structure was solved by direct methods and refined by full matrix least squares methods on F^2. Hydrogen atoms were placed geometrically and refined with a riding model (including torsional freedom for methyl groups) and with Uiso constrained to be 1.2 (1.5 for methyl groups) times Ueq of the carrier atom. Refinement converged at a final R = 0.0369 (wR2 = 0.0933, for all 3890 data, 183 parameters, mean and maximum δ/σ 0.000, 0.000) with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.340 and 0.516 $e.Å^{-3}$. A weighting scheme $w = 1/[s^2(Fo^2) + (0.0590*P)^2 + 2.3795*P]$ where $P=(Fo^2 + 2 * Fc^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXTL[Y] as implemented on the Pentium computer.

Reference Y SHELXTL version, An integrated system for solving and refining crystal structures from diffraction data (Revision 5.1), Bruker AXS LTD

Supplementary material

anisotropic thermal vibrational parameters with e.s.d.s

hydrogen atom position parameters

observed structure amplitudes and calculated structure factors.

Table 1. Crystal data and structure refinement for ns363.

Identification code	ns363	
Empirical formula	C15 H21 N O3 S	
Formula weight	295.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.7722(4) Å	α= 90°.
	b = 11.0799(6) Å	β= 90°.
	c = 17.1162(9) Å	γ = 90°.
Volume	1473.96(13) Å^3	
Z	4	
Density (calculated)	1.331 Mg/m^3	
Absorption coefficient	0.227 mm^{-1}	
F(000)	632	
Crystal size	0.21 x 0.21 x 0.10 mm^3	
Theta range for data collection	2.19 to 28.97°.	
Index ranges	-10<=h<=10, -14<=k<=15, -23<=l<=23	
Reflections collected	28817	
Independent reflections	3890 [R(int) = 0.0612]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9777 and 0.9540	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3890 / 0 / 183	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0876	
R indices (all data)	R1 = 0.0470, wR2 = 0.0933	
Absolute structure parameter	0.01(7)	
Largest diff. peak and hole	0.516 and -0.340 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for ns363. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	960(1)	7698(1)	8134(1)	23(1)
N(1)	2961(2)	7827(1)	8387(1)	23(1)
O(1)	127(2)	8800(1)	8350(1)	30(1)
O(2)	364(2)	6577(1)	8457(1)	29(1)
O(3)	4967(2)	6389(1)	7901(1)	29(1)
C(1)	848(2)	7602(2)	7107(1)	23(1)
C(2)	601(2)	8644(2)	6668(1)	30(1)
C(3)	592(2)	8557(2)	5858(1)	31(1)
C(4)	828(2)	7463(2)	5483(1)	31(1)
C(5)	1038(3)	6429(2)	5936(1)	31(1)
C(6)	1061(2)	6495(2)	6747(1)	27(1)
C(7)	4031(2)	6780(2)	8567(1)	24(1)
C(8)	5105(2)	7104(2)	9292(1)	27(1)
C(9)	5999(3)	8332(2)	9258(1)	32(1)
C(10)	4958(2)	9325(2)	8850(1)	30(1)
C(11)	4005(2)	8874(1)	8128(1)	24(1)
C(12)	5141(3)	8481(2)	7440(1)	29(1)
C(13)	6078(2)	7299(2)	7580(1)	30(1)
C(14)	848(3)	7384(2)	4604(1)	44(1)
C(15)	6361(3)	6099(2)	9493(1)	37(1)

Table 3. Bond lengths [Å] and angles [°] for ns363.

S(1)-O(1)	1.4303(13)
S(1)-O(2)	1.4361(13)
S(1)-N(1)	1.6198(14)
S(1)-C(1)	1.7646(16)
N(1)-C(7)	1.460(2)
N(1)-C(11)	1.484(2)
O(3)-C(7)	1.419(2)
O(3)-C(13)	1.437(2)
C(1)-C(6)	1.382(2)
C(1)-C(2)	1.391(2)
C(2)-C(3)	1.389(2)
C(2)-H(2)	0.9500
C(3)-C(4)	1.383(3)
C(3)-H(3)	0.9500
C(4)-C(5)	1.394(2)
C(4)-C(14)	1.507(2)
C(5)-C(6)	1.390(2)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-C(8)	1.538(2)
C(7)-H(7)	1.0000
C(8)-C(15)	1.520(3)
C(8)-C(9)	1.529(3)
C(8)-H(8)	1.0000
C(9)-C(10)	1.534(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.525(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.535(2)
C(11)-H(11)	1.0000

C(12)-C(13)	1.518(3)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800

O(1)-S(1)-O(2)	119.49(7)
O(1)-S(1)-N(1)	106.89(8)
O(2)-S(1)-N(1)	106.48(8)
O(1)-S(1)-C(1)	106.63(8)
O(2)-S(1)-C(1)	108.39(8)
N(1)-S(1)-C(1)	108.60(7)
C(7)-N(1)-C(11)	111.86(13)
C(7)-N(1)-S(1)	122.20(11)
C(11)-N(1)-S(1)	120.95(11)
C(7)-O(3)-C(13)	113.66(12)
C(6)-C(1)-C(2)	120.82(15)
C(6)-C(1)-S(1)	119.45(12)
C(2)-C(1)-S(1)	119.69(13)
C(3)-C(2)-C(1)	118.79(16)
C(3)-C(2)-H(2)	120.6
C(1)-C(2)-H(2)	120.6
C(4)-C(3)-C(2)	121.59(16)
C(4)-C(3)-H(3)	119.2
C(2)-C(3)-H(3)	119.2
C(3)-C(4)-C(5)	118.49(16)
C(3)-C(4)-C(14)	121.08(16)
C(5)-C(4)-C(14)	120.42(17)

