Diversity-Based Synthesis of Nitrogen Heterocycles

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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Declaration

The work in this thesis is my own unless otherwise stated in the text, and referenced accordinly.

Carolyn Austin, August 2006

Dedicated to my Family

Heather, Peter, Catriona, Andrew, the Austins, the Rosses, the McRaes and the Grays

Couldn't ask for better, couldn't want for more.

Acknowledgements

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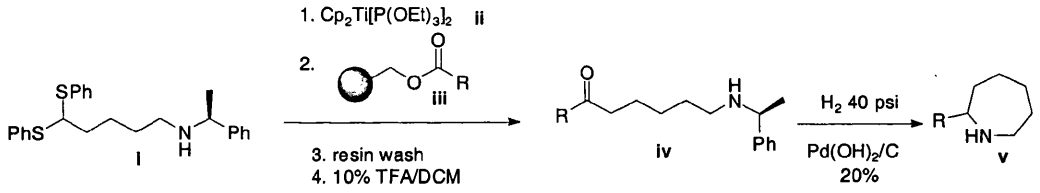
To everyone in the Henderson lab past and Louden lab present, I've had a ball, thank you for making it difficult for me to leave!

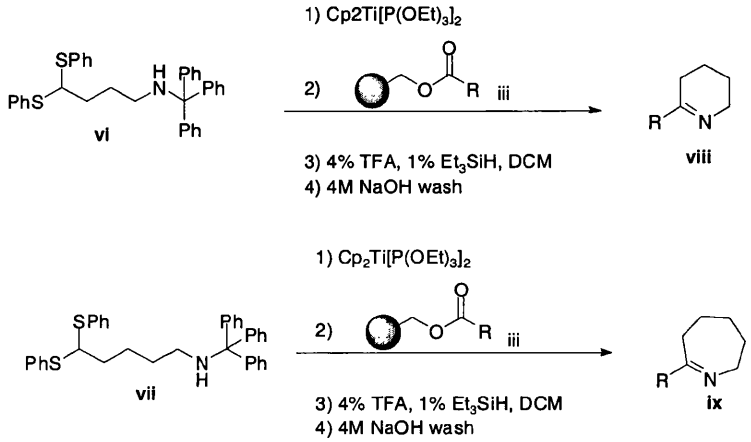
Abstract

Brief investigations were carried out towards the synthesis of 2,4-disubstituted quinolines and 2,6-disubstituted piperidines using titanium alkylidene chemistry, but these were unsuccessful.

A route towards the diversity based stereoselective synthesis of 2-substituted azepane derivatives was explored *via* titanium alkylidene chemistry. Thioacetals **i** were reacted with low valent titanium(II) species **ii** to produce titanium(IV) alkylidenes that were reacted with resin-bound esters **iii**. Cleavage of the resulting enol ethers led to a small library of amino ketones **iv**, but reductive amination to give azepanes, remained elusive. However, hydrogenation of the α-phenylethylamino group in ketones **iv** gave racemic azepanes **v**.



Diversity based synthesis of cyclic imines, both 6 and 7 membered, has been carried out using trityl protected amines **vi** and **vii**. Alkylidene formation followed by reaction with a range of resin-bound esters **iii** gave enol ethers. Cleavage and deprotection under mild acidic conditions followed by treatment with base cyclised aminoketone products to cyclic imines **viii** and **ix**.



Contents

Abbreviations

Å	angstrom
aa	amino acid
Ac	acetyl
AcOH	acetic acid
a.m.u.	atomic mass unit
aq.	aqueous
atm	atmosphere (pressure)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyl carbamoyl
n-Bu	normal butyl
t-Bu/ *tert*-Bu	tertiary butyl
b.p.	boiling point
bs	broad singlet (NMR spectroscopy)
°C	degrees centigrade
CAN	ceric ammonium nitrate
cat.	Catalyst
CI	chemical ionisation
cm	centimetre
conc.	concentrated
Cp	cyclopentadienyl anion
Cp'	pentamethylcyclopentadienyl anion
Cy	cyclohexyl
d	doublet (NMR spectroscopy)
dba	dibenzylideneacetone
DBU	1,8-diaza[undec-7-ene]
DABCO	1,8-diazabicyclo[2.2.2]octane
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	Dichlorodicyano quinone
DEAD	Diethyl azodicarboxylate
DIC	1,3-diisopropylcarbodiimide
DIEA	*N*,*N*-diisopropylethylamine
DIPEA	*N*,*N*-diisopropylethylenediamine
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	dimethylformamide
2,2-DMP	2,2-diazabicyclo[5,4,0]undec-7-ene
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EI	electron impact
eq.	equivalent(s)
FAB	fast atom bombardment
Fmoc	9-fluorenylmethyloxycarbonyl
h	hour(s)
HBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOBt	1,hydroxybenzotriazole
HPLC	high performance liquid chromatography
Hz	hertz

IR	infrared
LDA	lithium diisopropylamide
LDBB	lithium 4,4-di-*tert*-butylbiphenylide
Ln	ligand
L-Selectride	Lithium tri-*sec*-butylborohydride
M	molarity
m	multiplet (NMR spectroscopy)
MAD	methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)
MALDI-TOF	matrix assisted laser desorption ionisation- time of flight (mass spectrometry)
MALDI-SIMS	matrix assisted laser desorption ionisation secondary ion time of flight (mass spectrometry)
MAS	magic angle spinning
m-CPBA	*m*-chloroperbenzoic acid
meq	milliequivalents
MHz	megahertz
MOM	methoxymethyl
min(s)	minute(s)
m.p.	melting point
MS	molecular sieves
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
α-PEA	*alpha*-phenylethyl amine
PG	protecting group
Ph	phenyl
PhH	benzene
PhMe	toluene
Py	pyridine
PyBOP	benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate
PPTS	pyridinium *para*-toluenesulfonate
quant.	quantitative
q	quartet (NMR spectroscopy)
quin	quintet (NMR spectroscopy)
Rac	racemic
RCM	ring closing metathesis
rt	room temperature
SM	starting material
SPS	solid-phase synthesis
t	triplet (NMR spectroscopy)
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TfO	triflate (trifluoromethanesulfonate)
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
Ts	Tosyl (*para*-toluenesulfonyl)
TsOH	*p*-toluenesulfonic acid

Chapter 1: General Introduction

1.1 Why Make Small Molecules? – Chemical Biology

Small molecules are the life-source of pharmaceutical companies. It is low molecular weight biologically active molecules that comprise the majority of successful drugs on the market. Identifying and accessing biologically active compounds requires detection methods suitable for fast and accurate screening of vast numbers of compounds in order to increase the chance of finding a hit lead compound.

1.1.1 Method of Identification:- Assays how Biologically Active Compounds are Identified

Traditional drug discovery has relied on screening the drug candidates on known specific protein targets, after their function has been determined.[1] Small molecule targets that are biologically active can affect cellular processes by binding to proteins or protein receptors, as their nature determines and in doing so can produce a phenotypic response. In screening compounds on cell or organism-based assays, an insight into biological processes which are not fully understood can be gained.[1] In general, bioactive small molecules interfere with protein function, and this is how they modulate gene function giving rise to chemical genetics, although in some cases these molecules can also bind to nucleic acids and modulate their activity.[2] Chemical genetics is the use of bioactive small molecules to modulate gene function in an attempt to learn what that gene(s) does. This is in contrast to classical genetic techniques, that require manipulation of the genome of a subject to discover gene function, e.g. deletion of a gene to see what is missing. Chemical genetic screens probe the ability of small molecules to change any part of cell function, providing a usually controllable, rapid and reversible effect over the small molecule's target.[1,3]

1.2 Privileged Structures

Discovery of these bioactive small molecules, useful as potential therapeutic agents, can be carried out under two ideologies. Structure based rational design is a method based on understanding the mechanism of the potential action of the drug, through knowing the target protein and possible binding sites etc. This method requires detailed knowledge of the target pathway and protein. The second is to screen a large number of diverse compounds (library) and observe the hits that produce the desired response or phenotype in

the screens. In order do this a wide range of small molecules must first be synthesised, to provide a greater chance of finding a molecule which is bioactive, selective and potent. Previously, libraries were extremely diverse in an attempt to cover as much chemical space as possible.

Chemical space is a description of all the possible structures of low molecular weight drug-like compounds in relation to each other. There are a phenomenal number of these compounds, some estimates include 10^{30}-10^{200} (depending on the program used)[4], though only a proportion of these molecules are likely to have acceptable drug-like properties, and their position in chemical space depends upon the descriptors chosen to define the molecule. Multiple descriptors are used to pinpoint a molecule's exact location in chemical space. These descriptors annotate the small molecule's structure, observed activities and properties and produce a multidimensional plot of chemical space encompassing the molecules plotted for. The descriptors can be defined using computer programs and algorithms or phenotypically using cell assays.[5]

With this knowledge you would expect that companies screening greater numbers of more structurally diverse compounds than ever before, therefore covering more chemical space, would find an increase in the number of lead compounds discovered, proportional to this effort. This is not the case however, and the number of drugs reaching market has not increased accordingly.[6]

Recently, however, another approach to determining leads using chemical space has been employed. Libraries can be directed towards one core structural moiety that has been shown to have a high degree of success in binding to a range of receptors. This information can be gained from previous high-throughput screens in which certain structural motifs have been shown to have an increased percentage of hits in a variety of assays, compared to other structural motifs.[7] This appears to limit the range of the combinatorial chemistry reducing the coverage of chemical space, but in fact the practice focuses the synthesis in the direction of structures most likely to interact with biological targets.

These moieties are known as privileged structures and can provide a starting point for the synthesis of a directed library of diversity in the structure. The aim of directed libraries, is to target the diversity orientated synthesis towards privileged structures and therefore increase the chance of finding a useful lead compound. Natural products are also an important consideration for a starting point in both target orientated synthesis and the

combinatorial library approach, as well as the final drug product e.g. anthrcyclines, taxoids and vinca alkaloids.[1] However their complex structure and stereochemistry considerations often make them difficult targets for lead optimisation. Routes have to be redesigned to produce analogues and the physiochemical properties required for in *vivo* experiments and oral bioavailability all require consideration. Research into diversity orientated synthesis of natural product-like compounds is on going, however, and promises to yield structures which are diverse and naturally, bioactive.[8]

1.3 Chemical Genetics

1.3.1 Forward Chemical Genetics

Forward chemical genetics uses a cellular based assay to determine the bioactivity of small molecules. Cells are distributed onto plates, usually 96 well plates, and a dose of each library member is administered to an individual well. The plate is then given a set incubation time before it is screened for a phenotypic response to the library member. Cell based assays are useful for determining whether a compound has bioactivity. Knowledge of the specific target is not required at the beginning[3] as it can be determined later through affinity chromatography separations, common in biochemistry. The separation and identification of the target protein can be carried out, using a biochemical approach, by attaching the ligand or bioactive small molecule to a solid support, e.g. sepharose. The cell or tissue extracts are then exposed to this affinity column and proteins that bind to the ligand can be drawn out.[2,3] The gene coding for the bound protein can then be determined.[1]

Problems can arise from using biochemical target identification techniques. In immobilising small molecule substrates for the affinity columns, their function can be impaired so they behave differently from in *vivo*. The process of immobilisation can also cause trouble as functional sites are needed for immobilisation and, if present in the molecule, they may be needed to bind the target protein. Background protein binding is another issue, if the affinity for the target protein to the ligand is low, many proteins can bind, making isolation and identification of the desired target more difficult. In addition to this, more abundant proteins are more easily viewed, as less enrichment is required than less expressed ones, e.g. transcription factor proteins are less abundant than certain kinases, so even if a strong affinity occurs it will be difficult to observe transcription factor proteins above background.[9] Therefore affinity based separation is much easier and more useful for

characterising abundant protein targets that bind strongly to their ligands than for weaker binding and less prevalent protein targets.[9]

1.3.2 Reverse Chemical Genetics

If the desired bioactive molecule is to bind to a protein already known, another approach may be employed. This is called reverse chemical genetics and uses purified protein based assays. The target protein is expressed, isolated and screened to find a bioactive small molecule or ligand that binds to it. This protein-ligand interaction can then be used to identify a phenotypic response within a cell-based assay and hopefully if the function of the protein is not known it can be determined. If the function is known, the effect of the ligand on the other genes and receptors in the cell can be studied, providing valuable information on selectivity should the bioactive small molecule be a suitable drug candidate. Figure 1 is taken from a paper by Blackwell and Zhao[3] and provides a clear diagram of both forward and reverse chemical genetics.

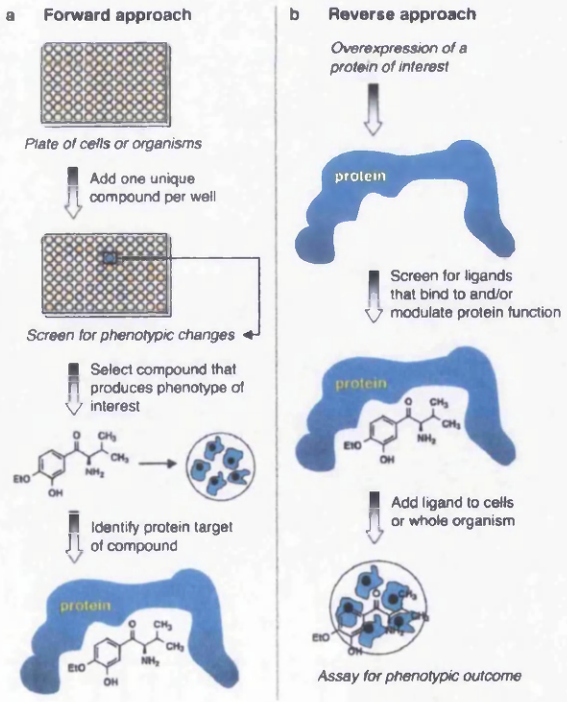


Figure 1.[3]

With these methods of evaluating the biological activity of large numbers of compounds, it is important to consider the methods of synthesising them. One of the greatest aids to library synthesis is solid-phase methodology. Several methods for providing libraries of

compounds exist using solid-phase and related technologies and they each create different degrees of diversity in the library.

1.4 Library Synthesis

1.4.1 Solid-Phase Chemistry

Combinatorial synthesis was first developed for the synthesis of small molecule drug candidates in the early 1990's. Previously, solid-phase chemistry - immobilisation of compounds onto solid supports inert to reaction conditions, had only been utilized in peptide synthesis.[4] This was developed by Merrifield in the early 1960's, and had the benefit of allowing easy purification by the removal of excess reagent by washing the compound attached to solid support, a chloromethylated co-polymer of styrene and divinylbenzene, with various solvents.[10] This support was successful because it allowed flow of reagents through its porous gel structure, providing access for reactants, particularly when solvents with swelling properties were used (e.g. DCM, THF). The advantages of solid-phase chemistry, ease of purification by filtration and use of excess reagent to drive reactions, fuelled research into expanding the methodology to small molecule synthesis.

The new field posed several challenges, differing from that of peptide chemistry. Optimisation on solid-phase now required a range of bond-forming reactions, instead of just peptide coupling and de-protection strategies, and limitations of heterogeneous reaction conditions and the small quantities of compounds produced were also challenges.[11] One major problem with using an insoluble support is the difficulty in observing reaction progress and intermediate compounds attached to resin.

Standard spectroscopic and analytical techniques give a little insight into the compounds loaded onto resin. IR provides an insight for certain marker functionalities, e.g. carbonyl groups, but does little to help with structure. Combustion analysis is useful for determining the heteroatom content, e.g. N, S, F, Cl, Br, and as such can provide a reasonably accurate indication of loading of a resin e.g. chloromethyl polystyrene, but is obviously ineffective for carbon and hydrogen. Mass Spectrometry is useful for the analysis of support-bound intermediates. Depending on the linker MALDI-TOF and TOF-SIMS techniques are available.[12] Gel-phase NMR is not very useful due to the broadening of the signals, but there has been research into this however, and magic angle spinning (MAS) gel phase NMR is a technique available which greatly aids the identification of

compounds bound to resin.[11,12] However, cleaving the product from the a sample of the resin after each step and then using standard analytical techniques can often be the simplest approach and is the one we adopted.

Traditionally there are two ways of producing libraries of compounds for high throughput screening by combinatorial synthesis. The first is parallel synthesis, a technique useful for the generation of small libraries, as it requires the synthesis of each compound to be carried out individually. Automation is possible however and this can speed up the time taken for production. The second is a process similar to genetic recombination,[4] the 'split and mix' technique, figure 2[11] shows three cycles, each with three different compounds, (3 x 3 x 3 = 27) member library. The latter approach requires deconvolution and has been steadily diminishing in popularity.

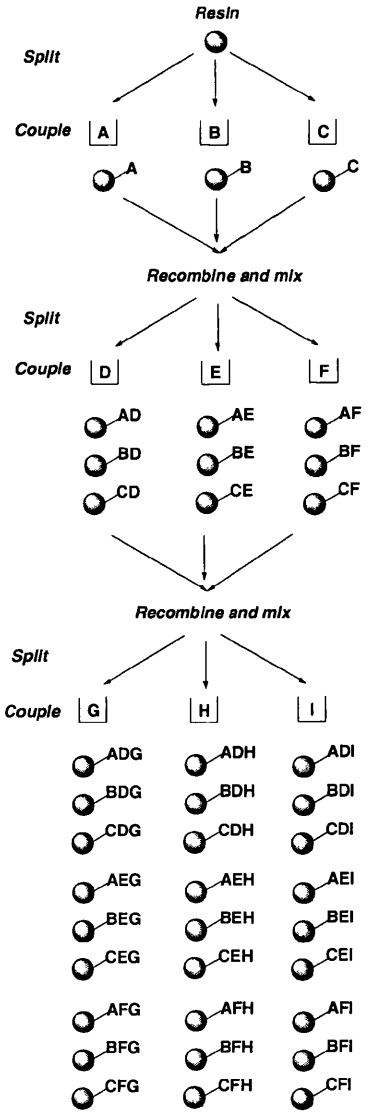


Figure 2.[11]

The solid-supports are usually small spherical beads of polymer and are used in the form of loose resin. This usually has to be weighed out and contained within individual reaction vessels, however a recent advancement discards the need for tedious weighing by the use of stratosphere® plugs. Figure 3 shows loose resin and plugs of resin.

Figure 3.[13]

The resin can be contained in 'tea-bag' containers that permit the reactions to take place while localising the resin to an easily handled container, and the used of specific solid-phase equipment is negated. The research carried out in this thesis utilised IRORI macrokans, figure 4.

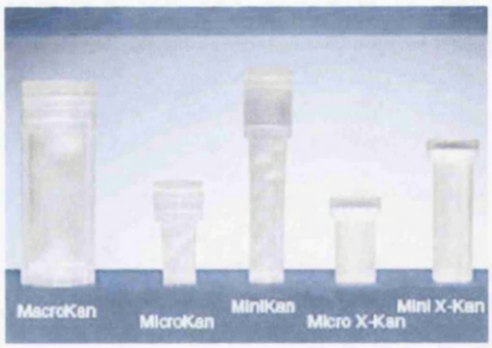


Figure 4.[14]

Other solid-supports include support sheets, crown-shaped pins and small disks.[12]

Since the advent of solid supports for small molecule synthesis, several different methods of 'support' have been developed as well as a wide range of polymers for solid support. These polymers provide a wide range of properties differing from Merrifield's original polymer, though chloromethylpolystyrene and hydroxymethyl polystyrene are still widely used today, and were used in the synthesis of nitrogen heterocycles detailed later in this work. Polymers have been developed which have varying swelling properties allowing

differing degrees of permeability of reagent into the polymer matrix. This permits controlled exposure to reagents, and aids in the purification process by swelling and squeezing the polymer support in different solvents, but is also a concern when choosing the solvent for a reaction, particularly if the ideal solvent for solution phase does not swell the resin. In general solvents that swell the majority of resins are dipolar aprotic solvents (e.g. DMF, DCM) as polystyrene is a hydrophobic polarizable substance, and swelling is poor in alkanes, protic solvents (e.g. MeOH) and water.[12]

1.4.2 Soluble Polymer-Supported Synthesis

The polymer chemistry used in solid phase synthesis has been expanded to the use of soluble polymers in liquid-phase synthesis also known as 'soluble polymer-supported synthesis'. Here the objective is to use a soluble polymer backbone attached to reagents or reactants. Separation is facilitated by the use of the macromolecular properties inherent in the bound compounds to separate the polymer bound substance at the end of the reaction.[15] The support, sometimes called a precipitation tag,[4] is usually a polyethylene glycol derived polymer, employed because they are soluble in a range of solvents e.g. DMF, DCM, toluene acetonitrile, water and methanol, but can be precipitated using ethers and higher alcohols.[16] Precipitation with solvent followed by washing excess reagents away provides the advantage of solid-phase. The tagged product can then be made soluble again providing a homogeneous medium for the following reactions. This negates problems associated with the solid supported substrates as the reaction is homogeneous and therefore unequal distribution of attachment and reaction on the polymer sites is avoided. As the reactions behave more like solution-phase reactions there is less optimisation required to get the reaction to go. However, optimisation is necessary to reduce the number of polymer bound side products, as this remains a problem, and the product will require further purification after cleavage.[15] Furthermore, different polymer-supported compounds have to be reacted in different flasks or separation and identification becomes a problem.

1.4.3 Fluorous Chemistry

Fluorous chemistry is a growing field of separation platform chemistry.[4] This technique involves tagging a compound with a cleavable perfluorocarbon side chain. The compound can then undergo standard reaction conditions homogeneously and the benefits of solid-phase chemistry can be conveyed during work-up. As the solubility of the compound is affected by the perfluorocarbon side chain, loading of the product onto a fluorous phase silica gel and elution with fluorophobic solvent systems (protic solvents) will remove all

non-fluorinated by-products. Subsequent elution with a fluorophilic solvent system (aprotic solvents) will elute all fluorous compounds from the column.

This methodology has been expanded to fluorous mixture synthesis, a technique that allows some of the advantages of combinatorial chemistry used in solid-phase library production detailed above to be extended to a solution-phase library synthesis.[17] This is achieved by tagging with varying degrees of perfluorocarbon side chain e.g. C_4F_9 to $C_{19}F_{21}$.[17] Once tagged, a series of one pot reactions can be carried out in an 'internal parallel' approach leading to no change in library size, or the mixture can be subjected to a number of one-pot reactions followed by separation into two other groups and further parallel reactions carried out on these new lines, figure 5.[18] This amplifies the number of compounds produced in the library and has been used to produce a library of 560 compounds in this manner.[18] Following the final reaction in the sequence the varying degrees of fluorination in the molecules can be used to separate out the mixture of products. Again using fluorous phase chromatography the compounds can be cleaned up by elution of a fluorophobic solvent and a concentration gradient in the elution of the fluorophilic solvent allows separation of the various tagged compounds eluted.

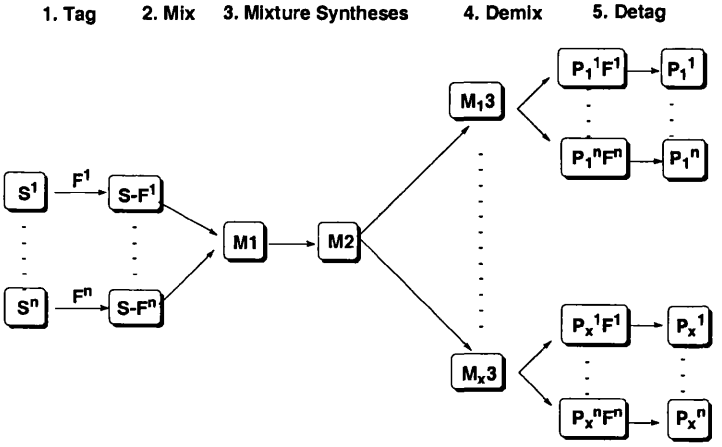


Figure 5.[18]

1.4.4 Linkers

An important factor in all of the above methods used to allow automation is the attachment and detachment of the compounds to the separation platform used. This is achieved in solid-phase chemistry, soluble polymer-supported synthesis and fluorous synthesis by the use of a cleavable linker. The linker is of great importance, as it must not interfere with the reactions carried out on resin until it is necessary to cleave it, and therefore the compound, from the support, figure 6. In the original work carried out by Merrifield, an ester linker

was utilised as the triethylammonium salt of a protected amino acid could be attached via O-alkylation with a chloromethylated polystyrene resin.[10] Cleavage was carried out using under ester hydrolysis conditions (NaOH and ethanol). The use of such strong hydrolysing conditions is acceptable when there is little other functionality that can be affected by it. However, the development of selective and easily cleavable linkers was essential for the use of solid-phase chemistry in small molecule synthesis. Research carried out by Wang into the synthesis of a more acid-labile linker provided the para-alkoxybenzyl linker, this was easily cleaved in the presence of trifluoroacetic acid and lead to products of higher purity.[19]

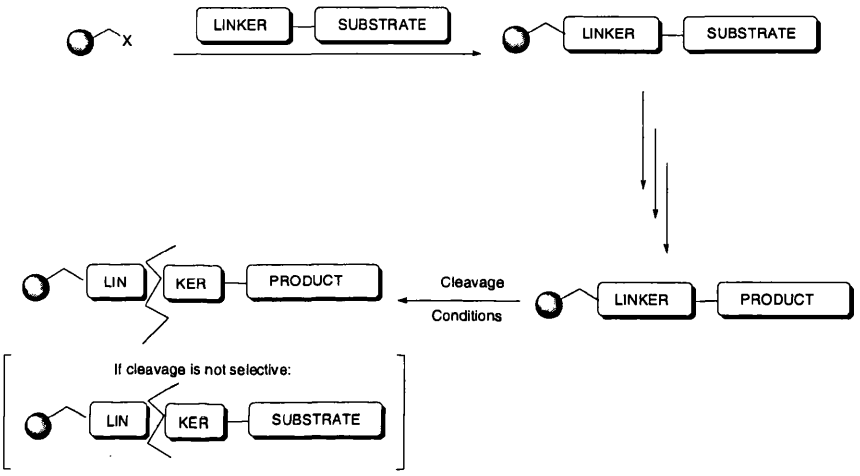


Figure 6.

The field was expanded by other methods used to introduce synthetically orthogonal cleavage conditions including the use of a photolabile linker. This, rather than relying on chemical compatibility with product functional groups, requires irradiation to secure cleavage.

An example of a development that has an interesting and important application, considering chemical genetics and the high throughput screening of libraries is that of biocompatible linkers. These linkers have been designed to allow cleavage of the compound into aqueous buffer following synthesis on solid support, and therefore permit the compounds to be screened directly from resin. This has important implications for automation as cleavage directly into screening wells for biological assays can be carried out. An example of a biocompatible linker is that of an enzyme-labile linker, designed to be cleaved by enzyme-initiated fragmentation, that leads to the release of the bound substrate.[20] The linker is attached to resin *via* a stable amide bond, figure 7. The linker contains an acylating arm that a nucleophilic atom on the substrate can bind to, to attach

the compound to resin, and an acyl handle for the enzyme, a lipase or esterase, to bind and cleave.

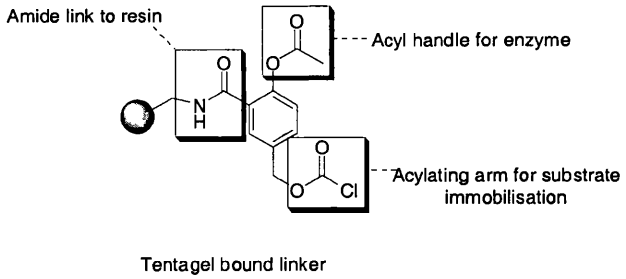
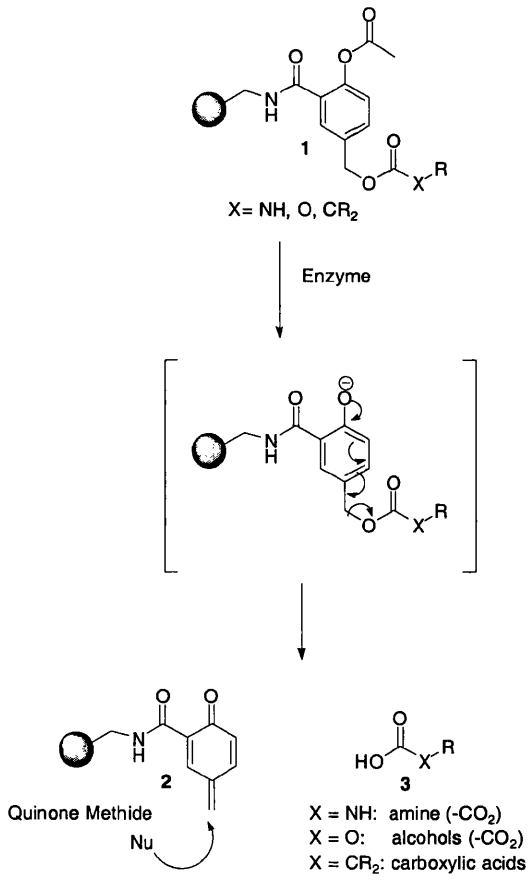


Figure 7.

Cleavage of the acetyl group in **1** initiates a fragmentation reaction that produces a quinone methide **2**, retained by the resin and quenched by water or another nucleophile, and releases the bound molecule **3** from the linker, (Scheme 1).



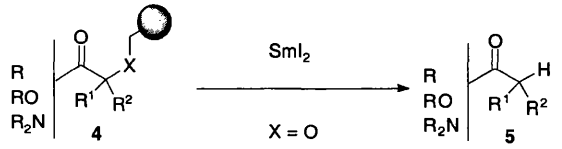
Scheme 1.

Other advances include asymmetric induction from the linker and partial or sequential release linkers.[11] It is not my intention to give a comprehensive review of linkers as these are available[11,21] but I will focus on three important developments relevant to our research: a) Linkers that leave no trace at the site of attachment. b) Safety catch linkers that require

activation before cleavage so ensuring the purity of products. c) Chameleon catch linkers that change their nature and maximise the diversity introduced.

A) Traceless Solid-Phase Synthesis

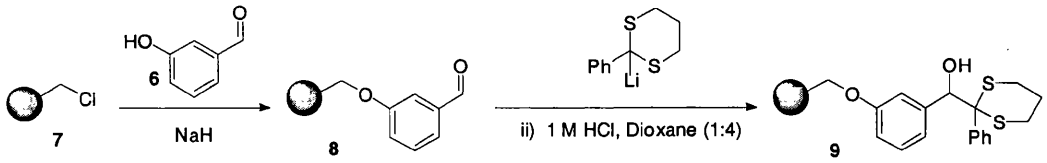
Linkers provide a handle or functionality to facilitate cleavage in the final step of the synthesis, but they also pose a problem: in cleaving the linker, trace functionality can be left behind, reminiscent of the attachment to resin, and this can affect the biological function of the small molecules synthesised. Traceless synthesis is the synthesis of compounds on resin, that once cleaved, leaves no obvious residue from the site of attachment that would interfere with structure activity studies. The term 'traceless' has been debated over and because what constitutes an 'obvious residue' varies, some have argued that it is not useful.[22] However if a synthesis avoids the presence of a single or small range of functionality at the site of cleavage we regard it as traceless. Generally what remains of the site of cleavage is an aliphatic or aromatic C-H.[23] The most widely used traceless linkers are silicon derived. Such linkers take advantage of the labile aryl-silicon bond, that is easily cleaved under acidic conditions.[11] However other examples exist including the recent development of linkers that can be cleaved under mild conditions using samarium diiodide. The strategy[24] utilises the ability of SmI_2 to reduce the heteroatom of α - heteroatom substituted carbonyl compounds **4** bound to solid phase, leaving C-H in its place **5**, (Scheme 2).



Scheme 2.

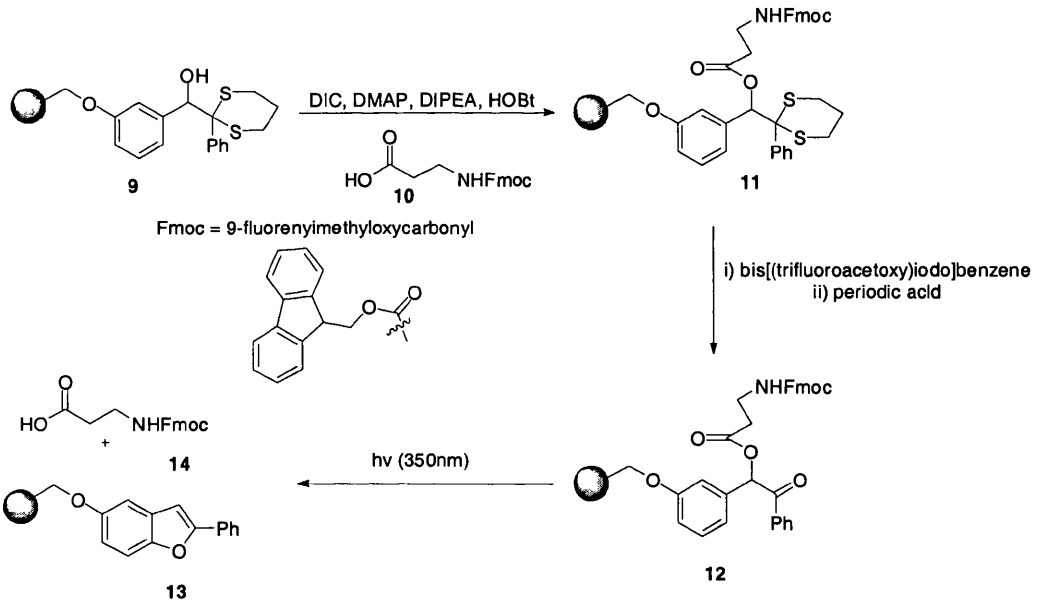
B) Safety Catch Linkers

An advancement that combined photolabile linkers with that of ensuring control of cleavage is the use of a photolabile safety catch linker. A safety catch is a masked handle for cleavage that can be revealed prior to administering the cleavage conditions. An example of such a safety catch mechanism is the dithiane protected benzoin photolabile linker, formed by alkylation of an *meta* hydroxybenzaldehyde **6** with chloromethylpolystyrene **7**, followed by addition of the lithiated dithiane **8** to complete the synthesis of linker **9** synthesis, (Scheme 3). [11,25]



Scheme 3.

This chemistry utilizes the benzoin ester's photosolvolytic cleavage with irradiation at 350 nm, which is possible only once the dithiane group has been removed. The linker was tested by coupling with a simple Fmoc-protected amino acid **10**, to form the safety catch protected and immobilised substrate **11.** Unmasking conditions revealed the cleavable benzoin ester **12**, which once subjected to irradiation produced the immobilised benzofuran **13** and the desired amino acid **14**, (Scheme 4).[25]



Scheme 4.

The linker **9** once constructed on resin can be attached to reactants *via* the secondary alcohol, this can be activated with a carbonyl-1,1-diimidazole to increase the reactivity of the linker, figure 8.[25]

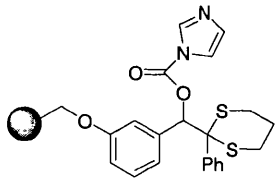
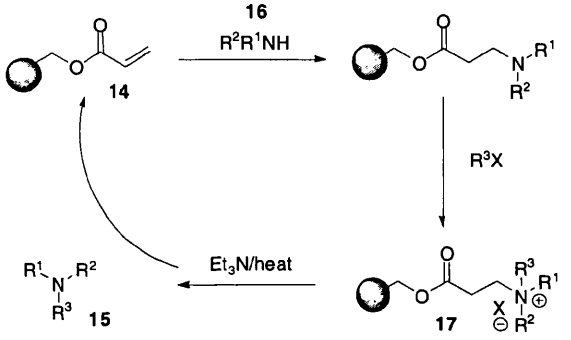


Figure 8.

A safety catch linker has also been used in the development of recyclable resins. This regeneration of the linker at the end of the reaction may be desirable to companies wishing to make many similar compounds. The first of these resins was the REM resin, an acrylate ester **14** immobilised onto hydroxymethyl polystyrene resin, and was used in the synthesis of tertiary amines **15**. Michael addition of a secondary amine **16** and alkylation with a primary alkyl halide provides a quarternised amine **17** and activates the linker towards cleavage. Elimination of the tertiary amine regenerates the α,β unsaturated ester linker, this can then be used in at least 4 cycles without deterioration in yields provided the quarterisation is driven to completion, (Scheme 5). Benzyl and aryl sulfone analogues, figure 9, that reduce undesired Hoffmann elimination prior to quarterisation and withstand far harsher reaction conditions, but work in exactly the same manner, have also been synthesised.[11]



Scheme 5.[11]

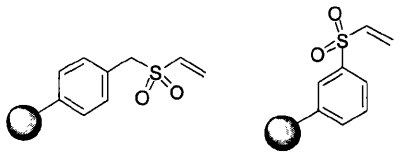
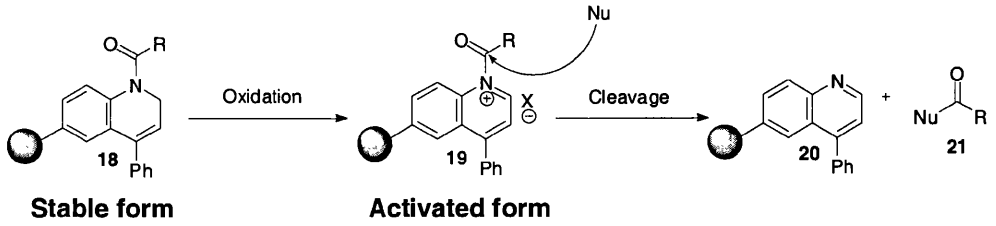


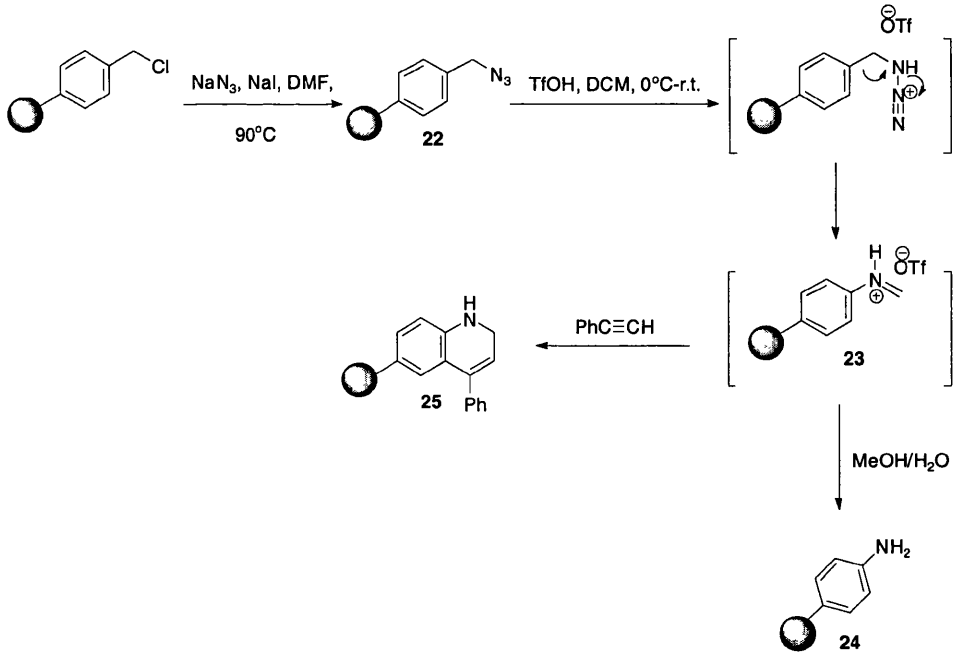
Figure 9.

Another example is the use of the dihydroquinoline core and its conversion to a resin bound quinoline, for use as a safety catch linker, (Scheme 6).[26] The linker **18**, attached to compounds through an amide bond to the quinoline nitrogen, has a two stage safety catch approach in that it will not cleave from the product molecule until activated **19** and then a second step effects cleavage from the altered linker to yield quinoline attached to resin **20** and the products **21**, (Scheme 6).



Scheme 6.

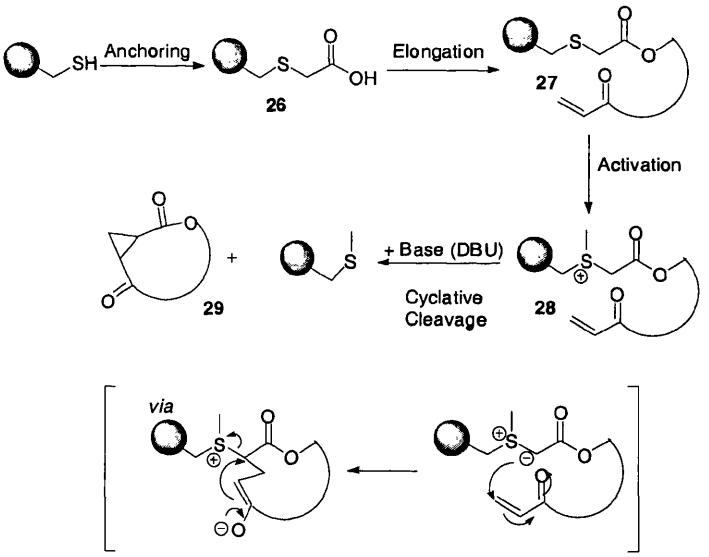
The starting resin used is chloromethyl polystyrene and the first step is formation of the azide **22** using Finkelstein and S_N2 displacement conditions. Treatment of the azide with trifluoromethanesulfonic acid provokes a one carbon degradative Schmidt rearrangement to form an imminium ion intermediate **23**. This intermediate can be treated to methanol and water to produce a resin bound aniline **24** or reacted with an alkyne group to produce resin-bound 4-phenyl-1,2-dihydroquinoline **25**, (Scheme 7). Acylation with substrates to be manipulated can then be carried out, forming the amide bond (**18** stable form) and following reaction sequences, the linker can be treated to oxidisers e.g. DDQ (dichlorodicyanoquinone), CAN ceric ammonium nitrate, and cleaved by addition of a nucleophile.[26]



Scheme 7.

One problem remains, however, if the nature of the linker remains unchanged in the synthesis, the final cleavage step can introduce impurity in the form of unreacted starting material or by-products attached to resin. Cyclative cleavage of compounds from resin is

an excellent technique for combating this problem, particularly important as many heterocycles are well known to be good pharmacophores, with many of them considered privileged structures. The method provides the advantages of a safety catch approach as products will only be released when functionality allowing cyclisation has been introduced and unmasked, and any by-products from incomplete transformations will be left behind.[11] An example of cyclative termination is shown in Scheme 8.[27] Acid **26** was elongated to include a Micheal acceptor **27**. Activation of the linker by conversion to a sulfonium salt **28** allowed cyclative cleavage via an addition followed by an elimination generating a cyclopropane **29**. No cleavage would occur unless both the sulfonium ylide and Micheal acceptor were present.



Scheme 8

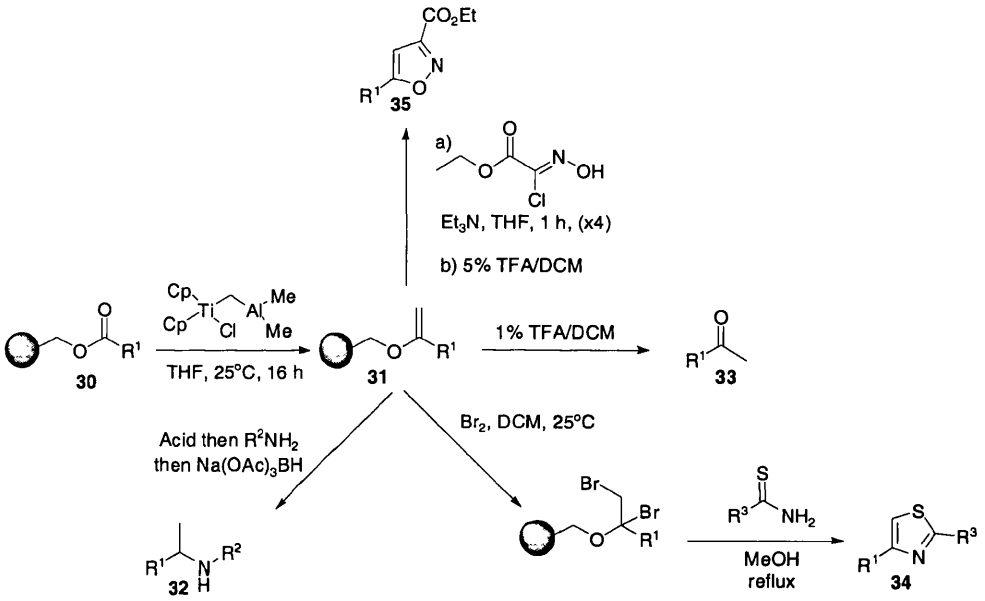
This cleavage could be regarded as traceless as there is no additional undesired functionality at the site of cleavage.

C) Chameleon Catch Methodology

Since the start of research into solid-phase linkers, more sophisticated techniques for cleaving have been developed. One example is the use of the cleavage step to introduce further diversity into the molecule. By using this method a wide range of functionality can be introduced. In the case of a simple ester linker **30**, hydrolysis, aminolysis, and reduction, provide access to acids, amides and alcohols respectively.[11]

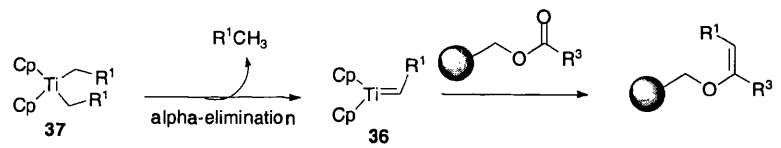
Thus ester linker **30** could be cleaved to give acids or alcohols but could also be converted to an acid labile enol ether linker **31** using the Tebbe reagent.[28] Switching the nature of an

easily accessible ester linker **30**, to an enol ether **31** is similar to a 'safety catch' activation, as only the enol ether is affected by mild acid conditions. It also provided direct access to amines **32** *via* reductive amination from the cleavage product ketone **33**, (Scheme 9). The enol ether could also be derivatised further on resin allowing access to thiazoles **34** as well as Diels-Alder products when the correct starting material was used and the method was later utilised in the synthesis of isoxazoles.[29]



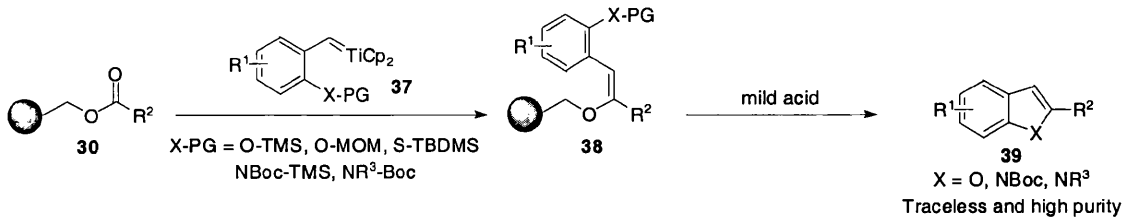
Scheme 9.

The alkylidenation step, which switches the nature of the linker was achieved using the Tebbe reagent. This has the disadvantage that only methylenation was possible and no other groups could be introduced during the alkylidenation step. Petasis alkylidenation, which involves generating a Schrock carbene **36** from a dialkyltitanocene **37** requires elevated temperatures and led to premature cleavage from resin, (Scheme 10).[23] This was unfortunate as benzylidenation as well as methylenation is possible with these reagents.[30] The main limitation to Petasis reagents is that there cannot be hydrogen atoms beta to the titanium in the dialkyltitanocene or β-elimination rather than α-elimination is the predominant process at raised temperatures.



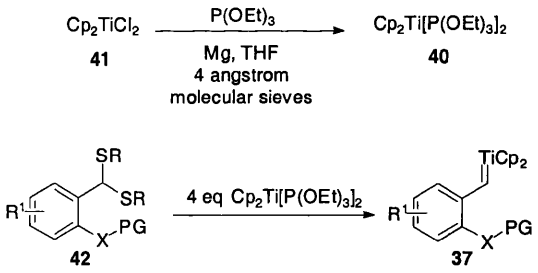
Scheme 10.

The Hartley group, however, combined cleavage diversification, with the traceless chameleon catch technique and took the methodology much further. The titanium alkylidene **37**, bearing functionality, was reacted with a range of ester groups **30** to give enol ethers **38**. Cleavage with possible concomitant cyclisation then gave a range of bicyclic aromatic heterocycles **39**, (Scheme 11).[31,36]



Scheme 11.

The titanium alkylidene was accessed through Takeda's method of reductive desulfurisation of dithianes or dithiophenyl thioacetals, with low valent titanium(II) complex **40** generated from titanocene dichloride **41**. The titanium alkylidene then reacted easily with ester groups in a Wittig-like manner to produce substituted enol ethers **38**. The Takeda method of generating the Schrock carbene **37** has the advantage that it tolerates a wide range of functionality and hydrogens β to the titanium are permissible, (Scheme 12). Furthermore a wide range of thioacetals **42** are easily accessed in one step from the corresponding aldehydes.



Scheme 12.

The solid-phase provides the advantage that the titanium by-products and impurities from the reaction, usually requiring a silica gel column to purify, can be easily washed away. In combination with the safety catch mechanism permitted by the chameleon catch linker, the methodology provides a route to a variety of products that are pure once cleaved from resin, and require little if any post cleavage modification to achieve the desired heterocycles. Through this traceless methodology a range of heterocycles were produced; benzofurans[31] e.g. **43**, benzothiophenes[35] e.g. **44**, indoles[33] e.g. **45**, alkylated indoles[33] e.g. **46** and quinolines[34] e.g. **47** have all been synthesised, figure 10.

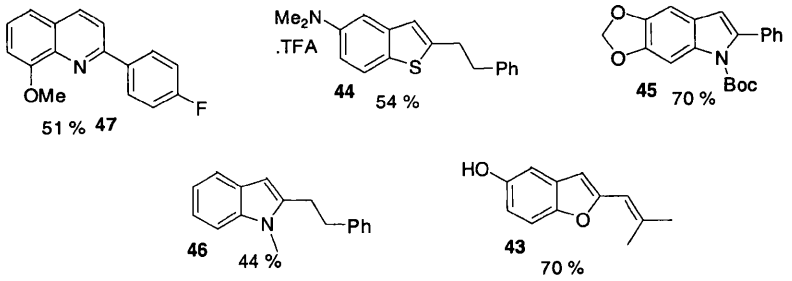
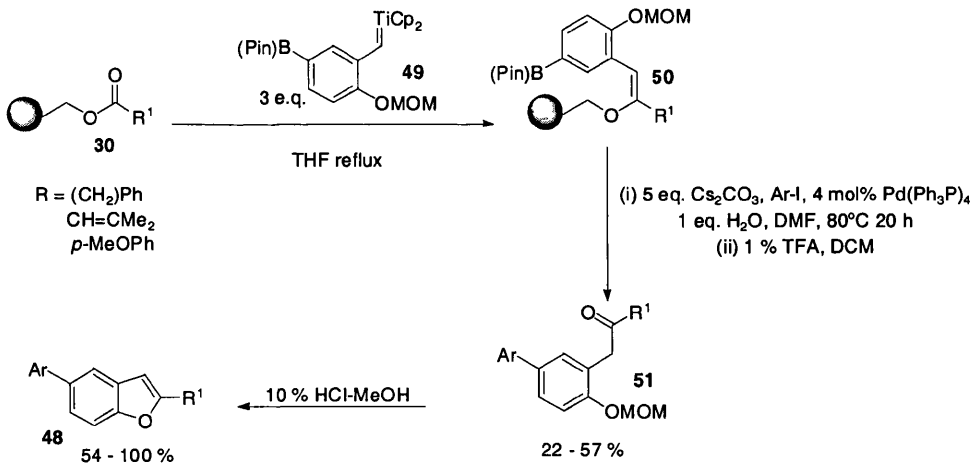


Figure 10.

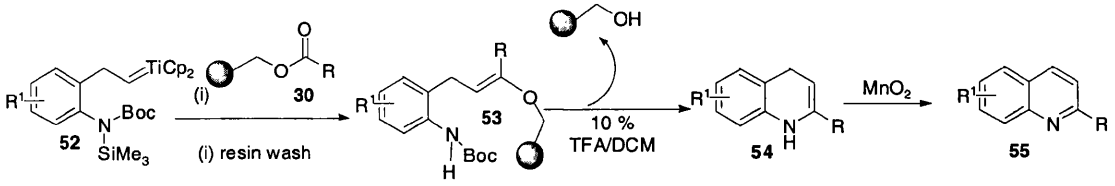
Recent advances in the benzofuran synthesis methodology within the Hartley group have provided a route to resin-bound substrates for Suzuki cross-coupling substrate. The synthesis was the first to incorporate an organoboronate with a Schrock carbene and allowed a greater opportunity for diversity in the synthesis of benzofurans.[33] Alkylidenation of the resin bound esters **30** with a titanium benzylidene **49** bearing a boronate group formed the enol ethers on resin **50**. Cross-coupling on resin, followed by cleavage then gave ketones **51** off resin. Deprotection and cyclisation under acid conditions gave the disubstituted benzofurans **48**, (Scheme 13). No chromatography was necessary at any stage and a range of benzofurans was produced in high purity.



Scheme 13.

Following these successes, the chemistry was extended to the formation of 2-substituted quinolines, an important class of medicinally relevant heterocyclic privileged structures.[34] Unlike the previous heterocycles formed using titanium benzylidenes, the route required the generation of titanium alkylidene **52** that did not benefit from benzylic stabilisation. Reaction with the resin-bound esters **30** gave resin bound enol ethers **53**, as before. These were cleaved under mild acid conditions to give dihydroquinoline derivatives **54**. Post-cleavage modification was required in the form of oxidation to form the quinoline ring

system **55**, (Scheme 14). The method used, however, provided the advantage of solid phase as separation platform, as the oxidant chosen was manganese dioxide, and could simply be filtered off following the mild oxidation reaction.[34]



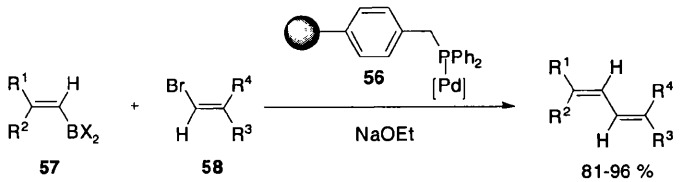
Scheme 14.

It was at this stage I began my research into novel titanium alkylidene reagents that would allow access to other heterocycles. However, before discussing my own research on solid-phase synthesis, I will briefly show that solid supports can be used in other ways to facilitate automated synthesis.

1.4.5 Polymer Supported Reagents

In addition to immobilising and manipulating what eventually becomes the desired product, the solid support methodology has also been extended to immobilisation of reagents and catalysts. This provides the benefits of removing catalysts or spent reagent and the possibility that major by-products can be immobilised onto a polymer support. The advantage of this method of polymer-assisted synthesis is that the products of each individual reaction are not immobilised on resin negating the need for an attachment step and a cleavage step in the synthesis. It has two other main advantages; the product can be purified for the next step, so no accumulation of by-products attached to the resin that could be cleaved with the final product occurs, and the intermediates can be characterised. This prevents a synthesis of many steps finishing with no cleavable product and little way of knowing which step went wrong. However when carrying out high throughput synthesis, purification by mass directed HPLC (high performance liquid chromatography) is generally reserved for the final product.

Another advantage of this methodology is that the reagent or catalyst recovered, where possible, can be recycled/regenerated, giving a greener approach to the chemistry in hand. An example of this would be in the Suzuki coupling, using polymer bound palladium complex **56** to couple organoboranes **57** and alkenyl bromides **58** to form allylic compounds **59**, (Scheme 15).[37,38]



Scheme 15.

There are three main methods for reagent and catalyst immobilisation:[37]

1. Entrapment of the catalyst or reagent within a preformed polymer network.

2. Ion-pairing, ionic bonding between corresponding cationic and anionic sites on the polymer support and reagent.

3. Covalent bonding, in which, the reagent is permanently bound to the polymer support

1.4.6 Scavengers

Another approach is to use solid supported scavengers, reactive species immobilised on resin to react with by-products or products of the reaction selectively and therefore provide a method of isolation by, as before, simple filtration. Below is a brief overview of methods based on this idea detailed in a review by S. Ley and co-workers[39]

1. Reactant sequestration: excess reagent is removed by the selective binding of scavenger resin to it.

2. Scavenging-enabling reagents: reaction of starting materials of low reactivity with an activating reagent, producing a compound of higher reactivity and therefore greater ability to bind to scavenging resin.

3. Tagged reagents: the presence of a functional group in a reactant that will not interfere in the reaction but will allow easy sequestration with a scavenging resin in the reaction work-up.

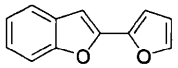
4. Molecular adsorption: addition of a large hydrophobic tag at the end of the synthesis to allow adsorption of the desired compound onto porous graphitised carbon to provide a support for extensive washing.

5. Catch and release purification: Selective binding of the desired product onto solid-phase to allow purification by washing and filtration. Subsequent cleavage from resin must not introduce further impurities.

Before turning to the main work of the thesis, i.e. the synthesis of heterocycles not previously tackled using titanium alkylidene chemistry; I shall first consider two small pieces of work where different uses of isotopic labelling were briefly explored.

1.5 ^{18}O-Labelling Experiments

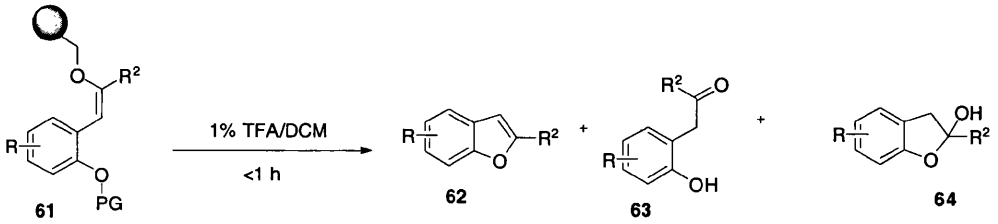
The earlier work by the Hartley group showed that heterocycles, including benzofurans, could be generated from resin-bound esters. I extended this work by synthesising benzofuran **60**, figure 11.



60 26 %

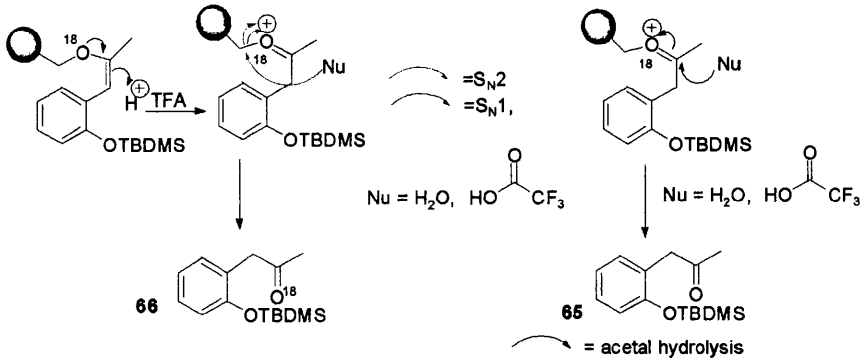
Figure 11.

Considering the cleavage of resin-bound enol ethers **61** to give benzofurans **62**, if cleavage could be made dependant on cyclisation , then only unmasked phenols would cyclise and induce product release. It had been shown that under the standard cleavage conditions, cyclisation occurred post cleavage as ketone **63** and hemiacetal **64** were present in the reaction mixture if exposure to acid was shorter than 1 h,[33] (Scheme 16).



Scheme 16.

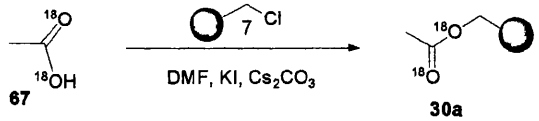
If the ketone had been generated by standard acetal hydrolysis, then cyclative termination might still be possible if water was excluded, but this did not seem to work, so we wished to confirm whether an S_N1 or S_N2 mechanism was competing. Consider the possible mechanism in Scheme 17, if oxygen 18 labelled acetate were used, an unlabelled ketone **65**, would be observed under standard acetal hydrolysis, but either S_N1 or S_N2 would lead to incorporation of an oxygen 18 label into ketone **66**.



Scheme 17.

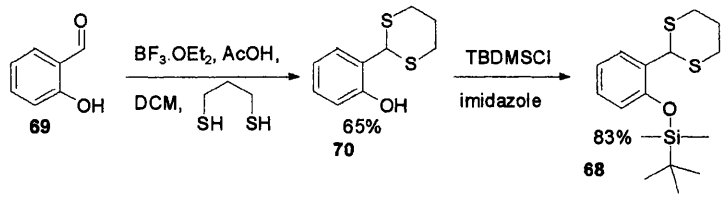
^{18}O labelled acetic acid was employed to determine exactly how the enol ether was cleaved. This is a good label as the mass spectrum must show a clear difference in the fragment peaks containing the label when compared to the unlabelled corresponding fragment. Use of an isotope with 1 a.m.u. more than the prevalent natural atomic mass is not desirable as depending on the results this can be confused with the natural abundance of carbon-13 within the molecule.

The labelled acetic acid **67** was immobilised onto Merrifield resin **7** using standard resin loading techniques, (Scheme 18).



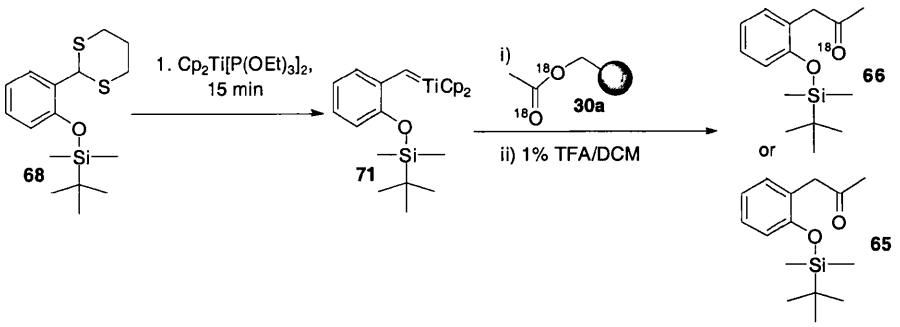
Scheme 18.

The ortho nucleophile of the thioacetal substrate **68** was blocked using TBDMS protection. This prevents the intramolecular attack needed for concomitant cyclisation, however other nucleophiles are present in the form of trifluoroacetate anion to compensate in the study, and this protection also allows a handle for the GCMS analysis and prevents a possible volatility problem. Salicaldehyde **69** was converted into dithiane **70** before protection with TBDMSCl to give the desired thioacetal, (Scheme 19).



Scheme 19.

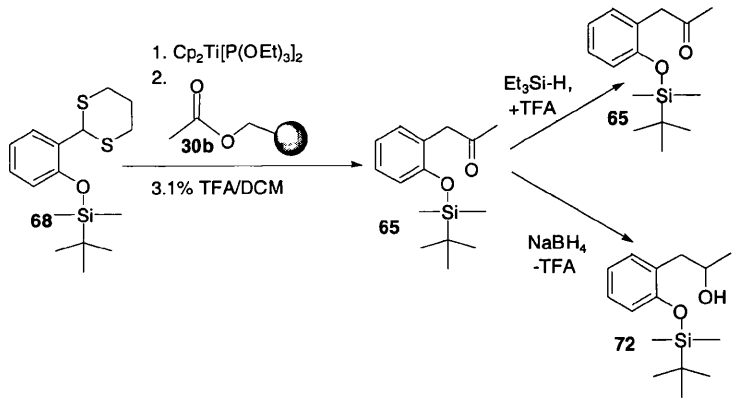
The labelled resin bound ester **30a** was reacted with the titanium alkylidene **71** formed from thioacetal **68** to give the ketone **65** or **66** and, depending on the method of cleavage, the ^{18}O would either be incorporated into the ketone or not, (Scheme 20).



Scheme 20.

Alkylidenation of unlabelled resin bound **30b** ester was carried out. An unlabelled standard was required for the GCMS. Cleavage was followed by a quick and simple reduction of the ketone **65** to the corresponding alcohol **72** so that exchange with atmospheric water did not cause loss of the label producing false results.

Two methods of reduction of the cleavage product, ketone **65**, were tried. Doyle and West reported a reduction of ketones in acidic media using silanes.[40] This was a particularly interesting reduction as it would have led to a one pot reduction and therefore less manipulation of the compound off resin. The reaction was unsuccessful, however, and only ketone **65** was observed. This was disappointing at the time but later investigations into the use of tiethylsilane to reduce a trityl cation produced under similar cleavage conditions, detailed in chapter 6, showed that this result was desirable in the long run. Sodium borohydride on the other hand was successful and enough alcohol **72** was isolated to provide a MS standard, (Scheme 21).



Scheme 21.

Both the ketone **65** and the alcohol **72** were analysed by GCMS in the hope that a fragment could be identified that contained the alcohol and ketone oxygen atoms, necessary to analyse the labelled experiment effectively. Suitable fragments **A** and **B** were produced from each, figure 12.

Figure 12.

The reaction was repeated with labelled rein-bound acetate. Cleavage and the immediate reduction of the product ketone **66** gave alcohol **72** or labelled alcohol **73.** The GCMS trace revealed a 1:4 ratio of 211 peak to 209, this represents a 20% inclusion of ^{18}O in the sample, figure 13.

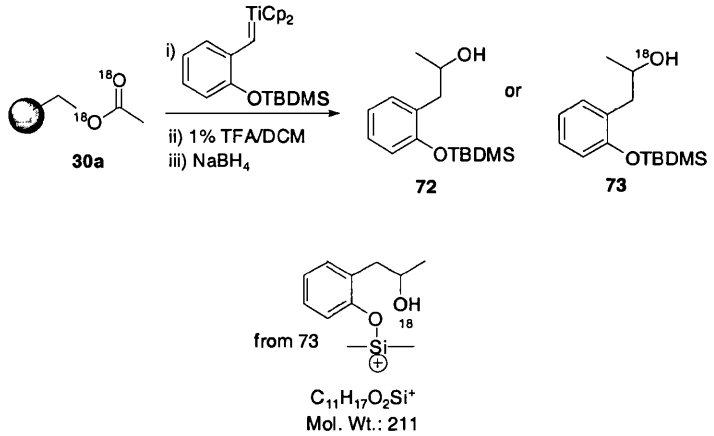


Figure 13.

It is clear therefore that 20% of the reaction does not follow the acetal hydrolysis mechanism and cleavage occurs at the benzylic position of the resin linkage. This mechanism could be either S_N1 or S_N2. The study does not distinguish between these mechanisms and it is possible that the exclusion of all other external nucleophiles, prohibiting S_N2 at the benzylic site could lead to cyclative cleavage. Carrying out cleavage from resin under these conditions however, is not possible giving limited value in distinguishing between the two mechanisms.

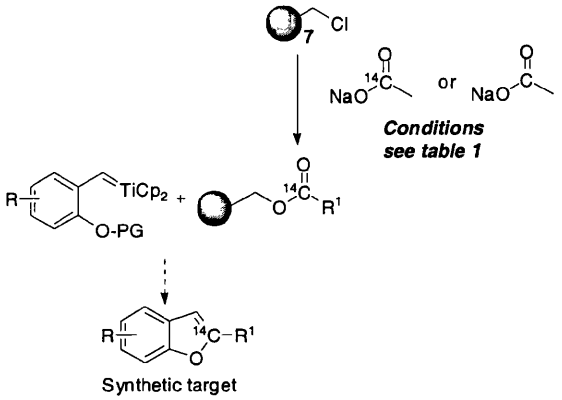
1.6 Radiolabel Immobilisation

In order for scientists to understand what metabolites are produced and where they affect the body, it is necessary to label drug candidates with radioactive isotopes before administering the compounds to test subjects. The choice of label depends on the position of the atom in the compound and on the information required. An example is PET (positron emission tomography) a method using a ^{11}C radioisotope to investigate the biodistribution of labelled materials around the body.[41] Tritium and ^{14}C are also commonly used isotopes, used to discover the structures of metabolites of drugs. Considerations important when designing an isotopic labelling sequence are the position of the isotope i.e. can you label in positions likely to be incorporated into the main pharmacophore of subsequent metabolites, and also the lability of the isotope used. ^{14}C is less labile than tritium but usually requires a more complicated process of incorporation, as carbon atoms are more difficult to introduce to compounds than hydrogen atoms.

In this research a method for loading ^{14}C radiolabelled carboxylate salts onto Merrifield resin was developed. This provides an easily accessible route to ^{14}C labelling in the 2 position of the heterocycles formed using our methodology. The route, in addition to labelling in an integral site of the heterocycle using non-labile ^{14}C, also incorporates the advantages of solid-phase technology.

A major advantage of using radiochemistry in combination with solid-phase technology is the ability to immobilise radioactivity to one site. Handling radioactive solids is far easier than volatile liquids or gases. In addition to this, the purification of solid-supported compounds in combination with the chameleon catch strategy employed with our methodology, should ensure radiochemical and chemical purity upon cleavage.

The salts of low molecular weight carboxylic acids are handled rather than the volatile free carboxylic acids. To avoid liberating the radiolabel under the standard resin loading conditions, using an excess of the free acid and Merrifield resin **7** at elevated temperatures, a modified method of immobilising carboxylate salts onto resin was developed, (Scheme 22, table 1).



Scheme 22.

Initial studies involved phase transfer catalysts and *in situ* conversion of the less reactive chloride on the resin to the more reactive iodide. However these were not successful based on colorimetric tests[42] and IR analysis. Loading was achieved finally by using crown ether sequestration of the sodium from the salt and then reaction of the naked carboxylate anion with chloromethylpolystyrene resin **7**, a procedure not commonly used for ester formation.[43]

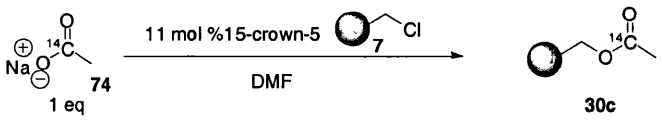
Table 1.

Resin	**Reaction Conditions**	**Result**
Cl Merrifield resin loading : 1.9 mmol/g	NaOAc (2 eq), KI (0.5 eq), DMF, 80°C, O/N	IR: CO stretch, Colour test: Cl +ve
Cl Merrifield resin loading : 1.9 mmol/g	NaOAc (2 eq), TBAI (0.5 eq), DMF, 80°C, O/N	IR: CO stretch, Colour test: Cl +ve
Cl Merrifield resin loading : 1.9 mmol/g	NaOAc (2 eq), 15-Crown-5 ether 4%, KI, DMF, RT, O/N	IR: CO stretch, Colour test: Cl +ve

Cl Merrifield resin loading : 1.9 mmol/g	NaOAc (2 eq), 15-Crown-5 ether 4%, DMF, 80°C, O/N	IR: CO stretch, Colour test: Cl +ve
Cl Merrifield resin loading : 1.9 mmol/g	NaOAc (2 eq), 15-Crown-5 ether 11%, DMF, 80°C, O/N	IR: CO stretch, Colour test: Cl -ve
Cl Merrifield resin loading : 1.9 mmol/g	NaOAc (1.1 eq), 15-Crown-5 ether 11%, DMF, 80°C, O/N	IR: CO stretch, Colour test: Cl +ve

From this it is clear that the conditions, which load the resin completely, are 11 mol% 15-crown-5 ether and the carboxylate salt (NaOAc), and that this is an improvement on the traditional method for loading carboxylic acids which requires 3 eq cesium carbonate, 0.5 eq potassium iodide and 2 eq carboxylic acid. Most importantly the use of a large excess of radioactive acetate can be avoided.

This technique was applied to the loading of ^{14}C -labelled sodium acetate **74** onto Merrifield resin **7**. The radioactivity was monitored and used as an indication of loading. All activity not accounted for in the scintillation samples of the reaction mixture, washings and NaOH traps (attached to catch volatile radioactivity), is presumed to be loaded onto the resin. This measurement is therefore an accurate account of the loading achieved, (Scheme 23).



Scheme 23.

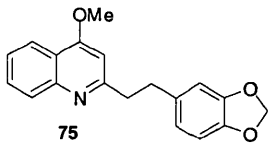
The washings contained 15 MBq of the 145 MBq used, indicating the resin **30c** is 90% loaded. Time constraints (the research was carried out during my industrial placement), prevented the synthesis of labelled heterocycles using this resin, however the clear benefits of immobilising radioactivity on resin makes this research worthwhile.

Chapter 2: Quinolines

2.1 Why Make Quinolines

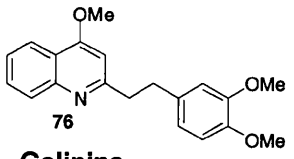
Quinolines are an extremely important core moiety used in medicinal chemistry. The moiety can be seen in drugs that treat everything from malaria to HIV. In addition to the therapeutic effects exhibited by these compounds, there is also a connection with the quinoline core and molluscacidal properties,[44] an application that could be of importance to the pesticide market.

Many of the natural product quinoline compounds isolated have been from the *Galipea* genus, and it is from a plant of this group, *galipea officinalis,* that cusparine and galipine were isolated.[45] Both cusparine **75** and galipine **76** figure 14, showed activity against mycobacterium tuberculosis, a relevant discovery due to the resurgence of this disease and the development of drug resistant strains.[46]



75

Cusparine

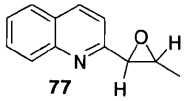


76

Galipine

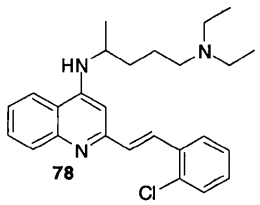
Figure 14.

Galipea longiflora provided a natural product that is a possible anti-leishmanial therapeutic agent, in the form of chimanine D **77**.[47] The compound is active against the fatal visceral form of the disease which is caused by the protozoan flagellate *leishmania.*[48] Another quinoline moiety drug used to treat leishmaniasis is aminoquinol **78**.[49]



77

Chimanine D



78

Aminoquinol

Other medicinal applications of quinoline based drug compounds include, local anaesthetics e.g. Cinchocaine **79**,[50] antifungal agents e.g. 5-Chloro-8-hydroxyquinoline

80,[50] anti-arthritic and anti-inflammatory agents e.g. Timegadine **81**,[50] and immunosuppressant drugs such as Brequinar **82**[50] used in organ transplant operations, figure 16.

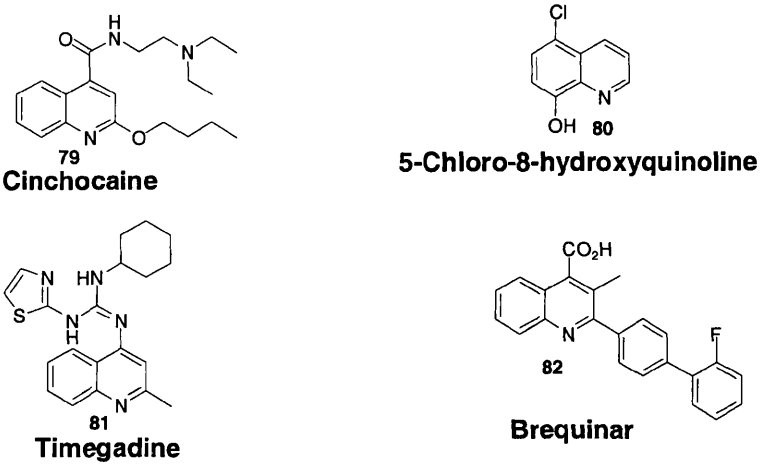


Figure 16.

Quinoline drugs are relied on heavily as the main therapeutic control of malaria.[51] The oldest treatment for malaria, dating back to the 16th century, is quinine **83**, figure 17 and contains the quinoline structure.[52,53] It is the basis for a wide range of anti-malarial drugs. Quinine is a natural product isolated from cinchona bark from *Cinchona officinalis* but has been isolated from most other *cinchona* species as well as a few other sources. It is used in tonic and bitter drinks, and its activity is stereochemistry independent. Quinine is effective against the *plasmodium falciparum* parasite, the most deadly form of malaria. The drug is important in the treatment of the disease as many of the more recent and widely used anti-malarial drugs on the market are now less effective due to the development of drug resistant strains.[54] Attempts to eradicate malaria with the wide spread use of chloroquine **84**, figure 17, described later, after the second world war and the use of pestisides and land drainage were unsuccessful. The subsequent chloroquine-resistant strains of malaria however, had not received prolonged exposure to quinine, as throughout history there had been complications with the widespread use and isolation of the drug. As a result drug resistance to quinine itself has been slow to develop.[54]

Figure 17.

Chloroquine **84** is an anti-malarial of some importance. As with quinine, the stereochemistry has little effect on the compounds biological activity. The development of drug-resistance in malaria has been a problem with this drug, due to its irresponsible use. The drug was incorporated in table salt in Brazil in an attempt to wipe out malaria, however this led to the emergence of chloroquine resistant strains of the parasite shortly after these measures were introduced. [54]

The therapeutic agent has been used to treat discoid lupus erythematosus and rheumatoid arthritis, due to is analgesic properties. Chloroquine is also useful in the treatment of HIV-1. The drug has an anti-retroviral effect by interfering with post-transcriptional production of the virus in the cell.[55] As well as the anti-retroviral effect, it has the advantage of decreasing the success of AIDS opportunistic pathogens. In addition to this the drug is socially more acceptable than other HIV-1 alone therapies, having a beneficial effect on patient compliance. It is cheap, and can convey the possibility of reducing the transfer of the virus from mother to child through breast-feeding. This is of great importance when the majority of HIV infections occur in sub Saharan Africa, where patients have little money to fight the infection, and an estimated 200000 new infections a year are caused by mother-child breast feeding.[56]

The wide range of therapies quinoline-based compounds provide demonstrate the ability of this core moiety to effect responses at many different biological targets. While it is clear the quinoline structure effects therapeutic action in many examples, the mechanism of action of the agent is unknown in many cases. The most accepted explanation of the anti-malarial effect of these compounds is that they interfere with heme detoxification in red blood cells, and that this has a range of knock on effects, mainly increasing the oxidative stress on the parasite. Other research[57] into the selectivity and selection of proteins that the quinoline based drugs affect has highlighted two enzyme targets the drugs interact with. The research was based on screening the quinoline drugs against the purine binding proteome of whole homogenized mouse, red blood cells, and red blood cells infected with *Plasmodium falciparum.*

The rationale behind this was that due to the similarity of structure between quinoline compounds and purine-based nucleotides, quinolines may be binding to proteins that would normally bind to purine nucleotide compounds. The two target proteins were identified as being human aldehyde dehydrogenase 1 and quinone reductase 2. These were identified as the targets of quinoline drugs from the red blood cells and red blood cells infected with *P. falciparum.* Interestingly, the targets are both within the human genome

and not the parasites. The aldehyde dehydrogenase 1 was shown to be only weakly inhibited by chloroquine, and it was postulated that this enzyme's inhibition may actually be responsible for some of the drugs side effects more than the anti-malarial effect.[57]

On the other hand the mechanism of action can be explained by the inhibition of the quinone reductase 2. Quinone reductase 2 is responsible for the metabolic detoxification of quinones, that are found in all respiring plant and animal cells and are potentially toxic compounds. The presence of increased levels of quinones puts the cell under higher oxidative stress, and the parasite is subjected to conditions it cannot withstand.[57]

It is unlikely that the other therapeutic effects of drugs like chloroquine (HIV therapy, discoid lupus and arthritis treatment) can be explained by the inhibition of quinone reductase 2 alone. The breadth of therapeutic targets means that the quinoline core is considered to be a privileged structure and therefore it is desirable to incorporate it into libraries for lead discoveries.

Most quinoline drugs and natural products are substituted in the 2 and 4 position of the quinoline ring. Methodology previously developed within the Hartley group provided a route to the traceless diversity orientated synthesis of 2-substituted quinoline structures on solid-phase. Initially I undertook to develop a route for the solid-phase synthesis of 2,4-disubstituted quinolines.

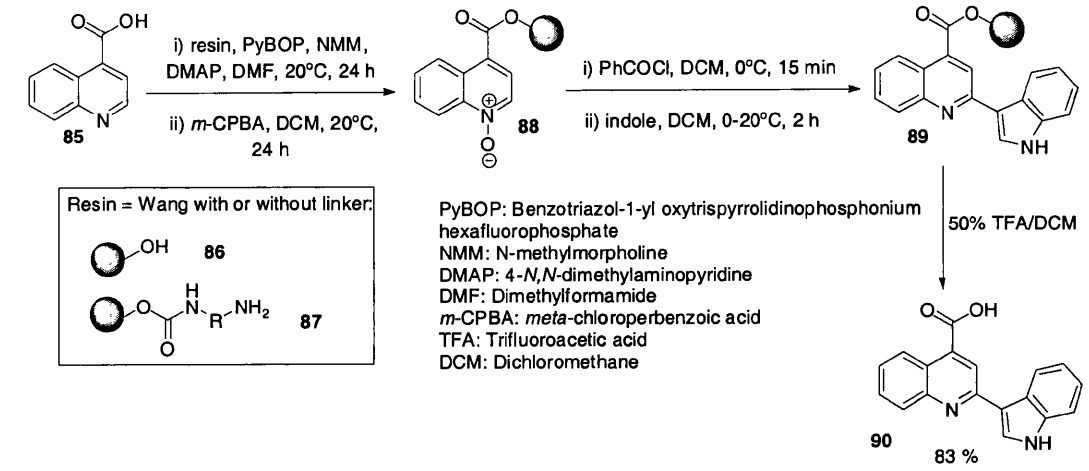
2.2 Previous Solid-Phase Syntheses of Quinolines

2.2.1 Decoration of Quinoline Structure on Solid-Phase

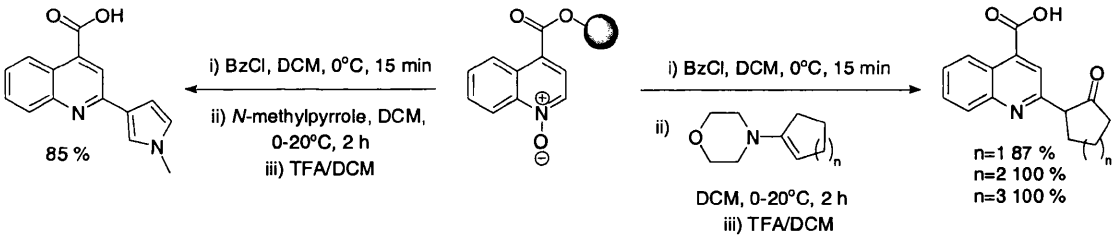
Methods exist both for the construction of quinolines on solid-phase and the decoration of the structure by immobilising the pre-constructed quinoline core. This section will deal with the embellishment of the structure on solid-phase.

2,4-disubstituted quinolines have been synthesised[58] on solid-phase by the immobilisation of quinoline-4-carboxylic acid **85** onto Wang resin[19] either directly *via* coupling to the hydroxyl group of the resin **86** or through a diamine linker **87**,[58] (Scheme 24). The immobilised quinoline core was then oxidised to the N-oxide **88** using *m*-CPBA and activated by acylation with benzoyl chloride. Nucleophilic attack at C-2 then gave a range of resin bound products including indole **89**. Following this the quinolines were cleaved

from resin using trifluoroacetic acid in DCM. A variety of substituted pyrroles and enamines were also used as nucleophiles, (Scheme 25).[58]

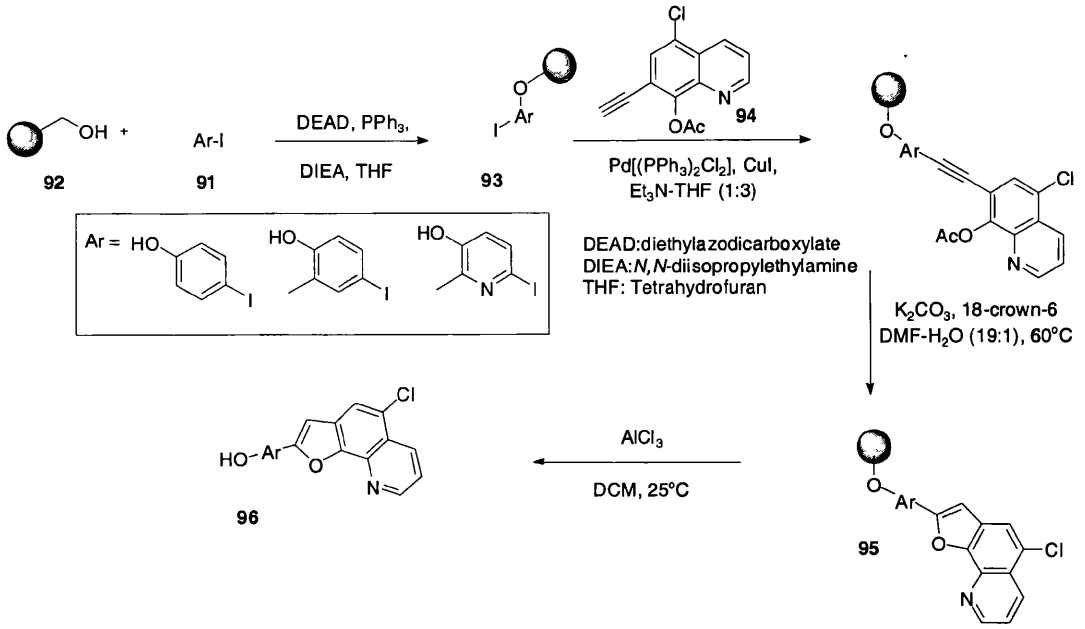


Scheme 24.



Scheme 25.

Other examples of immobilised quinolines include a quinoline moiety added to solid-phase *via* an alkyne group in a Sonogashira coupling, to furnish a substrate suitable for furan formation,[59] (Scheme 26). The starting aryl iodide **91** was immobilised by reaction with Merrifield hydroxymethyl polystyrene resin **92** using standard Mitsunobu conditions. Sonogashira coupling was then carried out between the resin-bound aryl iodide **93** and the quinoline moiety bearing an alkyne and an acetate group to protect the phenol functionality, **94**. Following coupling, deprotection and cyclisation was carried out using potassium carbonate and 18-crown-6, forming the furan ring **95**. Cleavage from resin was then achieved under Lewis acid conditions to reveal the tricyclic heterocycle **96**.

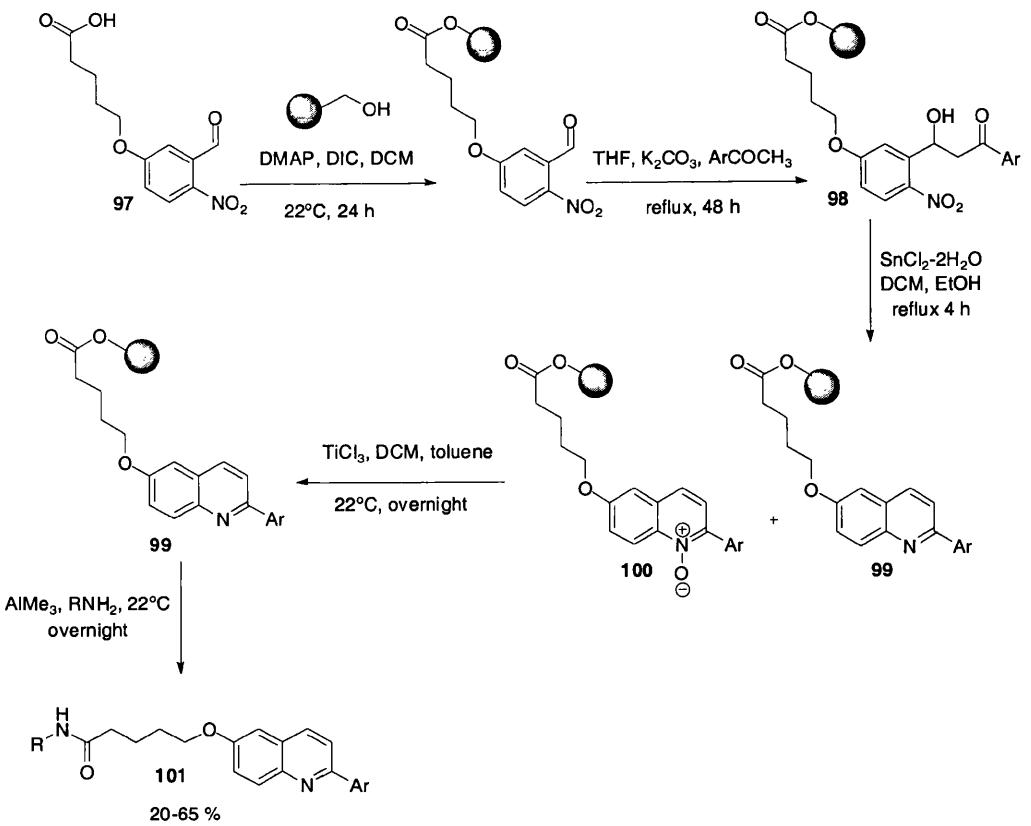


Scheme 26.

Another example is attachment of quinoline structures to oligonucleotides for the enhancement of the oligonucleotide's binding affinity. The object of this research was to develop oligonucleotides with quinoline appendages that would bind transiently to a complimentary strand of RNA from a target host.[60]

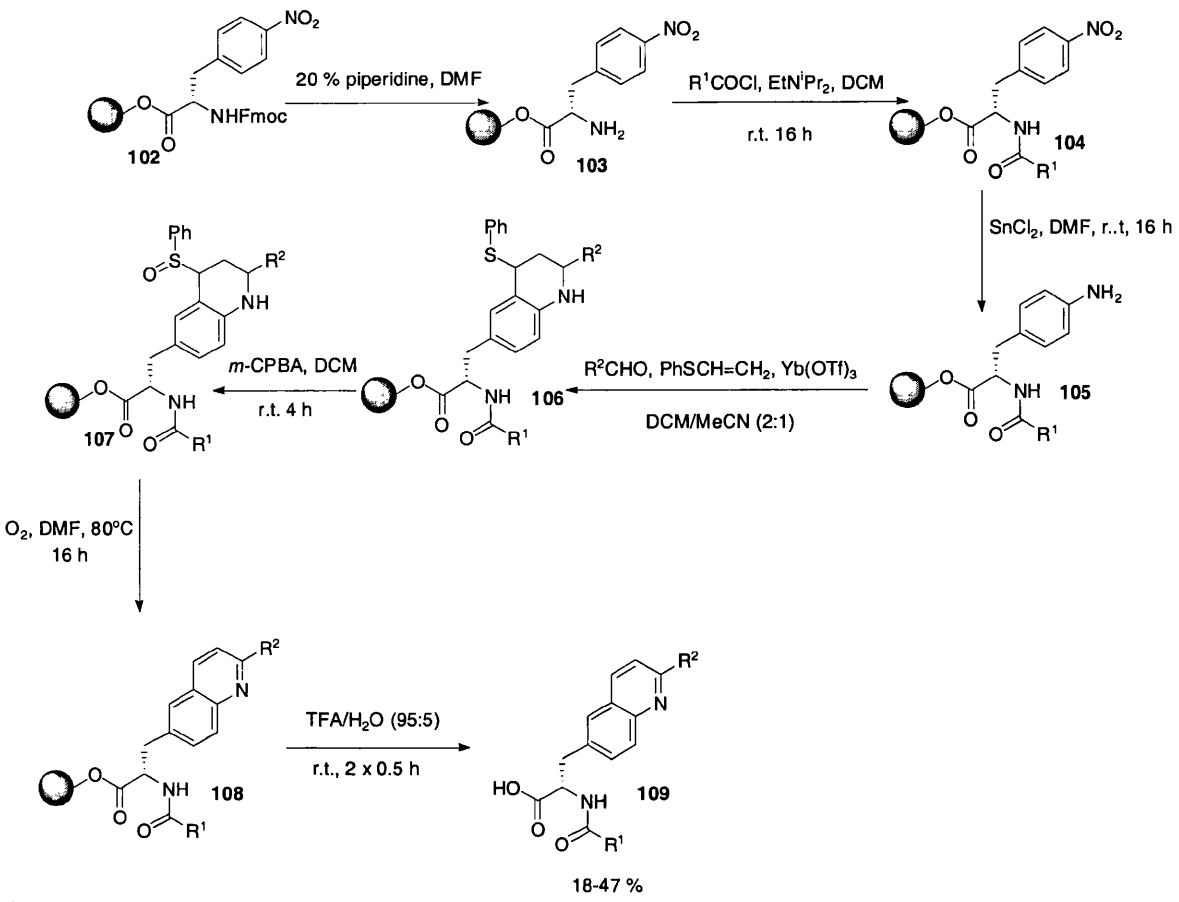
2.2.2 Synthesis of Quinoline Core on Solid-Phase

The development of syntheses for the formation of quinoline cores on solid-phase has been a recent addition to combinatorial chemistry. A route was developed using hydroxyethyl polystyrene resin as a solid support, (Scheme 27). A nitrophenol derivative **97** was attached *via* coupling conditions to resin. Aldol reaction using a range of aryl methyl ketones was carried out to form the β–hydroxy ketones **98**. This was followed by a tin(II) chloride mediated reductive cyclisation to form both the quinoline products **99** and the corresponding *N*-oxides **100**. The *N*-oxide products were converted to the quinolines **23** by reduction with titanium(III) chloride. Lewis acid mediated amide formation could be carried out with a variety of amines and cleaved the compounds from resin providing the quinolines **25**. Using this methodology there are two opportunities to introduce diversity into the molecule, through the ketone and primary amine components, but the synthesis is not traceless as there is always amide functionality left at the site of attachment.[61]



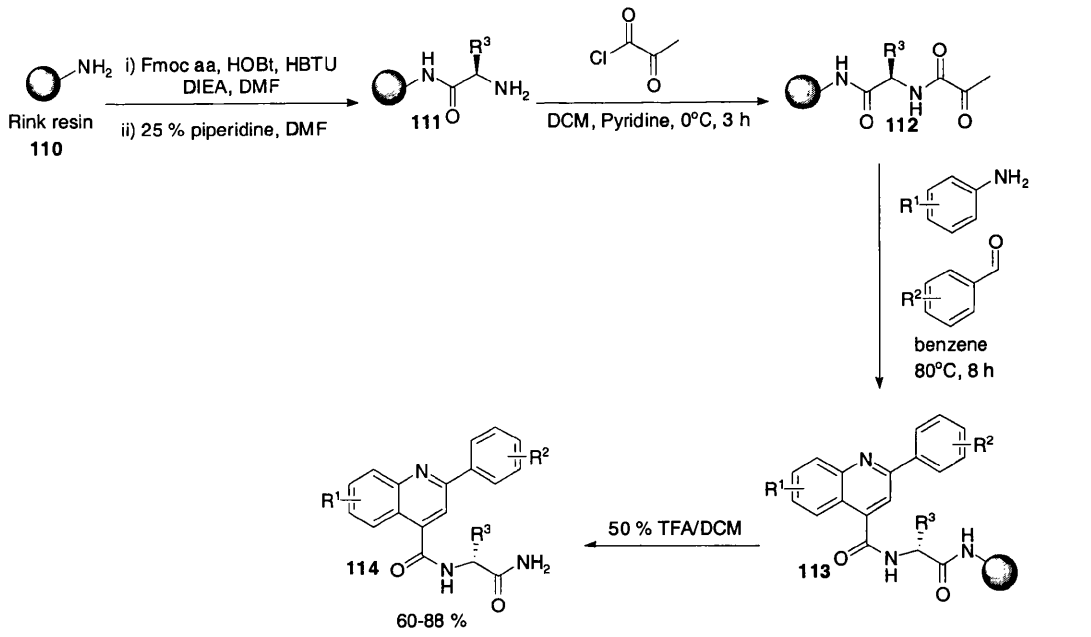
Scheme 27.

The simplest and most often used methodologies for quinoline synthesis on solid-phase are those adapted from their solution phase counterparts. The multicomponent reaction developed by Grieco and Bahsas[62] produced heterocycles using immonium salts as dienophiles and Diels-Alder conditions. This was extended by Kobayashi[63] to allow imines as dienophiles using lanthanide Lewis acids as catalysts, and has been developed and optimised for the solid-phase synthesis of quinolines,[64] (Scheme 28). The synthesis begins with a resin bound (*S*)-4-nitrophenylaniline. The immobilisation of this Fmoc protected compound **102** onto resin is followed by deprotection and acylation of the amine **103** to form the amide **104**. Reduction of the nitro group with tin chloride gave the aniline **105** which was used in the multicomponent reaction to yield resin bound tetrahydroquinolines **106**. The oxidation of the thioether was effected using m-CPBA to give the sulfoxide **107** and pyrolysis transformed the tetrahydroquinolines **107** into the resin-bound quinolines **40**. Cleavage from resin was achieved using TFA/water to yield quinolines **109**, with the opportunity to introduce diversity at the 2 position of the quinoline ring and the amide functionality present. The synthesis is not traceless however, as a carboxylic acid group is always left at the site of attachment to resin.[64]



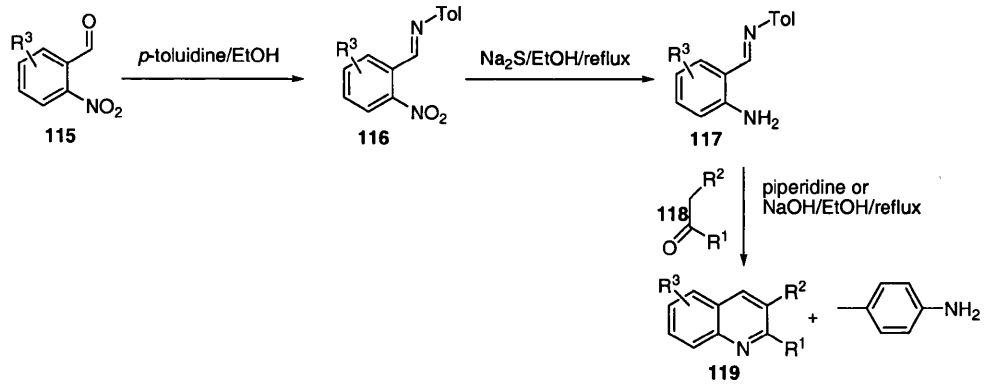
Scheme 28.

Another example of a solution phase synthesis, again based on the multicomponent approach, adapted for solid-phase, is the adaptation[65] of the Doebner quinoline synthesis.[66] The synthesis was achieved using Rink resin[67] **110** and immobilisation of an Fmoc-protected amino acids, followed by deprotection to give amine **111**, (Scheme 29). Acylation of the amino group with pyruvyl chloride gave tricarbonyl compounds **112** for the multicomponent reaction. The resin bound quinoline product **113** was then cleaved using TFA to give the final amides **114**. As all products contained the amide group at the site of cleavage, so this is not a traceless synthesis.[65]



Scheme 29.