C(6)-C(5)-C(4)	120.91(16)
C(6)-C(5)-H(5)	119.5
C(4)-C(5)-H(5)	119.5
C(1)-C(6)-C(5)	119.38(15)
C(1)-C(6)-H(6)	120.3
C(5)-C(6)-H(6)	120.3
O(3)-C(7)-N(1)	111.43(12)
O(3)-C(7)-C(8)	116.16(15)
N(1)-C(7)-C(8)	107.11(13)
O(3)-C(7)-H(7)	107.2
N(1)-C(7)-H(7)	107.2
C(8)-C(7)-H(7)	107.2
C(15)-C(8)-C(9)	111.63(15)
C(15)-C(8)-C(7)	111.12(15)
C(9)-C(8)-C(7)	115.04(13)
C(15)-C(8)-H(8)	106.1
C(9)-C(8)-H(8)	106.1
C(7)-C(8)-H(8)	106.1
C(8)-C(9)-C(10)	114.57(15)
C(8)-C(9)-H(9A)	108.6
C(10)-C(9)-H(9A)	108.6
C(8)-C(9)-H(9B)	108.6
C(10)-C(9)-H(9B)	108.6
H(9A)-C(9)-H(9B)	107.6
C(11)-C(10)-C(9)	113.02(14)
C(11)-C(10)-H(10A)	109.0
C(9)-C(10)-H(10A)	109.0
C(11)-C(10)-H(10B)	109.0
C(9)-C(10)-H(10B)	109.0
H(10A)-C(10)-H(10B)	107.8
N(1)-C(11)-C(10)	106.23(14)
N(1)-C(11)-C(12)	108.80(13)
C(10)-C(11)-C(12)	115.79(15)
N(1)-C(11)-H(11)	108.6

C(10)-C(11)-H(11)	108.6
C(12)-C(11)-H(11)	108.6
C(13)-C(12)-C(11)	113.58(14)
C(13)-C(12)-H(12A)	108.9
C(11)-C(12)-H(12A)	108.9
C(13)-C(12)-H(12B)	108.9
C(11)-C(12)-H(12B)	108.9
H(12A)-C(12)-H(12B)	107.7
O(3)-C(13)-C(12)	112.15(15)
O(3)-C(13)-H(13A)	109.2
C(12)-C(13)-H(13A)	109.2
O(3)-C(13)-H(13B)	109.2
C(12)-C(13)-H(13B)	109.2
H(13A)-C(13)-H(13B)	107.9
C(4)-C(14)-H(14A)	109.5
C(4)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(4)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(8)-C(15)-H(15A)	109.5
C(8)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(8)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

Symmetry transformations used to generate equivalent atoms:

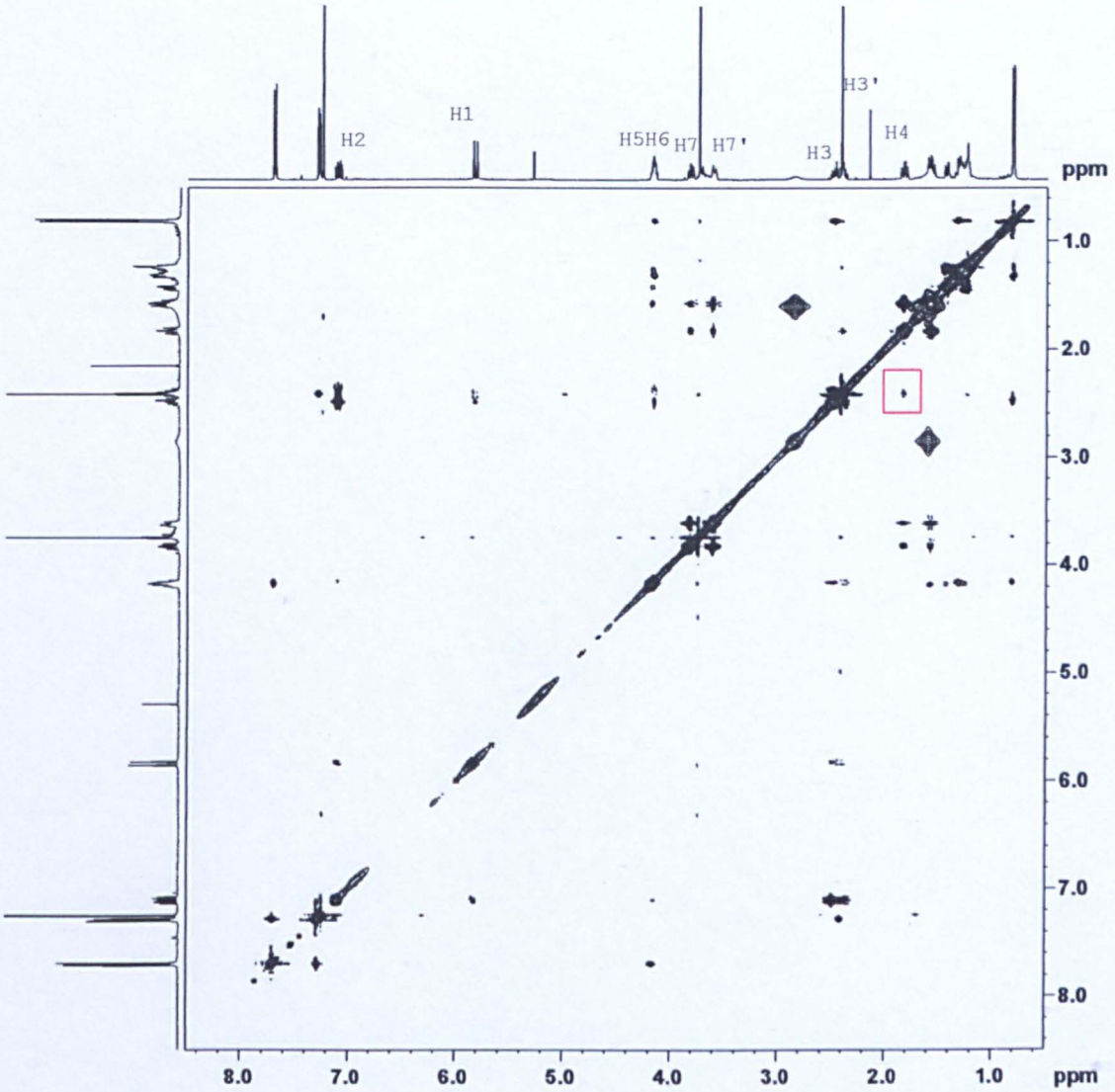
Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for ns363. The nisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