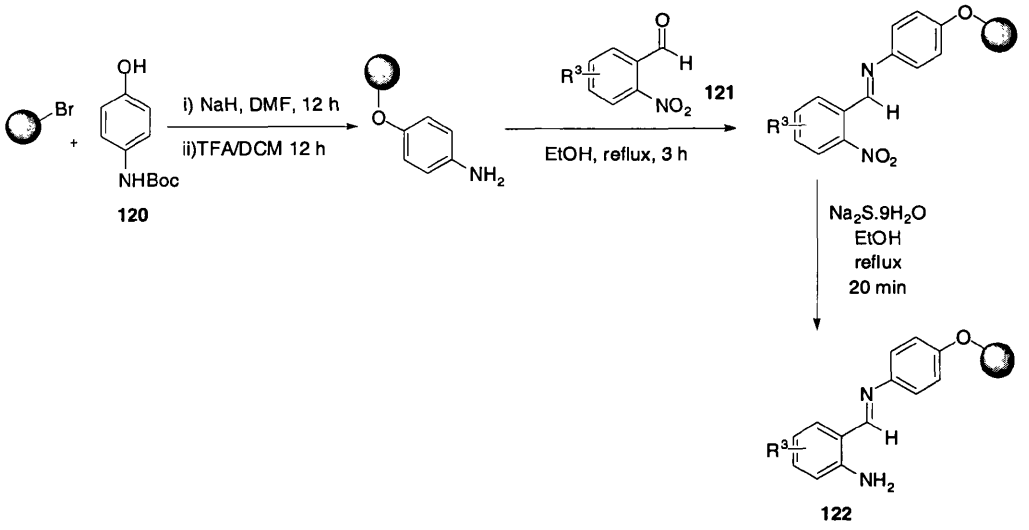
The most impressive synthesis of quinolines on solid-phase is also adapted from a solution phase route, the Borsche modification[68,69] of the Friedländer synthesis, (Scheme 30). In the Borsche modification the problem of self condensation of aniline bearing *ortho*-benzaldehydes **115** associated with the Friedländer synthesis[70] was avoided by converting the aldehyde functionality into an imine **116** by reacting with *p*-toluidine prior to generating the aniline functionality. Condensation of anilines **117** with the ketones **118** then produced quinolines **119**.



Scheme 30.

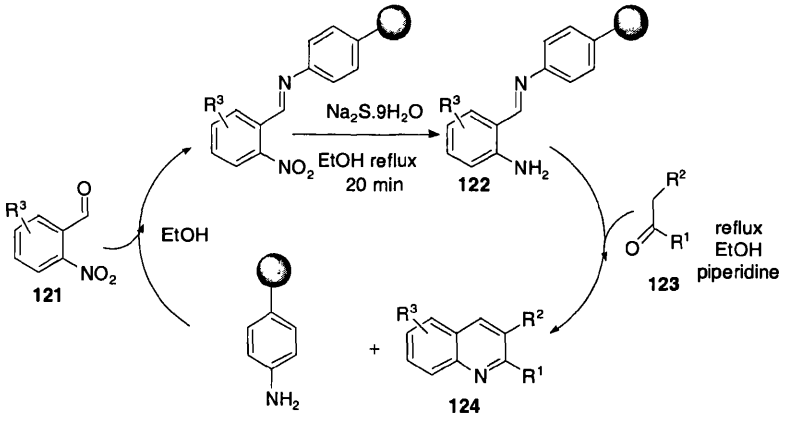
In the adaptation to solid-phase,[71] attachment to resin was carried out *via* the *p*-toluidine functionality and the resin used was TentaGel-Br, due to the compatibility of TentaGel and ethanol, the solvent used in quinoline formation. The toluidine was prepared by O-alkylation of Boc protected aminophenol **120**, followed by removal of the Boc group,

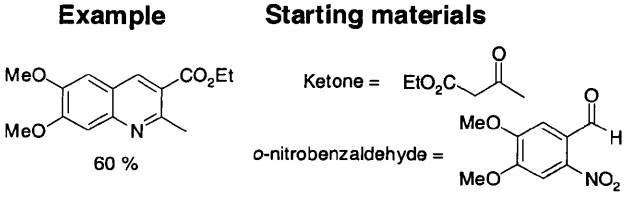
(Scheme 31). Condensation with *ortho*-nitrobenzaldehyde **121** was followed by the reduction of the nitro group to the aniline **122** using sodium sulfide in water and ethanol.



Scheme 31.

The reaction of the resin-bound aniline **122** with a range of ketones **123** gave a variety of substituted quinolines **124** and regenerated the toluidine resin to start the cycle again, (Scheme 32). [71]





Scheme 32.

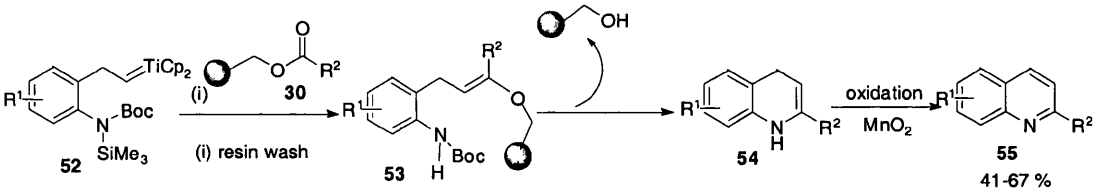
As can be seen from above, the previous synthesis of quinolines differ little from their solution phase routes. The methodology developed within the Hartley group however,

provides a solid-phase route to quinolines that is novel and unique.[34] A downside of the solid-phase Friedländer synthesis is that the products require post cleavage purification. This problem has been avoided in the Hartley groups methodology, and, as well as being considered a traceless synthesis, the route utilises one of the cheapest resins available, Merrifield's chloromethyl polystyrene resin.

2.3 Solid-phase Route to Quinolines

2.3.1 Route to 2-Substituted Quinolines

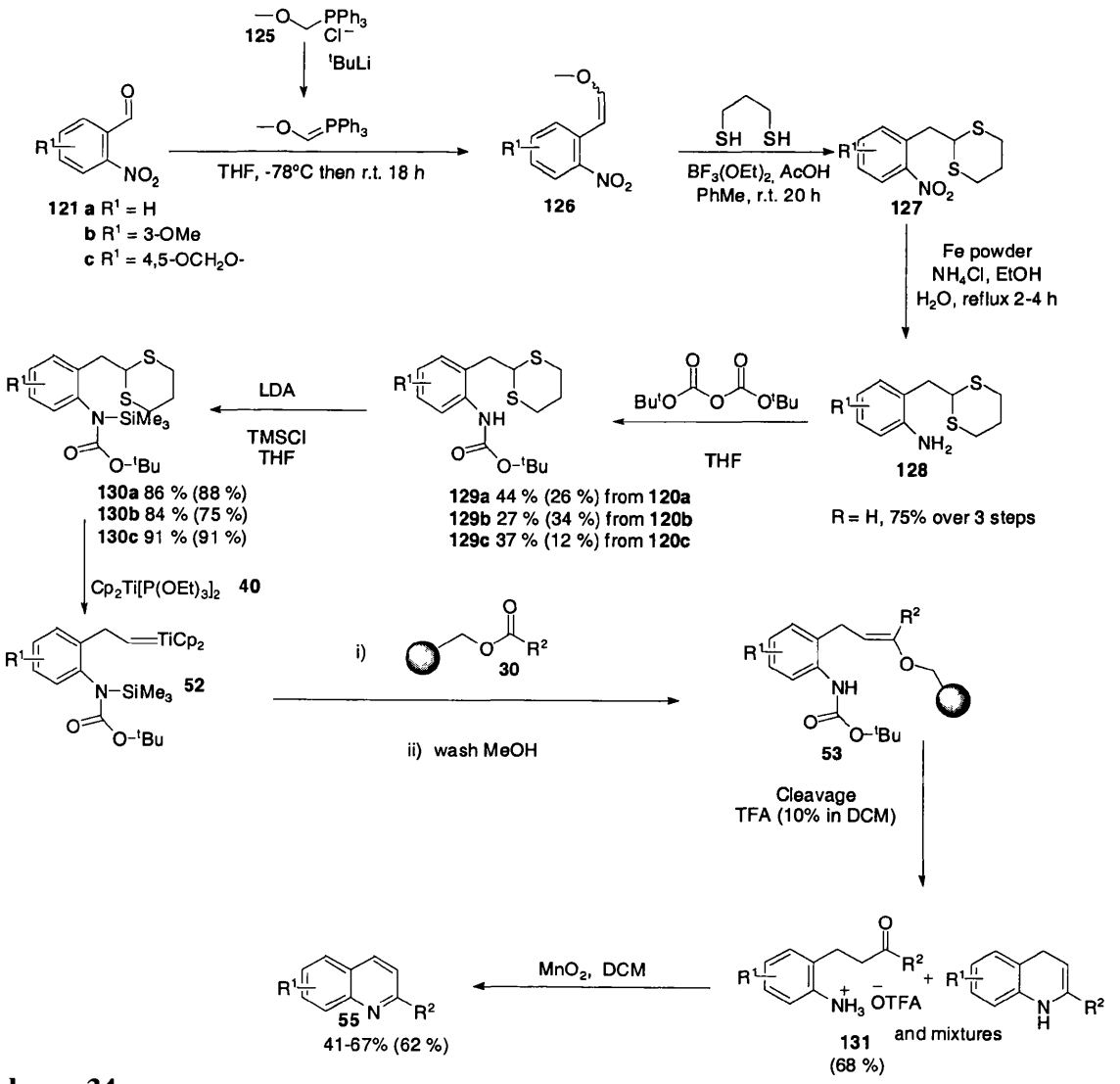
Previously quinolines had been synthesised by Calum Macleod and myself (as an undergraduate) using novel titanium alkylidenes **52** to react with resin-bound esters **30** to produce resin-bound enol ethers **53**.[34] This switch in the nature of the linker follows chameleon catch methodology and allows selective cleavage of only the reacted sites on the resin, preventing the need for further purification. The enol ether **53** is cleaved under mild acid conditions and the dihydroquinoline produced **54** was oxidised with the solid reagent manganese dioxide, preventing the need for elaborate purification as the oxidant is filtered off during work up, giving quinolines **55**, (Scheme 33).



Scheme 33.

The synthesis of the substrate for alkylidene formation was carried out using simple *ortho*-nitrobenzaldehyde starting materials **121**. The 2-nitrobenzaldehydes **121** were alkylidenated using the Wittig reaction with methoxymethyl-triphenylphosphine **125**. The resultant enol ethers **126** were a mixture of *cis* and *trans* isomers. Cleavage of the enol ethers with acid and the formation of the thioacetals **127** *in situ* was carried out in one procedure using acetic acid and boron trifluoride as activators / catalysts. Reduction of the nitro group yielded anilines **128**. Protection of the anilines with di-*tert*-butyl dicarbonate gave carbamates **129** after purification by re-crystallisation using isopropanol. Silyl carbamate **130** was formed by deprotonation of the carbamate in the presence of chlorotrimethylsilane. This was then used directly in the Takeda reaction following preparation of the low valent titanium(II) reagent, $Cp_2Ti[P(OEt_3)]_2$ **40** by reduction of titanocene dichloride with magnesium in the presence of triethyl phosphite and molecular

sieves. Reaction of the low valent titanium complex **40** with the thioacetal functionality of silyl carbamates **130** formed the alkylidenating reagents presumed to be titanium alkylidenes **52**. These were transferred into flasks, each containing a kan of Merrifield resin-bound ester **30**. Alkylidenation of the ester carbonyl group occurred overnight. The solution was then decanted and the resin-bound enol ether **53** was then washed thoroughly, dried and cleaved using 10% TFA in DCM for 1 h. Following cleavage the products were a mixture of the TFA salt **131**, dihydroquinoline **54** and possibly quinoline, though the NMR spectra were inconclusive. The yield at this point is a good indication of how well the alkylidenation worked. Oxidation was then carried out using manganese dioxide in DCM at reflux for 2 h to yield quinolines **55**. Scheme 34 shows the yields obtained by Calum Macleod and my own yields (in parenthesis), obtained in the work I carried out towards expanding the library.



Scheme 34.

A variety of quinolines were prepared using the above route and are detailed below, figure 18.[34]

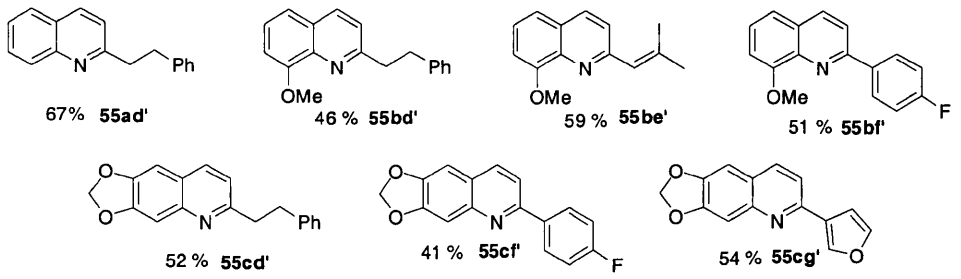
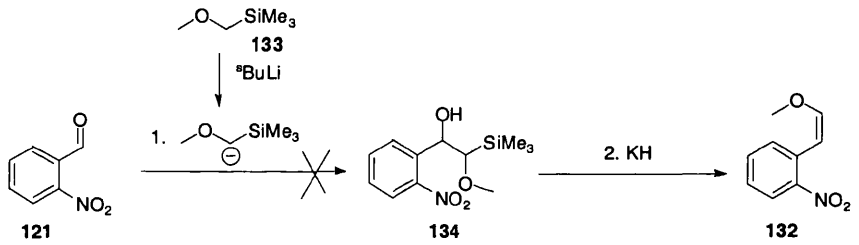


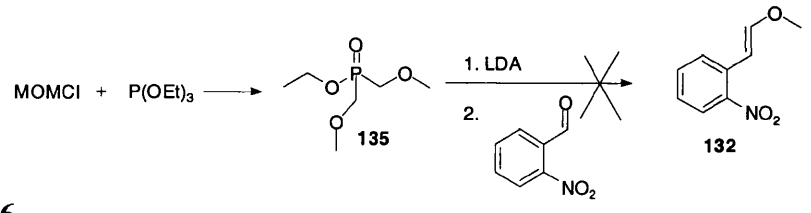
Figure 18.

As a postgraduate I initially repeated the synthesis of thioacetal **129a** in 26% overall yield. An improvement to the synthesis was sought to avoid the triphenylphosphine and triphenyl phosphine oxide by-products introduced in the first step by the Wittig reaction to form enol ether **132**. Two solutions were postulated to reduce the by-products. The first was a Peterson alkylidenation,[72] using lithiated methoxymethyl-trimethylsilane **133** and 2-nitrobenzaldehyde **121** (Scheme 35). However, the α-silylated adduct **134** failed to form.



Scheme 35.

Following this result the focus moved to producing easily removable, water-soluble by-products, and the formation of a phosphonate ester **135** was attempted using methoxymethyl chloride and triethylphosphite, (Scheme 16).[73]

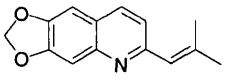


Scheme 16.

The Michaelis-Arbuzov[74] to form the phosphonate ester **135** was successful using an excess of MOMCl to triethyl phosphite, but reaction conditions could not be found which promoted formation of enol ether **132**. Had the reaction worked, the Horner-Wadsworth-

Emmons type reagent would have been ideal as the by-product would be easily removed during the work-up due to its water solubility.

I have extended the range of quinoline products by preparing quinoline **55ce'** in good yield from the resin-bound ester **30e**, figure 19.



62 % **55ce'**

Figure 19.

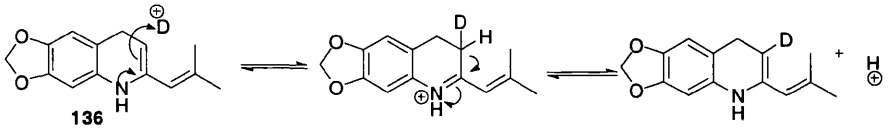
An interesting observation was that deuterium was incorporated into quinoline **55** to give 3-deuteroquinoline **D-55ce'**, on one occasion. This was clear from the integration of the doublet signal at 7.18 ppm in the ¹HNMR spectrum corresponding to H-3, and the presence of a small singlet at 7.87 ppm corresponding to H-4 of the deutero compound when the spectrum is taken in $CDCl_3$, figure 20.

D-55ce'

Figure 20.

Shaking the compound with DCl/D_2O failed to force the exchange to completion. The exchange had taken place when a ¹HNMR spectrum had been taken in CD_3OD prior to oxidation and repeating the synthesis without this intervention gave unlabelled quinoline.

Presumably enamines **136** had been deuterated by the mechanism shown in (Scheme 37).



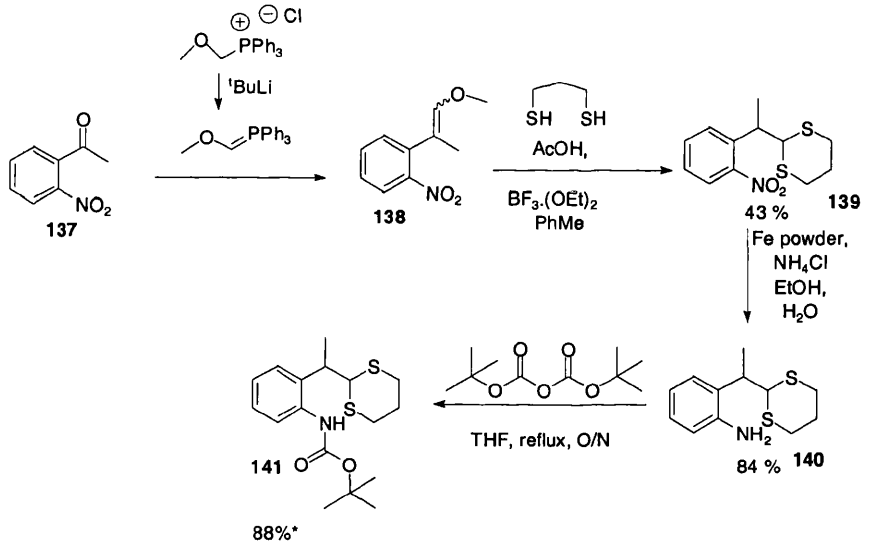
136

Scheme 37.

Quinoline **55ce'** was very insoluble in most deuterated solvents and the ¹HNMR and ^{13}CNMR spectra for characterisation were obtained in deuterobenzene.

2.3.2 Route to 2,4-Disubstituted Quinolines

The 2-substituted quinolines had been successfully prepared using the above route (Scheme 34). I then set out to investigate a variation of the route to permit the synthesis of 2,4 disubstituted quinolines. The new route started from 2-nitroacetophenone **137**, and used the same procedures to give aniline **140**, (Scheme 38). Purification was required after the thioacetal formation, as telescoping the reaction through to the *N*-Boc compound **141** yielded no desired product. Chromatography was necessary as there are large amounts of triphenylphosphine and triphenylphosphine oxide residues present from the Wittig reaction. Reduction of the nitro group went cleanly, with no need for further purification, and in good yield. Problems arose with the route after the Boc protection to form product **141**. The NMR spectra were complicated due to the presence of rotamers of the Boc group and diastereotopicity as a result of the chiral centre.



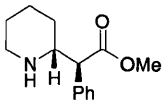
Scheme 38.

Attempts to remove impurities proved tedious and unsatisfactory and so the project was set aside in favour of new chemistry. At this time another member of the Hartley group, Mairi Gibson was undertaking research into the stereoselective synthesis of 2-substituted piperidines on solid-phase. Development of a route to produce 2,6-disubstituted piperidines offered an opportunity to expand the methodology and chemical knowledge.

Chapter 3: Piperidines

3.1 Why Synthesize Piperidines?

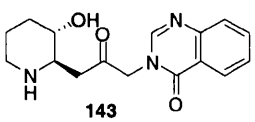
Piperidines are medicinally important privileged structures,[75] found within nature in abundance. In addition to being a widely used reagent in organic synthesis, piperidine itself is used in setting epoxy resins and in forming rubber as well as being the core structural moiety in wide range of pharmaceutical drugs. Drugs containing the piperidine ring include one of the most important and widely used analgesics, morphine, as well as Ritalin **142**, figure 21, a drug used in the treatment of attention deficiency/hyperactivity disorder (ADHD).[76]



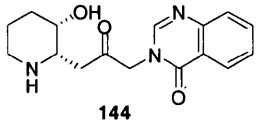
142

Figure 21.

An example of an isolated piperidine natural product is (+)-febrifugine **143**. This chiral piperidine compound is a potent antimalarial compound, the activity of which is similar to chloroquine, discussed earlier.[77]



143



144

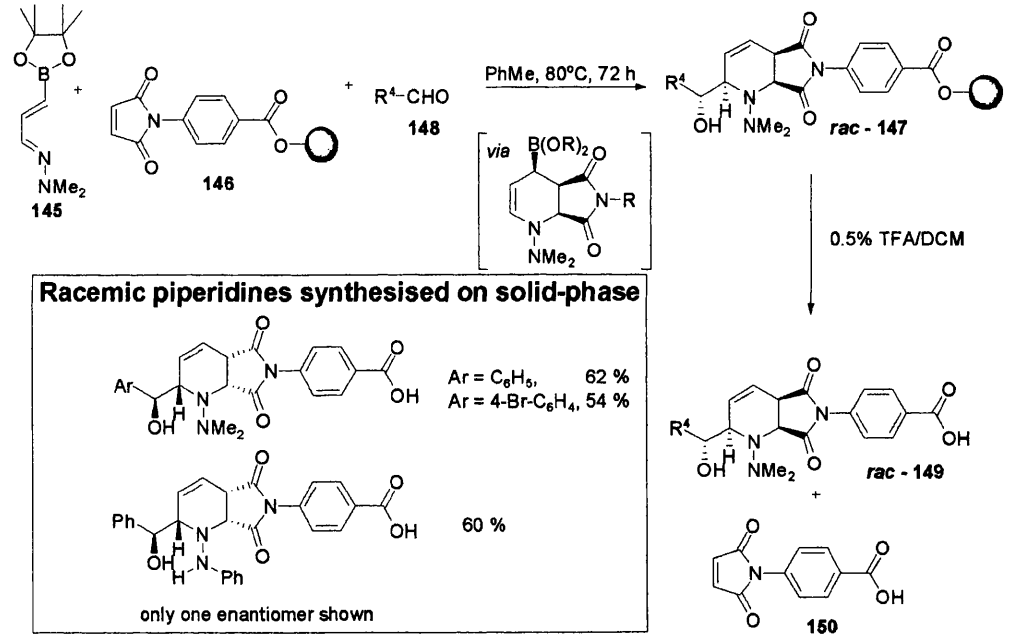
Figure 22.

Its racemate and the diastereomer, (+)-isofebrifugine **144**, show far less activity than (+)-febrifugine, illustrating the importance of enantiopurity, figure 22.

3.2 Previous Solid-Phase Routes to Piperidines

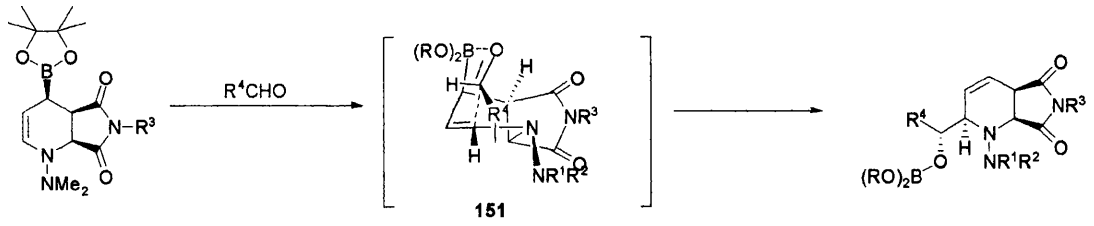
Research into the asymmetric synthesis of piperidines, has been extensive and is well reviewed.[78,79] Syntheses that employ the benefits of solid-phase and combinatorial technologies, however, have not been widely investigated. There are few examples of piperidines constructed on solid-phase and only one reported asymmetric route.[80] Research into the diversity oriented synthesis of piperidines has been carried out using a multicomponent reaction and solid phase technology to access a range of bicyclic piperidine derivatives. A hetero-[4+2]cycloaddition between 1-aza-4-borono-1,3-

butadiene **145** and resin-bound maleimide dienophile **146** produced solely the *endo*-products **147**, (scheme 39, only one enantiomer is shown though both are present throughout). In one pot, the multicomponent reaction sequence was continued with the allylboration reaction using aldehydes **148** as a source of diversity and the means of constructing the α-hydroxy functionality in alcohol **147**. The presence of the aldehyde during the [4+2] cycloaddition did not interfere the reaction. The α-hydroxy functionality is desirable as it is a motif present in biologically interesting alkaloids. Cleavage from resin using mild TFA/DCM conditions gave piperidine-like products **149**. One downside of this reaction sequence is that if the reaction is incomplete, the cleavage step will release the resin bound maleimide starting material, contaminating the product **150**.[75] Furthermore the sequence is not traceless as all products contain a carboxylic acid moiety.



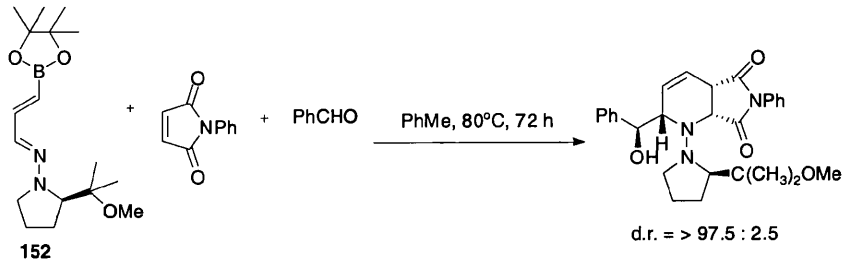
Scheme 39.

The selectivity of the allylboration, leading to only one stereoisomer, can be explained using the cyclic chair transition state **151**, and the formation of only the *endo* cycloadduct in the previous step, (Scheme 40).



Scheme 40.

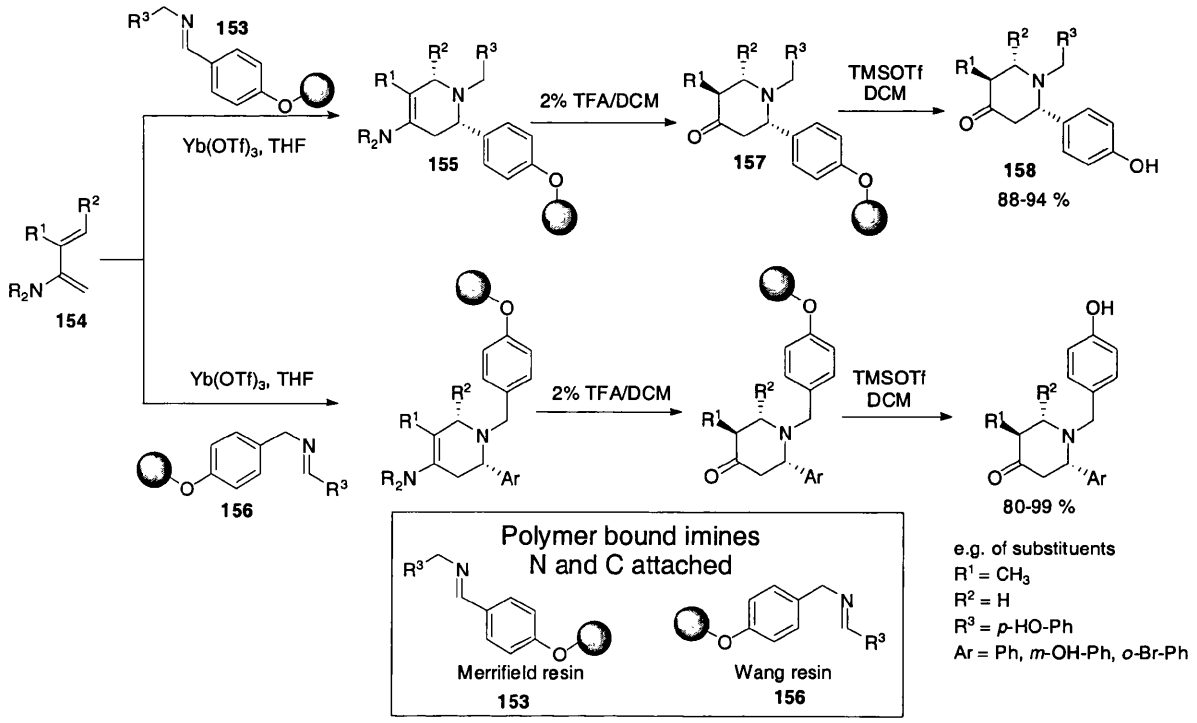
The reaction can be made asymmetric using a proline derived auxiliary **152** to selectively block one face, but this has not been applied to solid-phase, (Scheme 41).



152

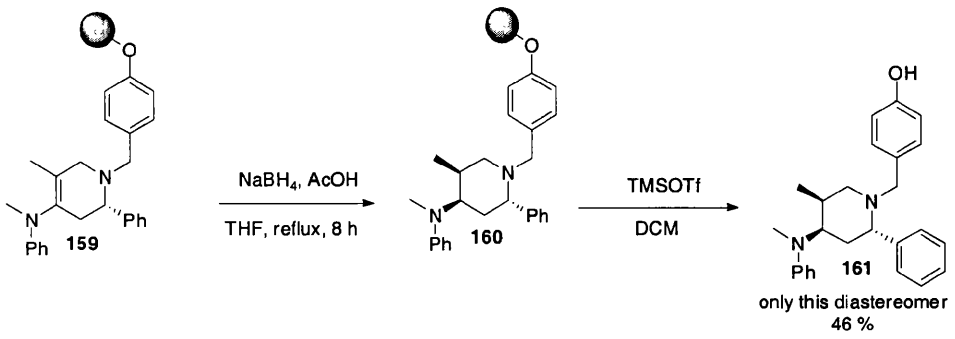
Scheme 41.

Other examples that exist of solid-phase synthesis of piperidines include the formation of polysubstituted piperidines again by Diels-Alder reaction but this time using a heterodienophile in the form of a benzylideneamine **153**, (Scheme 42). This imino-Diels-Alder cycloaddition of 2-amino-1,3-butadienes **154** forms resin-bound enamines **155** on solid phase using Wang resin-bound imines **156**, attached *via* the nitrogen or carbon atom, and a Lewis acid in the form of ytterbium triflate. Hydrolysis of the enamines to from the piperidinones **157** is followed by cleavage from resin to form piperidinones **158** with good diastereoselectivity. Again the sequence is not traceless with all the products containing a phenol. Reaction with resin bound imine **156** gives a different substitution pattern but the reaction is still not traceless.



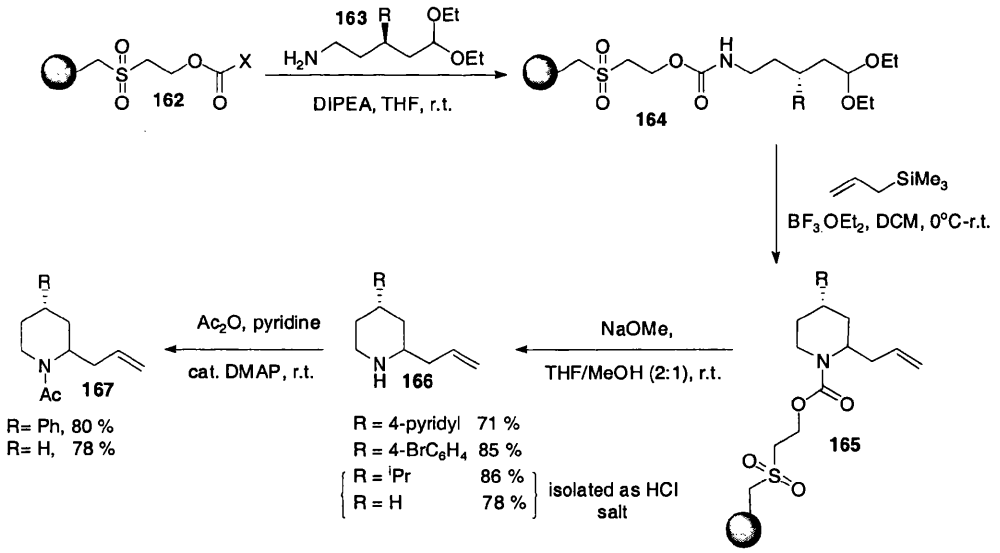
Scheme 42.

Reduction of the enamine moiety **159** could be carried out on resin to furnish piperidines **160** with total diastereoselectivity, (Scheme 43).[81]



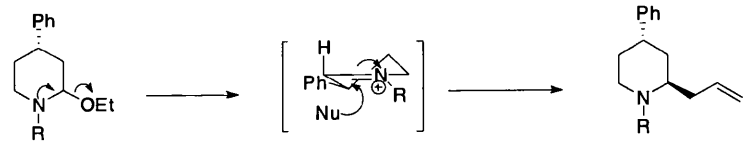
Scheme 43.

Sulfonylethoxycarbonyl-modified resin **162**, was used to immobilise amino acetals **163** prior to cyclisation and allylation to form resin-bound 2-substituted and 2,4 disubstituted piperidines **165**. Cleavage from resin was followed by acetylation of the nitrogen atom, giving free acetylated 2 and 2,4 disubstituted piperidines **167**, (Scheme 44).[76]



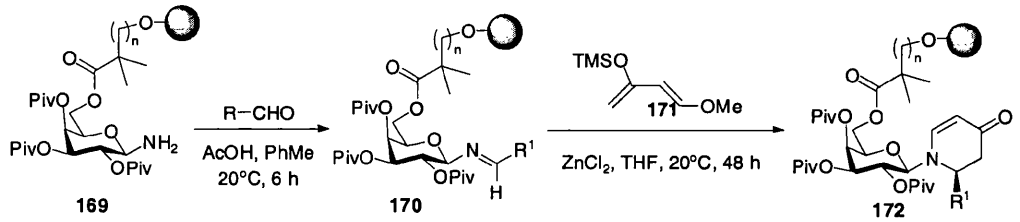
Scheme 44.

In the above example the 2,4-*anti* diastereomer was prepared selectively due to pseudoaxial nucleophilic attack on the iminium ion, shown below, (Scheme 45). The chiral centre in the starting amino acetal ultimately comes from a phenylethyoxy group (chiral pool), during its synthesis.[82]



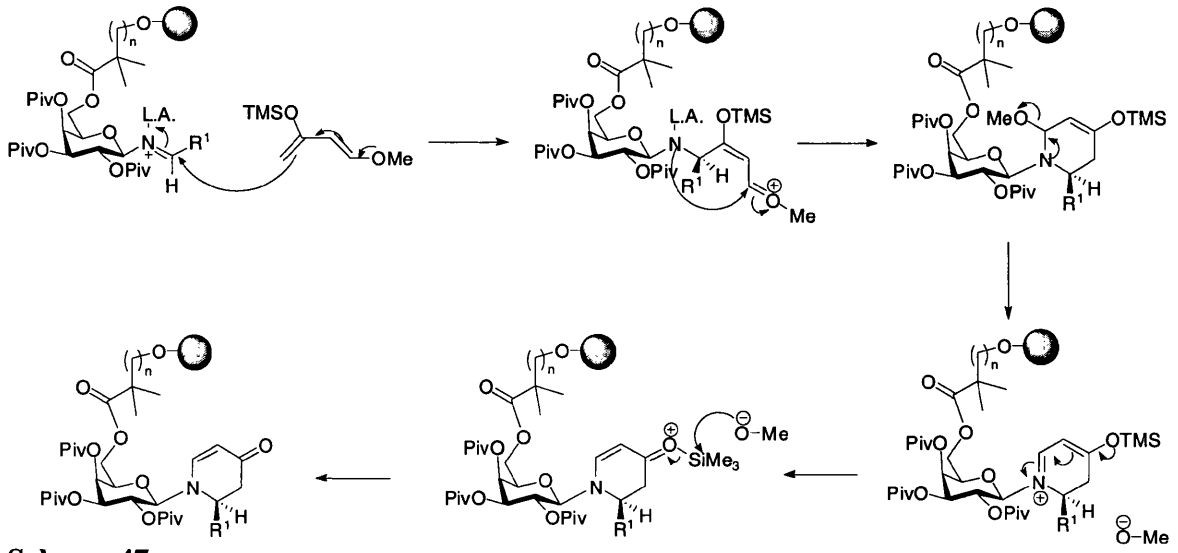
Scheme 45.

The only example of asymmetric solid-phase synthesis of piperidines during my Ph.D. was by Zech *et al.*[80] A polymer bound galactosylamine chiral auxiliary was condensed with aldehydes to form imines **170**. These were then reacted with Danishefsky's diene **171**[83] under Lewis acid conditions to form resin-bound dihydropiperidinones **172**, with control over the newly formed chiral centre, (Scheme 46).



Scheme 46.

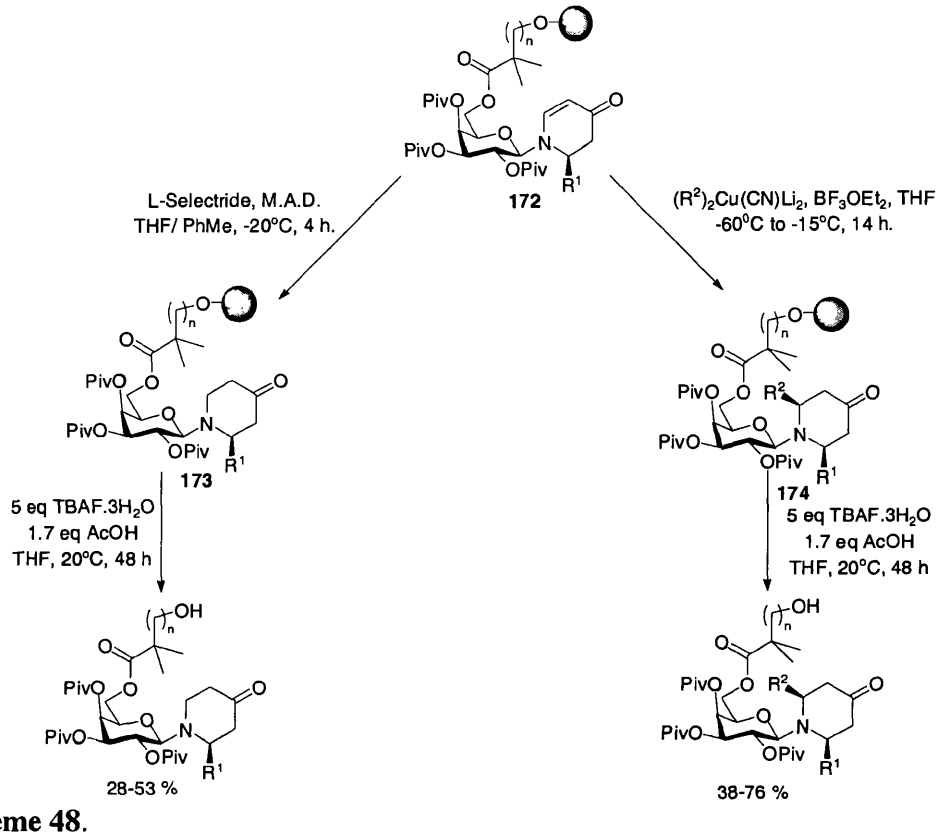
The mechanism for the reaction is postulated below, (Scheme 47). Attack is from the back as the pivalate group blocks the front face. The orientation of the iminium ion is controlled by $A^{1,3}$ strain.[84]



Scheme 47.

The dihydropiperidinones **172** could be reduced to the resin bound piperidinones **173** with acceptable purity using a sterically hindered oxygenophilic Lewis acid, methylaluminium bis(2,6-di-*tert*-butyl)-4-methylphenoxide (MAD), and bulky hydride source, L-Selectride.

Utilization of the enone functionality present in the dihydropiperidinone was also possible allowing the formation of 2,6-disubstituted piperidinones **174** by reaction with organocuprate reagents, (Scheme 48).



Scheme 48.

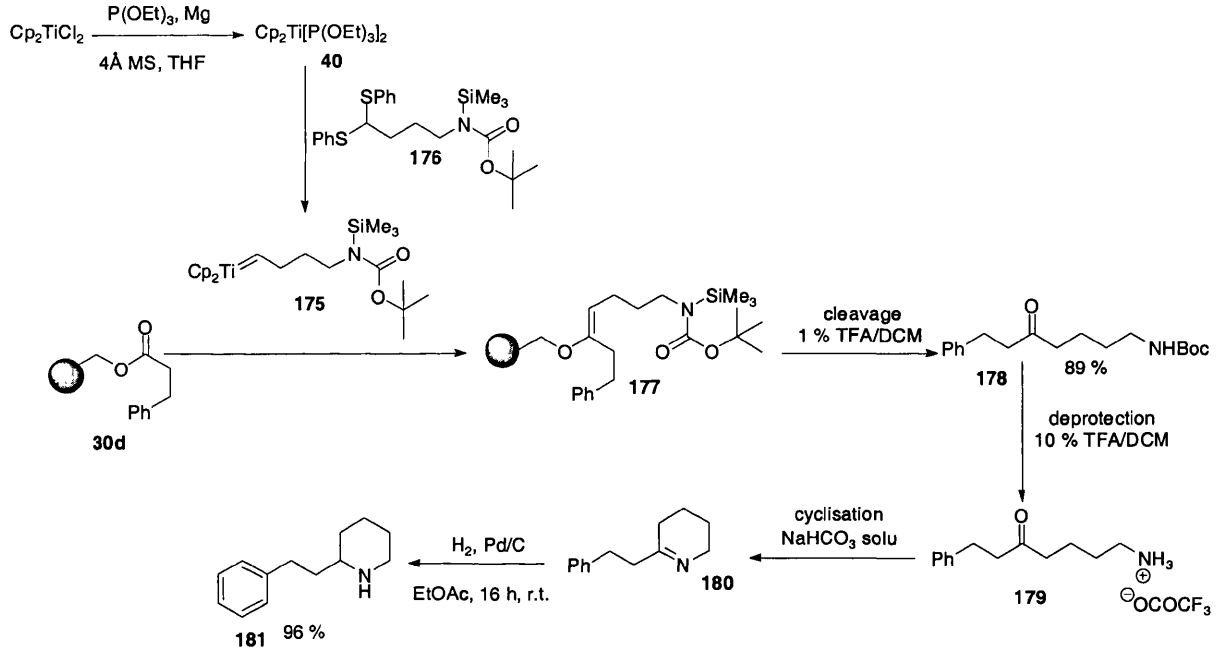
As a silyl linker was employed, cleavage from resin was achieved through a fluoride source, tetrabutylammonium fluoride (TBAF), giving dihydropiperidinones (piperidinones and 2,6-disubstituted piperidinones in 13-90%, 32-53% and 38-75% yields, respectively.[80] The auxiliary was not removed in this solid-phase synthesis but Kunz and co-workers recently carried out solution phase work with a related sugar auxiliary and published auxiliary cleavage conditions accordingly.[85]

3.3 Hartley Group Route to Piperidines

While the quinoline research was drawing to a close, another member of the Hartley group Mairi Gibson was researching the stereoselective synthesis of 2-substituted piperidines on solid-phase using the simple and cheap chiral auxiliary, α-phenylethylamine.[86]

Mairi's research started with the synthesis of racemic piperidines using titanium alkylidenes **175** and resin-bound esters as a source of diversity. Reduction of the dithiophenyl or thioacetal moiety in the *N*-silyl Boc protected substrate **27** using low valent

titanium complex **40**, produced the titanium(IV) alkylidene **175**. Reaction of this alkylidene with resin-bound ester **30d** gave resin-bound enol ether **177**, which could be monodeprotected and selectively cleaved using mild TFA/DCM conditions. The resulting Boc protected amine was further deprotected using stronger TFA conditions and cyclised to the imine **180** using sodium hydrogen carbonate solution. This was then reduced to the piperidine **181** on hydrogenation, (Scheme 49).



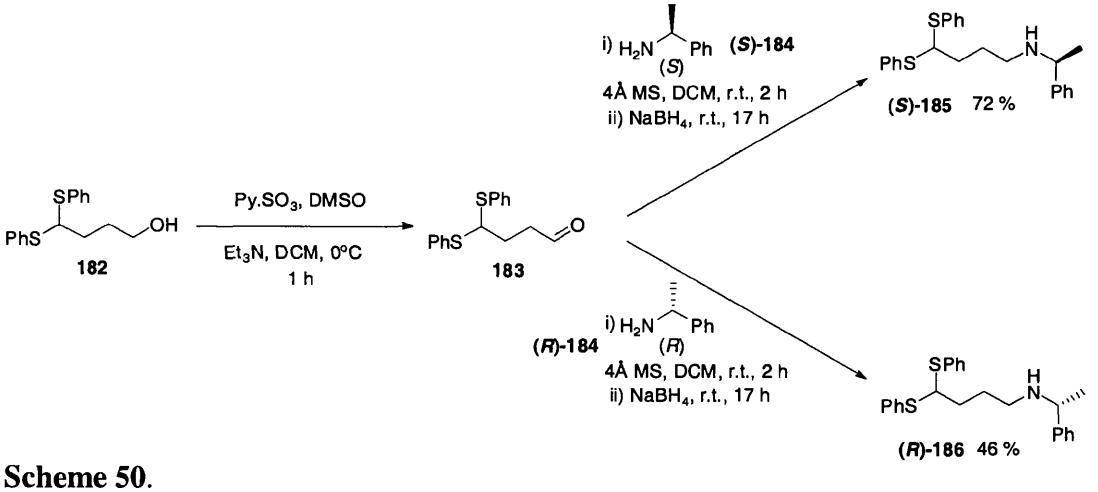
Scheme 49.

This procedure worked well for the formation of 2-phenethylpiperidine **181** but proved difficult for the synthesis of a library of piperidines using various resin-bound esters. The silyl carbamate protecting group is unstable and can form isocyanates and this instability was probably responsible for the variable results.[32,87]

With the problems of protecting groups hampering efforts to produce racemic piperidines, Mairi's research was refined in a manner that not only solved the protection problem, but also provided the considerable advantage of an asymmetric synthesis.[88] This is particularly important owing to the plethora of chiral piperidine drugs and medicinally interesting natural products containing the piperidine core reported in the literature. The major advantage of the synthesis over Zech *et al*'s asymmetric solid-phase synthesis with chiral control, is that the source of chirality is a simple and cheap chiral auxiliary available in both enantiomeric forms. The α-phenylethylamine auxiliary doubles as a protecting group and source of the nitrogen atom for the product piperidine ring. Furthermore, use of a chiral reagent rather than a chiral linker is much more versatile. Another important

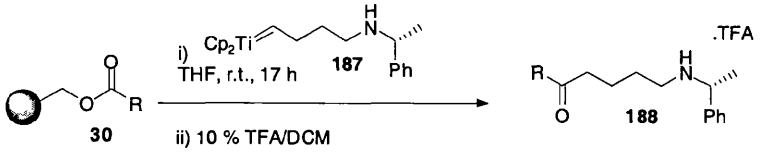
consideration is that one source of diversity in the synthesis, the resin-bound esters are produced from simple carboxylic acids ensuring a wide choice of appendages in the final products.[88]

The chiral substrates for the Takeda reaction were produced by Parikh-Doering modification[89] of the Swern oxidation[90] of the alcohol **182** produced by a literature procedure.[89] The resultant aldehyde **183** was then condensed with (*R*)-α-phenylethylamine (*R*)-**184** and (*S*)-α-phenylethylamine (*S*)-**184** as required, under reductive amination conditions, to produce two dithiophenyl thioacetals, (*S*)-**185** and (*R*)-**186** respectively, (Scheme 50).



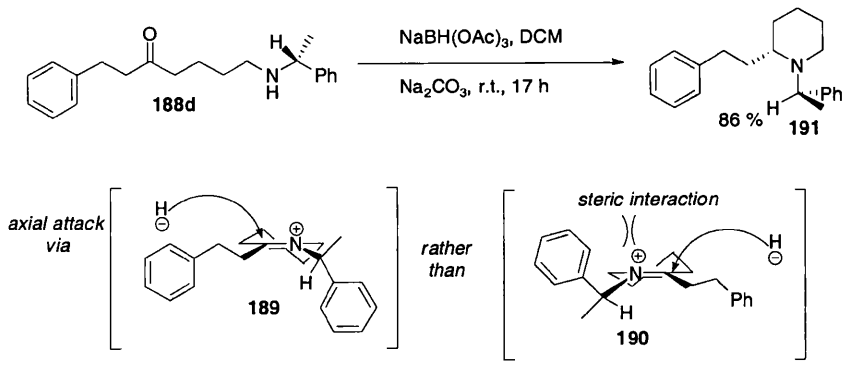
Scheme 50.

The substrates were then subjected to low valent titanium complex **40** to form a titanium reagent, presumably the titanium alkylidene **187** (from substrate (*R*)-**186**), again reaction with the resin-bound ester **30** followed by selective cleavage of the subsequent enol ether provides a range of ketones **188**, (Scheme 51).



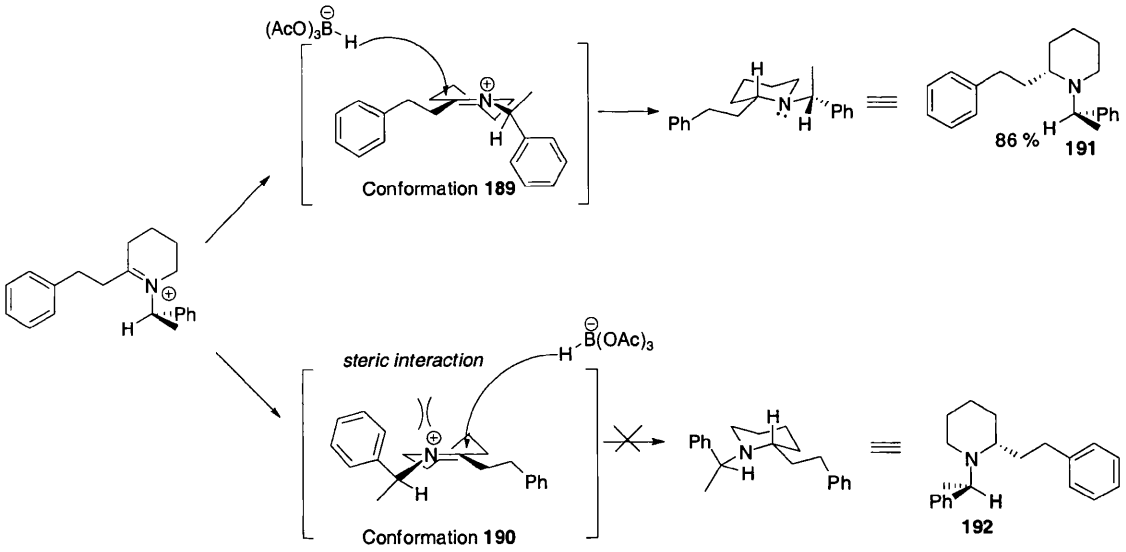
Scheme 51.

The ketones were then neutralised using potassium carbonate in dry DCM, cyclised using a large excess of sodium sulfate as a desiccant and the resulting iminium ion **189** was reduced diastereoselectivly to give auxiliary-bound piperidines **191** using sodium triacetoxyborohydride in a one pot procedure, (Scheme 52).



Scheme 52.

Stereocontrol arises from a number of factors. Axial attack is preferred because this leads directly to a chair conformation with the nitrogen lone pair antiperiplanar to the incoming group. The orientation of the α-phenylethylamine auxiliary, leading to the enantioselectivity, is controlled by $A^{1,3}$ strain.[86,91] The α-phenylethylamine auxiliary was used by Fujita and co-workers in the stereoselective synthesis of piperidines using iridium catalysis.[92] The same auxiliary has been used in the enantioselective synthesis of (S)-coniine by Shipman and co-workers,[84] who also used allylic 1,3 strain to anchor the α-phenylethylamine auxiliary into one conformation and therefore reduce the iminium ion with diastereoselevtivity. The lowest energy conformation for a system under $A^{1,3}$ strain is that in which the hydrogen atom, in this case of the auxiliary, is co-planar with the substituent of the imine, with our example the phenethyl group.[91] Therefore axial attack on conformation **190** is disfavoured due to the phenyl group of the auxiliary blocking the upper face, (Scheme 53). The removal of the chiral auxiliary under hydrogenation conditions was possible to give 2-substituted piperidines, however due to time constraints optimisation of the cyclisation and hydrogenation conditions and the determination of the enantioselectivities of the route were not possible within Mairi's PhD research. This work and further development of the route has subsequently been successfully carried out by Louis Adriaenssens, another member of the Hartley group.

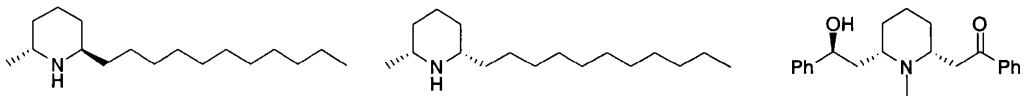


Scheme 53.

3.4 2,6-Disubstituted Piperidines

Following the success of Mairi's work and the lack of solid-phase asymmetric routes to 2,6-disubstituted piperidines in the literature in 2003, a route utilising much of Mairi's experience was devised to form this synthetically and medicinally interesting class of compounds.

2,6-Disubstituted piperidines are abundant in nature and are a core moiety in many drugs. They are common components of ant venom, e.g. solenopsin A **193** and isosolenopsin A **194** are alkaloids isolated from the fire ant and exhibit cytotoxic, haemolytic, necrotic, antibacterial, insecticidal and antifungal properties.[93] Another example is lobeline **195**, a nicotinic receptor antagonist that could have applications in the treatment of methamphetamine abuse, a field not catered for with current pharmaceutical products.[94]



(2R,6R)-(-)-Solenopsin A **193**

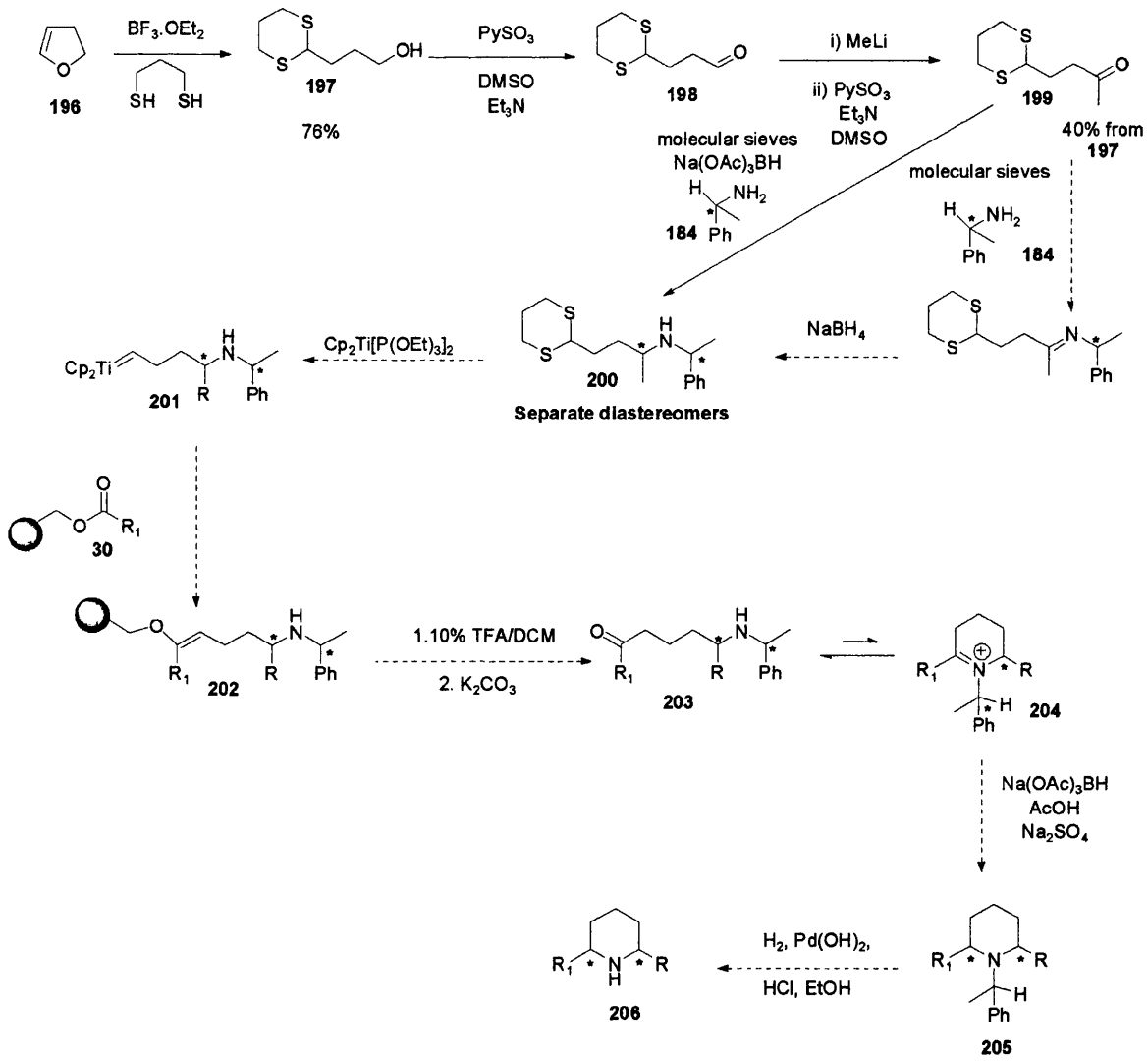
(2R,6S)-(-)-Isosolenopsin A **194**

(-)-Lobeline **195**

Figure 23.

My route started with a ring opening reaction on 2,3-dihydrofuran **196** to form the alcohol **197**, in good yield.[95] Swern oxidation under modified conditions[89] gave the aldehyde **198**. This could potentially be reacted with a variety of Grignard reagents or organolithium reagents to form the secondary alcohols. Initially, methyllithium was used and the resulting alcohols were oxidised back to give ketone **199**. Reductive amination with the

chiral auxiliary **184** gave amines **200**. The aim was then to separate diasteromers **200**, and subject both diastereomers separately to Takeda's conditions[95] to form alkylidenes **201** and then react these with the resin-bound esters **30** to give the enol ethers **202**. Selective cleavage, again, would follow under mild acid conditions and after neutralisation and cyclisation, the resultant iminium ion **204** would then be reduced selectively using a mild reducing agent to the auxiliary bound 2,6 disubstituted piperidines **205**. Hydrogenation conditions to remove the auxiliary would be the final step in the synthesis to provide 2,6-disubstituted piperidines **206**, (Scheme 54). Unfortunately the isolation of the separate diastereoisomers proved difficult. Attempts were made using crystallisation and trituration to separate the compounds but separation was not achieved. Problems with separation the diastereomers and a shift of focus in the research led to this route being left incomplete. At this time the opportunity to develop a route to a completely new moiety was presented and research into the asymmetric synthesis of 2-substituted azepanes was undertaken.



Scheme 54.

If the route to 2,6-disubstituted piperidines were to be further developed an important consideration in this methodology would be the reduction of the chiral iminium ion. It is a fundamental concern of this route as to how the two chiral centres would affect stereocontrol in the reduction of the iminium ion. It could be reasoned that one diasteromer **207** would work well with the (*R*)-auxiliary as the chiralities would be matched, while the other diastereomer **208** would give poor stereocontrol, figure 24.

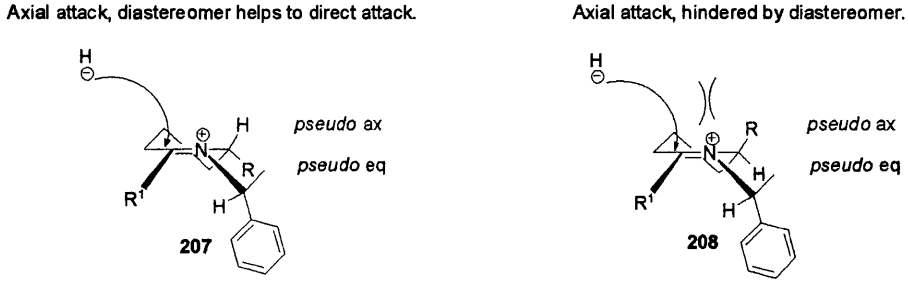
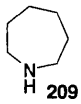


Figure 24.

Chapter 4: Literature Synthesis of 2-Substituted Azepanes

4.1 Why Synthesize Azepanes?



209

Figure 25.

The azepane structure **209**, figure 25, is a moiety present in many potential and proven biologically active alkaloids.[96] As such it has been the source of interest for medicinal applications, but also has other advantages e.g. chelating agents for paramagnetic MRI imaging metals,[97] discussed later. In addition to these applications, the ring formation is synthetically challenging due to loss of entropy and is therefore of interest to chemists developing synthetic methodology. Many enantioselective syntheses of azepanes rely on sugar starting materials,[98-100] in particular those derived from D-mannitol. These are important members of the chiral pool but limiting also, as the substitution of the ring with many hydroxyl groups is inevitable.

4.2 Previous Syntheses of Azepanes: Background

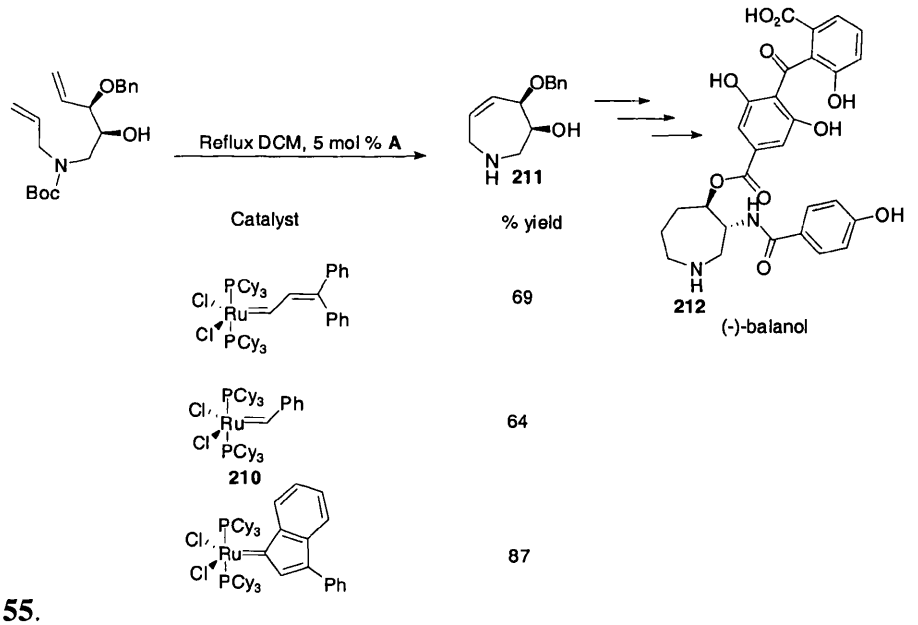
Accessing substituted azepanes asymmetrically has presented problems in the past.[96] Seven membered rings are on the verge of medium ring size and there is a loss of entropy in reaching the transition state of the ring-forming reaction, posing a challenge for those wishing to synthesize them. There are many non-productive conformations the linear precursors to seven membered rings can adopt, decreasing the percentage of molecules in the orientation needed for reaction and so slowing the rate of formation. One of the most popular method of preparing chiral azepanes is through the derivatisation of sugar analogues. Sugar-derived azepane structures by default have many hydroxyl groups attached to the ring. These can be desirable; as they increase the water solubility and prevent poor bioavailability,[101] but they can also be unwanted because of the effect they could have of structure activity relationships in drug design. Ring closing metathesis (RCM), is a fashionable and sophisticated alternative[102] leading to fewer appendages on the ring, if desired, as well as the ability to introduce functionality e.g. hydroxyl groups.[103] Azepanes can also be accessed *via* corresponding cyclic imines. However as the synthesis of cyclic imines will be dealt with in detail later on, the synthesis of these compounds shall

be omitted here. The synthesis of chiral 2-substituted azepanes and the solid-phase synthesis of azepanes will be the focus of this discussion.

4.3 Methods of Constructing Chiral 2-Substituted Azepanes

4.3.1 Ring Closing Metathesis

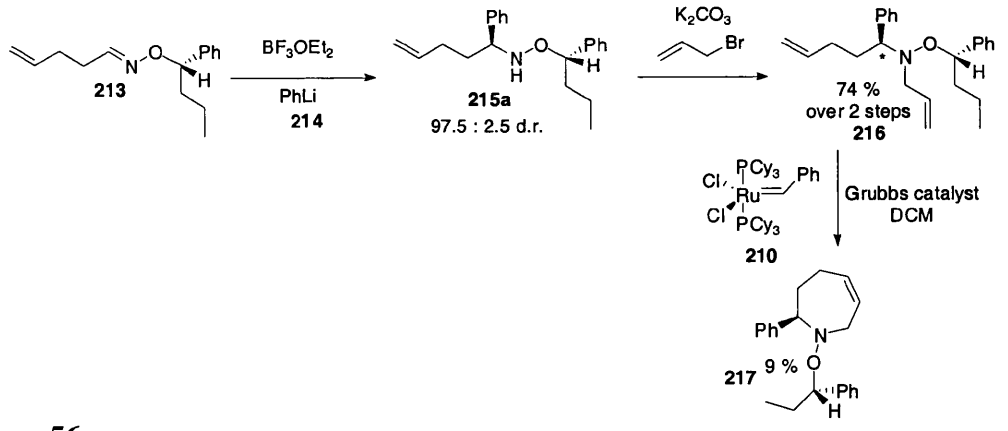
Ring closing metathesis (RCM) is one of the more frequent ways of constructing the azepane ring. Indeed, a range of Grubbs' catalysts **210** were effective in Fürstner and co-workers[102] synthesis of the chiral azepane segment **211** of (-)-balanol **212**, (Scheme 55).



Scheme 55.

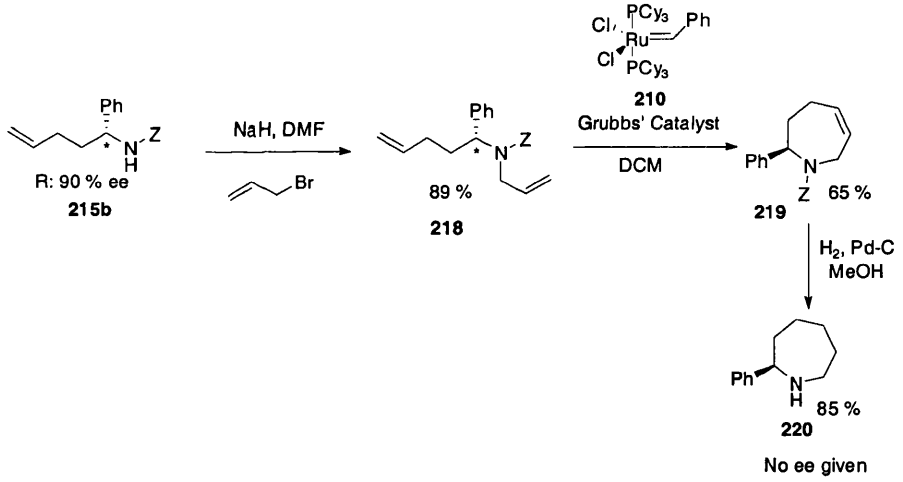
Azepanes synthesised using RCM include bacterial ribosome glycoside antibiotics,[104] potent glycoside inhibiting polyhydroxylated azepanes,[103] and the natural products (-)-tuberostemonine,[105] and (-)stemoamide.[106]

Chiral oxime ethers have been used to attach a chiral auxiliary in a synthesis of 2-substituted azepanes.[107] The chiral induction comes from oxime ethers **213** derived from (*R*) or (*S*)-O-(1-phenylbutyl)hydroxylamine and formed by condensing this auxiliary with unsaturated aldehydes. In the example given[107] oxime **213** was reacted with phenyllithium **214** to give only one alkoxylamine **215a**. Allylation of the amine **215** gave the diene **216** which was a substrate for the RCM reaction, (Scheme 56). This was carried out using Grubbs catalyst **210** and the alkene moiety created was hydrogenated under palladium on carbon conditions to give auxiliary bound **217** enantioselectively, but in poor yield.



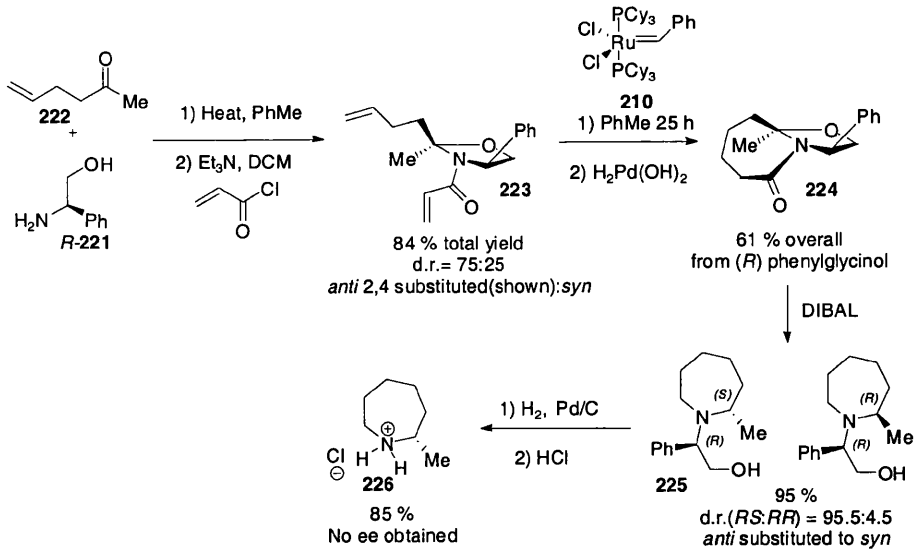
Scheme 56.

The low yield during the RCM gave rise to concerns that the basic nitrogen atom in amine **216** was coordinating to the ruthenium atom of the catalyst **210**. Therefore alkoxylamine **215** was converted into the benzyloxycarbamate **218**, (Scheme 57). The resulting diene **218**, cyclised smoothly in respectable yield to give alkene **219** and hydrogenation gave the corresponding enantomerically enriched azepane **220**.



Scheme 57.

An alternative auxiliary is phenylglycinol. Thus (*R*)-phenylglycinol **221** was condensed with 5-hexene-2-one **222** and the aminal produced immediately reacted with acryloyl chloride to form amide **223**, (Scheme 58). At this point the diastereomeric ratio was 75:25 in favour of the *anti* configuration of the methyl and phenyl groups and this major isomer was isolated to continue the sequence with. RCM using Grubbs' catalyst **210** followed by hydrogenation using palladium hydroxide gave the bicyclic lactam **224**. Reduction of the aminal bond and lactam carbonyl was carried out simultaneously using DIBAL as a hydride source to form auxiliary bound azepane **225**. Removal of the auxiliary was achieved by hydrogenation to give 2-substituted azepanes **226** in good enantiomeric excesses.[108]

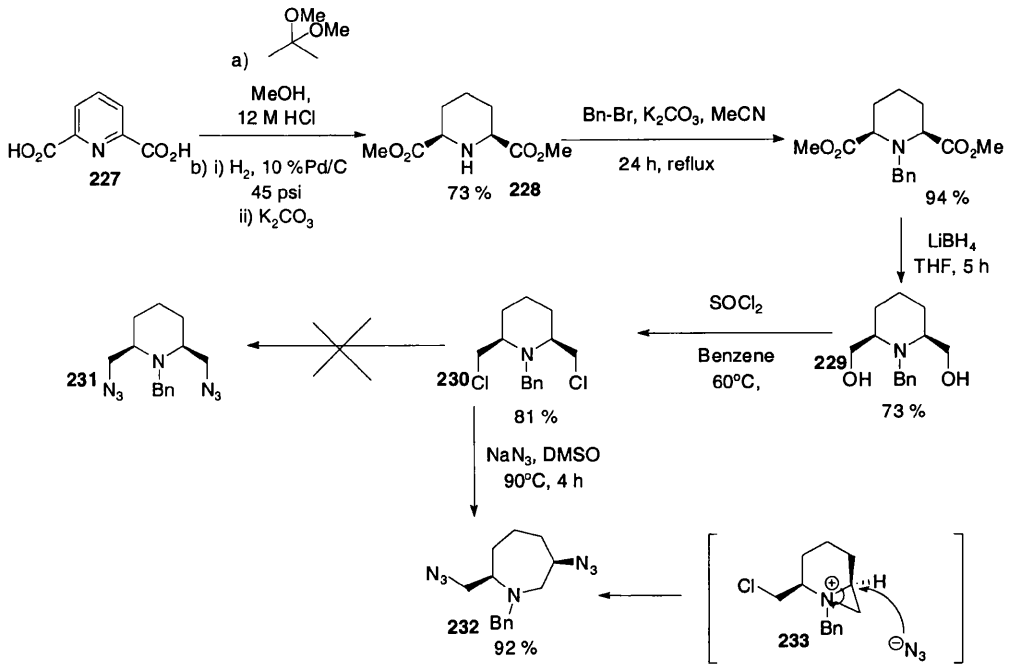


Scheme 58.

A small range of azepanes was prepared with the 2-alkyl group being either methyl or ethyl. Formation of 2-isobutyl azepane derivative gave very poor yields of the bicyclic lactam (8%), indicating the introduction of further diversity may be problematic. [108]

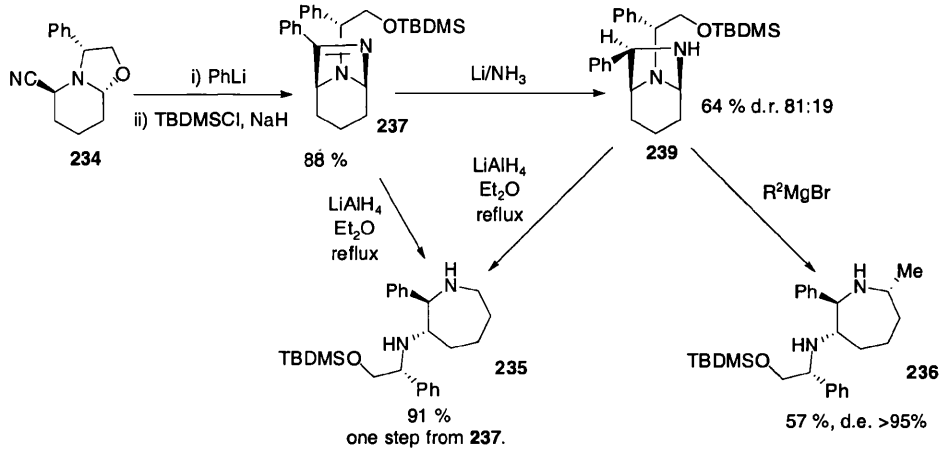
4.3.2 Ring Expansion

Formation of the azepane by ring expansion is a powerful method and Chong and co-workers used aziridinium ion formation and regioselective ring opening of this transitional species to provide a route to azepanes with total diastereoselectivity and in good yield. [97] The research aimed at preparing new azepane based agents to produce stable complexes and increase hepatobiliary clearance of toxic paramagnetic gadolinium (Gd) ions, used in MRI imaging.[96,97] The synthesis started with reduction of 2,6-pyridinedicarboxylic acid **227** to give *cis*-2,6-bis(methoxycarbonyl)piperidine[109] **228**, (Scheme 59). Benzyl protection of the nitrogen followed by reduction of the ester groups then gave the N-benzylated diol **229**. The diol was converted into the dihalide **230** using thionyl chloride, providing the substrate for azepane formation. The authors expected simple S_N2 displacement of both chlorine atoms with azide under the conditions used, however the piperidine derivative **231** was not isolated. Instead a seven membered azepane compound **232** was produced exclusively, presumably via the aziridinium ion intermediate **233**. [97]



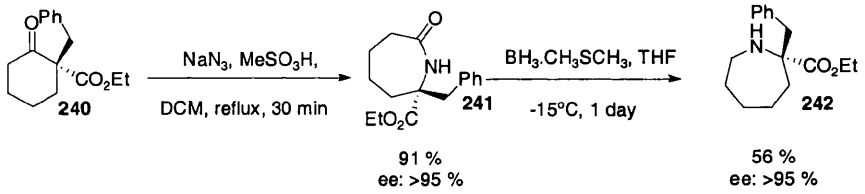
Scheme 59.

Another ring expansion that utilizes a bicyclic aminal **234** derived from the same chiral phenylglycinol auxiliary as used in the RCM routes above was used to produce 2,3-disubstituted azepane **235** and 2,3,7-trisubsituted azepane **236** diastereoselectively by addition of phenyllithium to the nitrile **234**. Reduction of the resulting cyclic imine **237** provided the bicyclic aminal **239** with a degree of stereoselectivity, (Scheme 60). This compound could then be treated to lithium aluminium hydride reduction to provide 2,3-disubstituted azepanes **235** or reacted with methyllithium to give 2,3,7-trisubstituted azepane **236**.[110,111] A range of similar azepanes were prepared by using other organolithiums and Grignard reagents in the two steps involving these.



Scheme 60.

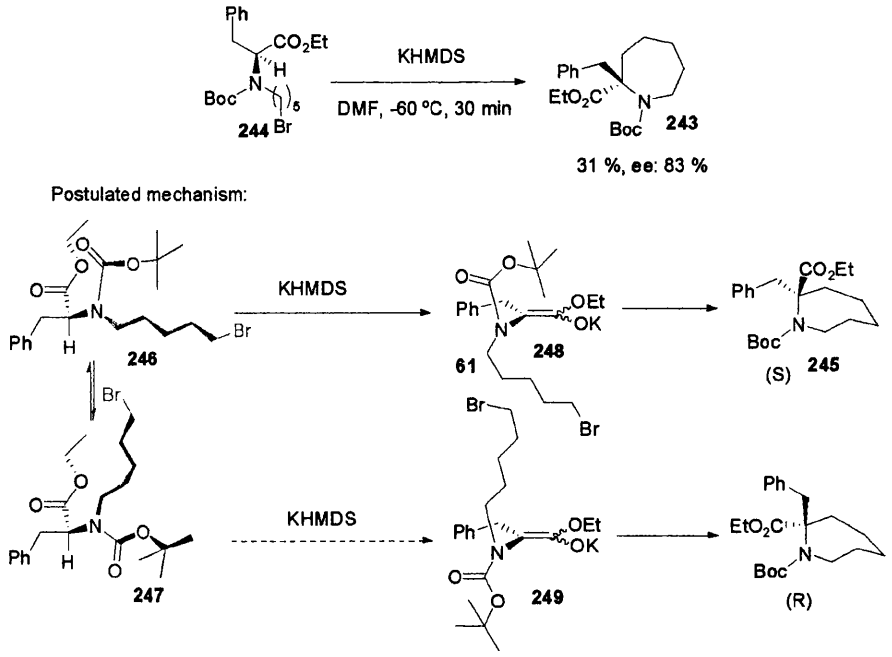
Azepane amino acids substituted at the α position have been synthesised using the Schmidt rearrangement.[112] This is a direct route to lactams from the chiral ketones, prepared by diastereoselective alkylation, avoiding the hydrazones required for the Beckmann rearrangement.[113] Thus chiral β-keto ester **240** was treated with sodium azide and methanesulfonic acid to effect the rearrangement to lactam **241**, (Scheme 61). Selective reduction of the lactam carbonyl group involved using borane-dimethyl sulfide complex to give the α-amino ester **242**. A range of alkyl groups could be used providing a variety of α-amino esters



Scheme 61.

4.3.3 Enolate Alkylation

Synthesis of α-alkylated α-amino acids **243** has been carried out by Kawabata *et al.* using memory of chirality in a deprotonation and subsequent intramolecular enolate alkylation step.[114] The key step is the cyclisation of bromoalkane **244**. Displacement of the halide by an enolate derived from the chiral parent Boc protected amino acid derivative gave the (*S*)-enantiomer **245** in 83% ee but low yield, (Scheme 62). The authors postulated a mechanism considering the memory effect of the enolate. Two stable confomers, **246** and **247** give rise to two different enolate conformations **248** and **249**. Conformation **248** arises from the deprotonation of a hydrogen that is eclipsed with the floppy and less sterically hindered N-$(CH_2)_3$Br group, whereas in conformation **247** the target hydrogen atom for the bulky KHMDS base is eclipsed with a sterically demanding Boc group, (Scheme 62). Alkylation then occurs more rapidly than interconversion of **248** and **249** by rotation about the C-N bond.

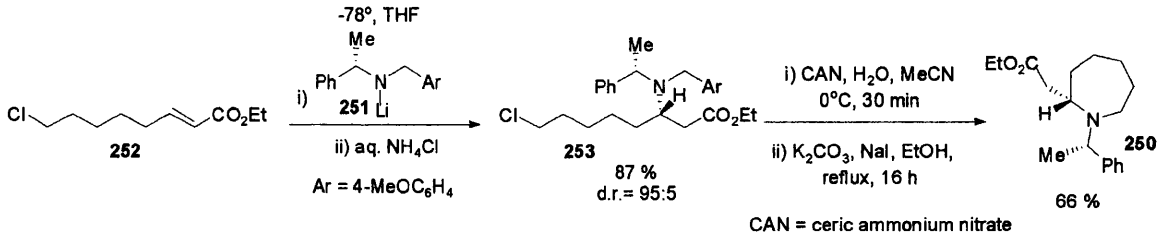


Scheme 62.

Solvent effects support this explanation, as decreased enantioselectivity is observed when a less coordinating solvent is used, e.g. PhMe instead of DMF, consistent with increased deprotonation of **247** due to the coordination of the potassium cation by the Boc group.[114]

4.3.4 *N*-Alkylation

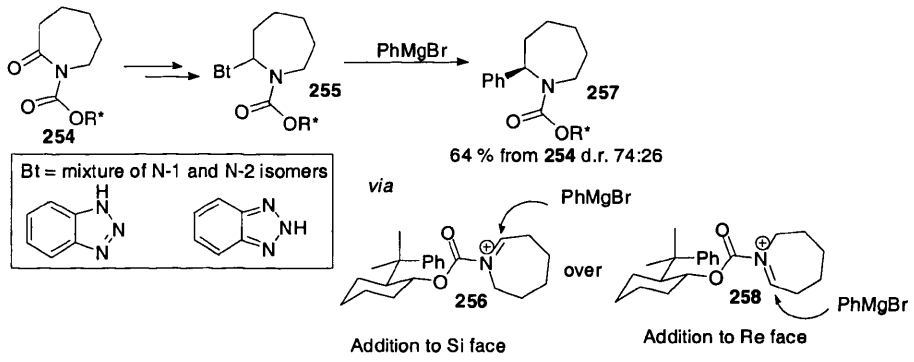
A route that used *N*-alkylation to access the azepane core employed the 2-phenylethylamine auxiliary to access cyclic β-amino acid derivative **250**.[115] The lithiated α-phenylethyl amine derivative **251** was reacted with α,β-unsaturated ester **252** in an asymmetric Michael addition reaction to form adducts **253** with 95% diastereoselectivity, (Scheme 63). Following the removal of the benzyl group using ceric ammonium nitrate (CAN) (hydrogenation cleaved the C-Cl bond) intramolecular alkylation was investigated using base and iodide as a catalyst to give the auxiliary-bound cyclic β-amino acid **250**. Removal of the auxiliary proved troublesome, an observation that concurs with our own research using the α-phenylethylamine auxiliary (see later).



Scheme 63.

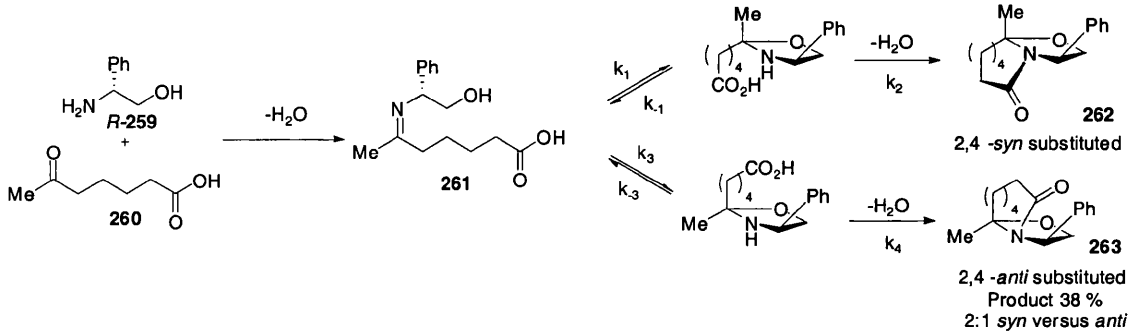
4.3.5 *N*-Acylation

A chiral auxiliary can also be introduced by acylation of a preformed lactam. Modification of TCC (trans-cumylcyclohexanol) auxiliary protected lactam **254**, by introduction of benzotriazole, a good leaving group occurs by reduction to the aminol and addition of benzotriazole as a nucleophile to give **255**. This provides access to *N*-acyl iminium ion **256**. Phenylmagnesium bromide alkylates this stereoselectively giving a route to 2-substituted chiral azepane **257**, (Scheme 64). The diastereoselectivity is dependent on the selective addition the *Si* face of the iminium ion as rotomer **256** is favoured over rotomer **258**. The TCC auxiliary then controls the face of attack by the organometallic reagent giving the auxiliary bound 2-substituted azepane **257**, (Scheme 64).



Scheme 64

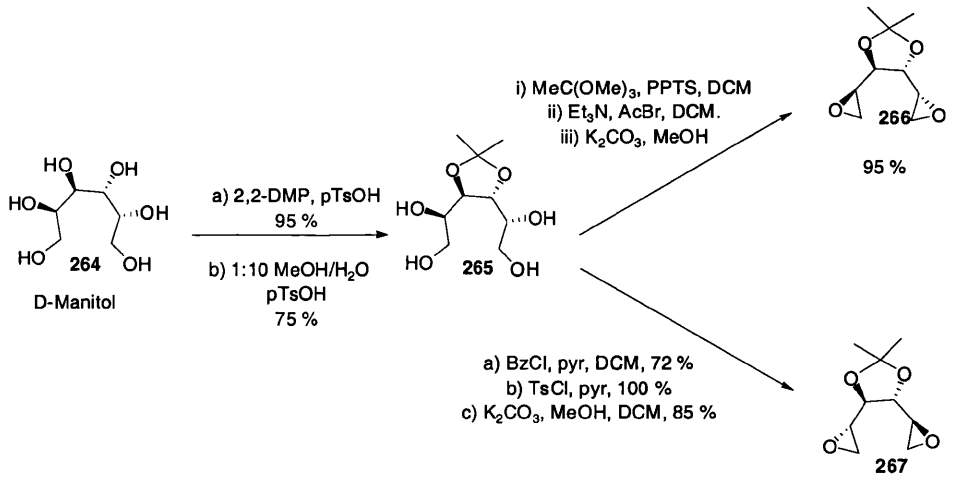
Another route that afforded 2-substituted azepanes enantioselectively used N-acylation and an auxiliary derived from (*R*) or (*S*)-phenylglycinol, (Scheme 65). The (*R*)-phenylglycinol **259** condensed with keto acid **260** to form imine **261**. Given time (3 days), the imine rearranged to a cyclic aminal that further cyclised to a bicyclic lactam products **262** and **263** with some degree of diastereoselectivity for the 2,4-syn product **262** (d.r. = 67:33 syn:anti).[108]



Scheme 65.

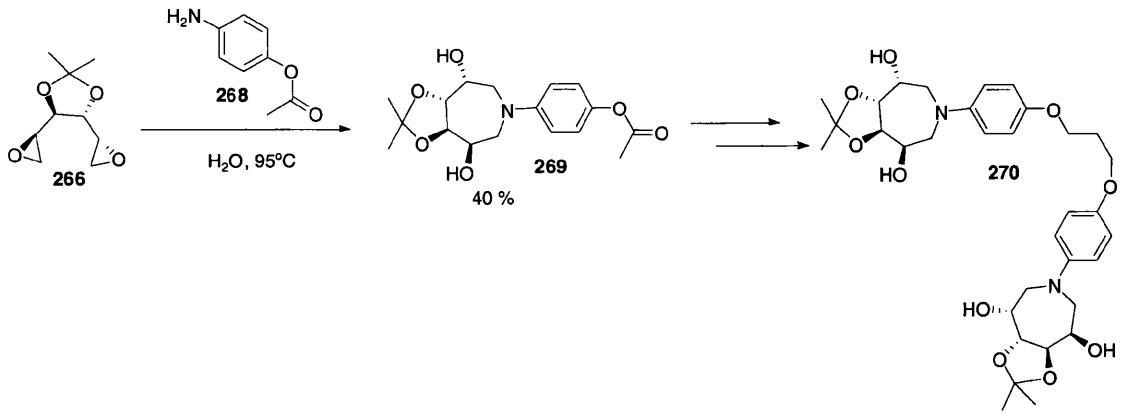
4.4 Methods for Constructing Azepanes on Solid-Phase

Hydroxyazepanes have been investigated as DNA minor groove-binding ligands.[100] As knowledge of the genome expands and the chemical understanding and manipulation provided by chemical biology continues to grow, therapeutic agents that bind directly to DNA to affect protein production are an increasing area of interest. Azepanes with hydroxyl appendages are thought to be flexible enough to allow the hydroxyl groups to interact and hydrogen bond with the N-3 of purine, a hydrogen-bond acceptor in the form of the urea carbonyl of the pyrimidine bases, or the 2-amino of guanine, directing the molecule attached into the minor groove.[99] The hydroxyl functionalities provide a high level of water solubility for the molecule, increasing the bioavailability of these structures. Such hydroxyazpanes are accessed, as in many other syntheses of azepanes, through epoxides derivatised from D-mannitol. An example of a DNA-binding molecule, derived from D-mannitol, was reported by Johnson and Thomas.[100] Protection of D-mannitol **264**, using dimethoxypropane and catalytic toluenesulfonic acid gave its triacetonide, which was selectively deprotected using acidic aqueous methanol to give monoacetonide **265**. This could be selectively converted into either one of two epoxides **266** and **267**, (Scheme 66).[116]



Scheme 66.

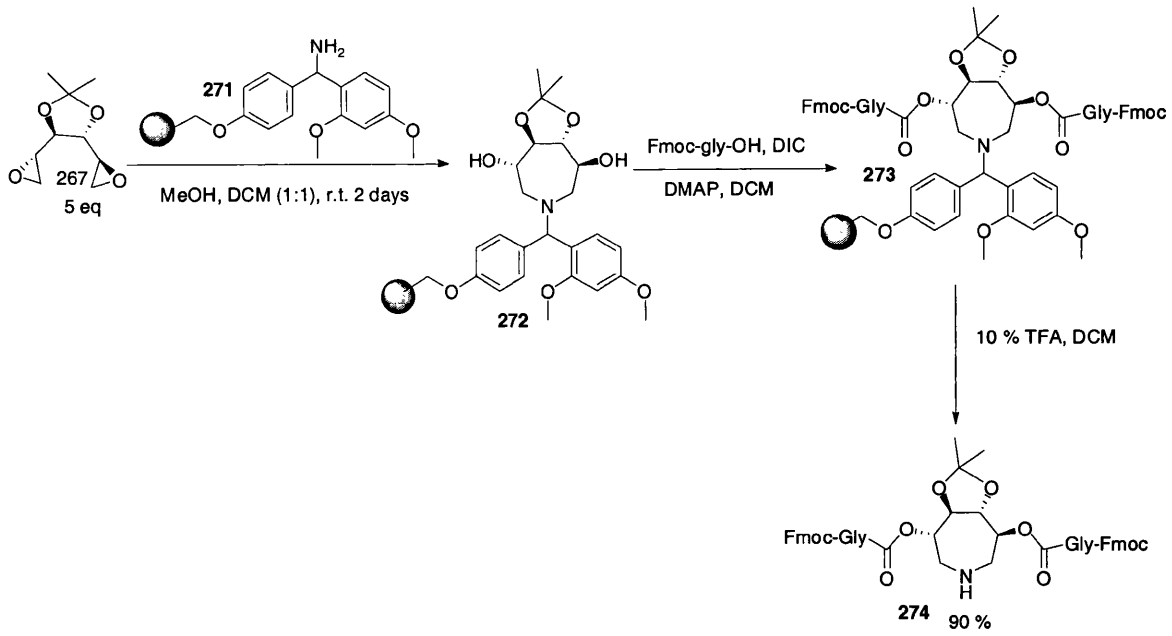
The epoxides **266** or **267** could then be treated with amine derivatives. For example epoxide **266** was reacted with aniline **268** to give polyhydroxyazepane **269**. Elaboration of the structure then provided the bis-azepane **270**, which was tested as a minor groove binding ligand, (Scheme 67).[100]



Scheme 67.

This built upon the research of Merrer and co-workers who discovered that the ring opening of bis-epoxides **266** and **267** could be controlled by the solvent used in the reaction.[116] Merrer found that in an aprotic medium the formation of the piperidine ring by 6-*exo* cyclisation was favoured, in accordance with Baldwin's rules and kinetics. The 7-*endo* ring closure yielding the azepane structure could be induced, however, by using protic media or aprotic conditions in conjunction with a Lewis acid. [116]

Merrer and co-workers later used solid-phase synthesis to access an azepane structure. The polyhydroxylated azepane moiety was constructed on resin to allow elaboration by peptide synthesis. The formation of the azepane structure was carried out as before, this time using a crowded amine derived from Rink resin **271** as the nucleophile to open the *bis*-epoxide **267** to give resin-bound azepane **272**. Following capping of the excess amine sites on resin, as complete loading was not desirable due to the reaction conditions required, derivatisation of the free hydroxyl groups was possible, illustrating the potential of producing libraries of peptide mimetics, when coupled to amino acids. The resin-bound functionalised azepane **273** was then cleaved from resin using standard conditions to give the compound **274**, (Scheme 68).[98]



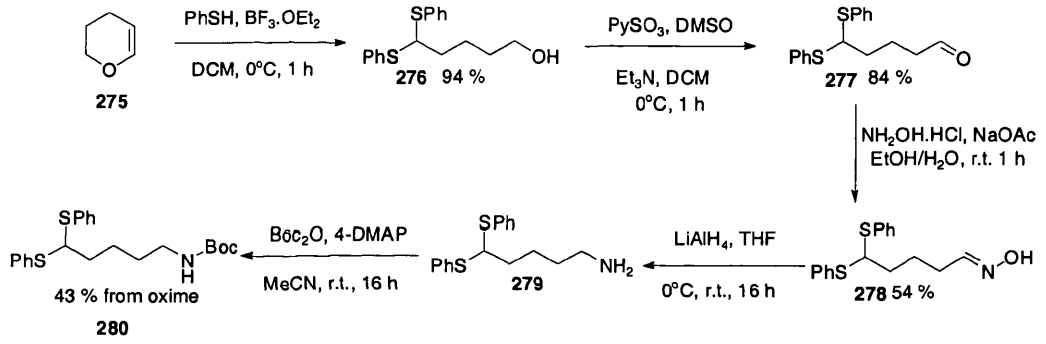
Scheme 68.

The route has the advantage of being traceless and in theory might be extended to employ other *bis*-epoxides. However it currently does not allow access to 2-substituted azepanes and its versatility has not been investigated.

Chapter 5: 2-Substituted Azepanes

5.1 Previous Hartley Group Work on Azepanes

Considering the success of Mairi Gibson's work in forming chiral 2-substituted piperidines and the gap in the literature concerning the diversity based synthesis of azepanes on solid-phase, an important tool for drug companies to cover chemical space, expansion of the methodology to the larger azepane ring system was undertaken. Mairi had started exploring the synthesis of racemic azepanes following the route shown, (Scheme 69). However the thioacetal **280** was never tested under Takeda conditions and the focus of her work remained the synthesis of chiral piperidines.[117]



Scheme 69.

5.2 Choice of Auxiliary

The chiral auxiliary chosen for the solid-phase synthesis of 2-substituted azepanes was α-phenylethylamine (α-PEA).[86] It is cheap, readily available in both enantiomers, and should be reductively cleaved with ease.[86] α-PEA has been used as a chiral resolving agent and as a chiral ligand in asymmetric catalysis, but we wished to use it as an auxiliary directing the reduction of a seven membered cyclic iminium ion in our synthesis. Stereocontrol over the chiral centre produced had already been demonstrated in the piperidine series[84] through 1,3 stereoinduction from the difference in size of the groups (CH_3 vs. Ph) around the benzylic carbon in the auxiliary, as has already been discussed.

The intermediate iminium ions **281** in our synthesis would be locked into a ring system and so *E* or *Z* depending on the R group (2-substituent) used. Alignment of the auxiliary

hydrogen atom in the same plane as the imine bond in the cyclic iminium ion of our intermediate and the consequent differentiation of the two faces of attack at the prochiral iminium ion centre, should provide the selectivity required, [91] figure 26.

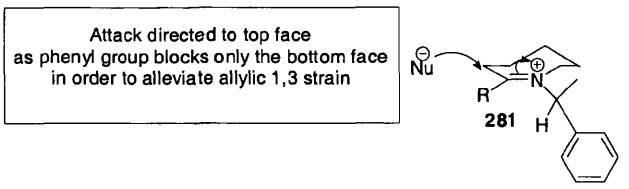
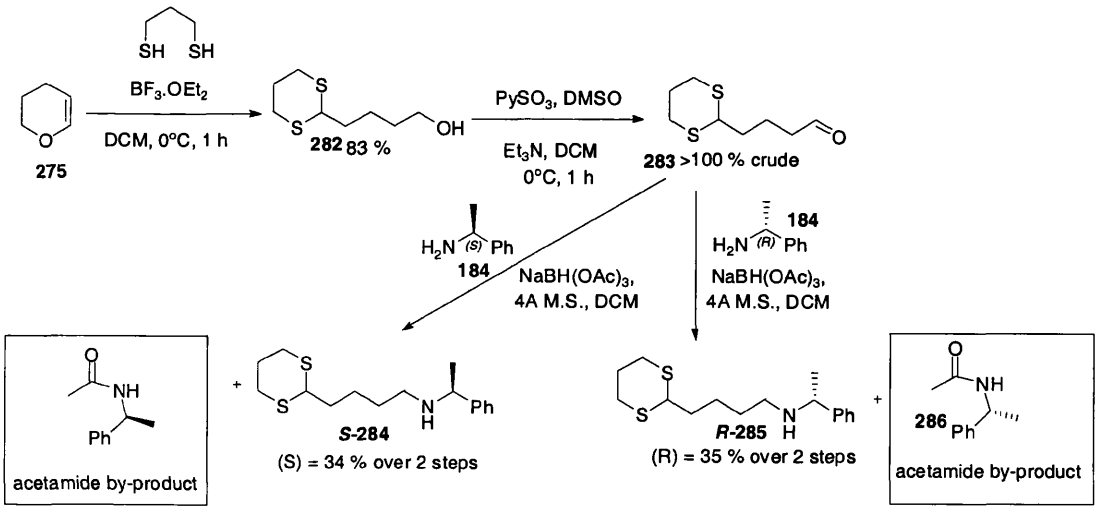


Figure 26.