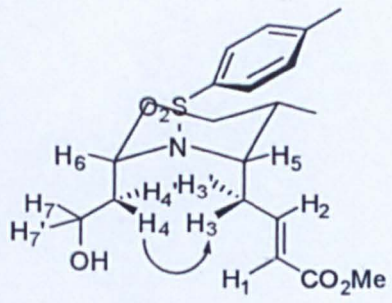
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	21(1)	23(1)	25(1)	0(1)	0(1)	0(1)
N(1)	23(1)	21(1)	25(1)	2(1)	-2(1)	-2(1)
O(1)	28(1)	27(1)	35(1)	-3(1)	4(1)	6(1)
O(2)	27(1)	28(1)	31(1)	5(1)	1(1)	-7(1)
O(3)	35(1)	24(1)	27(1)	-4(1)	1(1)	2(1)
C(1)	21(1)	24(1)	25(1)	1(1)	-3(1)	-2(1)
C(2)	33(1)	23(1)	33(1)	1(1)	-5(1)	2(1)
C(3)	36(1)	26(1)	33(1)	7(1)	-6(1)	-1(1)
C(4)	31(1)	35(1)	27(1)	4(1)	-5(1)	0(1)
C(5)	37(1)	26(1)	32(1)	-4(1)	-4(1)	-1(1)
C(6)	30(1)	21(1)	29(1)	2(1)	-5(1)	0(1)
C(7)	24(1)	22(1)	26(1)	3(1)	-1(1)	-1(1)
C(8)	26(1)	34(1)	22(1)	2(1)	0(1)	1(1)
C(9)	28(1)	42(1)	25(1)	-6(1)	-2(1)	-4(1)
C(10)	30(1)	28(1)	32(1)	-8(1)	2(1)	-7(1)
C(11)	26(1)	19(1)	27(1)	1(1)	1(1)	-1(1)
C(12)	33(1)	31(1)	24(1)	3(1)	3(1)	-4(1)
C(13)	30(1)	35(1)	25(1)	-4(1)	5(1)	1(1)
C(14)	60(1)	44(1)	27(1)	2(1)	-6(1)	1(1)
C(15)	32(1)	44(1)	35(1)	10(1)	-6(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for ns363.

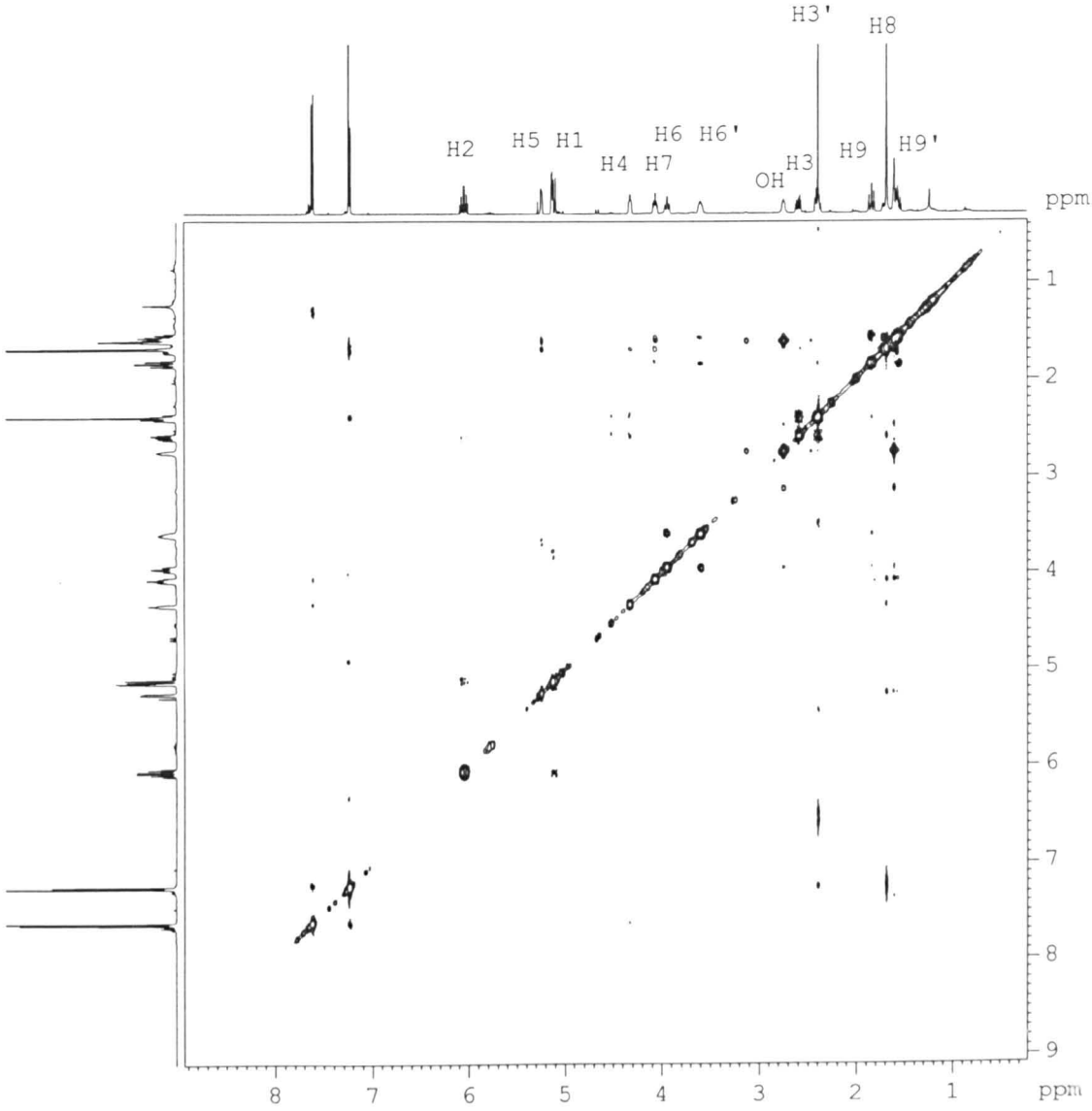
	x	y	z	U(eq)
H(2)	442	9402	6917	36
H(3)	418	9264	5555	38
H(5)	1168	5667	5687	38
H(6)	1221	5787	7051	32
H(7)	3240	6108	8719	28
H(8)	4275	7148	9738	33
H(9A)	7110	8237	8982	38
H(9B)	6254	8597	9798	38
H(10A)	4113	9661	9224	36
H(10B)	5746	9984	8695	36
H(11)	3210	9524	7944	29
H(12A)	4413	8399	6968	35
H(12B)	5999	9121	7336	35
H(13A)	6560	7005	7079	36
H(13B)	7049	7440	7943	36
H(14A)	1185	6567	4445	66
H(14B)	1675	7968	4394	66
H(14C)	-302	7564	4400	66
H(15A)	7273	6069	9098	56
H(15B)	5750	5325	9503	56
H(15C)	6869	6254	10007	56