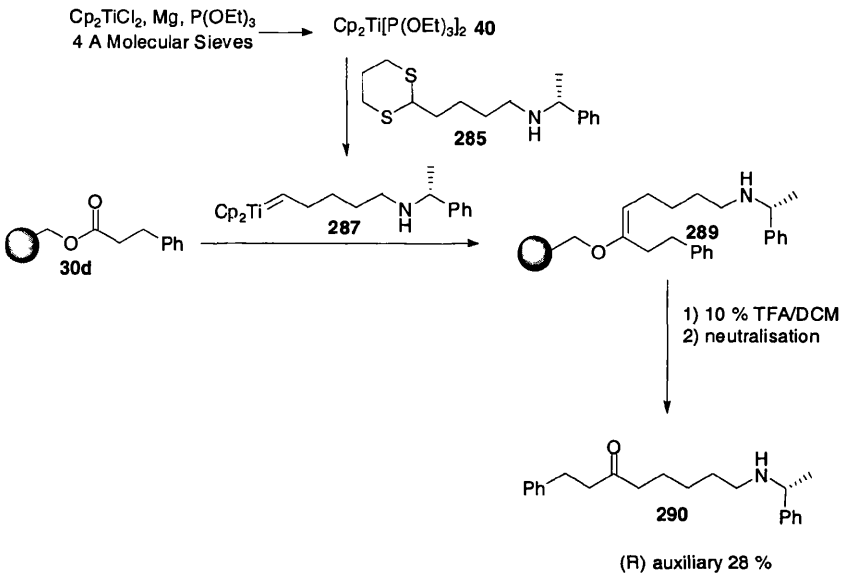
5.3 Synthesis of Thioacetal Substrates

The synthesis was started from the 2,3-dihydropyran **275**, which was ring opened in the presence of propanedithiol to produce thioacetal **282**. Swern oxidation[89] produced the crude aldehyde **283** contaminated with pyridine and triethylamine salts, which was used without further purification in a reductive amination reaction with the α-phenylethylamine auxiliaries **184**. The crude products were orange oils **284** and **285** that produced colourless crystals on standing. Unfortunately NMR and mass spectrometry showed that the crystals were amide **286**. This by-product was produced by the condensation of the auxiliary and acetic acid from the reducing agent used, and was easily removed along with the other impurities, salts carried on from the Swern oxidation, by column chromatography, (Scheme 70).



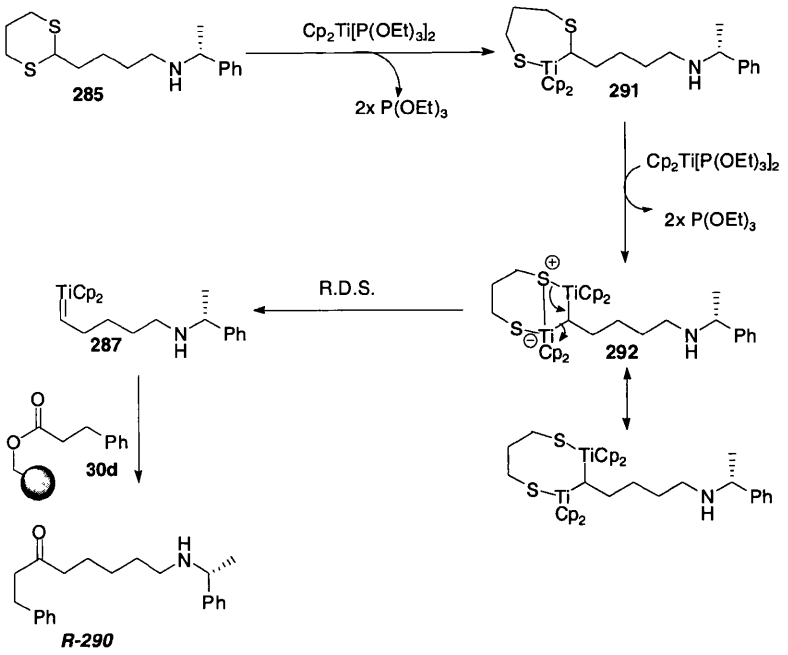
Scheme 70.

(*R*)-Substrate **285** was treated to 4 eq. of low valent titanium complex **40**, to generate an organotitanium reagent, presumably titanium alkylidene (R)-**287**. As before the low valent titanium(II) complex **40** was formed by reduction of titanocene dichloride by magnesium in the presence of triethyl phosphite. Reaction between 3 eq. of titanium(IV) alkylidene **287** and a resin-bound ester **30d** produced enol ether (*R*)-**289**, following a chameleon catch strategy. Selective cleavage of the enol ether moiety, leaving behind any unreacted resin-bound ester, provided the alkylammonium (*R*)-salt **290** in low yield, (Scheme 71).



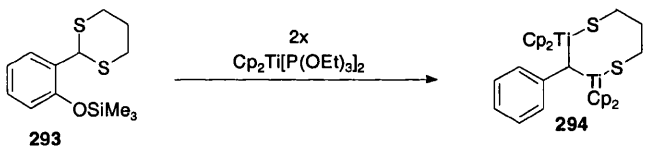
Scheme 71.

The modest yield indicated that there might be a problem with the formation of the titanium alkylidene reagent from the dithiane. The mechanism presumably involves step-wise reduction of the thioacetal (*R*)-**285** with a first oxidative addition giving rise to organotitanium **291** and a second oxidative addition resulting in bimetallic **292**. This is the reagent subjected to the resin-bound ester. Most probably formation of the Schrock carbene (*R*)-**287**, (Scheme 72), is the rate determining step in the alkylidenation reaction as have been shown for similar reactions.[118]



Scheme 72.

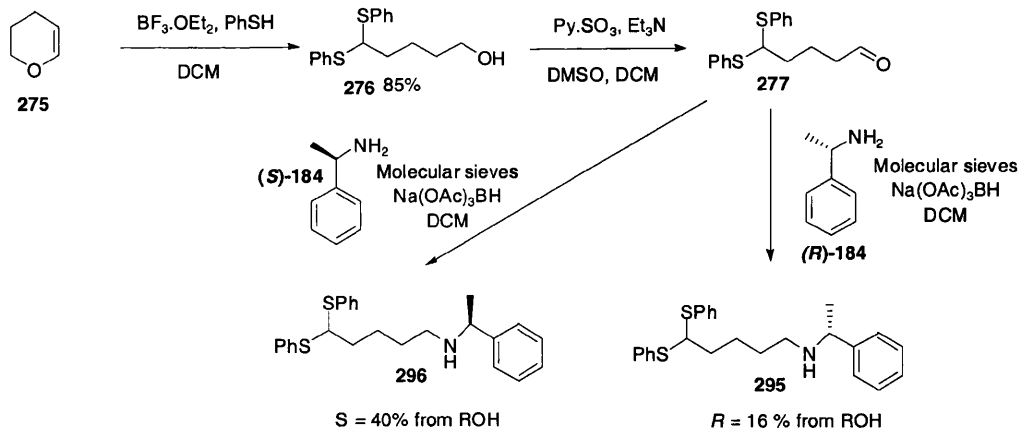
Unpublished results from other Hartley group members indicate that the first oxidative addition is generally instantaneous, while the second oxidative addition is slower. In the case of benzylic dithiane **293** stabilisation of the formed carbon dianion in bimetallic **294**, is achieved through conjugation with the aromatic ring and this is a good substrate for the Takeda reaction, (Scheme 73).



Scheme 73.

We reasoned that in the absence of this stabilisation it might be better to use a diphenyldithioacetal substrate as oxidative addition to the C-S bond would be easier because the phenylthiolate anion is more stable than an alkylthiolate.

Dithiophenyl thioacetals (*R*)-**295** and (*S*)-**296** were prepared from 2,3-dihydropyran **275**. This was converted into alcohol **276**. Swern oxidation then gave aldehyde **277** and this was followed by reductive amination with the α–phenylethylamine chiral auxiliary to produce thioacetals (*R*)-**295** and (*S*)-**296** in moderate yield following column chromatography. The low yield of the *R* substrate was due to an extended delay before purification, (Scheme 74).



Scheme 74.

It was possible that the low yield of ketone (*R*)-**290** was due to titanium alkylidene (*R*)-**287** failing to react with the resin-bound ester, so a complementary strategy using a lower loading resin was also investigated. This was pursued after re-treatment of one kan with titanium alkylidene (*R*)-**287** and doubling the equivalents of low valent titanium complex **40** both failed to increase yields. These experiments indicated that protection of the N-H of the auxiliary was not necessary because slow intramolecular protonation of the titanium alkylidene (*R*)-**287** would effectively decrease the amount of this species and increased equivalents would have increased the yield. The steric hindrance of the high loading Merrifield resin used could have contributed to low yields on the resin. This concern is also discussed by Kunz and co-workers in their work with galactose auxiliaries in chiral piperidine synthesis discussed earlier.[80]

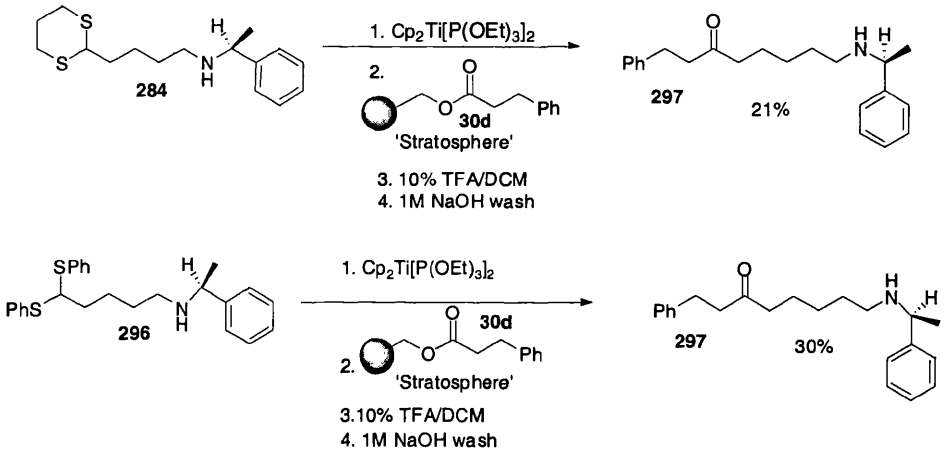
The resin was therefore changed from 1.89 meq $mmol^{-1}$ Merrifield resin to lower loading chloromethylpolystyrene stratosphere resin plugs, small pre-formed plugs of resin that can be treated as loose resin, but have the advantage of being a standard weight/quantity. The resin plugs were placed in the polypropylene IRORI ® macrokans. This has the benefit of avoiding mechanical degradation of the plug leading to loss of resin and yield, figure 27.

Loose Merrifield resin
loading 0.3 meq/kan

Stratosphere Plugs
loading 0.15 meq/ plug

Figure 27.

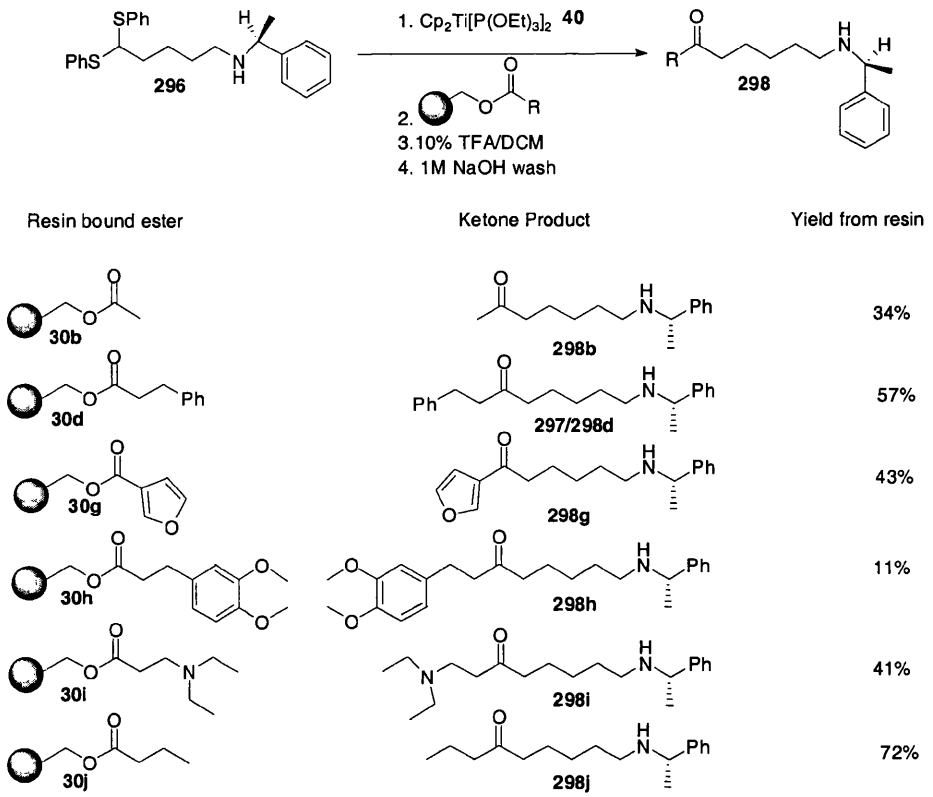
The loading was carried out as before using the caesium salt of the carboxylic acid and chloromethylpolystyrene Stratosphere ® plug. The resultant resin-bound ester **30d** was treated to alkylidenation conditions using the dithiane substrate **284**, to little effect, so increased equivalents and dithiophenyl derivative **296** were used, but the difference in yield remained low, (Scheme 75).



Scheme 75.

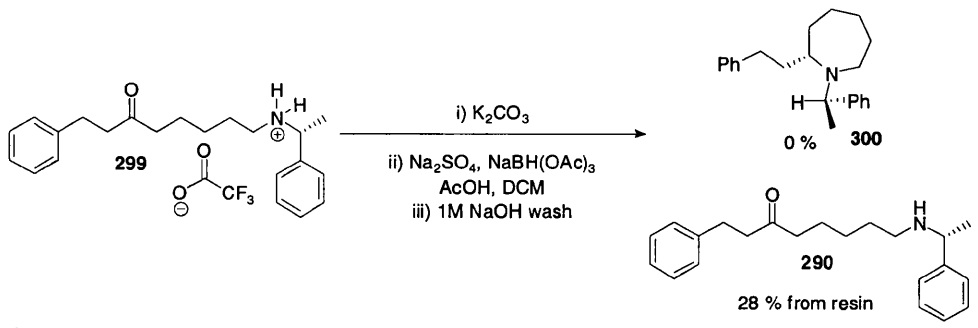
Following the lack of results concerning the resin and substrate conditions tried, extensive investigations into the extremely dry reaction conditions required for a successful Takeda reaction were carried out. The presence of even a small trace of water can affect the reduction of titanocene dichloride to give the low valent titanium species, $Cp_2Ti[P(OEt)_3]_2$ **40**. Removing every trace of water through extensive drying of reactants, glassware and solvents, and by heating the magnesium and the molecular sieves in a hot (250-300°C) oven overnight prior to the reaction being carried out solved the problem.

With the problem of low yields finally solved a small library of amino ketones was prepared in moderate to good yield off resin using a range of resin-bound esters. No post cleavage modification or purification was required, (Scheme 76).



Scheme 76.

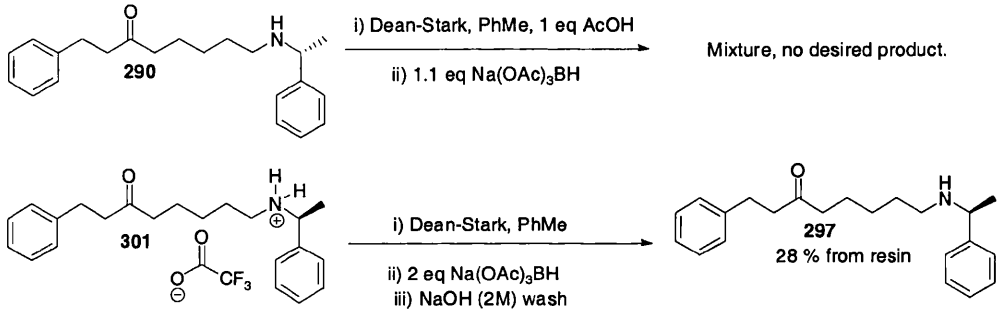
Having isolated the product in both the salt and free ketone form, initial attempts were made to cyclise and reduce the compounds using the same procedure as used in the piperidine chemistry previously described.[88] Following neutralisation of the TFA salt **299** off resin using potassium carbonate followed by sodium sulfate in excess and a mild reducing agent, sodium triacetoxy borohydride were used in the hope that the intermediate iminium ion would be reduced stereoselectively, as in the piperidines. The product obtained from the reaction however, was nothing more than the neutral ketone **290**, (Scheme 77).



Scheme 77.

As the recovered ketone was pure and there was enough material to work with again, further cyclisation attempts were made using mini Dean-Stark apparatus.

Dean-Stark removal of water from the ketone **290** followed by addition of the selective reducing agent sodium triacetoxyborohydride to the proposed cyclic iminium ion was the next alternative investigated. One equivalent of acetic acid was used to aid the formation of the iminium ion by facilitating dehydration and providing a counterion for the iminium cation. This reaction also failed to produce cyclised product, however due to excessive heating and a loss of toluene in the reaction set up this result is not surprising. The reaction was carried out again using no acetic acid and starting from the TFA salt as it comes off resin **301**. However, still ketone **297** was recovered, (Scheme 78).



Scheme 78.

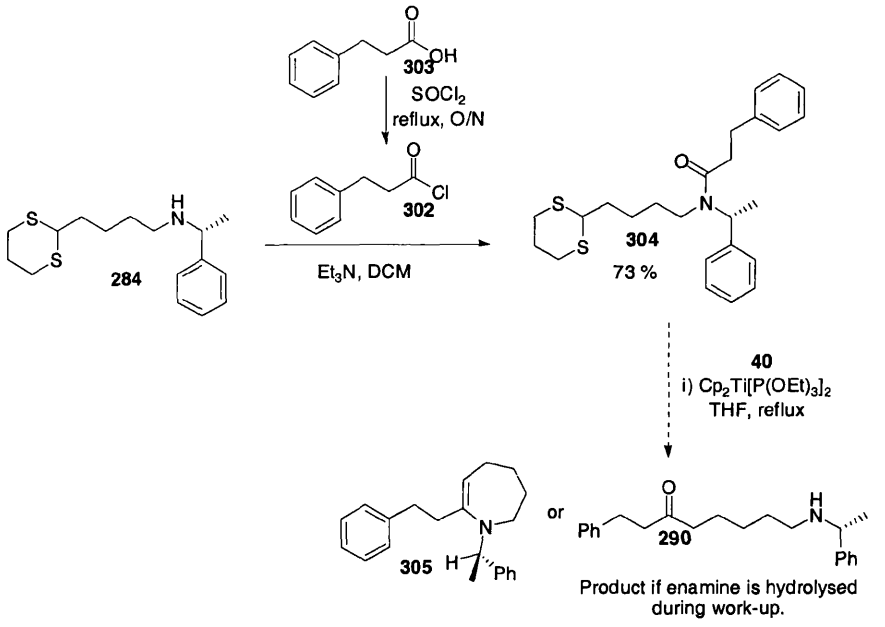
5.4 Alternative Routes to Amino Ketones

In order to investigate alternative methods of cyclisation and reduction, it was necessary to scale up the synthesis of amino ketones. The yields of the ketones from resin were now improved to the level of the substrates used to produce piperidine heterocycles. The yields of the Takeda reaction however, were not the only limiting factor in providing enough amino ketone to carry out research into cyclisation and reduction. Each polypropylene macrokan used in the solid-phase Takeda reaction could contain only ~0.3 meq (milliequivalents). Therefore scale up would be wasteful in kans and resin.

5.4.1 Intramolecular Takeda Reaction

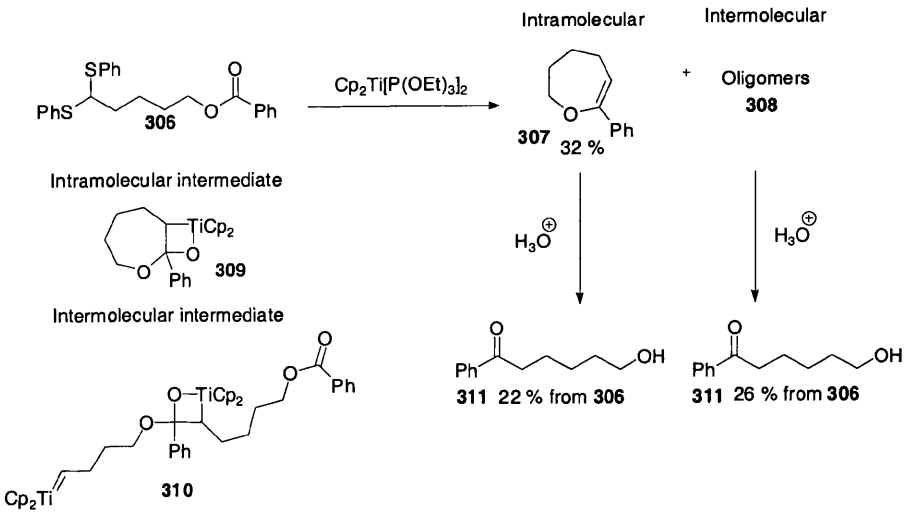
Two routes were explored in an attempt to access more ketone. The first was to utilise a solution-phase Takeda reaction by attempting an intramolecular alkylidenation of an easily obtained starting material. This was carried out by reacting the substrate **284** used for the solid-phase reaction with an acyl chloride **302**, formed by refluxing thionyl chloride with 2-phenylpropionic acid **303**. Ideally the dithiophenyl thioacetal substrate should have been used, but as it was a test reaction and the dithiane substrate was available **284** it was used. Formation of the amide substrate **304** was simple but it required column chromatography

before it was subjected to the low valent titanium complex **40** to produce the alkylidene, (Scheme 79).



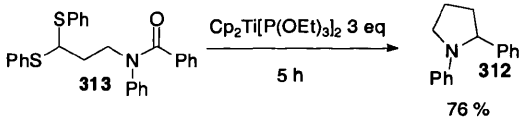
Scheme 79.

Previously work by Takeda and co-workers[95] have shown intramolecular alkylidenations are possible when the titanium alkylidene is formed from dithiophenyl thioacetal and reaction is with an internal ester moiety in substrate **306**. The product enol ether **307** was isolated but the intermolecular reaction competed and oligomers were also formed **308**. Attempts were made to decrease the chance of intermolecular reaction by using high dilution conditions, but this was not successful and the yield remained moderate. The reason for the preferred intermolecular reaction was assigned to the need for the intermediate in the reaction to form an oxatitanacycle **309**, this is greatly strained in the seven membered ring, but far less so in the intermolecular reaction intermediate **310**. The authors confirmed the nature of the oligomers isolated by hydrolysing them to the monomers obtaining the same hydroxyl ketone **311**, as from the hydrolysed enol ether **307**,[95] (Scheme 80).



Scheme 80.

Takeda and co-workers also showed that intramolecular alkylidenations in amides were possible in the synthesis of pyrrolidines **312** using the amide substrates **313**. The reaction proceeds as before forming the oxatitancyclobutane ring, however an unexpected result for the authors was direct reduction *in situ* giving the pyrrolidine ring directly. None-the-less the yields of the products were good and clearly the intramolecular reaction with the amide functionality had occurred, (Scheme 81).[119]



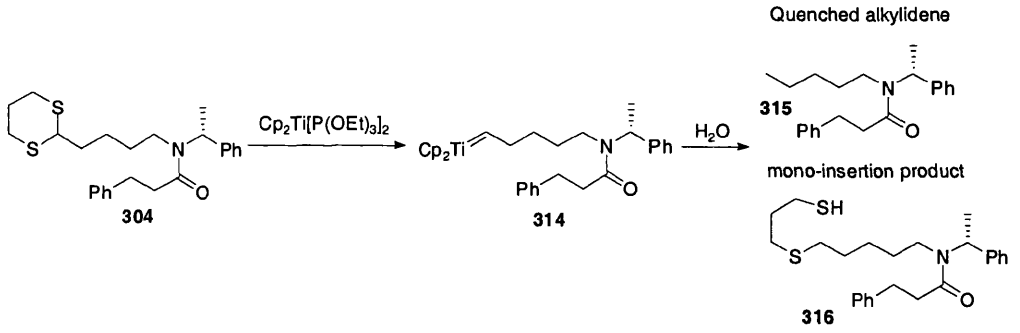
Scheme 81.

An important observation is that all the amides used in the above intramolecular alkylidenation research were benzanilides. This has implications on the reactivity of the substrate as the carbonyl group of the amide will be more electropositive owing to the competition of the aryl ring for the delocalisation of the lone pair on nitrogen. The subsrates in our synthesis are not benzanilides and therefore will be less reactive towards the nucleophilic Schrock carbene.

With this in mind reflux conditions were used, as had been implemented in the afore mentioned intramolecular ester alkylidenation, in the hope that it would encourage the reaction to go. The product desired from the reaction was the enamine **305** or the amino ketone **290** should it be hydrolysed on work-up. Unfortunately neither was produced and the reaction failed to give recognisable product after column chromatography, (Scheme 79).

The compounds or mixtures of compounds isolated provided two likely products, though neither was pure. The first was unreacted starting material **304** of which approximately 30 mg was recovered from the 321 mg used. This was important as it showed that the reaction had not fully formed the alkylidene needed to react intramolecularly. Only 30 mg was recovered, however, so the majority of substrate had been converted into the alkylidene and therefore the reaction could have produced some product albeit in low yield. The major recognisable product was amide **315** formed by quenching alkylidene **314**. Evidence for both rotomers present: δ_H (400 MHz, $CDCl_3$): 1.40 [$3H^A$, d, *J* 7.1 Hz, NCH(CH_3)], 2.00 ($3H^B$, d, *J* 7.8 Hz, NCHCH_3), 2.54 [$2H^A$, m, CH_2C(O)N], 2.65 [$2H^B$,m, CH_2C(O)N)], 2.73-2.90 ($2H^{A+B}$, m, CH_2CH_2N), 3.12-3.20 ($2H^{A+B}$, m, CH_2Ph), 4.97-5.04 ($1H^B$, m, NC**H**), 5.95-5.98 ($1H^A$, m, NC**H**), 7.07-7.26 (m, Ar-**H**).

This shows that the alkylidene did form, but did not react intramolecularly or intermolecularly and merely hung around until the work up of the reaction. Some evidence exists for a small proportion of material recovered being the product of monoinsertion **316**. δ_H (400 MHz), $CDCl_3$): 1.45 (3H, d, *J* 6.9, CHCH_3), 2.18 (2H, t, *J* 7.3, CH_2SCH_2), 2.26 (2H, t, *J* 7.4, HSCH_2), 5.21 (1H, bs/m, C**H**CH_3). None of these compounds were further purified or fully characterised, (Scheme 82).



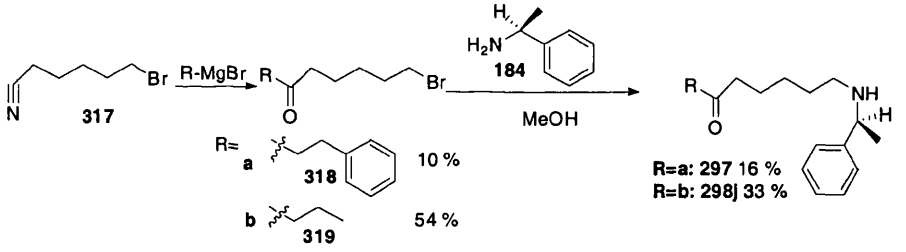
Scheme 82.

The failure of the reaction was not unexpected. The use of 1,3-dithiane instead of a dithiophenyl thioacetal would have contributed slightly to the problem, but as the main reaction products identified by ^{1}HNMR spectroscopy were those resulting from quenching of titanium alkylidene **314**, this was not the main reason for the reaction failing. The decreased reactivity of the amide with respect to benzanilides used in the literature could have been a considerable factor, with the alkylidene requiring a more electrophilic target than the amide used. The steric hindrance surrounding the carbonyl group of the amide bond could also have made it more difficult for the reacting centres to approach each other.

Had the reaction worked and the enamine **305** been isolated, it could have been treated to mild anhydrous acid to produce the cyclic iminium ion with greater ease and the reduction could have proceeded since the difficult step of ring closure had already occurred.

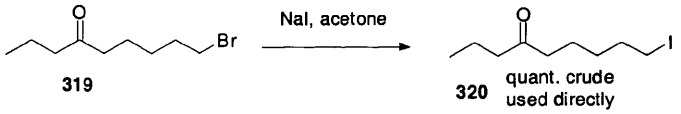
5.4.2 Grignard Addition to Nitriile Group and S_N2 Dispiacement

The second route was to form the ketone functionality by introducing diversity *via* a Grignard reaction to a nitrile group. Addition of an organometallic to the nitrile group of 6-bromocapronitrile **317**, following a procedure detailed by Buchwald and Reding[120] who used a similar route to access cyclic imines, bromo-ketones **318** and **319** could be achieved. The S_N2 displacement of the bromine using the chiral auxiliary **184** provides the amino ketone substrates **297** and **298j** for cyclisation in two steps from available starting materials, (Scheme 83).



Scheme 83.

Yields of the initial Grignard addition were poor in the case of the phenethyl derivative. Attempts to increase it were made by changing from the Aldrich supplied Grignard reagent to freshly prepared reagent. This increased the yield from 2% to 10%. While the yield for the phenethyl derivative was disappointing, the butyl derivative was isolated in reasonable yield, and after S_N2 displacement enough amino ketone **298j** was produced to test a wide variety of cyclisation conditions. The S_N2 displacement was also a problem however, and the yields were not optimal. A polar protic solvent, MeOH was used to solvate the transition state and encourage the reaction. An alteration was made in the route by using Finkelstein reaction conditions[121] to convert the bromide leaving group into an iodide leaving group, in the hope of increasing yields. Formation of the iodo ketone **320** was carried out using sodium iodide and the crude product was used (sodium iodide being the only contaminant) in the S_N2 displacement reaction, (Scheme 84).



Scheme 84.

Full conversion of the bromine-substituted ketone **319** to the iodo ketone **320** was observed and could be confirmed by the ^{13}CNMR analysis. The heavy atom effect applies to the iodine substituted compound and by using the equation for estimating the chemical shift of a carbon in an aliphatic chain (Eq 1), an approximation of the chemical shift of the carbon adjacent to the iodine can be obtained, using substituent constants, table 2.

Table 2

Substituent Constants : *z*			
α	**β**	**γ**	**δ**
I -7.2	Alkyl 9.4	Alkyl -2.5	Alkyl 0.3
H 0	H 0	H 0	H 0
H 0	H 0	H 0	H 0
Alkyl 9.1			

Equation 1: $\delta_C = -2.3 + \Sigma z + \Sigma S + \Sigma K$

Where z is the substituent constant (in this case the substituent constant changes from bromine in the starting material to iodine in the product), S is a steric correction (for

primary, secondary tertiary or quaternary substituted carbons), and ***K*** is a conformational increment for γ-substituents. ***K*** is 0 for freely rotating substitutents as in this case, and the sum of all the substituent constants *z*, can be obtained by adding the values apportioned to the α, β, γ, δ substituents of the carbon in question. In the case of the iodo compound the bonds from the carbon atom [-CH_2-CH_2-I] are freely rotating; there is a steric correction of 0 and the sum of the substituent constants *z* are obtained from table 1 [122] giving the equation 2:

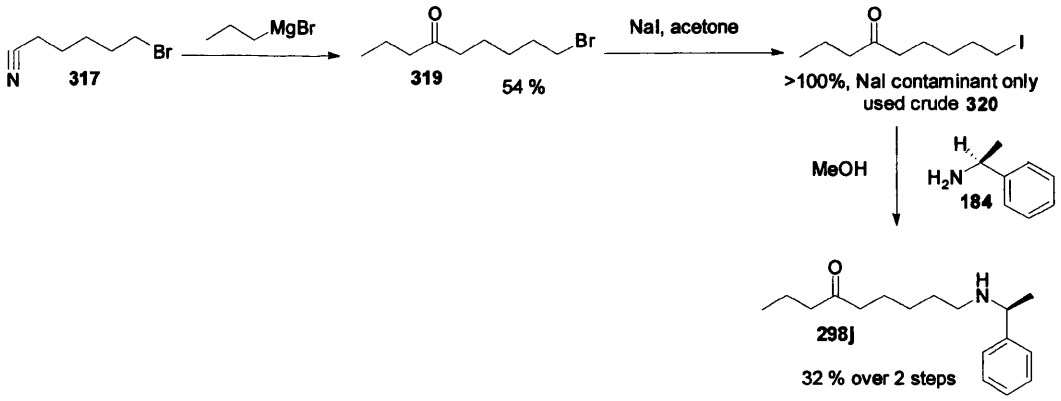
Equation 2: $\delta_C = -2.3 + (-7.2 + 9.1 + 9.4 + 0.3 + -2.5) + 0 + 0$

Predicted NMR δ_C for [-CH_2-CH_2-I] is 6.8 ppm

Observed NMR δ_C for [-CH_2-CH_2-I] is 6.82 ppm

Using the same equation with the bromine compound gives a predicted δ_C [-CH_2-CH_2-Br] of 32.9 ppm because of the α substituent change, bromine (*z* = 18.9) compared with iodine (*z* = -7.2). The observed chemical shift was 32.52 ppm.

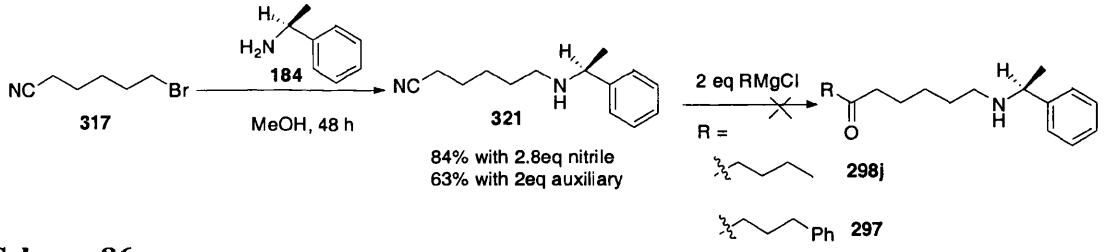
Unfortunately no difference in the overall yield was observed, (Scheme 85).



Scheme 85.

Once the amino- ketones **297** and **298j** were formed, simple purification was possible in the work-up by using acid/base extraction. Following solvent removal 1M HCl was added and an ether wash used to remove all non-amine by-products or starting materials. After this the aqueous acid layer was extracted with chloroform to remove the product as a salt, leaving behind the primary amine of the auxiliary **184**. The excess auxiliary **184** could be recovered by basification of the remaining solution and extraction with DCM .

The general problem of using alkyl halides with primary amines is over alkylation, but this did not occur. The recovery of halo ketone starting material **319** highlights this, and can be put down to the steric hindrance of the amine group.[123] Synthesis of the amino ketones **297** and **319** by carrying out the S_N2 displacement before addition of the Grignard reagent was also tried, and this drastically improved the efficiency of the S_N2 reaction, giving nitrile **321**. Even with increased equivalents of alkyl halide **317**, the by-products isolated were starting materials, not over alkylation products. The subsequent Grignard reaction failed however, probably due to the N-H present in the molecule, (Scheme 86), even though 2 eq of Grignard reagent were used.

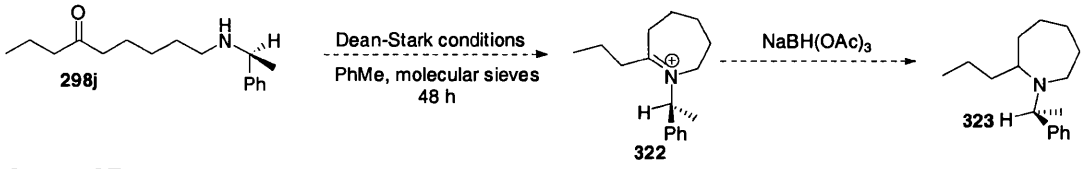


Scheme 86.

The successful route to amino ketones **297** and **298j** potentially provides access to a diversity based synthesis of chiral azepanes in solution phase and is complementary to the solid-phase enantioselective approach.

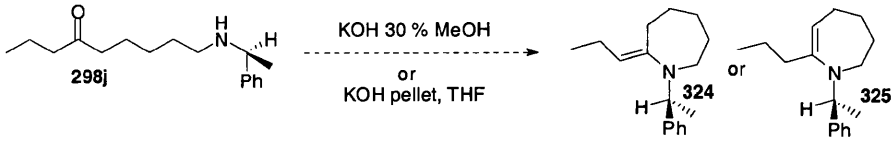
5.5 Cyclisation Methods Researched

With access to a larger quantity of substrate, research into the cyclisation-reduction of the amino ketones to give azepanes was carried out. It was hoped that the Dean-Stark removal of water under acidic conditions would give a mixture of cyclic enamine and iminium ion **322** that would be reduced by using sodium triacetoxy borohydride and give the azepane **323**. Unfortunately this was unsuccessful and starting material **298j**, was recovered.



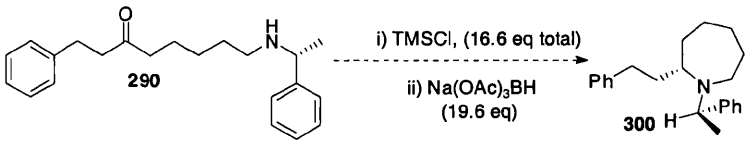
Scheme 87

A 30% solution of potassium hydroxide in MeOH and a solid pellet of KOH in THF were also used to encourage cyclisation-dehydration. The expected enamine products **324** and **325** were not obtained and under both conditions starting ketone was recovered, (Scheme 88).



Scheme 88.

Next the use of a Lewis acid to coordinate to the oxygen atom and encourage cyclisation of the amino group was investigated. The chosen Lewis acid was chlorotrimethylsilane. This reagent had the benefit of being oxyphilic, and being able to provide a chloride counterion for the iminium cation. Ketone **290** was treated with an excess of the TMSCl (3eq) and the mixture left stirring overnight during which time solvent evaporated. More DCM and TMSCl were added, a further 11.8 eq, (a total of 16.6 eq) and the reaction mixture stirred for 5 h. At this time the reducing agent was added in excess (19.6 eq) to account for the possible reaction with the TMSCl, and the reaction mixture stirred overnight, (Scheme 89).



Scheme 89.

Following work-up it appeared by the NMR data that the reaction had been successful. Having no data to compare it with the disappearance of the carbonyl ^{13}C in the carbon NMR seemed very promising and further attempts to optimise and induce stereoselectivity continued, pending the obtaining of full characterisation data. The reaction was repeated using lower temperatures and different reducing agents (e.g. L-selectride) in an effort to control the diastereoselectivity. Each reaction had to be repeated to effect conversion to what was thought to be cyclised product. The attempts to influence the diastereoselectivity of the reaction were unsuccessful, and following the acquisition of a mass spectrum, it was clear that the cyclised product **300** had not been produced.

GCMS gave rise to one fraction and the LRMS showed a peak that appeared to be the molecular ion at m/z ratio 248. Analysing the M.S. data in conjunction with the ^{1}H and ^{13}C NMR data, which was complicated due to diastereomers, led to the conclusion that the products were alcohols **326**. The m/z ratio was wrong for the molecular ion of these compounds, and 248 must be a fragment. A general fragmentation pattern in compounds

containing benzylic methyl substitution is loss of $^{\bullet}CH_3$. Loss of this from the alcohols **326**, would give the m/z fragment 248 due to ion **327**. Other m/z ratios present in the LRMS were 105 corresponding to **328** and 158 corresponding to **329**. HRMS was sought on that structure and this confirmed the analysis, figure 28

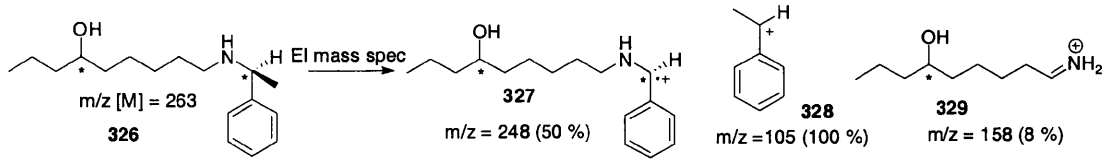


Figure 28.

Use of excess TMSCl had allowed the mild reducing agent sodium triacetoxyborohydride to reduce the ketone to an alcohol. In spite of investigating a range of conditions, cyclisation to the seven membered ring failed, table 3. Interestingly another group member however, Louis Adriaenssens has now successfully applied the TMSCl-sodium triacetoxyborohydride procedure to the cyclisation of 5-amino ketones to give chiral piperidines.

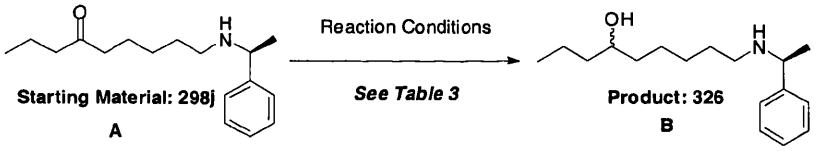
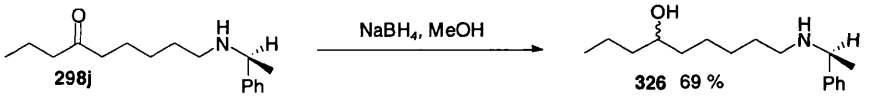


Table 3

Starting Material (scale in mol)	Reaction Conditions	Product/s Obtained	Yield
A 0.383 mmol	i) TMSCl (5 eq), DCM (2 mL), R.T. ii) $NaBH(OAc)_3$ (6 eq) i) TMSCl (10 eq), DCM (2 mL), R. T. ii) $Na(OAc)_3BH$ (12 eq)	**A+B** after first reaction. **B** only after second treatment	35% **B**

A 0.19 mmol	i) ii)	Microwave 50 W, 60 °C, 24 psi AcOH 1 drop, MS 4Å, MeOH, (2 mL) $NaBH_4$ (2 eq)	**A+B**	N/A
A 0.19 mmol	i) ii)	Microwave 200W, 85 °C, 94 psi, MS 4Å, tosic acid (1 crystal), MeOH. (2 mL) $Na(OAc)_3BH$ (2 eq)	**A**	51% Recovery
A 0.17 mmol	i) ii)	Microwave 150 W, 55-75 °C, 3 psi, TMSCl (18.5 eq), Et3N (1 eq), DCM (0.8 mL) $Na(OAc)_3BH$ (20 eq)	**B** + impurities	N/A
A 0.195 mmol	i) ii)	Microwave 200 W, 58 °C, 4 psi, TMSCl (8.1 eq), DCM $Na(OAc)_3BH$ (9.1 eq)	**B**	75% Crude

Finally with all cyclisation attempts failing, the structures of the alcohols **326** were confirmed by preparing an authentic sample by reducing the ketone **298j** with sodium borohydride, (Scheme 90).



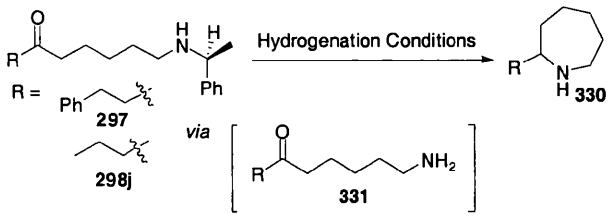
Scheme 90.

5.6 Proposed Route to Racemic 2-Substituted Azepanes

Attempts to produce azepanes enantioselectively were discontinued and the focus switched to producing racemic azepanes. Removal of the auxiliary by cleaving the benzylic C-N bond using hydrogenation was investigated. This would provide the free primary amino

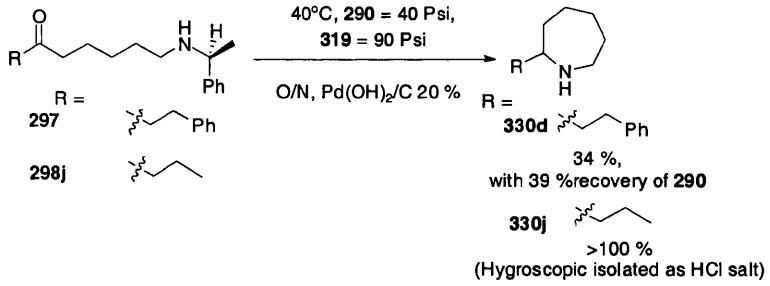
ketone, that would hopefully cyclise and reduction under the same conditions would produce racemic 2-substituted azepanes.

Amino ketones **297** and **298j** were subjected to a range of hydrogenation conditions in an effort to produce the primary amino ketones **331** that could cyclise with far greater ease than the sterically hindered amines **298j** and **297**, reducing in situ to racemic azepanes **330**, (Scheme 91).



Scheme 91.

Removal of the auxiliary at 40 psi and 40 °C using palladium hydroxide on carbon as a catalyst worked to some degree with ketone **297** giving azepane **330d** in 34% together with 38% recovered starting material after shaking overnight. This result shows that cyclisation once removal of the auxiliary has been accomplished is facile, but that the removal of the auxiliary is more problematic. When ketone **298j** was treated to a higher pressure of hydrogen under the same conditions, fully cyclised and reduced product **330j** was isolated. Though the exact yield was uncertain, as the product was isolated as a hygroscopic hydrochloride salt **330j** that resisted drying, it is assumed to be near quantitative, (Scheme 92).



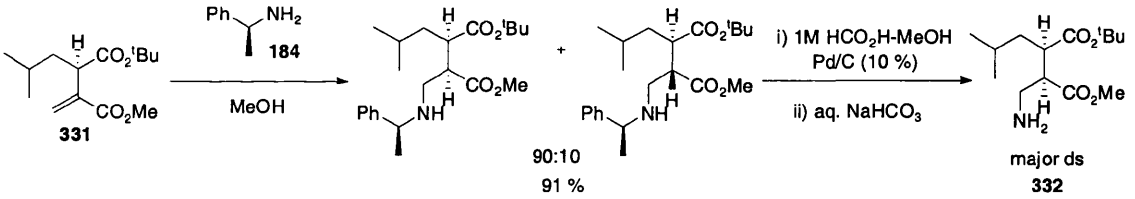
Scheme 92.

At this time a paper was published that reported removal of the same chiral auxiliary from piperidines using atmospheric hydrogenation conditions and HCl acid,[92] but application of this method was unsuccessful.

Another method for the removal of the benzyl group is catalytic transfer hydrogenation. This was not tried but could have yielded positive results. The use of formic acid and

palladium on carbon as a catalytic support was first described in the 1970's as a useful selective *N*-benzyl deprotection reagent for peptide synthesis. A paper by Jerina *et al* also describes using a short column of palladium on carbon and passing the reaction mixture over it and illustrates how this method is useful for automated systems. Using the column prevents the need to separate the catalyst from the product at the end of the reaction and the column can then be re-used once cleaned.[124]

Later examples using the phenylethylamine auxiliary **184** include its use in a stereoselective Michael addition to an acrylate derivative **331**, to produce a diastereoselective synthesis of inhibitors of enzymes linked to athritus. Giving matrix metalloproteinase analogues **332**[125] (Scheme 93).

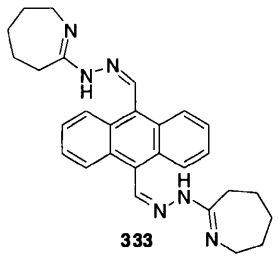


Scheme 93.

Clearly the use of a chiral auxiliary as a protecting group in the preparation of racemic azepanes was rather wasteful so an alternative route using a different protecting group and generating cyclic imine intermediates was investigated.

Chapter 6: Literature Routes to Cyclic Imines

Cyclic imines have applications for the pharmaceutical industry as potential leads for treatment of Alzheimer's disease[126] and examples have been reported to have anti-cancer[127] and anti-bacterial properties.[128] An example of a related amidine compound that exhibits anti-cancer activity against leukaemia and melanoma cell lines in mice is compound **333**, figure 29.[129]



333

Figure 29.

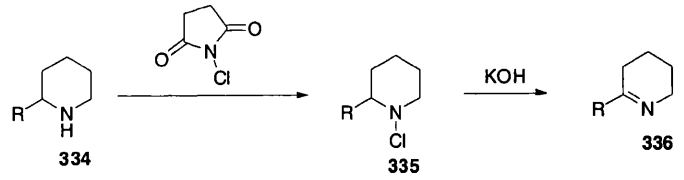
Cyclic imines are also extremely useful synthetic intermediates. They provide access to 2-substituted heterocycles, through nucleophilic addition to the imine bond[130] and chiral heterocycles, through stereoselective reduction of the imine bond.[131-133] Cyclic imines can also be used to generate aromatic heterocycles,[134] amino acid analogues[135] and as a substrates for the Ugi reaction.[136]

6.1 Previous Syntheses of Cyclic Imines

The following review of cyclic imine synthesis is designed as a general introduction to the types of reactions that have previously been used to produce them. For a full review of the synthesis of six membered cyclic imines up to 1998 please see the review by M-G. A. Shvekhgeimer.[137]

6.1.1 Halogenation of the Nitrogen Atom

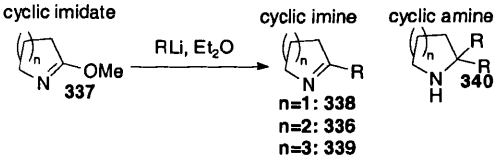
One of the oldest methods for preparing cyclic imines is *via* the addition of a halogen to the nitrogen atom of a saturated heterocycle **334** to give the corresponding *N*-chloropyrrolidine[138] or *N*-chloropiperidine **335**,[139] followed by base-induced elimination, (Scheme 94). The transformation can be carried out using a variety of reagents,[137] one example being *N*-chlorosuccinimide, and following treatment of base, the cyclic imine **336** can be isolated.