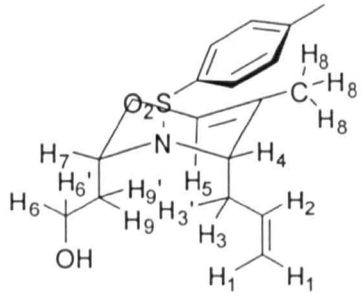
6.3.NOESY spectrum for compound 249



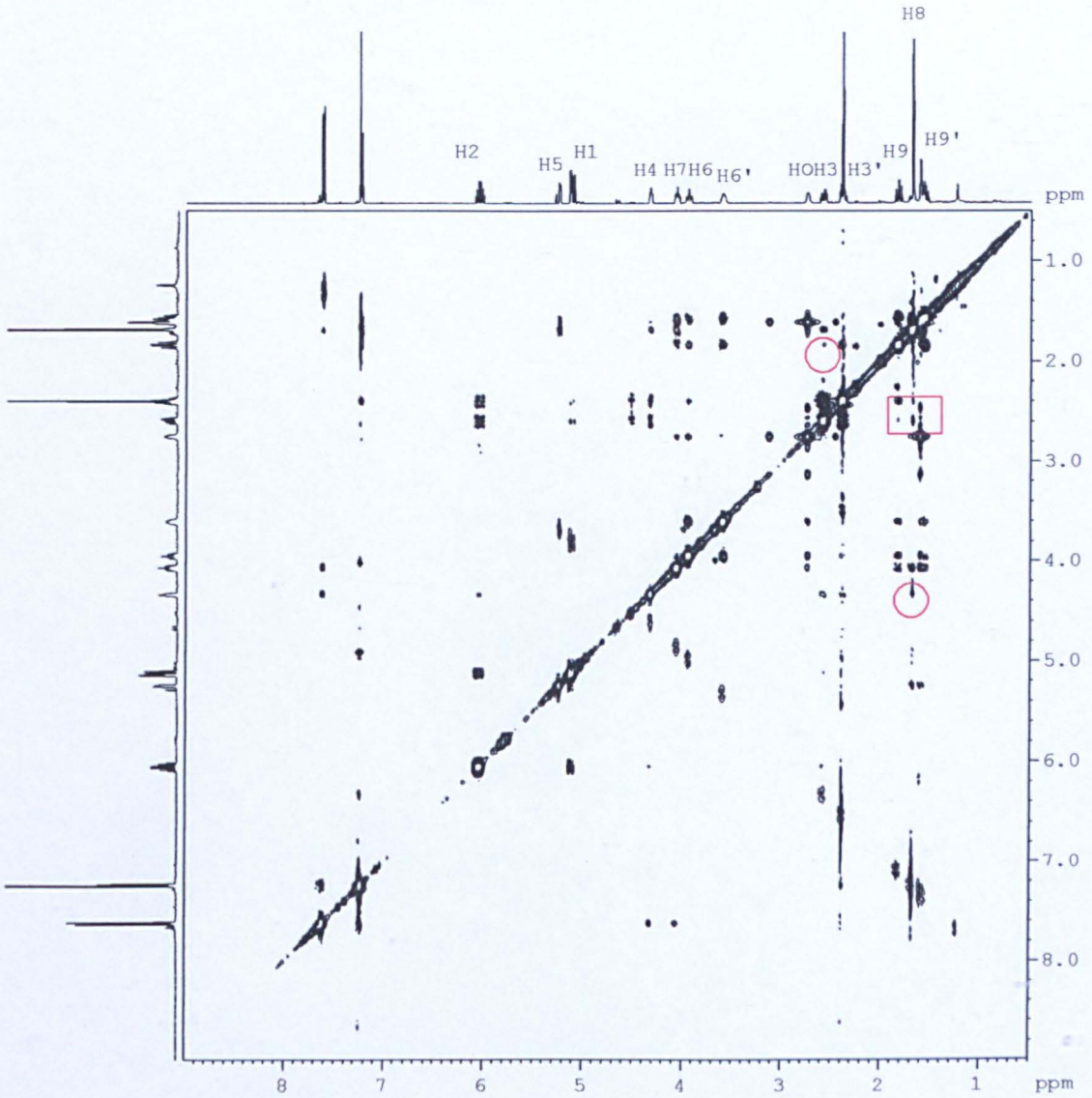


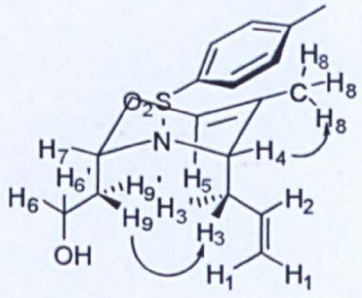
6.4.1H-1H Cosy NMR data for compound 254



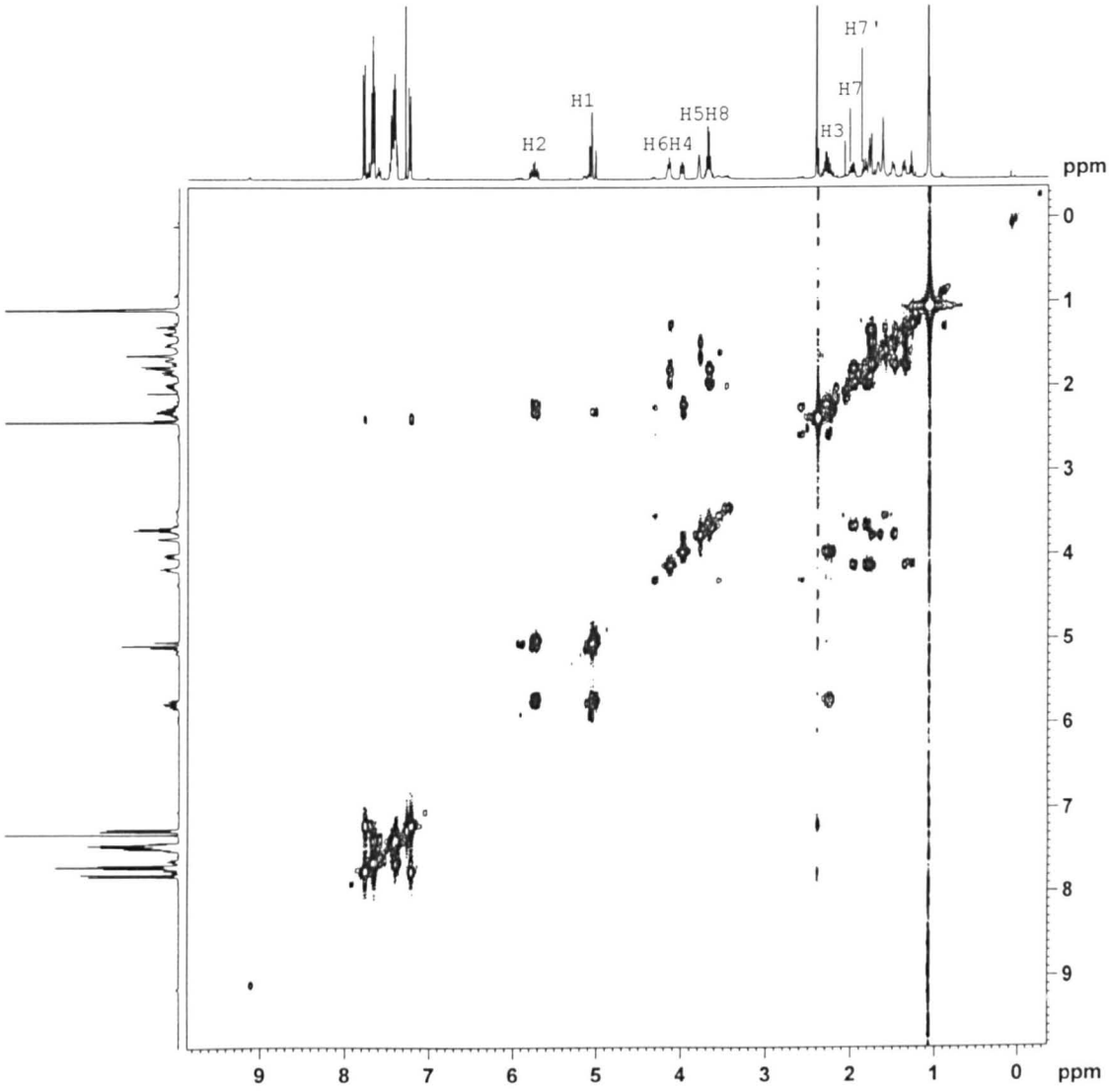


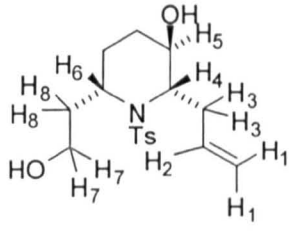
6.5.NOESY spectrum for compound 254



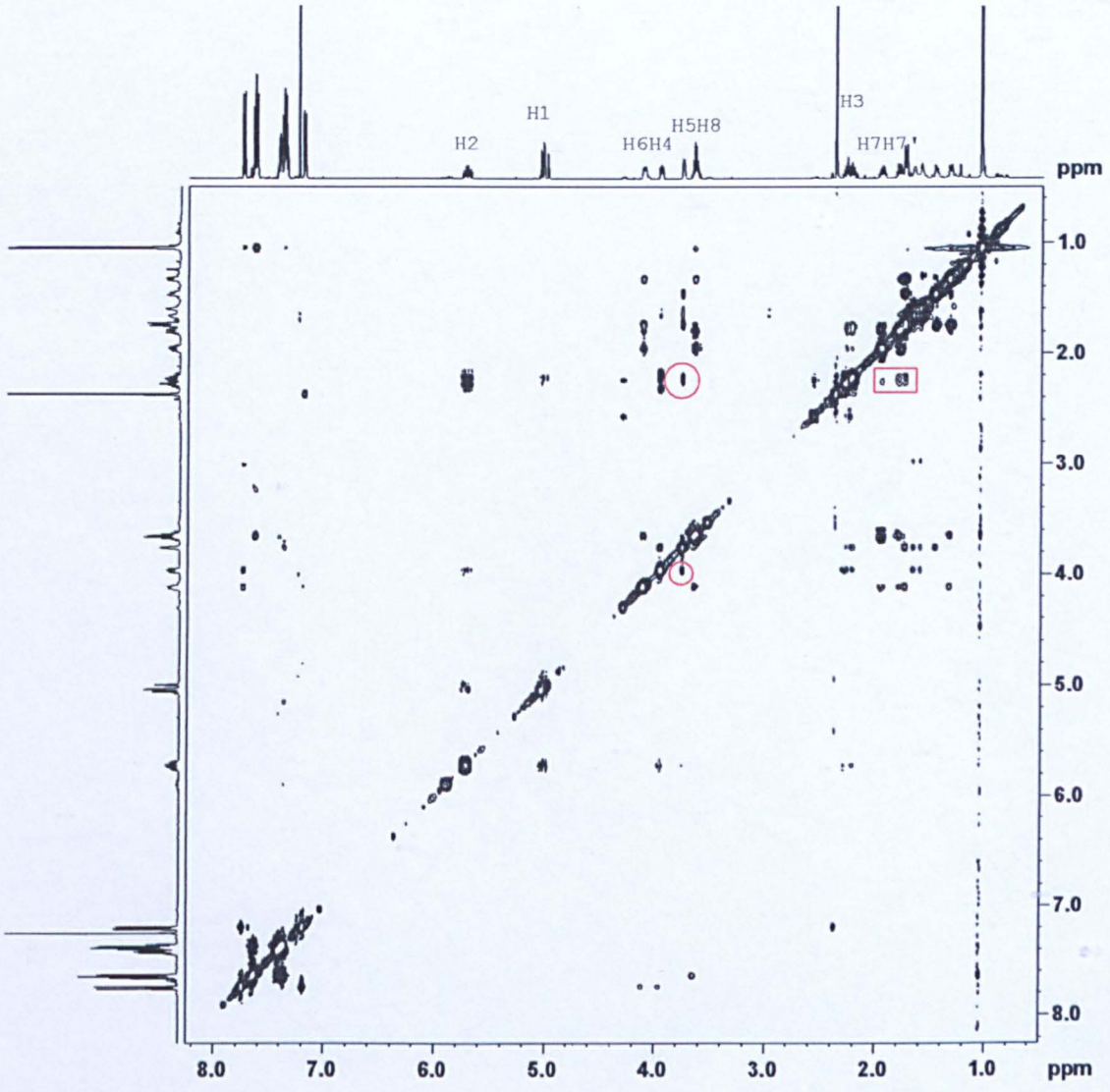


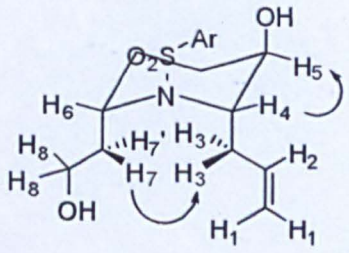
6.6.1H-1H Cosy NMR data for compound 267a