Scheme 94.

6.1.2 Organometallic Addition to Lactim Ethers

One of the most general methods for the preparation of 2-substituted cyclic imines is the reaction of lactim ethers **337** with nucleophiles, Grignard reagents or organolithium reagents being the most common,[130] (Scheme 95). The lactim ethers or cyclic imidates **337**, are synthesised *via* reaction of the corresponding lactams with dimethyl sulfate, methyl fluorosulfonate or trimethyloxonium tetrafluoroborate.[137] Reaction with an organolithium, a more effective nucleophile than Grignard reagents, proceeds through an addition/elimination sequence, liberating lithium methoxide. The reaction provides access to 5, 6, and 7 membered cyclic imines **338**, **336**, **339** in good yield, though the choice of organolithium reagent is limited to less reactive organolithiums to ensure the imine products over the amines **340**.[130]

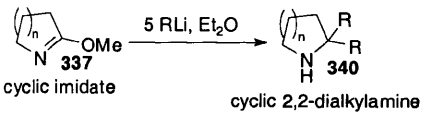


imidate	RLi	imine	yield	amine	yield
n = 1	*n*-BuLi	*n*-Bu	34 %	*n*-Bu, *n*-Bu	24 %
n = 2	*n*-BuLi	*n*-Bu	21 %	*n*-Bu, *n*-Bu	25 %
n = 2	Ph-Li	Ph	47 %	Ph, Ph	
n = 3	*n*-BuLi	*n*-Bu	9 %	*n*-Bu, *n*-Bu	33 %
n = 3	Ph-Li	Ph	67 %	Ph, Ph	

Scheme 95.

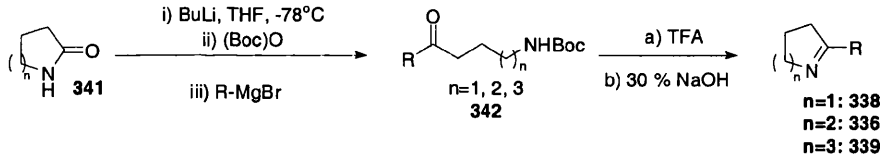
This is due to the problem of double addition of the alkylating reagent. The more reactive the organolithium reagent, the higher the quantity of double alkylated products **340**, though if this is the desired process it can be optimised by using 5 eq of organolithium reagent to yield cyclic 2,2-dialkyl amines,[130] (Scheme 96).

Scheme 96.



6.1.3 Organometallic Addition to Cyclic Imides

Surprisingly few examples rely on simple condensation of a carbonyl group with a primary amine.[140-142] This is the method of ring closure employed in our chemistry. An example of this method is demonstrated by Giovannini *et al*, who produced a range of 5, 6 and 7 membered cyclic imines **336**, **338**, **339** using the corresponding lactams **341** as starting materials[142], (Scheme 97). The authors removed the boc protecting group with acid before adding a 30% aqueous sodium hydroxide wash to form the cyclic imine from the amino ketone **342**. In addition to sodium hydroxide solution, sodium carbonate has also been used to effect ring closure successfully.[141]



Scheme 97.

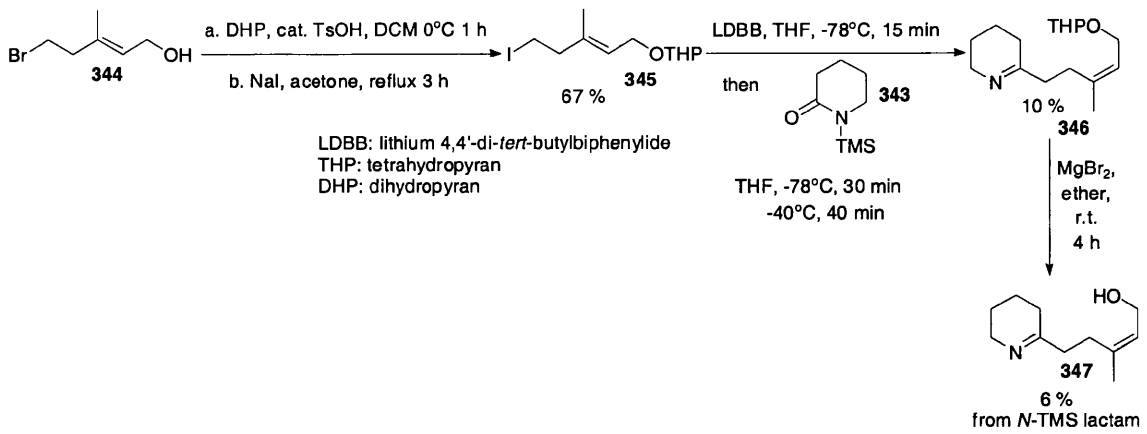
Hydroxylamines have been used as synthetic precursors to cyclic imines. The reaction of titanium trichloride with a cyclic hydroxylamine under anhydrous conditions, followed by a basic work-up with sodium hydroxide gives rise to cyclic imines. The dehydration reaction produces imine products in 53 – 99% yield.[143]

6.1.4 Organometallic Addition to *N*-trimethylsiiyl lactams

A similar method for the general synthesis of 2-substituted 5,[144,145] 6,[144,145] and 7[144,146] – membered ring, 2-substituted cyclic imines has been developed that utilises *N*-(trimethylsilyl)lactams **343** and a nucleophilic alkylating agent e.g. organolithiums to produce an adduct that then loses trimethylsilanol to form the cyclic imines.

An example, detailed below in Scheme 98, shows use of this chemistry in the synthesis of polonicumtoxins, that have ecological interest.[147] The cyclic imine core of the structure was synthesised by alkyllithium addition to *N*-TMS–lactam **343**. The alkylating agent was synthesised from a bromide **344**. THP protection of the alcohol was followed by Finkelstein conversion to the iodide **345**. Lithium-halogen exchange was carried out using LDBB (lithium 4,4'-di-*tert*-butylbiphenylide) as previous attempts with butyllithiums were unsuccessful. Nucleophilic addition of the alkyllithium to *N*-TMS-δ-valerolactam gave an adduct that is said to undergo a Peterson-type elimination to leave a cyclic imine **346**.

Removal of the THP protecting group is carried out giving the product, polonicumtoxin C **347**, in low overall yield.[147]

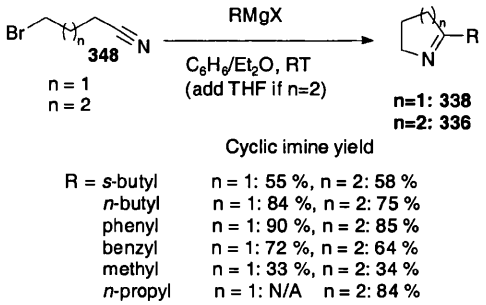


Scheme 98.

A more recent development in this chemistry has led to the development of a one-pot silylation and alkylation of the *N*-TMS-lactam, preventing the need for isolation of the highly labile silylated product.[145]

6.1.5 Grignard Addition to Nitriles

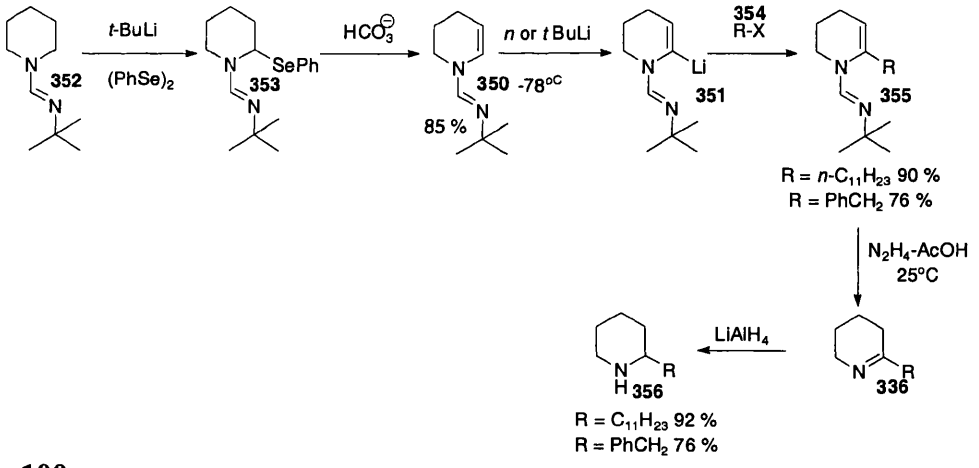
Another reaction which utilizes organometallic nucleophiles, employs a Grignard reagent. Addition of a Grignard reagent to a nitrile group **348** and subsequent intramolecular cyclisation *via* S_N2 displacement of a halide in **348** provides access to a range of 5 and 6 membered cyclic imines **338**, **336**,[148] (Scheme 99).



Scheme 99.

6.1.6 Functionalised Enamines as Starting Materials

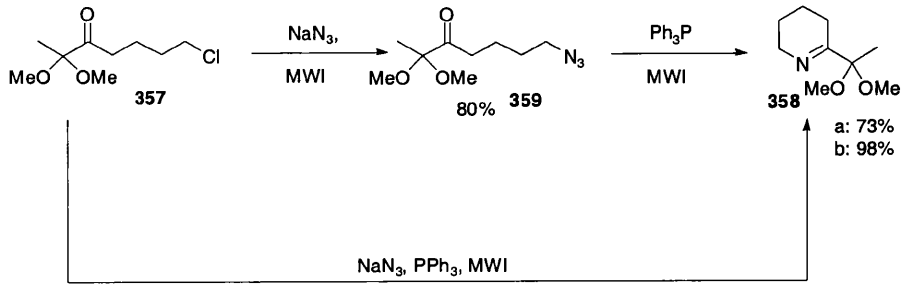
Cyclic imines **336** can be prepared from cyclic enamidine **350**, by turning the cyclic enamidine into an organolithium reagent **351**,[149] (Scheme 100). This synthetic intermediate is produced by α-lithiation of formamidine derived heterocycles **352** followed by selenation with diphenyl diselenide **353**. Elimination of phenylselenide with bicarbonate yields enamidate **350** in 70 – 90% yield. Cyclic enamidines **350** can then undergo α-lithiation, again, and alkylation **354** to give 2-substituted enamines **355**. Removal of the formamidine group follows, leaving 2-substituted cyclic imines **336**. These can be reduced directly to piperidines **356**. In the seven membered ring series the sequence was only taken to as far as to form the seven membered enamidine.[149] The chemistry has also been extended to give 2,6-disubstituted cyclic imines by repeating the lithiation / alkylation process.[149]



Scheme 100.

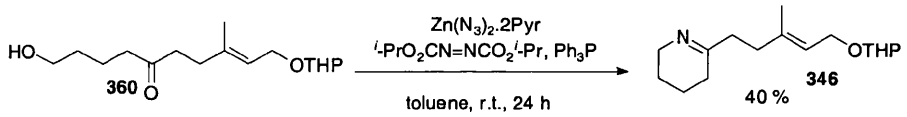
6.1.7 Aza-Wittig Reaction

The aza-Wittig is similar to the Wittig alkenation but with the α-anion on nitrogen instead of carbon. The result is an imine bond, and when the reaction is carried out intramolecularly on ketones, 2-substituted cylic imines are produced, (e.g. Scheme 101). Thus simple halo ketone **357** was converted into imine **358** in 2 steps *via* azide **359**,[136,150] and also in a one pot process.[150] The yield of imine **358** *via* this one pot reaction was superior to that of the aza-Wittig reaction using preformed azide **359**.



Scheme 101.

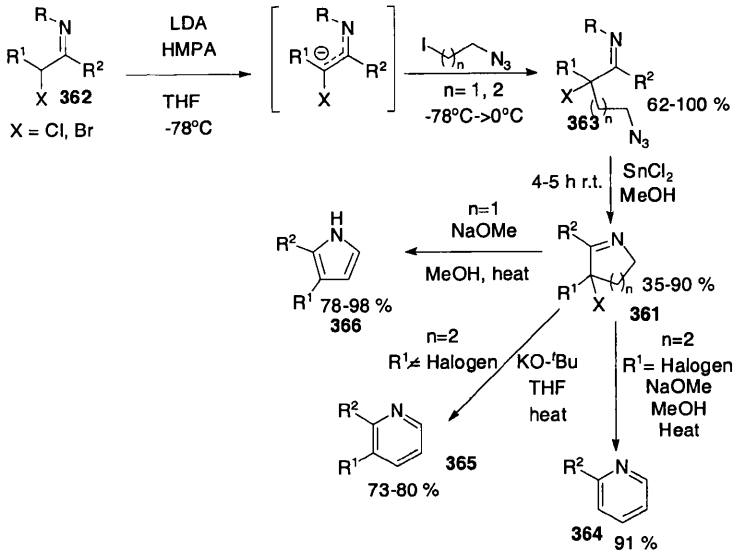
Synthesis from alcohols is also possible. Thus a one pot synthesis of the cyclic imine **346** from a primary alcohol **360** combined Mitsunobu conditions and Staudinger aza-Wittig conditions to give an in *situ* conversion of the alcohol **360** to azide followed by the intramolecular aza-Wittig reaction.[147] (Scheme102).



Scheme 102.

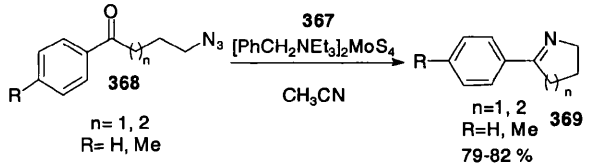
6.1.8 Other Reductive Cyclisations of Azides

Related reductive cyclisations of azides are also possible using other reducing agents. One example is a route to pyridines and pyrroles that avoid harsh conditions[151] by employing a dehydrohalogenation reaction, (Scheme 103). The halogenated cyclic imines **361** required for this reaction were synthesised from α-haloketimines **362.** Regioselective alkylation α to the imine with ω-iodo-alkyl azides was carried out to give azides **363.** The resultant α,γ- and α,δ- difunctionalised ketimines **363** were then subjected to chemoselective reduction and cyclisation using tin(II) chloride, forming 5 and 6 membered halogenated cyclic imines **361** cleanly.[151] The imines were then treated to base conditions to yield the desired pyridines **364** and **365** or pyrroles **366**.[151]

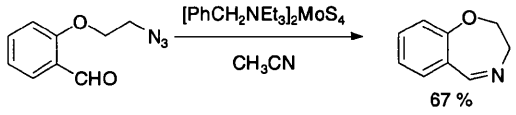


Scheme 103.

In a similar method to the tin(II) chloride reductive cyclisation, a tetrathiomolybdate complex **367** was used to reduce the azide **368** and form the cyclic imine **369** in one step[152] (Scheme 104). This procedure was useful for 5, 6 and 7 (benzene fused) cyclic imines[152] (e.q. Scheme 105).



Scheme 104.

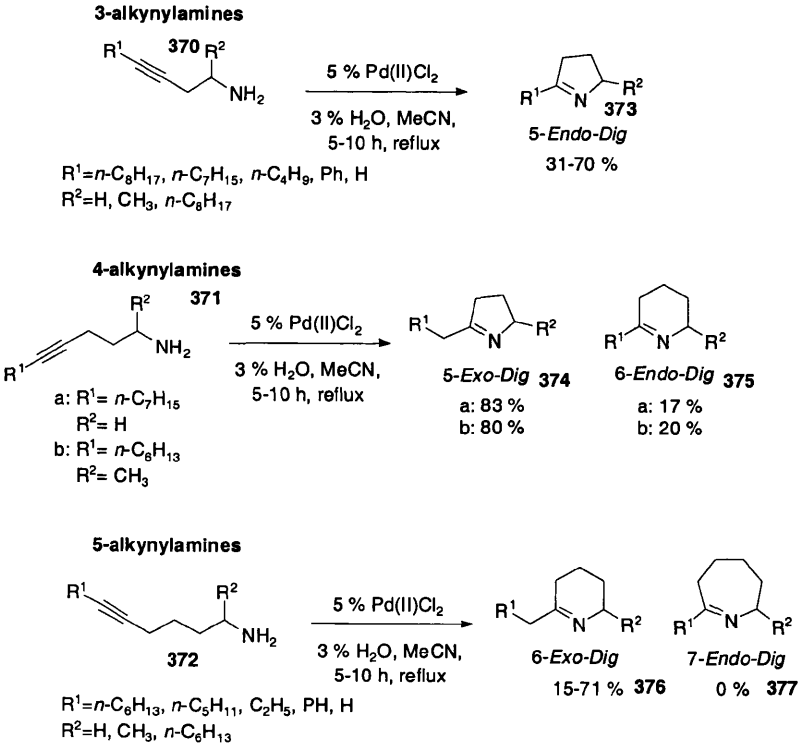


Scheme 105.

6.1.9 Transition Metal Catalysed Cyclisation of Alkenes and Alkynes

Transition metal promoted intramolecular amination of alkenes or alkynes is also a method for cyclic imine formation (e.g. Scheme 106). The use of an alkyne as the potential electrophile is superior to an alkene, as the substrate does not suffer the lack of regioselectivity that occurs with the alkene. The reaction can be carried out with the catalytic action of gold(III)[153] or with a palladium(II) source.[154]

In the examples shown palladium chloride is used, coordinating to a π bond of the alkynes **370**, **371**, **372**. This draws electron density to the electrophilic palladium(II) and allows nucleophilic attack, intramolecularly in this case, by the nitrogen nucleophile. Protonolysis of the resulting C-Pd bond is required, and this is encouraged with the addition of catalytic water. In the work carried out by Utimoto *et al,*[154] 3-alkynylamines **370** were treated to palladium chloride (5%) and water (3%). The favoured 5-*Endo-Dig* product **373** was obtained in 31-70% yield. 4-alkynylamines **371** were treated to the same conditions and the result was a mixture of 5-*exo-dig* product **374** and 6-*endo-dig* **375** product in a ratio of 80:20-83:17. 5-Alkynylamines **372** cyclise exclusively to the 6-*exo-dig* **376** product, although the 7-*endo-dig* **377** product is allowed by Baldwin's rules, it was not observed, (Scheme 106). In all cases, the initial products of addition to the alkynes were enamines. The *exo-dig* additions gave exocyclic enamines and the *endo-dig* additions endocyclic, however, the enamines rearranged to give the more stable cyclic imines **373**, **374**, **376**.[154].



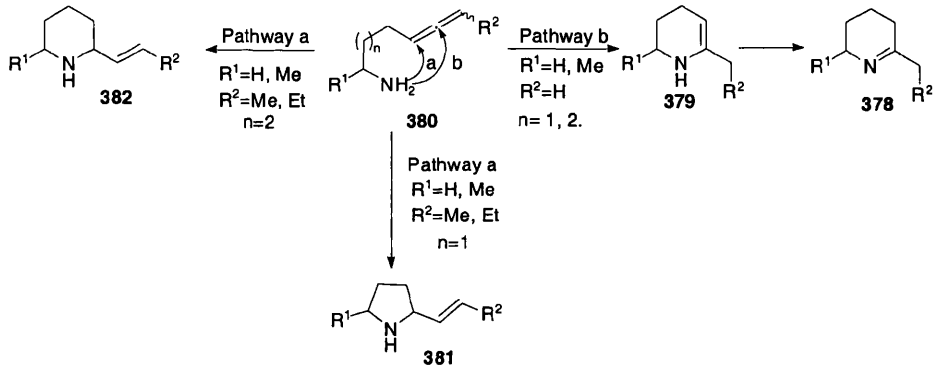
Scheme 11.

Similar cyclisations are possible using other transition metal catalysts.[155,157]

The hydroamination of allenes has also been investigated. Organolanthanide complexes of La, Sm, Y, and Lu, ($Cp'_2LnCH(TMS)_2$, $Cp'=\eta^5Me_5C_5$) have been used in the formation of cyclic imines **378** from amino allenes **380**. Alkene and alkyne moieties bearing an amine

functionality can insert into the σ metal-ligand bond once the amine coordinates to the metal centre in bis(cyclopentadienyl)lanthanide complexes.[158] There are two possible outcomes of aminoallene reaction with the organolanthanide complexes. The first is formation of vinyl pyrrolidines or piperidines **381** or **382** though pathway (a), and the second is formation of cyclic imines **378** *via* pathway (b), (Scheme 107). 1,3-disubstituted aminoallenes R^2 = alkyl, always gave cyclic allylamines, so a range of 2,6 substituted cyclic imines cannot be accessed through this route.

The only substrate to give exclusively six membered cyclic imine **378** was unsubstituted aminoallene (n=2), R^2=Me, with other substrates providing mixtures.[158]

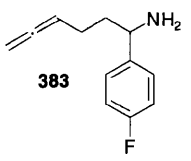
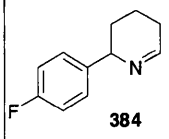
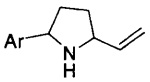
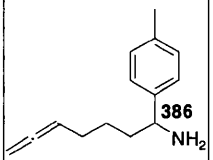
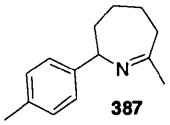
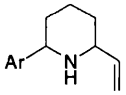


Scheme 107.

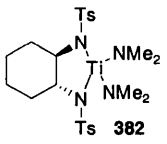
Aminoallenes have also been investigated as substrates for cyclic imine synthesis using titanium and zirconium complexes.[156] The choice of substrate was dictated by the authors requirement of a suitably challenging reaction to test the catalytic activity of the complexes synthesised. The study examined a range of catalysts starting from $CpTiMe_2$ and CpTi(NHAr)(NAr)py, (Ar = 2,6-dimethylphenyl), catalysts that both produced acceptable intermolecular hydroamination products, but proved less reactive for intramolecular reactions.[156] A tosyl-substituted complex **382** gave increased reactivity and regioselectivity reacting with amino allene **383** to form sixmembered cyclic imines **384** only, over allylamines **385**, table 4. The chemistry was extended to an aminoallene substrate **386** which gave rise to a 2,7-substituted cyclic imine **387** using the same tosyl substituted catalyst **382**. In this case the product did contain some allylamine **388** but the yield of cyclic imine **387** was excellent, table 4.[156]

Table 4.

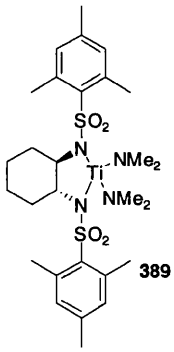
e.g.

entry	substrate	major product	cat.	t/h	isolated yield imine : allylamine
1	 **383**	 **384**	**382**	10	93 % : 0 %  **384** **385**
2	 **386**	 **387**	**382**	3	93 % : 7 %  **386** **388**

Steric congestion around the metal centre was investigated using mesitylene sulfonyl rather than tosyl ligands. The result was increased reactivity of the catalyst, giving better yields with the same catalyst loading and reaction time. The more sterically hindered mesityl ligand complex **389**, (figure 30) is also capable of reacting with 1,3-disubstituted allenes **392** giving greater yields than that of the tosyl-ligand, and of producing 2,6-disubstituted cyclic imines **393**, table 5.[156]



Ts **382**

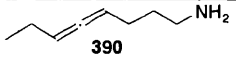
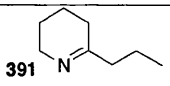
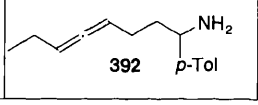
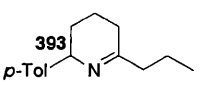


389

Mesityl-substituted catalyst

Figure 30.

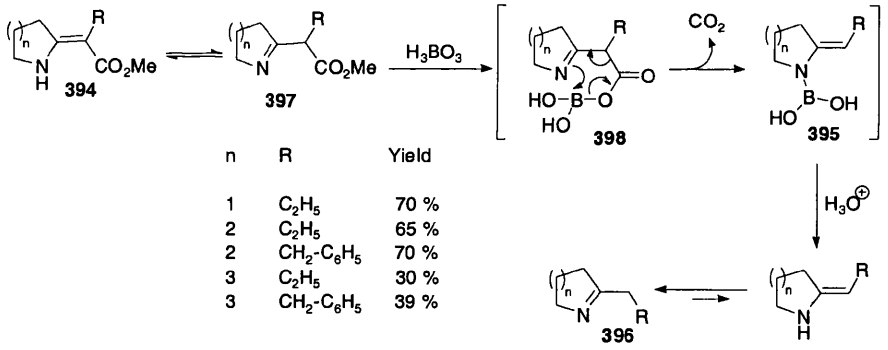
Table 5.

entry	substrate	major product	cat.	T °C	t/h	yield
1	 **390**	 **391**	MSC **389** TSC **383**	75 75	2 2	96 % 70 %
2	 **392** *p*-Tol	 **393** *p*-Tol	MSC **389**	105	2	100 %

Zirconium analogues of the titanium catalysts were synthesised. The mesityl-sulfonyl analogue showed improved reactivity compared to $Zr(NMe_2)_4$ but increased the production of the allylamine side product in comparison to the titanium catalyst.[156]

6.1.10 Decarboxylation Reactions

The decarboxylation of cyclic β-enaminoesters **394** using boric acid, followed by hydrolysis of the boron complex **395**, yields cyclic imines **396**, (Scheme 108).[159] β-Enaminoesters, synthesised from lactams, first undergo a boric acid catalysed conversion of tautomers giving imines **397** suitable for thermal rearrangement. Transesterification with boric acid occurs and a thermal rearrangement takes place with the correct tautomer **398**. The boron complex **395** is then hydrolysed using aqueous hydrochloric acid and the resultant compound is a 5, 6, or 7 membered cyclic imine **396** depending on the structure of the starting β-enaminoester.[160]

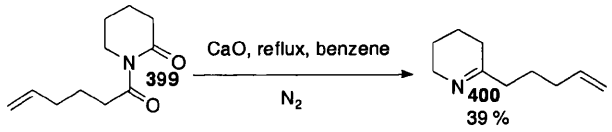


Scheme 108.

The methodology was subsequently expanded by the authors to form a route to geminal – disubstituted cyclic β-enaminoester compounds.[161]

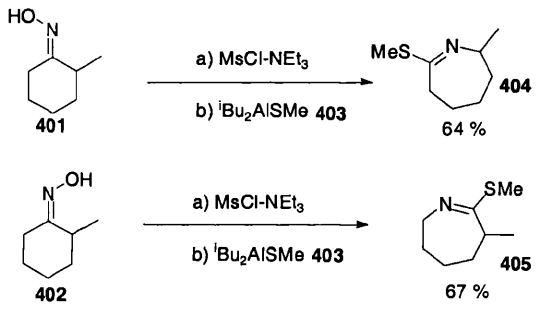
6.1.11 Rearrangement Reactions

Rearrangements comprise a significant portion of the routes available to cyclic imines. The rearrangement of *N*-acyllactams provides a realatively short route to 6 membered cyclic imines, (Scheme 109).[128] In one example simple acylation of 2-piperidinone with an acid chloride provided the substrate **399** for the rearrangement. The *N*-acyllactam was then heated under reflux in benzene with calcium oxide to give the cyclic imine product **400**. The yield however, was low.[128]



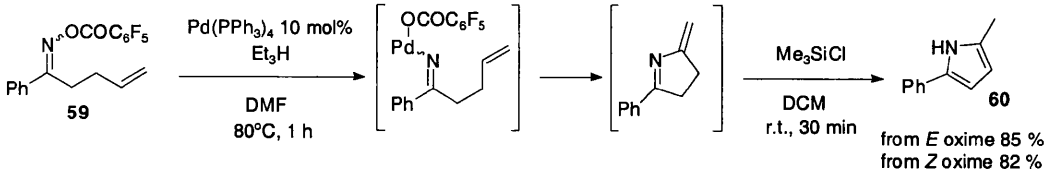
Scheme 109.

Beckmann rearrangement of oxime sulfonates **401** and **402** have also been used to produce cyclic imines. Maruoka *et al* used the derivatised oximes **401** and **402** with an organoaluminium reagent **403** to effect the Beckmann rearrangement and also provide a nucleophile to add to the intermediate iminocarbocation, (Scheme 110). In this manner six, and seven membered cyclic imines **404** and **405** were produced regioselectively depending on the geometry of the oxime used. This discrimination comes from the selective migration of the group anti to the oxime sulfonate.



Scheme 110.

Palladium catalysed intramolecular reaction of oximes, with an alkenes has also been reported, (e.g. Scheme 111). This amino-Heck method of ring closure has been used to access bicyclic compounds and spirocyclic compounds. An example of its use is in the synthesis of pyrroles **407** *via* oximes **407**, shown below.[162]



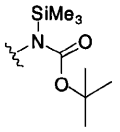
Scheme 111.

Chapter 7: Diversity Orientated Synthesis of Cyclic Imines

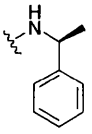
7.1 Proposed Route to Seven Membered Cyclic Imine Library

In chapter 5, I discussed the unsuccessful attempts at the asymmetric synthesis of azepanes, which concluded, with a successful synthesis of racemic azepanes by reduction of imines produced from amino ketones. A phenethyl group derived from enantiopure phenylethylamine had been employed but its removal had proved capricious and the use of an enantiopure protecting group seemed strange in a racemic synthesis. Consequently alternative protecting groups were considered that might allow access to the key imine intermediates. Not only are imines useful targets in themselves but asymmetric reduction would allow enantioselective access to chiral azepanes.

The route towards cyclic imines required a new protecting group strategy. Previously the silyl carbamate group, (Figure 30), had been employed to protect amines during the Takeda reaction and deprotection was facile. However this protecting group was unstable and required formation immediately prior to use. A new protecting group that could withstand the Takeda conditions was needed. In addition, we wanted to keep the benefits of previous protecting groups: ease of removal, preferably under cleavage conditions, was highly desirable so as to avoid the need for post cleavage modification and ease purification of the products without use of chromatography. The α–phenylethylamine auxiliary had provided insight into the protection strategy as it showed that sterically hindered amines were tolerated in the titanium reagent.



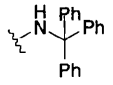
Silyl carbamate protecting group



alpha-phenylethylamine auxiliary

Figure 30.

The protecting group chosen was the bulky trityl protecting group, (Figure 32), as it is easily cleaved under mildly acidic conditions like those used for cleavage of the enol ether from resin.

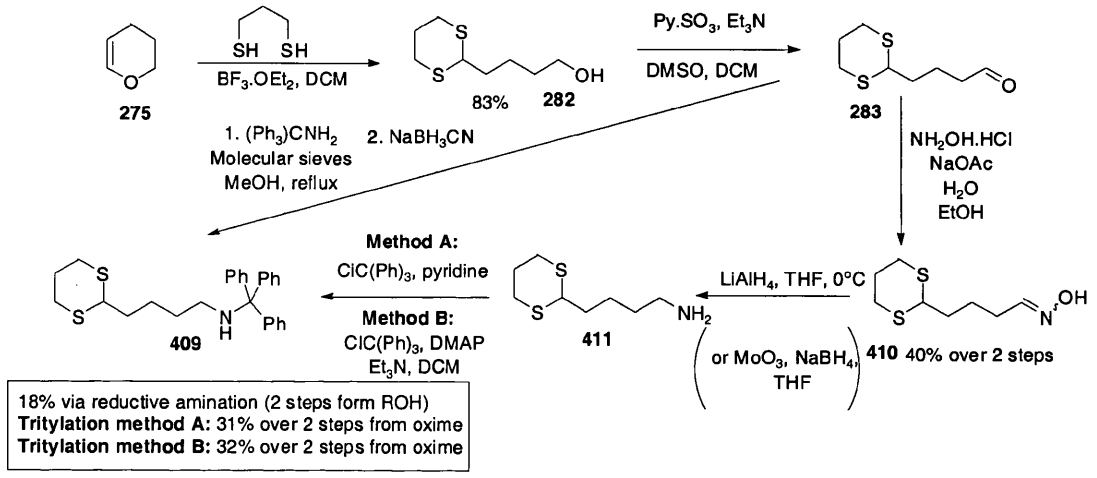


Amine proteced with a trityl protecting group

Figure 32.

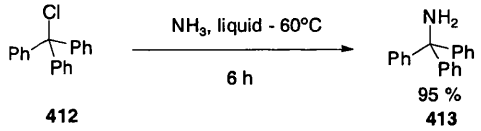
7.1.1 Seven Membered Imine Route

Two routes to a suitable thioacetal substrate were investigated with a view to forming seven membered cyclic imines, (Scheme 112). Formation of the alcohol **282** by ring opening of 2,3 dihydropyran **275** was followed by Swern oxidation to give the aldehyde **283**. This could then be treated in two ways: firstly, a direct reductive amination of the aldehyde with tritylamine provided the tritylated substrate **409** for the Takeda reaction; secondly formation of the oxime **410** using hydroxylamine hydrochloride, sodium acetate, water and ethanol worked well (40%), providing a mixture of *E* and *Z* isomers visible in the NMR spectrum. Reduction of the oxime **410** to the amine **411** was carried out using lithium aluminium hydride. The alternative of using sodium borohydride with molybdenum trioxide gave a lower yield.[163] Tritylation of the amine **411** using tritylchloride, which is considerably cheaper than tritylamine, was carried out under two conditions, with little difference between the yields (see below) to form the substrate **409**, (see appendix 1a), for the Takeda reaction. The route via oximes **410** was initially preferred as tritylamine is expensive and the relative cost of materials *via* the oxime **410** in spite of the extra steps, was cheaper. Formation of the oxime[164] was facile and the reaction produced an easily managed crystalline compound. This was advantageous as the Swern oxidation used prior to the oxime formation produced a number of impurities and the aldehyde was not suitable for purification. Crystallisation of the oxime removed these without the need for column chromatography.



Scheme 112.

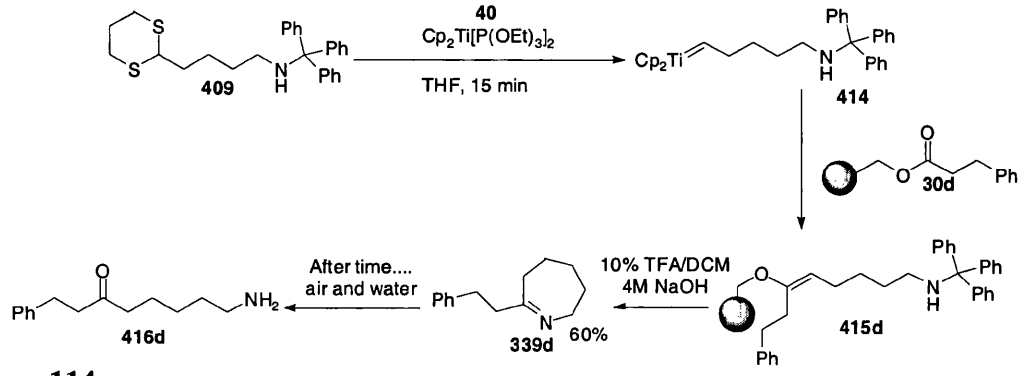
However, although large scale production of the oxime **410** was simple, large scale reduction of the oxime to the primary amine **411** proved problematic. The time taken to quench large quantities of lithium aluminium hydride and the subsequent task of isolating the product amine from large amounts of aluminium salts was frustrating. At this time it was important to produce a large quantity of the substrate in a short time and a literature search revealed a method for converting trityl chloride **412** into tritylamine **413** by refluxing in liquid ammonia, (Scheme113).[165] A large quantity of tritylamine **413** was then produced from the inexpensive trityl chloride **412** making the one step reductive amination reaction more attractive.[166]



412 413

Scheme 113.

Having obtained a reasonable quantity of substrate **409**, a test Takeda reaction was carried out, (Scheme 114). Subjecting the substrate to low valent titanium complex **40** produced the titanium alkylidene **414** that then reacted with a resin-bound ester **30d** to form an enol ether **415d**. Cleavage of the enol ether using 10% TFA in DCM solution gave the TFA salt of the primary amine **416d**. Treatment of the salt under concentrated basic conditions (4 M NaOH), provided the free base and dehydrated in one step, cyclising the primary amine **416d** to a cyclic imine **339d** (for sample ^{1}HNMR see appendix 2a) completely in good yield. Following prolonged exposure to air the imine ring opened again to form the amine **416d**, so it was important to treat all subsequent imines under anhydrous and inert gas conditions.



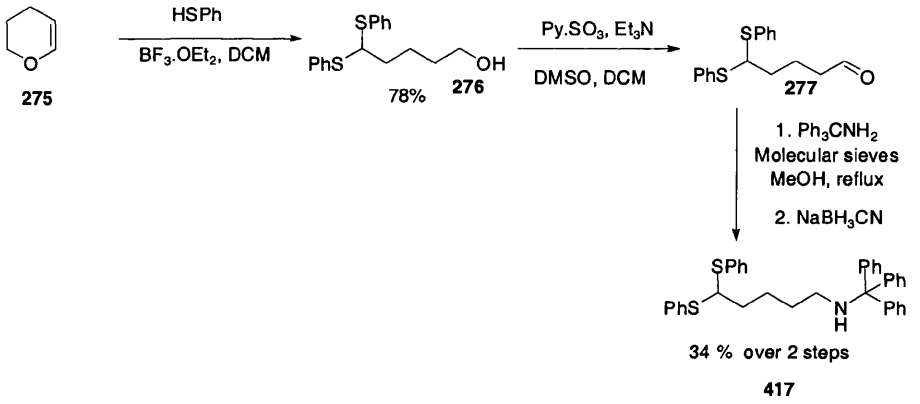
Scheme 114.

This first test reaction allowed access to synthetically valuable cyclic imines, and showed the use of the trityl group under Takeda conditions was possible. This was a relief as

investigation into the trityl group showed that one method of deprotection used for it, developed for chemoselectivity reasons, was the use of low valent titanium reagents.[167]

7.1.2 Investigation into Substrate Synthesis

Diphenyldithioacetals are more easily reduced than dithianes so the thioacetal functionality was switched from dithiane to dithiophenyl functionality to aid alkylidene formation, (Scheme 115). Ring opening of the 2,3-dihydropyran **275** to form the alcohol **276**, was followed by Swern oxidation to the aldehyde **277** that was used without purification in a reductive amination reaction[166] to produce the tritylated substrate **417**, (see appendix 1b).



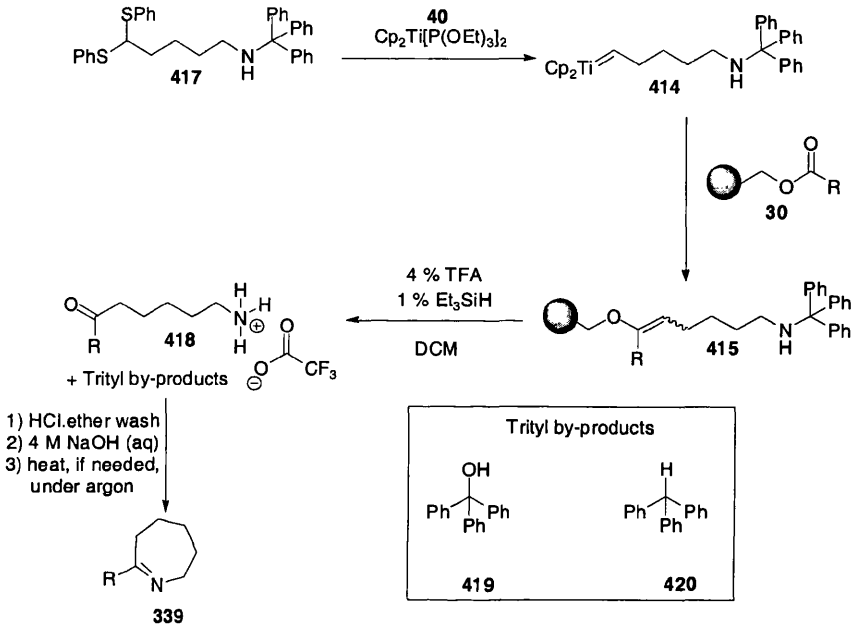
Scheme 115.

7.1.3 Seven-Membered Imine Library Synthesis

The production of a large quantity of substrate facilitated the production of a small library of diverse cyclic imines, (Scheme 116). The titanium alkylidene **414** was formed by reduction of the thioacetal **417** with the low valent titanium complex **40** and used to alkylidenate resin-bound esters **30** to form enol ethers **415**. The enol ether moiety was cleaved selectively using a trifluoroacetic acid, triethylsilane, DCM mixture to give the free alkylammonium salts **418**.

The trityl derived side products were removed by washing with non-polar solvents. The addition of triethylsilane to the cleavage mixture[168] was necessary as without it the cleaved trityl cation picked up water and produced trityl alcohol **419**. This side product was considerably more difficult to remove by washing from the TFA salt **418** than triphenylmethane **420**, produced when the triethylsilane additive was used, that could be washed away in hexane. Conversion to the HCl salts prior to cyclisation was achieved by washing the trifluoroacetic acid with saturated ethereal HCl and was carried out to increase the purity and because the HCl salt was a solid and easier to handle than the TFA salt,

which was an oil. The HCl salt also provided a characterisation possibility, should the imine fail to form. Following removal of the trityl side products the mixture was treated to a 4 M NaOH wash, producing mainly ring closed imines **339**. In some cases it was necessary to gently warm the imine under a flow of argon if there was a small proportion of ring opened primary amine present. This produced only ring closed product.



Scheme 116.

The library below was produced using the above method, table 6.

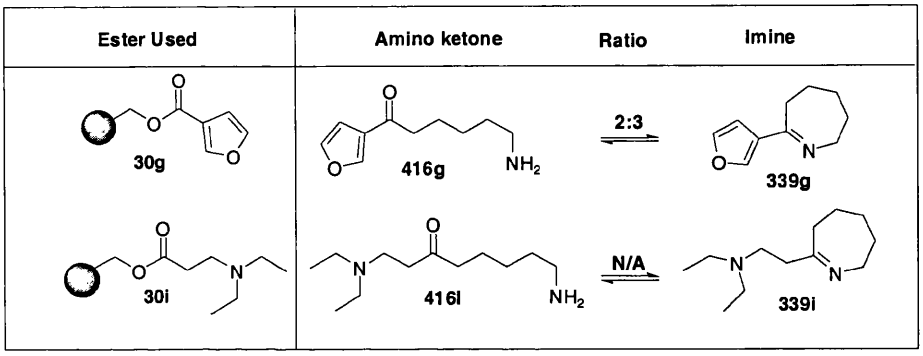
Table 6.

Ester Used	30f	30d	30k	30j
Imine Produced	339f 24 %	339d 60%	339k 27 %	48 % 418j → 339j

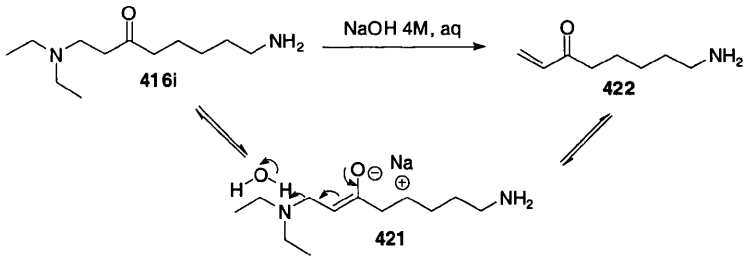
Yields for the propyl substituted imine **339j** were taken at the HCl salt phase **418j** to avoid an artificially low yield due to the volatility of the imine product.

The following compounds were prepared partially closed, complete formation of the imine was not possible. The ratio was determined by ^{1}HNMR spectroscopy. Determination of the ratios for the diethylamino substituted imine were not possible as the ^{1}HNMR spectrum was not clean. The ^{13}CNMR spectrum did show signals for both the imine **339i** (167.85 ppm) and the ketone **416j** (195.14 ppm), table 6.

Table 6.

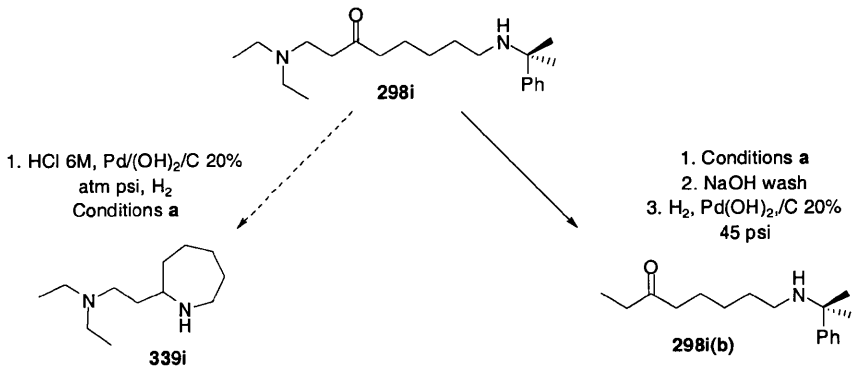


One reason for the complicated signals in the NMR and the impurity of the compounds **339i** and **416i** is that treatment of this compound under basic conditions, e.g. the sodium hydroxide wash needed for cyclisation, causes elimination to occur, (Scheme 117).



Scheme 117.

Evidence supporting this process comes from the treatment of (*S*)-1-diethylamino-8-(1-phenylethylamino)octan-3-one **298i** to hydrogenation conditions in an attempt to synthesis the racemic azepane **339i**. It was hopped that hydrogenation conditions detailed earlier, in the presence of hydrochloric acid[92] would remove the auxiliary and form the azepane. However the first hydrogenation reaction was unsuccessful and to neutralise the HCl salt formed, sodium hydroxide solution was used. The resultant mixture was subjected to a second set of hydrogenation conditions before ketone **298i(b)** was isolated assuming from hydrogenation of the intermediate alkene, (Scheme 118).



Scheme 118.

This process, combined with the failure to fully close and form the ring, can then lead to a wide range of products present in the final mixture, (Figure 33).

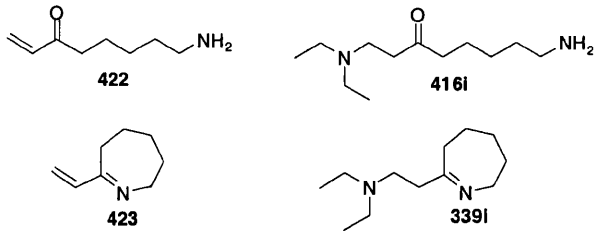


Figure 33.

7.2 Six-Membered Cyclic Imines

In order to fully demonstrate the versatility of the methodology, we had investigated preparation of six-membered cyclic imines in parallel. Examples have been shown of the pharmaceutical value of seven-membered cyclic imines,[129] however their six-membered counterparts are of equal value as potential therapeutic leads.[128] One of the more notorious compounds is coniceine **391**, synthesised by our methodology (detailed later) along with coniine **424**, figure 34, they are the active ingredients in the hemlock drink used to execute the Greek philosopher Socrates.[120]

Figure 34.

Other examples include the ecotoxic compound **425**, figure 35, an antifungal compound that has activity against barley and wheat mildews.

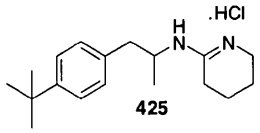
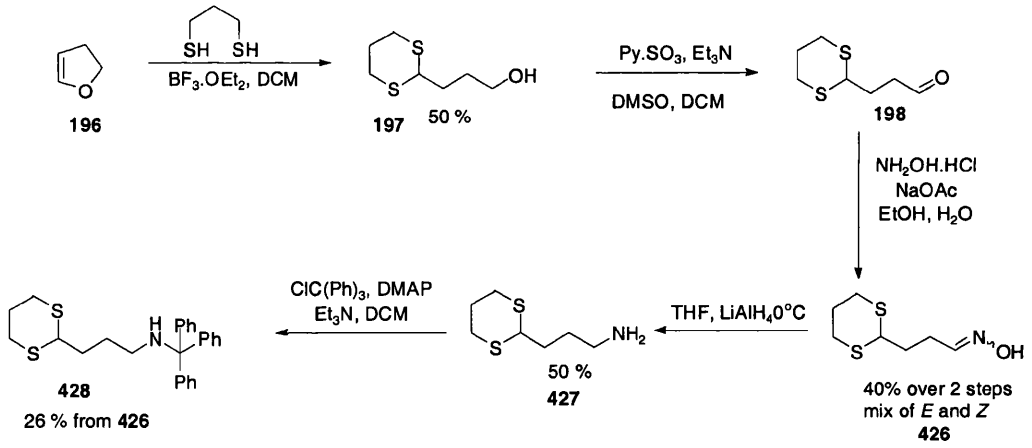


Figure 35.

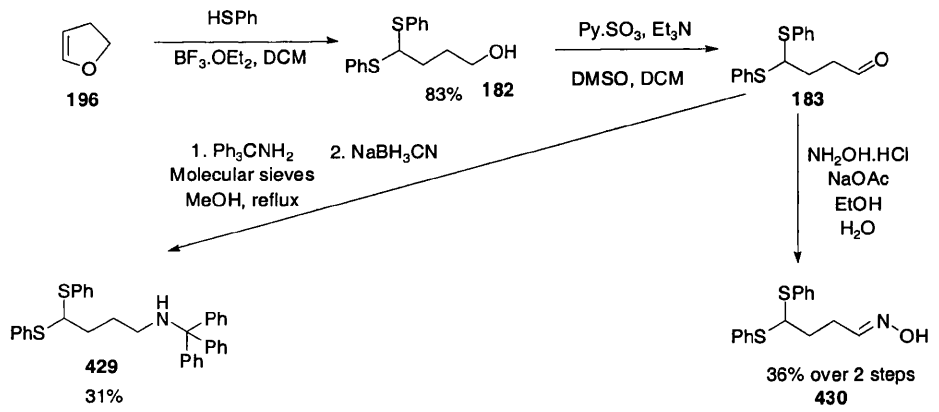
7.2.1 Synthetic Route

The synthetic route was analogous to that for the seven membered series, (Scheme 119). As before, initially the dithiane substrate was synthesised. Dihydrofuran **196** was treated with propanedithiol to give the alcohol **197**. Oxidation of this product under Swern oxidation conditions gave the aldehyde **198** which was converted into the oxime **426** using hydroxylamine hydrochloride and sodium acetate. Reduction of the oxime **426** with lithium aluminium hydride gave the primary amine **427** which was then tritylated using trityl chloride and DMAP conditions to give substrate **428**.