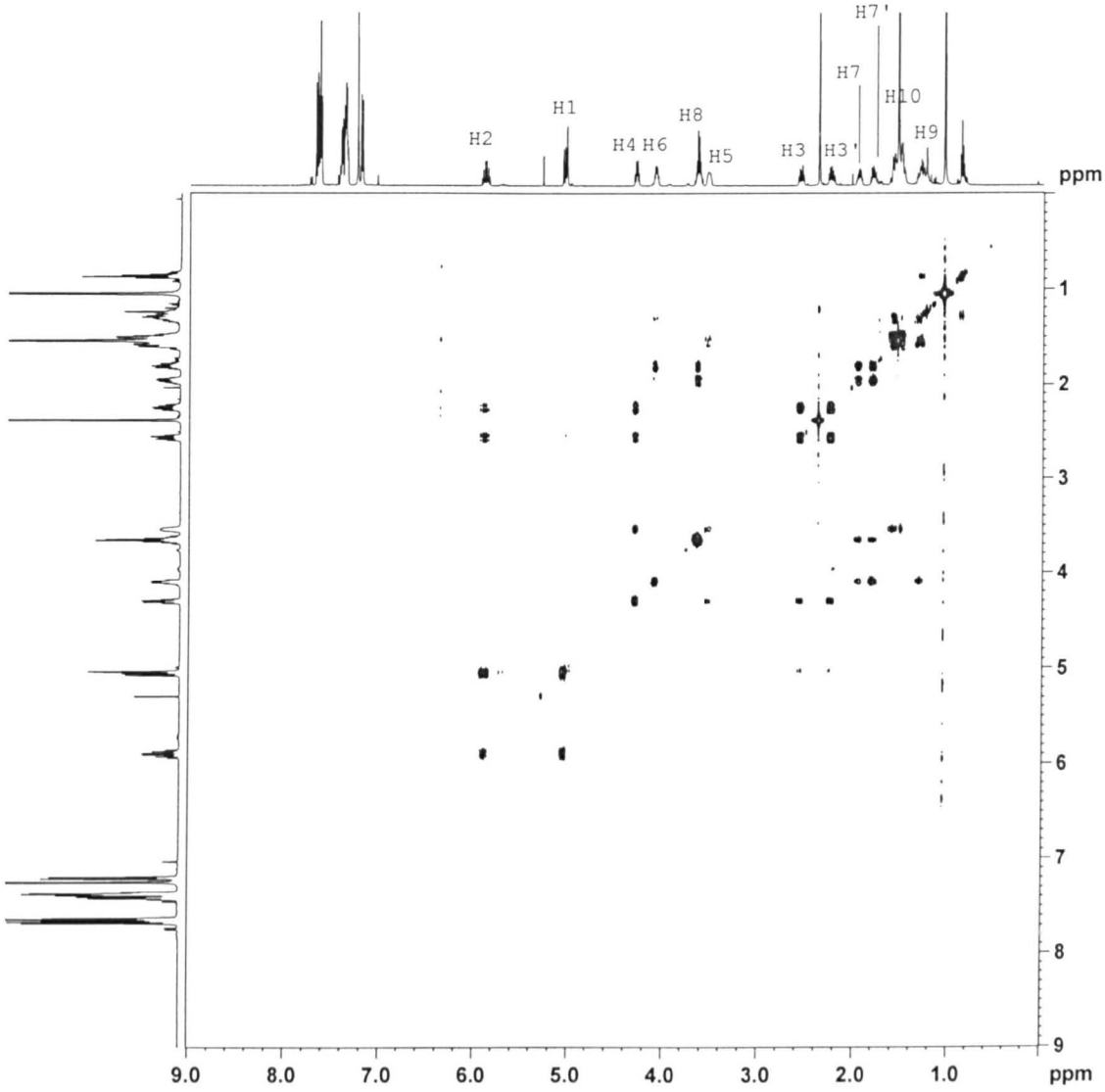


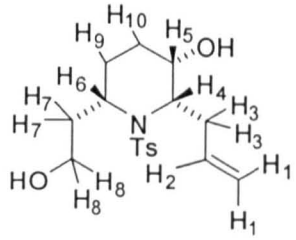
6.7.NOESY spectrum for compound 267a



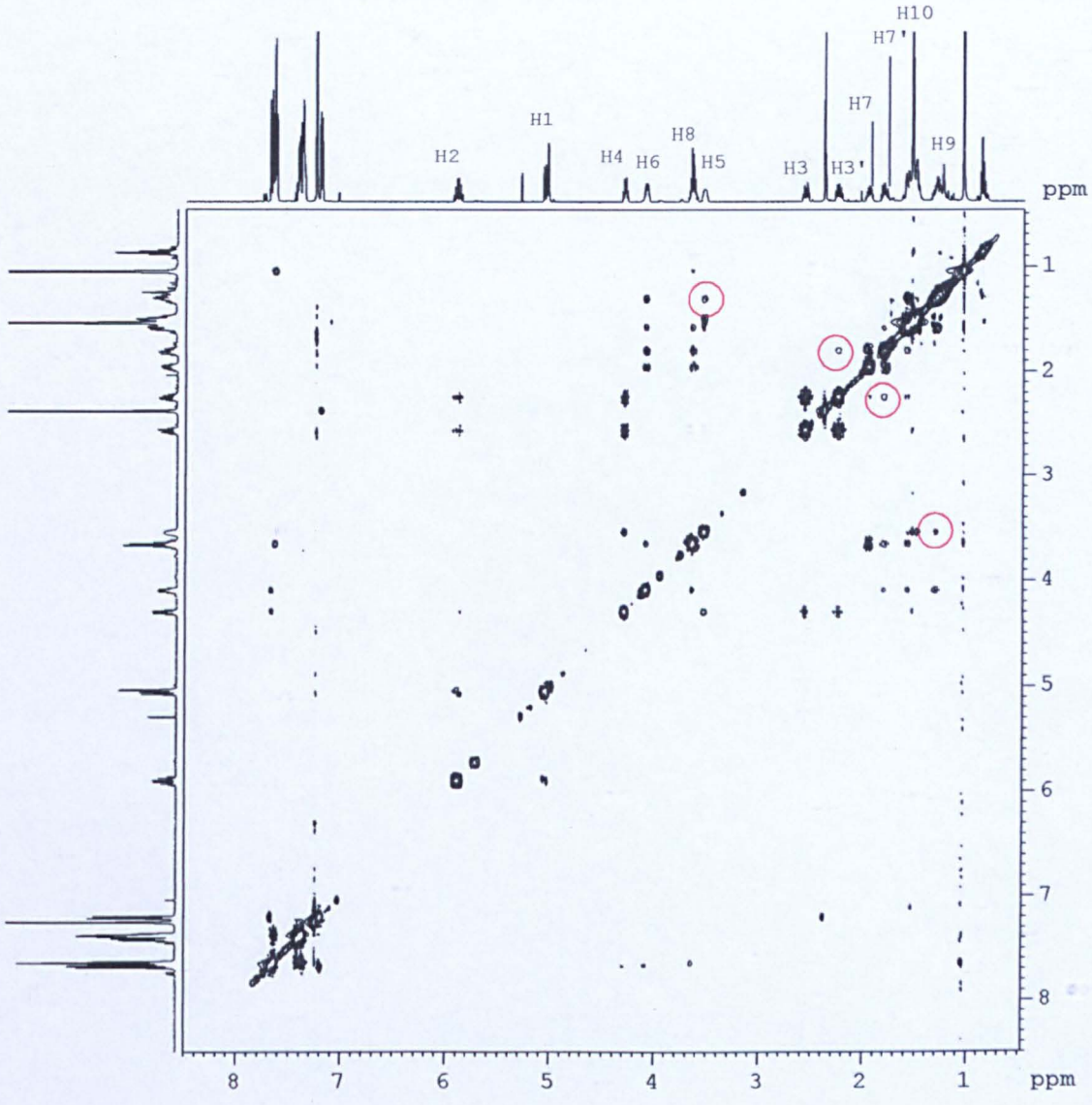


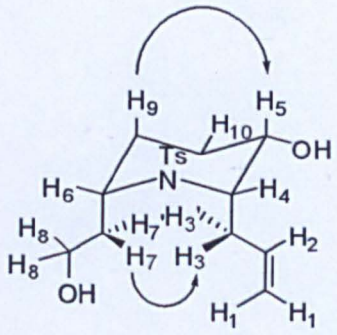
6.8.1H-1H Cosy NMR data for compound 267b