Scheme 119.

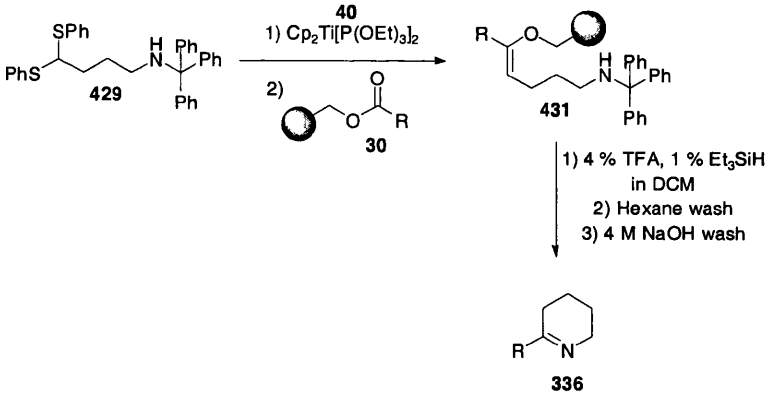
The dithiophenyl substrate was then made for the library production, (Scheme 120). Ring opening of dihydrofuran **196** gave thioacetal **182**. Swern oxidation of the resulting alcohol **182** gave the aldehyde **183**, and reductive amination with triylamine then yielded the trityl-protected substrate **429**, (see appendix 1c). In this manner, large quantities of substrate for the Takeda reaction were produced in three simple steps. The oximes **430** were also made but their conversion to trityl derivatives **429** not investigated.



Scheme 120.

7.2.2 Library Production of Six-Membered Series

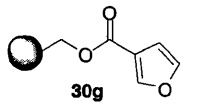
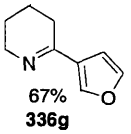
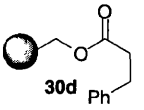
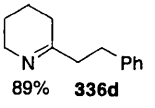
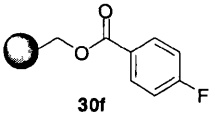
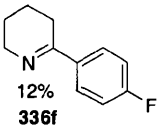
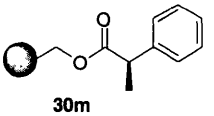
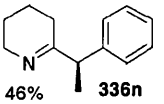
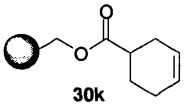
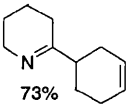
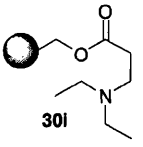
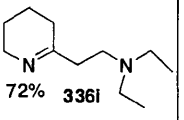
The substrate **429** was then treated with low valent titanium complex **40** to form the alkylidene, which was reacted with resin-bound esters **30** to form enol ethers **431**, (Scheme 121). The enol ethers were then selectively cleaved from resin using a TFA and triethyl silane mixture to ensure the by-product of deprotection was triphenylmethane. After washing away side products, sodium hydroxide solution neutralised and cyclised the TFA salt products to form cyclic imines **336**.



Scheme 121.

Using this procedure the following library of six-membered cyclic imines were produced, (for sample ^{1}HNMR of **336g** see appendix 2b) table 7.

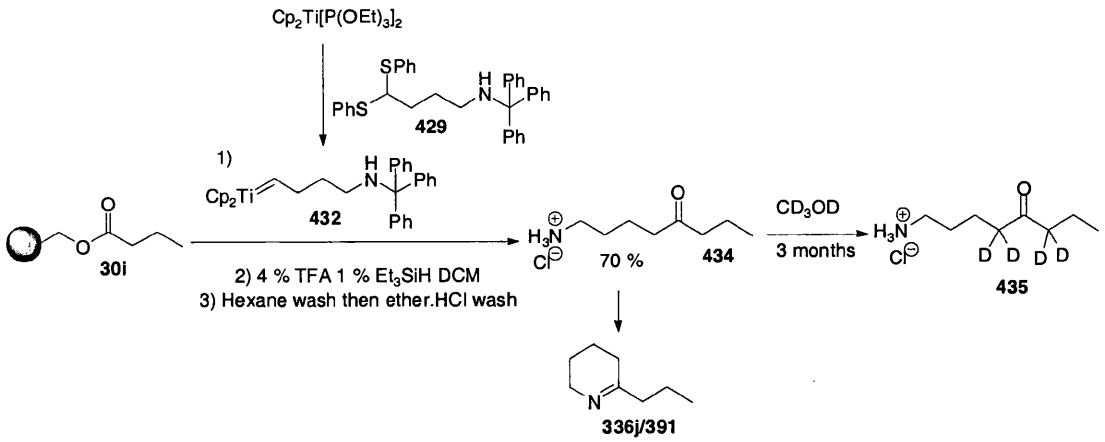
Table 7.

Ester Used	Imine Produced	Ester Used	Imine Produced
 **30g**	 67% **336g**	 **30d**	 89% **336d**
 **30f**	 12% **336f**	 **30m**	 46% **336n**
 **30k**	 73% **336k**	 **30l**	 72% **336i**

Imine **336e** was also produced under these conditions but the purity was not as good as those in table 7.

Figure 36.

Coniceine was also prepared and its yield was based on isolation of the ketone **434** as the imine is volatile. An interesting observation was the deuterium incorporation into the HCl salt **434** that gives coniceine upon cyclisation, (Scheme 122). Exposure for a prolonged time, one month, to deuterated methanol caused exchange in the CH_2 groups α to the carbonyl position of the ketone **434**. This conversion was complete when the salt was left in deuterated methanol for 2 more months to provide the fully deuterated compound **435**, with notable absence of the triplet for the α protons ($CH_2C{=}OCH_2$) in the ^{1}H NMR spectrum and near complete loss of the CH_2 signal in the ^{13}C NMR. Attempts to convert the deuterated compound back to the unlabelled form using MeOH and aqueous HCl stirring for two weeks, failed. This method of incorporation is perhaps unsurprising as a favourite method of labelling metabolites synthesis is stirring the compound to be labelled with deuterated trifluoroacetic acid.



Scheme 122.

Anabaseine **436** is a six membered cyclic imine that has been isolated from a pheromone cocktail of ants belonging to the *aphaenogaster* genus.[169] It is an ant recruitment pheromone used to lead ants from the same colony to a food source. Biological testing of the compound has shown it increases levels of the neurotransmitter dopamine in the brain. It is an agonist with selective binding for the nicotinic receptors.[126] With this efficacy it is a potential lead for treatment of Alzheimer's disease[126] and so a good synthetic target for testing the methodology.

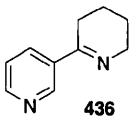
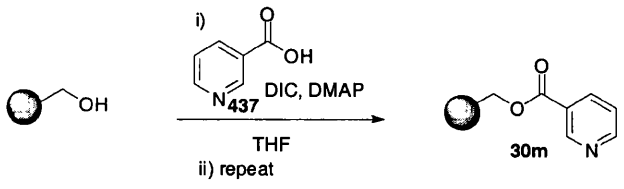


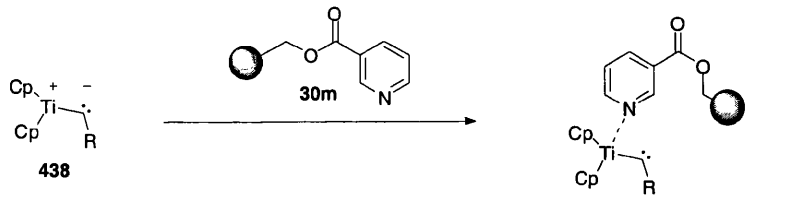
Figure 37.

The synthesis of this compound was attempted using resin-bound nicotinic acid **30m**, prepared by coupling 3-nicotinic acid **437** with hydroxymethylpolystyrene resin, (Scheme 123).



Scheme 123.

Unfortunately when this resin was treated under the above conditions, it failed to give the desired anabaseine product. The lone pair of the pyridine nitrogen atom may coordinate with the titanium alkylidene **438** preventing reaction with the carbonyl group of the resin-bound ester, figure 38.



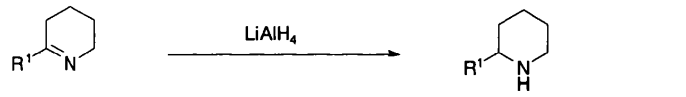
Titanium Alkylidene

Coordination
and steric bulk restricting reaction

Figure 38.

7.2.3 Reduction of the Imine Bond

Time constraints only allowed a brief investigation of the reduction of the imines **336** produced using the route detailed above, to give piperidines **439** and **440**, (Scheme 124). Lithium aluminium hydride gave poor un-optimised yields, but a wide range of manipulations including asymmetric reduction would have been possible.



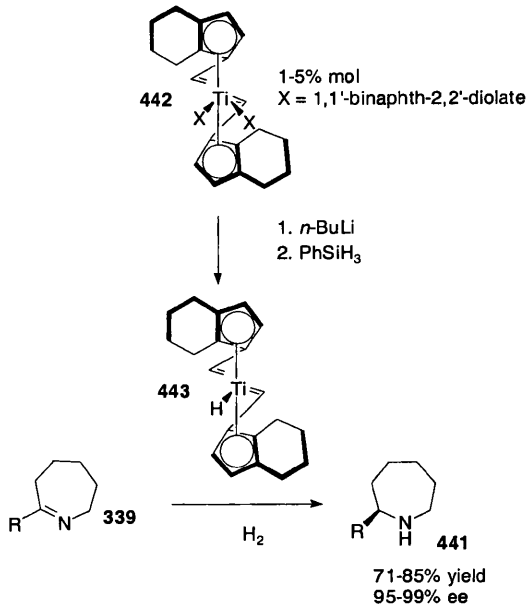
R = CH_2CH_2Ph **336d**
R = $CH_2CH_2CH_3$ **336j**

R = CH_2CH_2Ph 20 % **439**
R = $CH_2CH_2CH_3$ 9 % (HCl salt) **440**

Scheme 124.

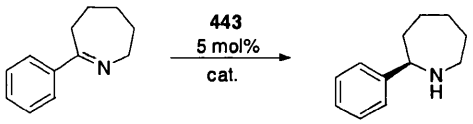
7.3 Utility of Cyclic Imines: Future Work and Applications

The imines produced using this methodology could have been functionalised in a variety of ways. The simplest is asymmetric hydrogenation of the imine bond **339** to produce 2-substituted heterocycles **441** selectively, (Scheme 125). This can be carried out with many catalysts, one example is Buchwald's titanium catalyst the precursor **442** being converted into an active titanium hydride species before coordination of the imine bond of **339** to the metal centre occurs.[170]



Scheme 125.

Examples of hydrogenation of five, six and seven-membered imines to their corresponding nitrogen heterocycles using Buchwald's catalyst have been demonstrated. In all cases however, a high pressure of hydrogen is required, (Scheme 126), table 8.

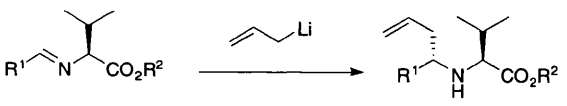


Scheme 126.

Table 8.

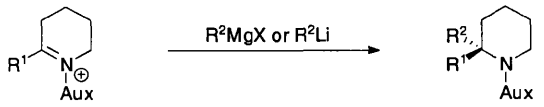
Time	Psi	T °C	Yield	ee
24 h	500	45	71	98
30 h	80	65	74	97

Other manipulations can also be carried out using the imine bond. Grignard or alkyl lithium additions can form a new chiral centre and provide greater diversity as shown by Basile *et al.*[171] (Scheme 127).



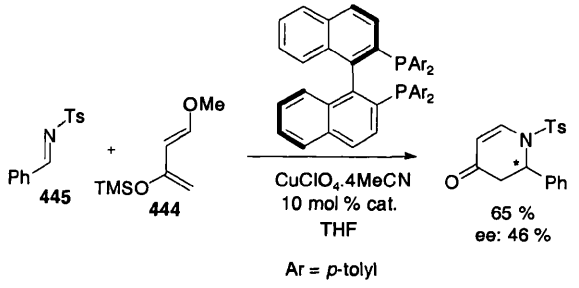
Scheme 127.

Grignard reagents and organolithiums would also add to iminium ions and use of a chiral auxiliary attached to the nitrogen atom might provide selectivity but is only useful if the auxiliary chosen can be removed easily.[171] (Scheme 128).



Scheme 128.

Aza-Diels Alder reactions could provide a route to bicyclic systems. There are examples of aza-Diels Alder reactions using Danishefsky's diene **444** and tosylated benzylideneimides e.g. **445**. C_2 chiral BINAP-derived copper catalyst can be used to obtain a small degree of control over the chiral centre formed in the reaction,[172] (Scheme 129).



Scheme 129.

Applied to our substrates, the following compounds could be accessed, (Scheme 130), though conditions would need to be harsher as there is no electron withdrawing group activating the imine.

Scheme 130.

In summary, a general route for the high throughput synthesis of diverse imines has been successfully demonstrated. These intermediates should be of great utility in the synthesis of alkaloids and may have interesting biological properties themselves.

Chapter 8: Experimental

All reactions were carried out under an atmosphere of nitrogen or argon, using oven-dried glassware. All solutions were added *via* syringe unless otherwise stated. THF was freshly distilled from sodium and benzophenone. Dichloromethane, triethyl phosphite and pyridine were distilled from CaH_2 prior to use. DMF was distilled from calcium hydride and stored over 4Å molecular sieves. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Purification by column chromatography was carried out using Fisher Matrix TM silica gel, mesh size 35-70μm, the stationary phase. Melting points are uncorrected. IR spectra were recorded using a JASCO FT-IR 410 or a Nicolet Impact 410 FTIR spectometer and Golden gate apparatus where indicated and NMR spectra were recorded using a Bruker DPX-400 spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane using residual $CHCl_3$ as an internal standard (7.26ppm). J values are given in Hz. The multiplicities of C nuclei were determined using the DEPT pulse sequence. Mass spectra were recorded on a JEOL JMS700 spectrometer. Combustion analysis was carried out using a Carlo-Erba 1106 elemental analyser.

Solid-phase Takeda reaction – General Method A

Titanocene dichloride (1.00 g, 4.02 mmol, 12 eq), magnesium turnings (108 mg, 4.42 mmol, 13.2 eq) and 4Å molecular sieves (200 mg) were heated briefly under vacuum. Following cooling, the reaction flask was flushed with argon, and THF (4 mL) and triethylphosphite (1.38 mL, 8.04 mmol) were added and the reaction mixture was stirred, with cooling using a water bath for 30 min. After stirring for a further 2-2.5 h, a THF (10 mL) solution of the thioacetal (286 mg, 1.01 mmol) was added, and the solution was stirred for 15 min. The reaction mixture was added *via* syringe into a flask containing 1 kan of resin-bound ester (0.280-0.335 meq equal to 1 equivalent). The mixture was stirred under argon for 15-18 h. After this time, the kan was removed and then washed with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and finally with diethyl ether. The resin was then dried under vacuum.

Solid Phase Takeda reaction – General Method B

Titanocene dichloride (981 mg, 3.936 mmol), magnesium turnings (105 mg, 4.33 mmol) and 4Å molecular sieves (200 mg) were heated briefly under vacuum. Following cooling,

the reaction flask was flushed with argon, and THF (4 mL) and triethyl phosphite (1.35 mL, 7.87 mmol) were added and the reaction mixture was stirred for 3 h. At this time a THF (10 mL) solution of the thioacetal or dithiophenyl compound (0.984 mmol) was added, and the solution stirred for 15 min. The reaction mixture was added *via* syringe into a flask containing one of resin-bound ester (0.328 meq). The mixture was stirred under argon for 15-18 h. After this time, the kan was removed and then washed with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and finally with diethyl ether. The resin was then dried under vacuum.

Solid Phase Takeda reaction – General Method C

Titanocene dichloride (981 mg, 3.94 mmol) was added to a flask cooled under high vacuum containing magnesium turnings (105 mg, 4.33 mmol) and 4Å molecular sieves (200 mg) that had been placed in the oven overnight. The mixture was then heated briefly under vacuum. Following cooling, the reaction flask was flushed with argon 3 times, and THF (4 mL) and triethylphosphite (1.35 mL, 7.87 mmol) were added and the reaction mixture was stirred for 3h. At this time a THF (6 mL) solution of the thioacetal (0.984 mmol) was added, and the solution stirred for 15 min. The kan containing resin-bound ester (0.328 meq) flushed with argon was quickly added to the reaction mixture under a flow of argon. The mixture was stirred under argon for 15-18 h. After this time, the kan was removed and then washed with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and finally with diethyl ether. The resin was then dried under vacuum.

Cleavage from resin – General Method A

A solution of TFA in DCM (1%, 5 mL) was added to a tube containing 1 kan of Merrifield resin-bound ester, which had been subjected to the Takeda reaction conditions. This was then shaken for 1-2 h before the contents were removed and the kan washed with DCM (x 4). The combined organics were then neutralised with potassium carbonate and concentrated under reduced pressure.

Cleavage from resin – General Method B

A solution of TFA in DCM (10%, 5 mL) was added to a tube containing 1 kan of Merrifield resin-bound ester, which had been subjected to the Takeda reaction conditions. This was then shaken for 1-2 h before the contents were removed and the kan washed with

DCM (x 4). The combined organics were then washed with NaOH (1M), water (x 1) and brine (x 1), dried over sodium sulfate, filtered and concentrated under reduced pressure.

Cleavage from resin – General Method C

A solution of TFA in DCM (4%, 5 mL) was added to a tube containing 1 kan of Merrifield resin-bound ester, which had been subjected to the Takeda reaction conditions. This was then shaken for 1-2 h before the contents were removed and the kan washed with DCM (x 4). The combined organics were then washed with NaOH (1M), water (x 1) and brine (x 1), dried over sodium sulfate, filtered and concentrated under reduced pressure.

Cleavage from resin – General Method D

A solution of TFA (4%) and Et_3SiH (1%) in DCM (5 mL), was added to a tube containing 1 kan of Merrifield resin-bound ester, which had been subjected to the Takeda reaction conditions. This was then shaken for 1-2 h before the contents were removed and the kan washed with DCM (x 4). The combined organics were then concentrated under reduced pressure, washed with cold hexane then treated to a NaOH (4 M) wash and extracted with DCM. The combined organics were then dried over sodium sulfate, filtered and concentrated under reduced pressure.

kan loading

General Method A : Resin-bound ester

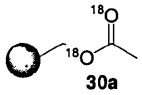
IRORI mackrokans® (kans) containing a known quantity of chloromethylpolystyrene polymer (Merrifield resin), were treated with a solution of 3 eq caesium carbonate, 2 eq of corresponding carboxylic acid and 0.5 eq potassium iodide in dry DMF (0.08 Mol L^{-1}), based on the loading of the resin chosen. The reaction mixture was heated to 80 °C under argon overnight.

Work-up: the kans were washed with 3 x DMF: water (9:1), 2 x THF, 2 x MeOH and DCM alternately, 1 x MeOH and 1 x Ether. The kans containing resin-bound ester are then dried under high vacuum.

General Method B : Carboxylate salt immobilisation

kans containing 1 equivalent of chloromethylpolystyrene polymer, based on polymer loading, were treated in dry DMF with 2 equivalents carboxylate salt (sodium acetate) and 11% 15-crown-5 at 80 °C overnight under argon. The kans were then treated to the same work up as general method A.

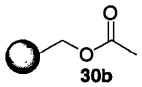
Resin-bound ^{18}O-labelled acetic acid 30a



30a

Following resin loading, general method A, using ^{18}O-labelled acetic acid (110 mg, 1.56 mmol) and stratosphere® resin plugs of chloromethylpolystyrene with resin loading 0.15 mmol/plug, 4 kans of resin-bound^{18}O-labelled acetic acid **30a** were prepared.

Resin-bound acetic acid 30b



30b

Method A

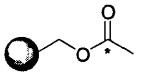
Following resin loading, general method A, using acetic acid (0.075 mL, 1.31 mmol) and Merrifield resin (chloromethylpolystyrene), 0.328 meq/kan, 1 kan of resin-bound acetic acid **30b** was prepared.

Method B

Following resin loading general method B, using sodium acetate (59 mg, 0.719 mmol) and chloromethylpolystyrene resin (170 mg/kan, 0.328 meq/kan), 2 kans of resin-bound acetate **30b** were prepared.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 3027 (CH), 2985 (CH_2, CH_3), 1731 (C=O).

Resin-bound radiolabelled sodium acetate 30c

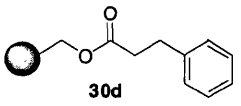


*= ^{14}C

30c

^{14}C Sodium acetate (53.93 mg, 145.63 MBq, 0.656 mmol) was placed in a round bottom flask from the vial used for accurate measurement, with 2 kans containing Merrifield resin (170 mg/kan, 0.328meq/ kan), DMF was used to wash out radioactive starting material (5 mL), and an air condenser, connected two 2 sodium hydroxide traps attached. To this DMF (15 mL) and solution of 15-crown-5 (1 mL, 0.722 Mol/L^{-1}) in dry DMF was added. This was heated to 80°C over 3 nights. The kans were then worked-up as for resin loading general method A giving **30c** and all washings and the reaction mixture kept separate for scintillation counting. From the counts of these and the sodium hydroxide traps it was taken that the resin was 89.7% loaded with radiolabelled sodium acetate. The kans were then treated to sodium acetate (27 mg, 0.329 mmol) and 15-crown-5 (0.5 mL, 0.722 Mol/L^{-1}) in dry DMF, under exactly the same conditions. Following the counting of all washings, the reaction mixture and the NaOH traps, 0.36 MBq of activity was obtained showing no transesterification taking place

Resin-bound 3-phenyl propionic acid 30d

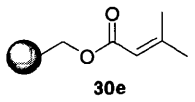


30d

Following resin loading general method A, 3-phenylpropionic acid (990 mg, 6.56 mmol) was loaded onto 10 kans containing chloromethylpolystyrene resin (170 mg each) giving a loading of 0.328 meq / kan. 10 kans containing Stratosphere ® plugs (0.15 mmol/kan) were also loaded separately using general method A with 3-phenyl propionic acid (316 mg, 3.00 mmol). The resin-bound ester **30d** was also prepared under the same conditions using loose chloromethylpolystyrene resin of loading 1.93 meq/g (170 mg, 0.328 meq/kan).

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 3053 (CH), 2986 (CH_2, CH_3), 1731 (C=O).

Resin-bound dimethyl acrylic acid 30e

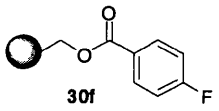


30e

Dimethyl acrylic acid (0.47 g, 3.10 mmol), caesium carbonate (5.04 g, 15.5 mmol) and potassium iodide (0.26 g, 1.55 mmol) were placed in a dry flask with 10 kans containing chloromethylpolystyrene resin (0.170 g, 0.311 meq/kan) in DMF (100 mL). The reaction mixture was then stirred at 80 °C under argon overnight. The reaction mix was decanted and the kans washed as follows, DMF:water 9:1 (x 3), THF (x 5), MeOH and DCM alternately (x 3), MeOH and finally diethyl ether. The kans **30e** were then dried on the high vacuum.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 2989 (CH_3), 1650 (C=O).

Resin-bound 4-fluorobenzoic acid 30f

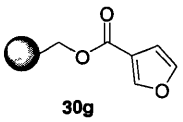


30f

Following resin loading general method A, 4-fluorobenzoic acid (919 mg, 3.28 mmol) was loaded onto 10 kans (170 mg/kan, 0.328 meq/kan), giving **30f**, using chloromethylpolystyrene resin (0.170 g / kan).

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 3050 (CH), 1711 (C=O).

Resin-bound furan-3-carboxylic acid 30g



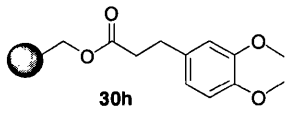
30g

3-Furoic acid (520 mg, 4.67 mmol), caesium carbonate (5.04 g, 15.5 mmol) and potassium iodide (260 mg, 1.55 mmol) were placed in a dry flask with 10 kans containing chloromethylpolystyrene resin (170 mg/kan, 0.311 meq/kan) in DMF (100 mL). The reaction mixture was then stirred at 80 °C under argon overnight. The reaction mix was

decanted and the kans washed as follows, DMF:water 9:1 (x 3), THF (x 5), MeOH and DCM alternately (x 3), MeOH and finally diethyl ether. The kans, **30g**, were then dried on the high vacuum.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 3055 (CH), 1675 (C=O).

Resin-bound 3-(3,4-dimethoxy)(phenyl)propionic acid 30h

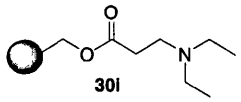


30h

Following kan loading general method A, using resin of loading 1.93 meq/g, 10 kans containing (170 mg/kan, 0.328 meq/kan). Chloromethylpolystyrene resin was loaded with 3-(3,4-dimethoxy)(phenyl)propionic acid (1.38 g, 6.56 mmol) using caesium carbonate (3.21g, 9.84 mmol) and potassium iodide (270 mg, 1.64 mmol) in DMF, giving **30h**.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 2988 (CH), 1719 (C=O).

Resin-bound 3-(diethylamino)-propionic acid 30i

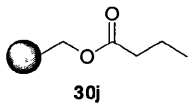


30i

Following kan loading general method A using resin of loading 1.93 meq/g, 10 kans of Merrifield resin (170 mg/kan, 0.328 meq/kan) were loaded with the 3-(diethylamino)-propionic acid hydrochloride (715 mg, 3.94 mmol). Using caesium carbonate (3.21g, 9.84 mmol, 5 eq) in a larger excess to neutralise the starting acid, and potassium iodide (163 mg, 0.984 mmol), in DMF, the kans **30i** were successfully loaded.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 2990 (CH), 1744 (C=O).

Resin-bound butyric acid 30j

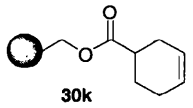


30j

Following resin loading general method A using resin of loading 1.93 meq/g, butyric acid (0.36 mL, 3.93 mmol) was loaded onto 6 kans containing chloromethylpolystyrene resin (170 mg/kan, 0.328 meq/kan), giving kans **30j**.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 3062 (CH), 1730 (C=O).

Resin-bound cyclohex-3-enecarboxylic acid 30k

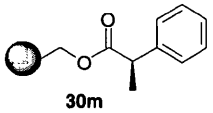


30k

Following resin loading general method A, 3-cyclohexene carboxylic acid (0.72 mL, 3.10 mmol) was loaded onto chloromethylpolystyrene resin. 10 kans loading (170 mg/kan, 0.310 meq/kan), **30k** were synthesised.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 2988 (CH_2), 1719 (C=O), 1602 (C=C).

Resin-bound (*R*)-(-)-2-phenylpropionic acid 30m

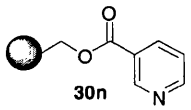


30m

Following resin loading general method A using resin of loading 1.93 meq/g, (*R*)-(-)-2-phenylpropionic acid (493 mg, 3.28 mmol) was loaded onto 10 kans loading (170 mg/kan resin giving 0.328 meq/ kan of **30m**, using chloromethylpolystyrene resin.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 3053 (CH), 2986 (CH_2, CH_3), 1735 (C=O).

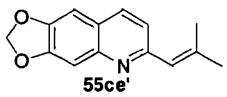
Resin-bound 3-nicotinic acid 30n



Hydroxy-Merrifield resin with a loading of 2.0 meq / g was weighed out into 6 IRORI macrokans (170 mg/kan, 0.340 meq/kan). The kans were placed in a dry flask and nicotinic acid (3.01 g, 24.5 mmol), DMAP (76.0 mg, 0.623 mmol) and THF (40 mL) added. To this DIC (3.80 mL, 24.5 mmol) was added and the reaction mixture was stirred overnight. The resin was subjected to the work-up before being re-treated with the same conditions. Work-up: the kans were washed with THF (x 3), MeOH and DCM alternately (x 4), MeOH and diethyl ether, then placed under high vacuum to dry giving kans **30n**.

ν_{max} (swollen with DCM on NaCl plate)/cm^{-1}: 1713 (C=O), 1601 (pyridine).

6,7-Methylenedioxy-2-(2'-methylpropenyl)quinoline 55ce'



2-[2'-(*N-tert*-Butoxycarboxyamino)-4',5'-methylenedioxybenzyl]-1,3-dithiane **127c** (340 mg, 0.93 mmol) was dissolved in THF (7 mL) and TMSCl (0.14 mL, 1.12 mmol) was added. To this LDA (0.56 mL, 1.12 mmol, 2M) was added drop-wise at –78 °C. The mixture was allowed to warm slowly over 1 h to room temperature and then stirred for a further 45 min. The THF was then removed and diethyl ether (7 mL) was added. The reaction mix was then filtered and concentrated under reduced pressure, and used without further purification to form the corresponding titanium alkylidene under standard Takeda reaction conditions B. When reacted with the corresponding resin-bound ester **30e** the enol ether was produced. Subsequent cleavage using 10% TFA/DCM (5 mL) solution gave the TFA salt (73.8 mg, 68%). The salt was then subjected to manganese dioxide (90 mg) with DCM (10 mL) as the solvent. After 2 h heating under reflux in air, solid sodium carbonate was added and the solution filtered though wet-packed celite, washing with ethyl acetate. The solvent was removed under reduced pressure to give the quinoline **55ce'**[173] (73.8 mg, 62%). The quinoline was insoluble in a number of solvents however deuterated benzene was successful as an NMR solvent.

ν_{max} (GG)/cm^{-1}: 1650 (CH=CH), 1573+1502 (benzene/pyridine C=C)

δ_H (400 MHz: C_6D_6): 1.92 (3H, d, *J* 1.2, CCH_3), 2.45 (3H, d, *J* 1.1,CCH_3), 5.30 (2H, s, OCH_2O), 6.58 (1H, d, *J* 1.4, **H**-1'), 6.82 (1H, s, **H**-8), 7.02 (1H, d, *J* 8.4, **H**-3), 7.50 (1H, d, *J* 8.4, **H**-4), 7.70 (1H, s, **H**-5).

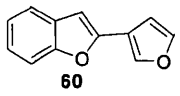
δ_H (400 MHz: $CDCl_3$): 1.98 (3H, s, CCH_3), 2.12 (3H, s, CCH_3), 6.08 (2H, s, OCH_2O), 7.01 (1H, s, **H**-8), 7.18 (1H, d, *J* 8.4, **H**-3)*, 7.34 (1H, s, **H**-5),7.87 (1H, d, *J* 8.4, **H**-4)*, 7.87 (1H, s, **H**-4)*.

*= signals affected by D-H exchange.

δ_C (100 MHz: C_6D_6): 19.0 (CH_3), 26.4 (CH_3), 99.9 (CH_2), 101.4 (CH), 105.1 (CH), 119.8 (CH), 121.8 (C), 124.3 (CH), 133.0 (CH), 139.9 (C), 145.5 (C), 146.0 (C), 149.5 (C), 154.5 (C).

m/z, (CI): 228 [$(M+H)^+$, 100%], 85 (27%). HRMS: 228.1024. $C_{14}H_{16}NO_2$ requires (M+H) 228.1025.

2-(3'-furyl)benzofuran 60



60

2-(2'-Trimethylsiloxyphenyl)-1,3-dithiane (265 mg, 0.93 mmol), prepared by a literature procedure[31] was reacted under general Takeda reaction conditions **B** using resin-bound 3-furanoate **30g**. The resin-bound enol ether was cleaved using 1% TFA/DCM (5 ml) and the benzofuran neutralised onto solid potassium carbonate, filtered and concentrated in under reduced pressure to give *benzofuran* **60** (15.2 mg, 26%).

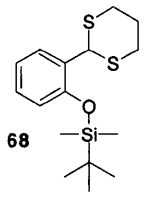
ν_{max} (NaCl)/cm^{-1}: 3118 (CH), 2960 (CH).

δ_H (400 MHz: $CDCl_3$): 6.58 (1H, dd, *J* 2.0, 0.8, **H**-4'/**H**-5'), 7.07-7.17 (1H, m, **H**-4'/**H**-5'), 7.21 (1H, td, *J* 7.2, 1.3, **H**-5/**H**-6), 7.26 (1H, td, *J* 7.2, 1.6, **H**-5/**H**-6), 7.47 (1H, m, **H**-4), 7.49 (1H, d, *J* 2.0, **H**-2'), 7.54 (1H, ddd, *J* 0.8, 1.6, 7.4, **H**-7), 7.91 (1H, s, **H**-3).

δ_C (100 MHz: $CHCl_3$): 101.4 (CH), 108.0 (CH), 110.9 (CH), 117.6 (C), 120.5 (CH) 122.9 (CH), 124.0 (CH), 138.1 (C), 139.8 (CH), 143.8 (CH), 150.1 (C), 154.5 (C).

m/z, (EI): 184 ($M^{\bullet+}$, 100%), 155 (30%). HRMS: 184.0522. $C_{12}H_8O$ requires 184.0524.

2-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]-1,3-dithiane 68



68

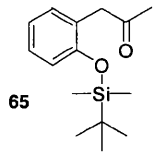
Following a literature procedure[31] 2-(2'-hydroxyphenyl)-1,3-dithiane was prepared. TBDMSCl (2.55 g 16.9 mmol) was added to a solution of 2-(2'-hydroxyphenyl)-1,3-dithiane (2.99 g 14.23 mmol) and imidazole (2.12 g, 31.1 mmol) in anhydrous DMF (30 mL). This was left stirring overnight. The DMF was then removed on the rotary evaporator and DCM (30 mL) and water (30 mL) added. The aqueous layer was extracted with DCM and the combined organic extracts washed with water (x 2) and brine (x 1) and then dried over sodium sulfate, filtered and concentrated under reduced pressure. A portion of the resultant mixture (1.85 g) was purified using silica gel chromatography eluting with ethyl acetate and hexane (1:8). This gave 2-[2'-(*tert*-butyldimethylsilyloxy)phenyl-1,3-dithiane[31] **68** (1.75 g, 83%) as an oil. R_F (Al_2O_3, 1:8 EtOAc:hexane): 0.68

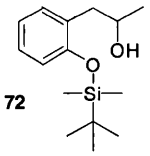
δ_H (400 MHz: $CDCl_3$): 0.26 [6H, s, $Si(\mathbf{CH_3})_2$], 1.06 [9H, s, $SiC(\mathbf{CH_3})_3$], 1.87-1.99 (1H, m, $CHSCH_2C\mathbf{H}_{ax}$), 2.13-2.19 (1H, m, $CHSCH_2C\mathbf{H}_{eq}$), 2.87-2.03 [2H, m, $CHSC\mathbf{H_2}$], 3.00-3.07 [2H, m, $CHSC\mathbf{H_2}$], 5.60 (1H, s, $C\mathbf{H}S_2$), 6.79 (1H, dd, *J* 8.2 Hz, 1.1 Hz, **H**-3′), 6.96 (1H, td, *J* 7.7 Hz, 1.1 Hz, **H**-5′), 7.15 (1H, m, **H**-4′), 7.54 (1H, dd, *J* 7.7 Hz, 1.8 Hz, **H**-6′).

δ_C (100 MHz: $CDCl_3$): -4.30 (CH_3), 18.30 (C), 25.32 (CH_2), 25.80 (CH_3), 32.54 (CH_2), 44.78 (CH), 118.83 (CH), 121.69 (CH), 129.05 (CH), 129.13 (CH), 129.76 (C), 151.78 (C).

1-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]propan-2-one[31] 65

1-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]propan-2-ol 72





Following solid phase Takeda reaction general method A, using 2-[2'-(*tert*-butyldimethylsilyloxy)phenyl]-1,3-dithiane (643 mg, 1.97 mmol) **68** and 2 kans (loading 0.15 meq/kan), containing resin-bound acetic acid and ^{18}O-labelled resin-bound acetic acid **30a** individually, were reacted to form resin-bound enol ether. The unlabelled enol ether was stirred in dry DCM (10 mL) for 1.5 h in dry glassware. At this point TFA (0.1 mL) was added and the reaction mixture left for 1.5 h under argon, at which time 5 mL of the cleavage solution was removed and treated with triethylsilane (13 μL, 1.1 eq) in an attempt to reduce the ketone. After water addition and the organic layer washed with water (x 2), brine (x 1), dried over sodium sulfate and concentrated under reduced pressure to give 1-[2′-(*tert*-butyldimethylsilyloxy)phenyl]propan-2-one[31] **65** (18 mg 42%) as yellow oil. The remaining cleavage mixture transferred to another dry flask and the TFA/DCM removed under high vacuum. Dry MeOH (5 mL) was then added followed by sodium borohydride (6 mg, 0.16 mmol) and the reaction left stirring for 2 h. This was then quenched with water and DCM was added. The water was extracted with DCM and the organics washed with water (x 2), brine (x 1), dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave *1-[2'-(tert-butyl-dimethylsilyloxy)-phenyl]propan-2-ol* **72** (20.4 mg, 47% over 2 steps) as an oil.

1-[2'-(*tert*-Butyldimethylsilyloxy)phenyl]propan-2-one 65

ν_{max} (NaCl)/cm^{-1}: 2929 (CH_2, CH_3), 1713 (C=O),1253 (Si-CH_3).

δ_H (400 MHz: $CDCl_3$): 0.24 [6H, s, Si($\mathbf{CH_3}$)$_2$], 0.99 [9H, s, SiC($\mathbf{CH_3}$)$_3$], 2.11 [3H, s, C(O)$\mathbf{CH_3}$], 3.66 [2H, s, $\mathbf{CH_2}$C(O)], 6.84 (1H, dd, *J* 7.8 Hz, 1.1 Hz, **H**-3′), 6.92 (1H, td, *J* 7.6 Hz, 1.1 Hz, **H**-5′), 7.12 (1H, dd, *J* 7.6 Hz, 1.6 Hz, **H**-6′), 7.16 (1H, td, *J* 7.8 Hz, 1.6 Hz, **H**-4′).

δ_C (100 MHz: $CDCl_3$): -4.18 (CH_3), 18.22 (C), 25.75 (CH_3), 29.04 (CH_3), 45.87 (CH_2), 118.41 (CH), 121.24 (CH), 125.67 (C), 128.30 (CH), 131.33 (CH), 153.76 (C), 206.76 (C).

m/z, (CI): 265 [$(M+H)^+$, 100%]. HRMS: 265.1627. $C_{15}H_{25}O_2Si$ requires 265.1624.

1-[2′-(*tert*-Butyldimethylsilyloxy)phenyl]propan-2-ol 72

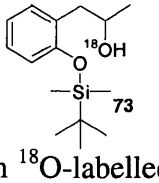
ν_{max} (GG)/cm^{-1}: 2955 (CH_2, CH_3), 1489 (CH), 1250 ($SiCH_3$).

δ_H (400 MHz: $CDCl_3$): 0.14 [3H, s, $Si(CH_3)_2$], 0.15 [3H, s, $Si(CH_3)_2$], 1.03 [9H, s, $SiC(CH_3)_3$], 1.24 [3H, d, *J* 6.4 Hz, $CH(OH)CH_3$], 2.66 [1H, dd, *J* 13.3 Hz, 8.2 Hz, $CH_2C(OH)$], 2.86 [1H, dd, *J* 13.3 Hz, 4.3 Hz, $CH_2C(OH)$], 4.03-4.08, (1H, m, CHOH), 6.83 (1H, d, *J* 8.0 Hz, **H**-3'), 6.92 (1H, td, *J* 7.4 Hz, 1.0 Hz, **H**-5'), 7.11-7.17 (2H, m, **H**-4', **H**-6').

δ_C (100 MHz: $CDCl_3$): -4.10 (CH_3), 18.23 (C), 22.98 (CH_3), 25.80 (CH_3), 40.64 (CH_2), 68.05 (CH), 118.59 (CH), 121.24 (CH), 127.61 (CH), 129.23 (C), 131.54 (CH), 153.87 (C).

m/z, (CI): 267 [$(M+H)^+$, 95%], 249 (55%), 135 (100%). HRMS: 267.1779. $C_{15}H_{27}O_2Si$ requires 267.1780.

1-[2-(*tert*-Butyl-dimethyl-silanyloxy)-phenyl]-propan-2-ol ^{18}O-labelled 73

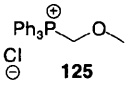


Resin-bound enol ether derived from ^{18}O-labelled acetic acid **30a**, contained in an IRORI macrokan® was stirred under argon for 1 h in dry DCM (10 mL). DCM (5 mL) was then added followed by TFA (0.15 mL). This was left to cleave for 1 h. At this time the contents were removed and placed in a dry 100 mL flask. This was then attached to a vacuum pump and cooled with a water bath. The DCM and TFA were removed using the pump and the compound left on the pump for a further hour to remove all TFA residues. At this time the flask was placed under argon and dry MeOH (4 mL) was added, followed by sodium borohydride (248 mg, 0.656 mmol). This was left stirring overnight. Water

was added to reaction mixture to quench, the mixture was then extracted with DCM (x 3), and the combined organics washed with water (x 3) and brine (x 1), dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave *alcohol* **73** (17.4 mg, 19.9%) as an oil.

GCMS was used to compare the samples of alcohols and the analyse the % of ^{18}O-labelled alcohol.

Methoxymethyl triphenylphosphonium chloride 125



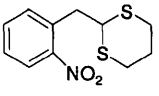
125

MOMCl (8.35 mL, 110 mmol) was added to a stirred solution of triphenylphosphine (26.23 g, 100 mmol) in DCM (150 mL). The mixture was stirred under reflux for 40 h. after which time the MOMCl was removed under reduced pressure and the resultant white powder dried by azeotropic distillation with toluene to give salt **125** (33.66 g, 98%).[34]

δ_H (400 MHz: $CDCl_3$) 3.72 (3H, d, *J* 0.6, OCH_3), 5.92 (2H, d, *J* 3.9, CH_3OCH_2), 7.65-7.73 (6H, m, Ar-**H**), 7.78-7.85 (9H, m, Ar-**H**).

Data agrees with literature.[174]

2-(2-Nitrophenylmethyl)-1,3-dithiane 127a



127a

tert-Butyllithium (27 mL of a 1.7 M solution) was added drop-wise to phosphonium salt **125** over 7 min.at –78 °C. The reaction mixture was stirred for a further 15 min at this temperature, then allowed to warm to –40 °C over 30 min. The mixture was cooled again to –78 °C for 15 min before a solution of 2-nitrobenzaldehyde (5.0 g, 33 mmol) in THF (27.5 mL) was added. The reaction mixture was allowed to warm to room temperature and left stirring under argon overnight. After the reaction was completed, a small amount of water was added to the reaction flask and some of the THF removed under reduced

pressure. The reaction mixture had water (275 mL) added to it and was then extracted with DCM (3x140 mL). The combined organic extracts were then washed with water (3 x 200 mL) and brine (200 mL), dried over sodium sulphate filtered, and concentrated under reduced pressure to yield crude enol ether product (18.12 g) as a mixture of *Z* and *E* isomers **126a**. δ_H (400MHz: $CDCl_3$) 3.74 ($3H^E$, s, OCH_3), 3.80 ($3H^Z$, s, OCH_3), 5.70 ($1H^Z$, d, *J* 7.2, CH=C**H**OCH_3), 6.31 ($1H^Z$, d, *J* 7.2, C**H**=CHOCH_3), 6.39 ($1H^E$, d, *J* 12.8, CHC**H**OCH_3), 7.01 ($1H^E$, d, *J* 12.8, C**H**CHOCH_3). This product was taken on without further purification. The enol ether was dissolved in toluene (55 mL) and acetic acid (33 mL) and 1,3-propanedithiol (3.65 mL, 36.3 mmol) was added. Boron trifluoride diethyl etherate (12.55 mL, 99 mmol) was added drop-wise and the reaction left stirring overnight. The triphenylphosphine oxide residues were then filtered off and the eluent poured into water (110 mL) and extracted into ethyl acetate (2 x 55 mL). The combined organic extracts were then washed with water (55 mL), aqueous NaOH (2x55 mL, 2M), water (110 mL) and then brine (110 mL), dried over magnesium sulfate and concentrated under reduced pressure. The product was recrystallised from toluene to give the thioacetal **127a** (1.04 g, 14%), as yellow prisms. [34]

mp: 77-81 °C.

ν_{max} (KBr)/cm^{-1}: 1517 (NO_2), 1340 (NO_2).

δ_H (400 MHz: $CDCl_3$) 1.83-1.94 (1H, m, SCH_2CH_{ax}), 2.07-2.17 (1H, m, SCH_2CH_{eq}) 2.83-2.85 (4H, m, SCH_2), 3.40 (2H, d, *J* 7.5, CH_2CHS) 4.36 (1H, t, *J* 7.5, CHS) 7.42-7.45 (2H, m, Ar-**H**), 7.56 (1H, td, *J* 7.6 and 1.2 Hz Ar-**H**) 8.00-8.02 (1H, m, Ar-**H**).

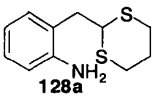
δ_C (100MHz: $CDCl_3$) 26.03 (CH_2), 30.49 (CH_2), 39.31 (CH_2), 47.09 (CH), 125.55 (CH), 128.70 (CH), 128.70 (C), 132.78 (C), 133.20 (CH), 133.94 (CH).

m/z, (CI): 256 [$(M+H)^+$, 100%], 226 (40%), 119 (72%).

Microanalysis:- C, 51.8; H, 5.12; N, 5.43%. $C_{11}H_{13}NO_2S_2$ requires C,51.74; H, 5.13; N, 5.49%.

Data agrees with literature. [174]

2-(2-Aminophenylmethyl)-1,3-dithiane 128a



128a

A mixture of 2-(2-nitrophenylmethyl)-1,3-dithiane **127a** (530 mg, 2.1 mmol), iron powder (350 mg, 6.3 mmol), and ammonium chloride (560 mg, 10.5 mmol), in ethanol (14 mL) and water (7 mL) were heated under reflux. After 2 h 15 min, the mixture was filtered through Celite and concentrated under reduced pressure. The amine was taken up in ethyl acetate and the solution washed with water (25 mL) and brine (2 x 25 mL), dried over magnesium sulfate and concentrated under reduced pressure to give dithiane **128a** as a pure yellow/orange oil (410 mg, 87%).[34]

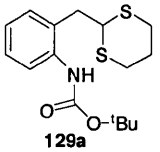
ν_{max} (NaCl)/cm^{-1}: 1623 (Ar C=C), 752 (A,r C-H, bending)

δ_H (400MHz: $CDCl_3$) 1.81-1.92 (1H, m, SCH_2CH_{ax}), 2.05-2.17 (1H, m, SCH_2CH_{eq}), 2.79-2.84 (4H, m, SCH_2), 2.94 (2H, d, *J* 7.2, CH_2CHS), 4.33 (1H, t, *J* 7.2, **CH**S), 6.70 (1H, d, *J* 8.1, **H**-3), 6.75 (1H, t, *J* 7.4, **H**-5), 7.07-7.10 (2H, m, Ar-**H**).

δ_C (100MHz: $CDCl_3$) 26.1 (CH_2), 31.02 (CH_2), 38.06 (CH_2), 47.12 (CH), 116.60 (CH), 119.21 (CH), 123.80 (C), 128.68 (CH), 131.51 (CH), 145.0 (C),

m/z, (EI): 225 ($M^{\bullet+}$, 5%), 119 ($M^{\bullet+}$-$C_3H_6S_2$, 20%), 83.0 (100%). HRMS: 225.0646. $C_{11}H_{15}NS_2$ requires 225.0646.

2-[2-(*N-tert*-Butyloxycarboxyamino)phenylmethyl]-1,3-dithiane 129a



129a

2-(2'-Aminobenzyl)-1,3-dithiane **128a** (580 mg, 2.58 mmol), di-*tert*-butyl dicarbonate (620 mg, 2.84 mmol) and THF (3.3 mL), were heated under reflux under nitrogen overnight. Water (10 mL) and DCM (6 mL) were added. The mixture was extracted with DCM (6 mL) and all the organic extracts combined and washed with water (2 x 10 mL), dried over

sodium sulfate and concentrated under reduced pressure. Crystallisation from cyclohexane gave the thioacetal **129a** as fine needles (630 mg, 75%). [34]

mp: 130-133 °C.

ν_{max} (KBr)/cm^{-1}: 3400 (N-H), 2927 (CH), 1677 (CO)

δ_H (400 MHz: $CDCl_3$) 1.54 [9H, s, $(C\mathbf{H}_3)_3$], 1.87-1.95 (1H, m, $SCH_2C\mathbf{H}_{ax}$), 2.11-2.16 (1H, m, $SCH_2C\mathbf{H}_{eq}$), 2.86-2.89 (4H, m, $SC\mathbf{H}_2$), 3.05 (2H, d, *J* 7.1, $C\mathbf{H}_2CHS$), 4.23 (1H, t, *J* 7.1, C**H**S), 6.53 (1H, br s, N**H**), 7.25-7.29 (4H, m, Ar-**H**)

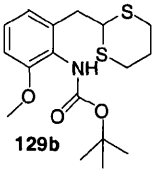
δ_C (100 MHz: $CDCl_3$) 25.92 (CH_2), 28.75 (CH_3), 30.77 (CH_2), 37.78 (CH_2), 48.20 (CH), 80.88 (C), 124.36 (CH), 125.04 (CH), 127.9 (CH), 128.28 (C), 130.97 (C), 136.47 (CH), 153.94 (C).

m/z, (EI): 325 ($M^{\bullet+}$, 10%), 268 ($M^{\bullet+}$-C_4H_9, 12%), 119 (100%). HRMS: 325.1175. $C_{16}H_{23}NO_2S_2$ requires 325.1170.