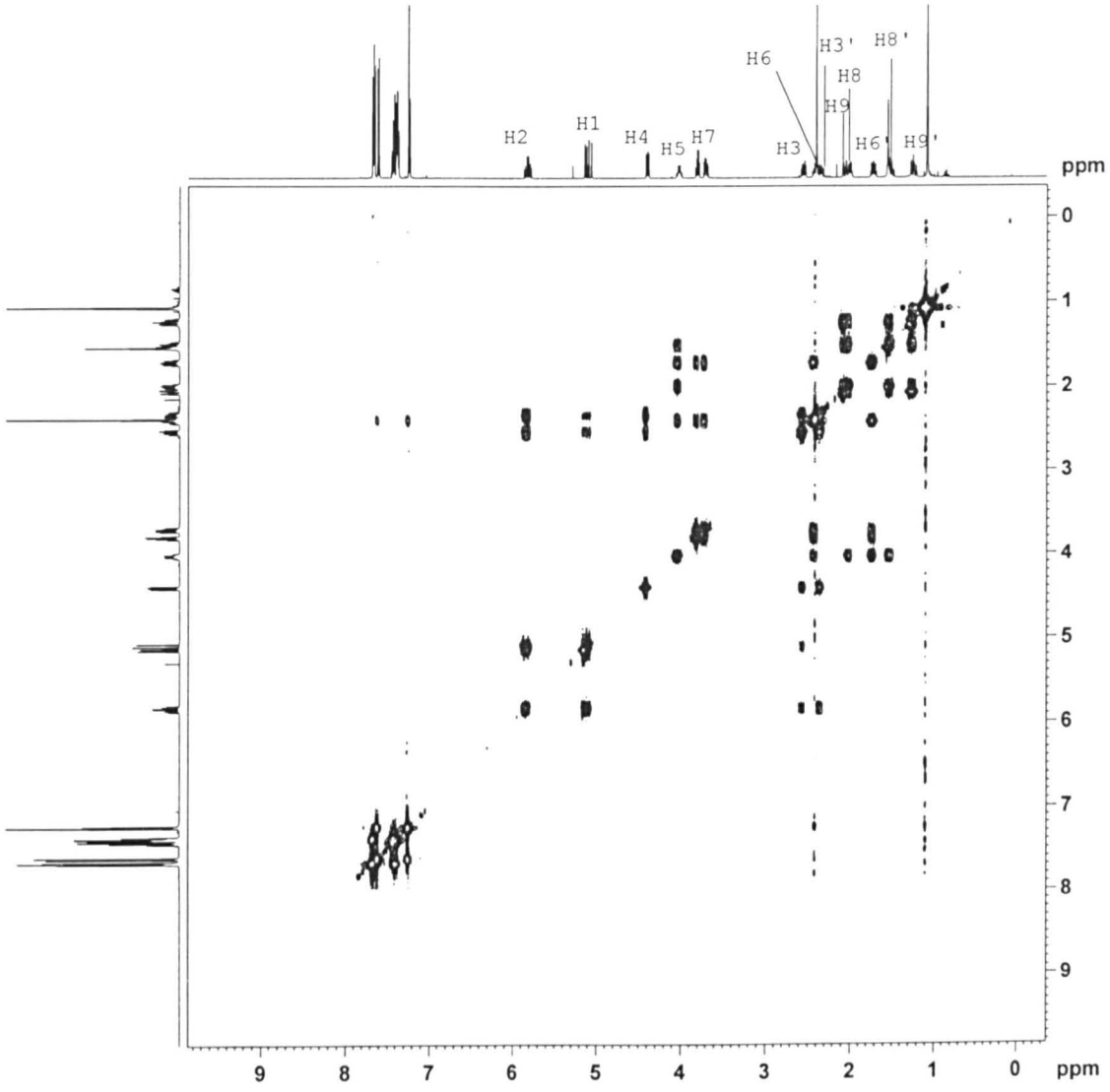


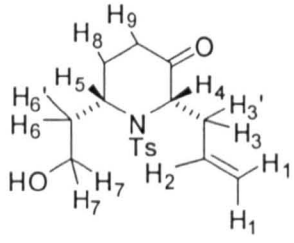
6.9.NOESY spectrum for compound 267b



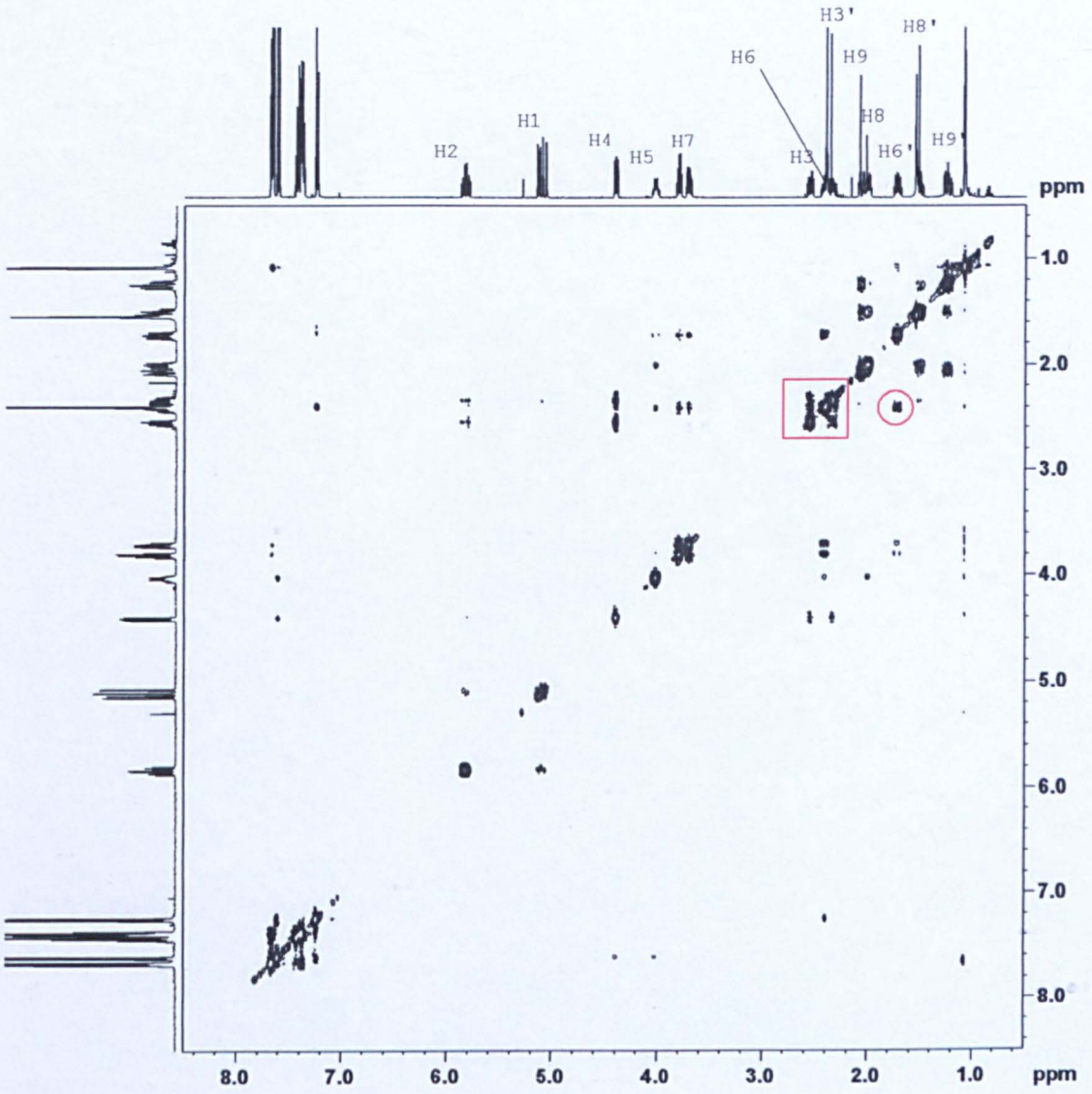


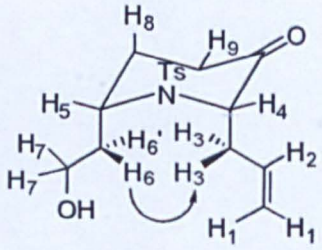
6.10.1H-1H Cosy NMR data for compound 269





6.11.NOESY spectrum for compound 269





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