Microanalysis:- C, 59.14; H, 7.12; N, 4.31%. $C_{16}H_{23}NO_2S_2$ requires C, 59.05; H, 7.12; N, 4.30%.

Data agrees with literature. [174]

2-[2-(*N-tert*-Butyloxycarboxyamido)-3-methoxyphenylmethyl]-1,3-dithiane 129b



129b

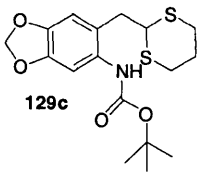
2-(3'-Methoxy-2'-nitrophenylmethyl)-1,3-dithiane **127b** was formed by adding ^{t}BuLi (12.8mL, 21.7 mmol) drop-wise to a suspension of methoxymethyltriphenylphosphonium chloride **125** (8.13 g, 23.76 mmol) in THF (40 mL) at –78 °C. After stirring for 15 min at -78 °C, the reaction mixture was allowed to warm to –40 °C over 30 min. The reaction was cooled again to -78 °C for 15 min and then 3-methoxy-2-nitrobenzaldehyde (2.87g, 15.84 mmol) in THF (13 mL), was added drop-wise. After stirring at room temperature

overnight, the reaction was quenched with water (130 mL) and the compound extracted with DCM (2 x 70 mL). The organic extracts were washed with water (3 x 100 mL) and brine (100 mL), dried using sodium sulphate, filtered, and concentrated under reduced pressure to give enol ether **126b**, which was taken on without further purification. The ^{1}HNMR spectrum showed a 1:1 mixture of *Z* and *E* isomers δ_H (400 MHz: $CDCl_3$): 3.45 ($3H^Z$, s, OCH_3), 3.66 ($3H^E$,s, OCH_3), 5.04 ($1H^Z$, d, *J* 7.2, $CHCHOCH_3$), 5.62 ($1H^E$, d, *J* 12.8, $CHCHOCH_3$), 6.26 ($1H^Z$, d, *J* 7.2, $CHCHOCH_3$), 7.08 ($1H^E$, d, *J* 12.8, $CHCHOCH_3$). The enol ether was dissolved in toluene (26 mL), acetic acid (16 mL) and 1,3-propanedithiol (1.75 mL, 17.42 mmol) was added. Borontrifluoride diethyletherate (6.02 mL, 47.5 mmol) was added drop-wise and the reaction mixture left stirring under argon overnight. The precipitate was filtered off, the solution poured into water (55 mL) and the organic layers extracted with ethyl acetate (2 x 30 mL). The organic extracts were then washed with water (30 mL), aqueous sodium hydroxide (2 x 30 mL, 2M), water (55 mL), and brine (55 mL) dried over magnesium sulfate and concentrated under reduced pressure. ^{1}HNMR analysis confirmed that this was the desired thioacetal, 2-(3'-Methoxy-2'-nitrobenzyl)-1,3-dithiane **127b** (3.92 g) and was taken on directly to the next step without further purification. [34], δ_H (400 MHz, $CDCl_3$): 1.81-1.92 (1H, m, CH_{ax}), 2.07-2.12 (1H, m, CH_{eq}), 2.82-2.84 (4H, m, CH_2S), 3.03 (2H, d, *J* 7.7, CH_2CHS), 3.88 (3H, s, OCH_3), 4.23 (1H, t, *J* 7.7, CHS), 6.95 (1H, d, *J* 7.8, **H**-4'), 7.16-7.18 (1H, m, **H**-6'), 7.36 (1H, t, *J* 8.1, **H**-5'). Data agrees with literature.[174] Iron powder (2.30 g, 41.23 mmol) was added to a solution of 2-(3'-Methoxy-2'-nitrobenzyl)-1,3-dithiane (3.92g) in ethanol (59 mL) and water (29 mL) with ammonium chloride (3.68 g, 68.73 mmol) and the mixture was heated under reflux for 2 h. After this time the reaction mixture was filtered through celite and washed with ethyl acetate. The ethanol was removed under reduced pressure and the compound dissolved in ethyl acetate (170 mL) and washed with water (170 mL), then brine (2 x 170 mL). The organic extracts were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. ^{1}HNMR analysis confirmed the amine **128b**. The compound was taken up in THF (22 mL) and di-tert-butyl dicarbonate (3.67 g, 16.8 mmol) was added. The reaction was then refluxed overnight under nitrogen. Column chromatography (SiO_2) eluted with hexane-ethyl acetate (1:1), gave dithiane **129b** (1.07g, 34% over 4 steps). R_F [SiO_2 hexane-ethyl acetate (1:1)] = 0.39. [34]

δ_H (400 MHz: $CDCl_3$): 1.53 [9H, s, $(CH_3)_3$], 1.84-1.90 (1H, m, CH_{ax}), 2.06-2.11 (1H, m, CH_{eq}), 2.80-2.83 (4H, m, CH_2S), 3.13 (2H, d, *J* 7.4, CH_2CHS), 3.81 (3H, s, OCH_3), 4.30 (1H, t, *J* 7.4, CHS), 6.00 (1H, s, NH), 6.81 (1H, dd, *J* 8.2, 1.1, **H**-4'), 6.89-6.90 (1H, m, **H**-6'), 7.17 (1H, t, *J* 8.0, **H**-5').

Data agrees with literature. [174]

2-[2'-(*N-tert*-Butyloxycarboxyamino)-4',5'-methylenedioxyphenylmethyl]-1,3-dithiane 129c



129c

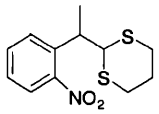
2-(4',5'-Methylenedioxy-2'-nitrophenylmethyl)-1,3-dithiane **127c** was formed by adding ^{t}BuLi (28.21 mL, 47.95 mmol, 1.7 M) drop-wise to a suspension of (methoxymethyl)triphenyl phosphine chloride **125** (17.97 g, 52.5 mmol) in THF (87 mL) at –78 °C. After stirring for 15 min at –78 °C, the reaction was allowed to warm to –40 °C over 30 min before being cooled again to –78 °C for 15 min. 6-Nitropiperonal (6.83 g, 35 mmol) in THF (30 mL) was then added drop-wise. This was left stirring at room temperature overnight. The reaction was quenched with water (290 mL) and the compound extracted with DCM (2 x 160 mL). The organics were washed with water (3 x 290 mL) and brine (290 mL). The compound **126c** was then dried using sodium sulphate, filtered, and concentrated under reduced pressure. The ^{1}HNMR spectrum shows a 1:1 mixture of *Z* and *E*. δ_H 3.73 (3H^{ZorE}, s, OC**H**$_3$), 3.79 (3H^{EorZ},s, OC**H**$_3$), 5.83 (1H^{Z}, d, *J* 7.3, CHC**H**OCH$_3$), 6.07 (2H^{ZorE}, s, OC**H**$_2$O) 6.07 (2H^{EorZ}, s, OC**H**$_2$O) 6.23 (1H^{Z}, d, *J* 7.3, C**H**CHOCH$_3$), 6.52 (1H^{E}, d, *J* 12.8, CHC**H**OCH$_3$), 6.93 (1H^{E}, d, *J* 12.8, C**H**CHOCH$_3$). The crude enol ether was dissolved in toluene (58 mL), acetic acid (35 mL) and propanedithiol (3.83 mL) was added. To this boron trifluoride diethyletherate (13.30 mL) was added drop-wise and the mixture left stirring under argon overnight. The precipitate was filtered off, the solution poured into water (130 mL) and the organic layers extracted with ethyl acetate (2 x 65 mL). The organic extracts were then washed with water (65 mL), aqueous sodium hydroxide (2 x 130 mL, 2 M), water (130 mL), and brine (130 mL), dried over magnesium sulfate and concentrated under reduced pressure to give thioacetal **127c** 2-(4,5-Methylenedioxy-2-nitrophenylmethyl)-1,3-dithiane (4.00 g, 38%) as the major product, which was used without further purification.[34] δ_H (400 MHz: $CDCl_3$): 1.92-1.88 (1H, m, C**H**$_{ax}$), 2.83-2.86 (1H, m, C**H**$_{eq}$), 2.83-2.86 (4H, m, C**H**$_2$S), 3.34 (2H, d, *J* 7.5, C**H**$_2$CHS), 4.37 (1H, t, *J* 7.7, C**H**S), 6.12 (2H. s, OC**H**$_2$O) 6.8 (1H, s, Ar-**H**), 7.56, (1H, s, Ar-**H**). 2-(4',5'-Methylenedioxy-2'-nitrobenzyl)-1,3-dithiane **127c** was dissolved in Ethanol (58 mL) and water (28 mL) and treated to iron powder (2.24 g) ammonium chloride (3.58 g) and heated under reflux for 2 h. The reaction mixture was filtered though

celite and the ethanol removed under reduced pressure. The resulting mixture was dissolved in ethyl acetate and (165 mL) and washed with water (2 x 165 mL) and brine (165 mL). The organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resultant amine **128c** was solvated in THF (15 mL) and di-tert-dibutyl dicarbonate was added (2.4 g, 11 mmol) and the reaction refluxed under nitrogen overnight. Sodium hydroxide (100 mL, 1 M) was added to the reaction flask along with DCM (25 mL). The layers were separated and the organics washed with water (3 x 40 mL) and brine (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave a brown solid, which was re-crystallisation twice from cyclohexane to isopropanol (4:1) to give dithiane **129c** (1.58 g, 12% over 4 steps) as an olive green solid.[34]

δ_H (400 MHz: $CDCl_3$): 1.50 [9H, s, $(CH_3)_3$], 1.84-1.93 (1H, m, CH_{ax}), 2.09-2.14 (1H, m, CH_{eq}), 2.81-2.86 (4H, m, SCH_2), 2.94 (2H, d, *J* 7.1, CH_2CHS), 4.16 (1H, t, *J* 7.1, CHS), 5.93 (2H, s, OCH_2O), 6.32 (1H, s, NH), 6.70 (1H, s, H-6′), 7.04 (1H, s, H-3′)

Data agrees with literature.[174]

2-[1'-(2'-Nitrophenyl)ethyl]-1,3-dithiane 139



139

Phosphonium salt **125** (30.4 g, 90 mmol) in THF (150 ml) under argon was cooled to –78 °C and ^{t}BuLi (49 ml, 82 mmol, 1.7 M) was added drop-wise by canula over 15 min. The reaction was stirred for a further 15 min at this temperature, then allowed to warm to –40 °C over 30 min. The mixture was cooled again to –78 °C for 15 min before a solution of 2-nitrophenyl acetophenone (10 g, 60 mmol) in THF (50 ml) was added. After stirring at room temperature the reaction was completed, a small amount of water was added to the reaction flask and some of the THF removed under reduced pressure. Water (275 ml) was added to the reaction mixture and the organic mixture extracted with DCM (3 x 280 ml). The combined organic extracts were then washed with water (3 x 400 ml) and brine (400 ml), then dried over sodium sulphate filtered and concentrated under reduced pressure to give impure enol ether **138** product as a 2:1 mixture of *E* and *Z* isomers (31.76 g). δ_H (400MHz: $CDCl_3$) 1.89, ($3H^E$, d, *J* 1.3, $CHCH_3$,), 1.95 ($3H^Z$, d, *J* 1.4, $CHCH_3$,) 3.49 ($3H^Z$,

s, OCH_3), 3.69 ($3H^E$, s, OCH_3), 5.98 ($1H^E$, d, *J* 1.4, $CCHOCH_3$), 6.05 ($1H^Z$, d, *J* 1.3, $CCHOCH_3$). This product was taken on without further purification. Toluene (100 mL) was added to the crude enol ether, along with acetic acid (60 mL) and propane dithiol (6.63 mL, 66 mmol). Boron trifluoride diethyl etherate (22.81 mL, 180 mmol), was added drop-wise and the mixture left stirring overnight. The triphenylphosphine oxide residues were then filtered off and the filtrate poured into water (220 mL) and extracted with ethyl acetate (2 x 110 mL). The combined organic layers were then washed with water (110 mL), NaOH (2 x 110 mL 2M), water (220 mL) and brine (220 mL), dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography (SiO_2) eluting with hexane - ethyl acetate (2:1) gave *thioacetal* **139** as a yellow oil (6.89 g, 43%). R_F [(SiO_2) hexane :ethyl acetate (2:1)] = 0.53.

ν_{max} (NaCl)/cm^{-1}: 3066 (CH), 2900 (CH), 1523 ($ArNO_2$), 1353 (NO_2).

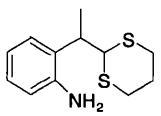
δ_H (400 MHz: $CDCl_3$) 1.55 (3H, d, *J* 7.0, $CHCH_3$), 1.81-1.91 (1H, m, SCH_2CH_{ax}), 2.02-2.09 (1H, m, SCH_2CH_{eq}), 2.78-2.90 (4H, m, SCH_2), 3.79 (1H, quin, *J* 7.1, $CHCH_3$), 4.27 (1H, d, *J* 7.9, CHS), 7.38 (1H, td, *J* 7.0 and1.8 **H**-4'), 7.52-7.59 (2H, m, Ar-**H**), 7.77 (1H, dd, *J* 8.2 and 1.2, **H**-3')

δ_C (100 MHz: $CDCl_3$) 18.80 (CH_3), 25.61 (CH_2), 29.65 (CH_2), 30.24 (CH_2), 38.54 (CH), 52.98 (CH) 124.15 (CH), 127.62 (CH), 129.06 (CH), 132.30 (CH), 137.57 (C), 150.24 (C).

m/z, (CI): 270 [$(M+H)^+$, 100%], 240 (20%). HRMS: 270.0619. $C_{12}H_{16}S_2NO_2$ requires (M+H) 270.0622.

Microanalysis:- C, 53.54; H, 5.49; N, 5.09% $C_{12}H_{15}NO_2S_2$ requires C, 53.50; H, 5.61; N, 5.20%.

2-[1'-(2'-Aminophenyl)ethyl]-1,3-dithiane 140



140

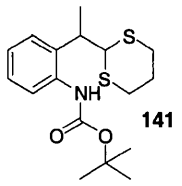
2-[1'-(2'-Nitrophenylmethyl)ethyl-1,3-dithiane **139** (413 mg,1.53mmol) was dissolved in ethanol (6.5 mL) and water (3.25 mL). Iron powder (257 mg, 4.59mmol) was added, followed by ammonium chloride (410 mg, 7.67mmol). The reaction was then heated under reflux under nitrogen for 3 h. After this time the reaction mixture was filtered through celite to remove the iron residues, washing with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The mixture was then dissolved in ethyl acetate and washed with water (1 x 19 mL), and brine (2 x 19 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give *aniline* **140** (310 mg 84 %)as an orange oil.

ν_{max} (NaCl)/cm^{-1}: 3345 (NH), 2894 (CH), 1619.

δ_H (400MHz: $CDCl_3$) 1.48 (3H, d, *J* 7.0, $CHCH_3$), 1.76-1.87 (1H, m, SCH_2CH_{ax}), 2.04-2.11 (1H, m, SCH_2CH_{eq}), 3.16 (1H, quin, *J* 6.9, $CHCH_3$), 4.35 (1H, d, *J* 6.8, CHS), 6.7 (1H, dd, *J* 7.9 and 1.2, **H**-3'), 6.81 (1H, td, *J* 7.6 and 1.2, **H**-5'), 7.07 (1H, td, *J* 7.8 and .1.5, **H**-4'), 7.17 (1H, dd, *J* 7.7 and 1.5, **H**-6').

m/z, (EI): 239 ($M^{\bullet+}$, 20%), 119 (100%), 83 (80%). HRMS: 239.0801. $C_{12}H_{17}NS_2$ requires 239.0802.

2'-(1-1,3-Dithian-2-yl-ethyl)-phenyl]-carbamic acid tert-butyl ester 141



141

2-[1'-(2'-Aminophenyl)ethyl]-1,3-dithiane **140** was dissolved in THF (15 mL), di-*tert*-dibutyl dicarbonate was added (2.4 g, 11 mmol) and the reaction mixture was heated under reflux under nitrogen overnight. Aqueous sodium hydroxide (100 mL, 1 M) was added to the reaction flask along with DCM (25 mL). The organic layer was then washed with water (3 x 40 mL) and brine (40 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave an 8:1.8 mixture of *dithiane* **141** (324 mg, 88%), as a yellow solid to Boc anhydride.

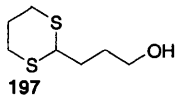
ν_{max} (GG)/cm^{-1}: 3338 (CONH), 2967 (CH).

δ_H (400 MHz: $CDCl_3$) 1.46 (3H, d, *J* 7.0, $CHCH_3$), 1.51 (9H, s, CCH_3), 1.52 (18H, s, Boc anhyd.)*, 1.79-1.86 (1H, m, SCH_2CH_{ax}), 2.05-2.10 (1H, m, SCH_2CH_{eq}), 3.31 (1H, quin, *J* 7.4, $CHCH_3$), 4.21 (1H, d, *J* 8.1, CHS), 6.45 (1H, bs, NH), 7.16 (1H, td, *J* 7.6 and 1.3, Ar-H), 7.23 (1H, dd, *J* 7.8 and .1.5, Ar-H), 7.30 (1H, dd, *J* 7.7 and 1.6, Ar-H), 7.56-7.58 (1H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$) 18.83 (CH_3), 25.64 (CH_2), 27.41 (CH_3)*, 28.36 (CH_3), 30.46 (CH_2), 30.77(CH_2), 38.32 (CH), 54.14 (CH), 125.24 (CH), 126.99 (CH), 127.33 (CH), 153.01 (C).

*=Boc anhydride signals in NMR.

3-(1,3-Dithian-2-yl)propan-1-ol 197



197

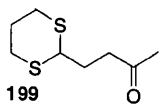
Boron trifluoride diethyletherate (35.9 mL, 285 mmol) was added drop-wise to a solution of 2,3-dihydrofuran (10.8 mL, 143 mmol) and 1,3 propane dithiol (14.3 mL, 143 mmol) in DCM (127 mL) stirring at 0 °C. [95] This was then stirred overnight. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM (3 x 40 mL). The organics were then combined and washed with water (3 x 90 mL), brine (1 x 90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave alcohol **197**[95] (19.3 g, 76%) as an oil, taken on without further purification.

δ_H (400 MHz: $CDCl_3$): 1.65 (1H, s, OH), 1.75-1.95 [5H, m, $CH(CH_2)_2CH_2OH$ and $CH_{ax}H_{eq}CH_2S$], 2.09-2.16 (1H, m, $CH_{ax}H_{eq}CH_2S$), 2.81-2.93 [4H, m, $CHS(CH_2)$], 3.68 (2H, t, *J* 6.2 Hz, CH_2OH) 4.08 (1H, t, *J* 6.8 Hz, CHS_2).

δ_C (100 MHz: $CDCl_3$): 25.9 (CH_2), 29.6 (CH_2), 30.3 (CH_2), 31.8 (CH_2), 47.2 (CH), 62.2 (CH_2).

Data in agreement with literature.[117,95]

4-(1,3-Dithian-2-yl)butan-2-one 199



199

Pyridine sulphur trioxide (33.9 g, 213 mmol) was added to a solution of 3-(1,3-Dithian-2-yl)propan-1-ol **197** (10.00 g, 178 mmol), triethylamine (51.5 mL, 370 mmol), and DMSO (37.2 mL, 560 mmol) in DCM (187 mL) and the solution stirred overnight. The reaction was quenched with water (270 mL) and the aqueous layer extracted with DCM (3 x 350 mL). The organic phases were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. This gave the 3-(1,3-dithian-2-yl)propionaldehyde **198** (17.7 g), though large amounts of DMSO and triethylamine salts were present. This compound was taken on without further purification. δ_H (400 MHz: $CDCl_3$): 1.82-1.96 (1H, m, $CH_{ax}H_{eq}CH_2S$) 2.08-2.16 (3H, m, $CH_{ax}H_{eq}CH_2S$ and $CHCH_2$) 2.72 (2H, td, *J* 7.2 Hz, 1.0 Hz, CH_2CHO) 2.84-2.87 [4H, m, $CHS(CH_2)$] 4.05 (1H, t, *J* 7.0 Hz, CHS_2) 9.81 (1H, s, CHO). Methyllithium (17.5 mL, 28.0 mmol) was added drop-wise to a solution of crude 4-(1,3-dithian-2-yl)-propionaldehyde **198** (4.43 g) in THF at –78 °C and left stirring to warm to room temperature overnight. The reaction mix was cooled to 0 °C before quenching with aqueous saturated sodium hydrogen carbonate. This reaction yielded 4-(1,3-dithian-2-yl)butan-2-ol (3.41 g) however there was also staring material present in the mixture, which gave a complicated proton 'HNMR spectrum. This was taken on directly for oxidation. Selected product signals: δ_H (400 MHz: $CDCl_3$): 1.21 (3H, d, *J* 6.2 Hz, CH_3CHOH), 3.83 (1H, q, *J* 6.1 Hz, $CH_3CH(OH)CH_2$). Pyridine sulphur trioxide (8.47 g, 159 mmol) was added to a solution of 4-(1,3-dithian-2-yl)butan-1-ol (3.41 g), triethylamine (12.9 mL, 92.4 mmol), and DMSO (9.90 mL, 140 mmol) in DCM (47 mL) and the solution stirred overnight. The reaction was quenched with water (70 mL) and the aqueous layer extracted with DCM (3 x 50 mL). The organic phases were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Column chromatography (silica) eluting with hexane and ethyl acetate (2:1) gave *4-(1,3-dithian-2-yl)butan-2-one* **199** as a pale yellow oil (1.058 g, 40% over 3 steps). R_F (SiO_2, 2:1 hexane:ethyl acetate): 0.47

ν_{max} (GG)/cm^{-1}: 2896 (CH), 1710 (C=O).

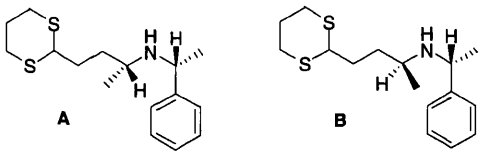
δ_H (400 MHz: $CDCl_3$): 1.81-1.92 (1H, m, $CH_{ax}H_{eq}CH_2S$), 2.05-2.15 [3H, m, $CH_{ax}H_{eq}CH_2S$ and $CHCH_2$], 2.17 (3H, s, CH_3), 2.68 [2H, t, *J* 7.2 Hz, $CH_2C(O)$], 2.83-2.86 [4H, m, $CHS(CH_2)$], 4.05 (1H, t, *J* 7.0 Hz, CHS_2).

δ_C (100 MHz: $CDCl_3$): 25.8 (CH_2), 29.0 (CH_2), 29.9 (CH_2), 30.0 (CH), 40.1 (CH_2), 46.4 (CH_3), 207.4 (C).

m/z, (EI): 190 ($M^{+\bullet}$, 8%), 132 (30%), 84 [$^{+\bullet}C_5H_8O$, 100%]. HRMS: 190.0487. $C_8H_{14}OS_2$ requires 190.0486.

Microanalysis: C 50.61%, H 7.51%; Theoretical $C_8H_{14}OS_2$: C 50.48%, H 7.51%

3-(1,3-Dithian-2-yl)-1-methyl-propyl-(1-phenylethyl)-amine 200



R, R- diastereomer S, R- diastereomer

200

Sodium triacetoxyborohydride (970 mg, 4.58 mmol) was added to a solution of 4-(1,3-dithia-2-yl)butan-2-one **199** (851 mg, 4.47 mmol), (*R*)-(+)-α-phenylethyl amine (1.06 mL, 8.32 mmol) and molecular sieves (210 mg) in DCM (15 mL). This was left stirring overnight. The reaction mixture was cooled to 0 °C before water (17 mL) was added and the organics separated from the aqueous, washed with water (3 x 30 mL), brine (2 x 15 mL). The organics were then dried over magnesium sulfate, filtered and concentrated under reduced pressure, to give *diastereoisomers* **200** (126 mg, 100%) as a 3:5 mixture of the two isomers **A**:**B** as an orange oil. Separation attempts were unsuccessful.

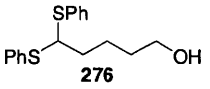
ν_{max} (NaCl)/cm^{-1}: 2956 (CH_2, CH_3)

δ_H (400 MHz: $CDCl_3$): 1.16-1.27 [$6H^{A+B}$, m, $NCH(CH_3)CH_2$], 1.61-2.17 [$9H^{A+B}$, m, CH_3CPh, $S_2CH(CH_2)_2$], $CH_{ax}H_{eq}CH_2S$], 2.57 ($1H^A$, bs/m, $NCHCH_2$), 2.72 ($1H^B$, bs/m, $NCHCH_2$), 2.75-2.80 ($4H^A$, m, $CHSCH_2$), 2.83-2.86 ($4H^B$, m, $CHSCH_2$), 3.84 ($1H^A$, t, *J* 6.8 Hz, CHS_2), 3.92 ($1H^B$, t, *J* 6.6 Hz, CHS_2), 4.12 ($1H^A$, bs/m, NCHPh), 4.18 ($1H^B$, bs/m, NCHPh), 7.28-7.54 ($5H^{A+B}$, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 25.95 (CH_2), 30.31 (CH_2), 31.36 (CH_2), 31.74 (CH_2), 47.32 (CH_3), 47.40 (CH), 50.04 (CH_3), 55.09 (CH), 55.28 (CH), 126.90 (CH), 127.38 (C), 127.64 (CH).

m/z, (EI): 269 ($M^{\bullet+}$, 100%), 280 (30%), 173 (65%), 148 (90%), 105 (83%). HRMS: 295.1427. $C_{16}H_{25}NS_2$ requires 295.1428.

5,5-Bis(phenylsulfanyl)pentan-1-ol 276



276

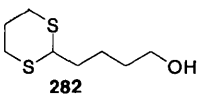
Following a literature procedure [175], boron trifluoro diethyletherate (13.1 mL, 105 mmol) was added drop-wise to a solution of 2,3 dihydro-2H-pyran (8.00 g, 95.1 mmol) and thiophenol (19.5 mL, 190 mmol) in DCM (85 mL) stirring at 0 °C. This was then stirred overnight. The reaction was quenched with water (75 mL) and the aqueous layer extracted with DCM (3 x 40 mL). The organic phases were then combined and washed with water (3 x 90 mL), brine (1 x 90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give alcohol **276**[95] (24.6 g, 85%) as an oil, which was taken on without further purification.

δ_H (400 MHz: $CDCl_3$): 1.31 (1H, s, O**H**) 1.50-1.57 [2H, m, (CH_2)$_3$$CH_2$OH] 1.64-1.72 [2H, m, ($CH_2$)$_3$$CH_2$OH] 1.85-1.90 [2H, m, ($CH_2$)$_3$$CH_2$OH] 3.60 (2H, t, *J* 6.5 Hz, CH_2OH) 4.40 (1H, t, *J* 6.6 Hz, CHS) 7.25-7.33 (6H, m, Ar-**H**) 7.44-7.47 (4H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 23.27 (CH_2), 32.05 (CH_2), 35.51 (CH_2), 58.35 (CH), 62.56 (CH_2), 127.69 (CH), 128.88 (CH), 132.72 (CH), 134.18 (C).

Data agrees with literature. [95]

4-(1,3-Dithian-2-yl)butanol 282



282

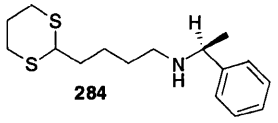
Boron trifluoride diethyletherate (35.1 mL, 279 mmol) was added drop-wise to a solution of 2,3 dihydro-2H-pyran (11.8 mL, 140 mmol) and 1,3-propane dithiol (14.0 mL, 140 mmol) in DCM (125 mL) stirring at 0 °C. This was then stirred overnight. The reaction was quenched with water (100 mL) and the aqueous layer extracted with DCM (3 x 40 mL). The organics were then combined and washed with water (3 x 90 mL), brine (1 x 90 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave 4-(1,3-dithian-2-yl)butanol **282,**[117] (22.4 g, 83%) as an oil , which was taken on without further purification.

δ_H (400 MHz: $CDCl_3$): 1.56-1.63 (4H, m, $CH_2CH_2CH_2OH$), 1.66 (1H, s, **OH**), 1.76-1.81 (2H, m, $CHCH_2$), 1.82-1.91 [1H, m, $CH_{ax}H_{eq}(CH_2)_2S_2$], 2.09-2.16 [1H, m, $CH_{ax}H_{eq}(CH_2)_2S_2$], 2.80-2.92 [4H, m, $CHSCH_2$], 3.63-3.66 (2H, m, CH_2OH), 4.06 [1H, t, *J* 6.9 Hz, CHS_2].

δ_C (100 MHz: $CDCl_3$): 22.81 (CH_2), 25.91 (CH_2), 30.36 (CH_2), 32.13 (CH_2), 35.07 (CH_2), 47.39 (CH), 62.44 (CH_2).

Data agrees with literature. [117]

(*S*)-(1,3-Dithian-2-yl-butyl)-*N*-(1-phenylethyl)amine 284



284

Pyridine sulphur trioxide (84.5 g, 531 mmol) was added to a solution of 4-(1,3-Dithian-2-yl)butan-1-ol **282** (140 mmol), triethylamine (51.5 mL, 370 mmol), and DMSO (37.2 mL, 560 mmol) in DCM (187 mL) and the solution stirred overnight. The reaction was quenched with water (270 mL) and the aqueous layer extracted with DCM (3 x 350 mL). The organic phases were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. This gave 4-(1,3-dithian-2-yl)butanal **283** (50.8 g), though large amounts of DMSO and triethylamine salts were present. This compound was taken on without further purification. δ_H (400 MHz: $CDCl_3$): 1.76-1.97 [5H, m, $CH_{ax}H_{eq}CH_2S$, $(CH_2)_2CH_2CHO$], 2.09-2.15 [1H, m, $CH_{ax}H_{eq}CH_2S$], 2.48 [2H, t, *J* 6.6 Hz, CH_2CHO], 2.81-2.92 (4H, m, $CHSCH_2$), 4.05 (1H, t, *J* 6.6 Hz, CHS_2) 9.77 (1H, s, **CHO**). Sodium triacetoxyborohydride (16.3 g , 76.8 mmol) was added to a solution of 4-(1,3-dithian-2-yl)butanal **283** (69.8 g, 25.4 mmol),(*S*)-(-)-α-phenyl ethylamine (17.9 mL, 140 mmol) and 4Å molecular sieves (33 g) in DCM (200 mL). This

was left stirring overnight. As before on standing after work up similar crystals of (S)-*N*-(1-Phenylethyl)acetamide formed, chromatography (alumina) using ether and hexane (2:1) yielded pure *amine* **284** (7.00g, 41% over 2 steps) as a yellow oil. R_F (Al_2O_3, 2:1 diethyl ether:hexane): 0.5.

ν_{max} (GG)/cm^{-1}: 2929 (CH or NH), 2854 (CH).

δ_H (400 MHz: $CDCl_3$): 1.34 [3H, d, *J* 6.6 Hz, NCH($\mathbf{CH_3}$)], 1.44-1.53 [4H, m, $NCH_2(\mathbf{CH_2})_2$], 1.70-1.75 (2H, m, $CHC\mathbf{H_2}$), 1.83-1.89 [1H, m, $C\mathbf{H}_{ax}H_{eq}CH_2S$], 2.07-2.13 [1H, m, $CH_{ax}\mathbf{H}_{eq}CH_2S$], 2.13-2.45 (1H, m, $NC\mathbf{H_2}$), 2.47-2.51 (1H, m, $NC\mathbf{H_2}$), 2.77-2.89 (4H, m, $CHSC\mathbf{H_2}$), 3.74 (1H, q, *J* 7.0 Hz, NC**H**), 4.01 (1H, t, *J* 6.9 Hz, C**H**S), 7.20-7.25 (1H, m, Ar-**H**), 7.26-7.34 (4H, m, Ar-**H**).

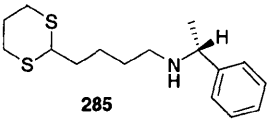
δ_C (100 MHz: $CDCl_3$): 24.29 (CH_3), 24.37 (CH_2), 25.97 (CH_2), 29.82 (CH_2), 30.41 (CH_2), 35.25 (CH_2), 47.47 (CH), 47.48 (CH_2), 58.34 (CH), 126.47 (CH), 126.77 (CH), 128.35 (CH), 145.77 (C).

m/z, (EI): 295 ($M^{\bullet+}$, 32%), 105 (34%), 82 (100%). HRMS: 295.1427. $C_{16}H_{25}NS_2$: requires 295.1428.

Microanalysis: C, 65.05; H, 8.49; N, 4.82%. $C_{16}H_{25}NS_2$ requires C, 65.02; H, 8.52; N, 4.76%.

Optical Rotation: $[\alpha]_D$ –3.79 concentration : 0.1 dm^{-3} taken at 22 °C in DCM

(*S*)-(1,3-Dithian-2-yl-butyl)-*N*-(1-phenylethyl)amine 285



285

Following the above procedure sodium triacetoxyborohydride (16.3 g , 76.8 mmol) was added to a stirred solution of 4-(1,3-dithian-2-yl)butanal (25.4 g), (*R*)-(+)-α-phenylethylamine (17.9 mL, 140 mmol) and 4′ molecular sieves (33.0 g) in DCM (200 mL). This was left stirring overnight. The reaction mixture was cooled to 0 °C before water (200 mL) was added, the organic phases were then separated from the aqueous, and washed with water (3 x 150 mL) and brine (1 x 150 mL). The organic phases were then

dried over magnesium sulfate, filtered and concentrated under reduced pressure. On standing large clear colourless crystals formed, further purification and spectroscopic investigation lead to the side product determined as *N*-(1-phenylethyl)acetamide **286**. [176] The majority was crystallised out (4:1 cyclohexane, isopropanol), and chromatography (alumina) using diethyl ether and hexane (2:1 solvent system) gave the *amine* **285** (7.29 g, 35% over 2 steps) as a yellow oil. R_F (Al_2O_3, 2:1 diethyl ether:hexane): 0.4.

ν_{max} (GG)/cm^{-1}: 2929 (CH), 2855 (CH or NH), 1601 (NH).

δ_H (400 MHz: $CDCl_3$): 1.34 [3H, d, *J* 6.6 Hz, NCH($\mathbf{CH_3}$)], 1.38-1.52 [4H, m, $NCH_2(\mathbf{CH_2})_2$],1.69-1.75 (2H, m, SCH$\mathbf{CH_2}$), 1.81-1.88 [1H, m, $\mathbf{CH}_{ax}\mathbf{H}_{eq}CH_2S$], 2.06-2.12 [1H, m, $CH_{ax}\mathbf{H}_{eq}CH_2S$], 2.40-2.44 (1H, m, N$\mathbf{CH_2}$), 2.47-2.57 (1H, m, N$\mathbf{CH_2}$), 2.78-2.85 [4H, m, CHS$\mathbf{CH_2}$], 3.47 (1H, q, *J* 7.0 Hz, N**CH**), 4.01 (1H, t, *J* 6.9 Hz, **CH**S), 7.20-7.22 (1H, m, Ar-**H**), 7.24-7.36 (4H, m, Ar-**H**).

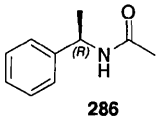
δ_C (100 MHz: $CDCl_3$): 24.3 (CH_3), 24.3 (CH_2), 25.9 (CH_2), 29.8 (CH_2), 30.4 (CH_2), 35.2 (CH_2), 47.4 (CH), 47.4 (CH_2), 58.3 (CH), 126.4 (CH), 126.7 (CH), 128.3 (CH), 145.7 (C).

m/z, (EI): 295 ($M^{\bullet+}$, 32%), 105 (100%). HRMS: 295.1426. $C_{16}H_{25}NS_2$: requires 295.1428.

Microanalysis: C, 64.51; H, 8.48; N, 4.72%. $C_{16}H_{25}NS_2$ requires C, 65.02; H, 8.52; N, 4.76%.

Optical Rotation: $[\alpha]_D$ 5.02 concentration : 0.1 dm^{-3} taken at 22 °C in DCM

N-(1-Phenylethyl)acetamide[176] 286

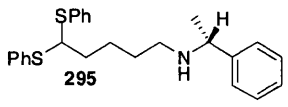


286

δ_H (400 MHz: $CDCl_3$): 1.49 (3H, d, *J* 6.9 Hz, NCH) 1.99 [3H, s, $\mathbf{CH_3}C(O)$] 5.14 [1H, q, HNC**H**(CH_3)] 5.65 (1H, bs, N**H**) 7.28-7.37 (5H, m, Ar-**H**)

m/z, (EI): 163 ($M^{+\bullet}$, 68%), 106 [$C_6H_5CH_2(CH_3)^{\bullet+}$ 100%].

(*R*)-*N*-[5,5-Bis(phenylsulfanyl)pentyl]-*N*-(1-phenylethyl)amine 295



Pyridine sulphur trioxide (47.3 g, 297 mmol) was added to a solution of 5,5-Bis(phenylsulfanyl)pentanol **276** (23.8 g, 78.3 mmol), triethylamine (72.0 mL, 517 mmol), and DMSO (56.0 mL, 783 mmol) in DCM (260 mL) and the solution stirred overnight. The reaction was quenched with water (200 mL) followed by aqueous sodium hydrogen carbonate solution and the aqueous layer extracted with DCM (3 x 100 mL). The organics were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. This gave 5,5-Bis(phenylsulfanyl)pentanal **277** (31.7 g), containing large amounts of DMSO and triethylamine salts. This compound was taken on without further purification . δ_H (400 MHz: $CDCl_3$): 1.83-1.89 [2H, m, $CH(CH_2)_2$], 1.91-1.98 [2H, m, $CH(CH_2)_2$], 2.41 (2H, td, *J* 7.1 Hz, 1.4 Hz, CH_2CHO), 4.38 (1H, t, *J* 6.4 Hz, CHS_2), 7.28-7.35 (6H, m, Ar-**H**), 7.44-7.47 (4H, m, Ar-**H**), 9.71 (1H, t, *J* 1.5 Hz, **CHO**). Sodium triacetoxyborohydride (9.12 g , 43.0 mmol) was added to a solution of 5,5-Bis(phenylsulfanyl)pentanal (11.8 g) at 0 °C, (*R*)-(+)-α -phenylethylamine (10 mL, 78.3 mmol) and molecular sieves (18.5 g) in DCM (200 mL). The reaction was left stirring overnight. The reaction mixture was cooled to 0 °C before water (200 mL) was added and the organic phases separated from the aqueous, washed with water (3 x 150 mL), then brine (1 x 150 mL). The organic phases were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. Chromatography (silica) eluting with DCM and hexane (4:1) followed by EtOAc elution gave (2.54 g, 16% over 2 steps) *(R)-N-[5,5-Bis(phenylsulfanyl)penty]-N-(1-phenylethyl)amine* **295** as an orange oil. R_F (SiO_2, 4:1 DCM:hexane): 0.41.

ν_{max} (NaCl)/cm^{-1}: 3316 (NH), 2931 (CH_3, CH_2).

δ_H (400 MHz: $CDCl_3$): 1.33 (3H, d, *J* 6.6 Hz, $NCHCH_3$) 1.36-1.46 [2H, m, $NCH_2(CH_2)_2$] 1.55-1.63 [2H, m, $NCH_2(CH_2)_2$] 1.79-1.84 (2H, m, $CHCH_2$) 2.32-2.40 (1H, m, CH_2N) 2.42-2.48 (1H, m, CH_2N) 3.71 (1H, q, *J* 6.6 Hz, $NCHCH_3$) 4.37 (1H, t, *J* 6.7 Hz, **SCH**) 7.21-7.33 (11H, m, Ar-**H**) 7.42-7.46 (4H, m, Ar-**H**).

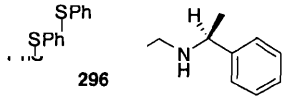
δ_C (100 MHz: $CDCl_3$): 24.31 (CH_3), 24.71 (CH_2), 29.61 (CH_2), 35.57 (CH_2), 47.45 (CH_2), 58.19 (CH), 58.32 (CH), 126.46 (CH), 126.79 (CH), 127.58 (CH), 128.35 (CH), 128.81 (CH), 132.60 (CH), 134.18 (C), 145.68 (C).

m/z, (FAB+/NOBA): 408 [$(M+H)^+$, 100%], 298 (70%), 106 (98%). HRMS: 408.1825. $C_{25}H_{30}NS_2$: requires 408.1820.

Microanalysis: C, 73.44; H, 6.95; N, 3.38%. $C_{25}H_{29}NS_2$ requires C, 73.66; H, 7.17; N, 3.44%.

Optical Rotation: $[\alpha]_D$ 2.23 concentration : 0.1 dm^{-3} taken at 22 °C in DCM

(*S*)-*N*-[5,5-Bis(phenylsulfanyl)pentyl]-*N*-(1-phenylethyl)amine 296



296

Following the above procedures and employing L-(-)-α-phenyl ethylamine (10.0 mL, 78.3 mmol), *(S)-[5,5-Bis-phenylsulfanyl-pentyl]-(1-phenylethyl)amine* was prepared and purified as follows: Chromatography (silica) DCM and hexane (4:1) solvent elution followed by EtOAc elution. This gave *amine* **296** in (6.38 g 40% over 2 steps) as an orange oil. R_F (SiO_2, 4:1 DCM:hexane): 0.12

ν_{max} (GG)/cm^{-1}: 2926 (CH_3, CH_2).

δ_H (400 MHz: $CDCl_3$): 1.34 (3H, d, *J* 6.4 Hz, NCHC**H**$_3$), 1.38-1.47 [2H, m, NC**H**$_2$(C**H**$_2$)$_2$], 1.54-1.63 [2H, m, NC**H**$_2$(C**H**$_2$)$_2$], 1.79-1.84 (2H, m, CHC**H**$_2$), 2.35-2.41 (1H, m, C**H**$_2$N), 2.43-2.49 (1H, m, C**H**$_2$N), 3.72 (1H, q, *J* 6.6 Hz, NC**H**CH$_3$), 4.37 (1H, t, *J* 6.6 Hz, SC**H**), 7.21-7.34 (11H, m, Ar-**H**), 7.42-7.44 (4H, m, Ar-**H**).

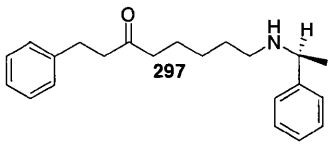
δ_C (100 MHz: $CDCl_3$): 24.26 (CH_3), 24.75 (CH_2), 29.59 (CH_2), 35.61 (CH_2), 47.47 (CH_2), 58.24 (CH), 58.37 (CH), 126.51 (CH), 126.87 (CH), 127.63 (CH), 128.41 (CH), 128.85 (CH), 132.5 (CH), 134.22 (C), 145.60 (C).

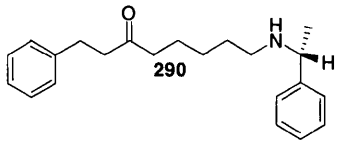
m/z, (EI): 407 ($M^{\bullet+}$, 20%), 298 ($M^{\bullet+}$-SPh, 90%), 105 ($CH_3CHPh^{\bullet+}$,100%). HRMS: 4071739. $C_{25}H_{29}NS_2$: requires 407.1741.

Microanalysis: C, 73.40; H, 7.17; N, 3.48%. $C_{25}H_{29}NS_2$ requires C, 73.66; H, 7.17; N, 3.44%.

Optical Rotation: $[\alpha]_D$ –2.23 concentration : 0.1 dm^{-3} taken at 22 °C in DCM

1-Phenyl-8-(1'-phenylethylamino)octan-3-one 297





Titanocene dichloride (930mg, 3.72 mmol), magnesium turnings (90 mg, 4.09 mmol) and 4Å molecular sieves (200 mg) were heated briefly under vacuum. Following cooling, the reaction flask was flushed with argon, and THF (4 mL) and triethylphosphite (1.28 mL, 7.20 mmol) were added and the reaction mixture was stirred for 3h. At this time a THF (10 mL) solution of (S)-*N*-{4-(1,3-dithian-2-yl)-butyl}-*N*-(1-phenylethyl)amine **284** (0.900 mmol) was added, and the solution stirred for 15 min. The reaction mixture was added *via* syringe into a flask containing 1 kan of resin-bound ester (0.150 mmol). The mixture was stirred under argon for 15-18 h. After this time, the kan was removed and then washed with THF (x 5), alternately with MeOH and DCM (x 5), then MeOH and finally with diethyl ether. The resin was then dried under vacuum. Following cleavage from resin using general method B, *(S)-1-Phenyl-8-(1-phenylethylamino)octan-3-one* **297** was obtained cleanly (37.3 mg, 37%yield. The enantiomer of this compound was also prepared using (*R*)-*N*-[4-(1,3-dithian-2-yl)-butyl]-*N*-(1-phenylethyl)amine **285** and solid phase Takeda reaction: general method B with a kan of resin-bound ester containing 0.310 meq. Again following the general cleavage procedure B, *(R)-1-Phenyl-8-(1-phenylethylamino)octan-3-one* **290** was produced (18.8 mg, 19%) as a yellow oil.

(*S*)-1-Phenyl-8-(1-phenylethylamino)octan-3-one 297

ν_{max} (NaCl)/cm^{-1}: 2924 (CH or NH), 2854 (CH or NH), 1713 (C=O), 1603 (NH).

δ_H (400 MHz: $CDCl_3$): 1.19-1.24 [2H, m, $NCH_2(CH_2)_3$], 1.35 [3H, d, *J* 6.6 Hz, $NCH(CH_3)$], 1.40-1.49 [2H, m, $NCH_2(CH_2)_3$], 1.48-1.55 [2H, m, $NCH_2(CH_2)_3$], 2.35 (2H, t, *J* 7.4 Hz, $PhCH_2$), 2.38-2.43 (1H, m, NCH_2), 2.46-2.52 (1H, m, NCH_2), 2.70 [2H, t, *J* 7.6 Hz, $C(O)CH_2$], 2.88 (2H, t, *J* 7.6 Hz, $C(O)CH_2$], 3.76 [1H, q, *J* 6.6 Hz, NCH], 7.15-7.20 (2H, m, Ar-H), 7.22-7.34 (8H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 23.49 (CH_2), 24.02 (CH_3), 29.69 (CH_2), 29.74 (CH_2), 31.90 (CH_2), 42.81 (CH_2), 44.22 (CH_2), 47.44 (CH_2), 58.41 (CH), 126.04 (CH), 126.56 (CH), 126.98 (CH), 128.28 (CH), 128.44 (CH), 140.09 (C), 145.10 (C), 210.13 (C).

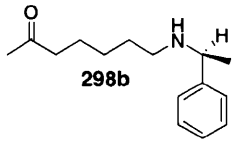
m/z, (EI): 323 ($M^{\bullet+}$, 8%), 308 (78%), 105 (100%). HRMS: 323.2252. $C_{22}H_{29}NO$ requires 323.2249.

(*R*)-1-Phenyl-8-(1-phenylethylamino)octan-3-one 290

δ_H (400 MHz: $CDCl_3$): 1.14-1.23 [2H, m, $NCH_2(CH_2)_3$], 1.28 [3H, d, *J* 6.4 Hz, $NCH(CH_3)$], 1.32-1.39 [2H, m, $NCH_2(CH_2)_3$], 1.41-1.48 [2H, m, $NCH_2(CH_2)_3$], 2.23 (2H, t, *J* 7.4 Hz, $PhCH_2$), 2.31-2.43 (1H, m, NCH_2), 2.37-2.41 (1H, m, NCH_2), 2.62 [2H, t, *J* 7.6 Hz, $C(O)CH_2$], 2.81 (2H, t, *J* 7.6 Hz, $C(O)CH_2$], 3.67 [1H, q, *J* 6.6 Hz, NCH], 7.05-7.12 (2H, m, Ar-H), 7.19-7.26 (8H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 23.56 (CH_2), 24.23 (CH_3), 26.86 (CH_2), 29.68 (CH_2), 29.93 (CH_2), 42.86 (CH_2), 44.23 (CH_2), 47.51 (CH_2), 58.37 (CH), 126.05 (CH), 126.52 (CH), 126.86 (CH), 128.29 (CH), 128.40 (CH), 141.11 (C), 145.63 (C), 210.13 (C).

(*S*)-7-(1-Phenylethylamino)heptan-2-one 298b



298b

Following solid phase Takeda reaction general method C, using resin-bound acetic acid, and general cleavage procedure B, gave *7-(1'-Phenylethylamino)heptan-2-one* **298b** was prepared as an orange oil (26 mg 43%) as a yellow oil.

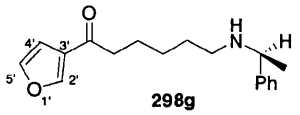
ν_{max} (NaCl)/cm^{-1}: 2926 (CH_2, CH_3), 1715 (C=O).

δ_H (400 MHz: $CDCl_3$): 1.24-1.31 [2H, m, $(CH_2)_3CH_2N$] 1.35 (3H, d, *J* 6.6 Hz, $NCHCH_3$) 1.40-1.49 [2H, m, $(CH_2)_3CH_2N$] 1.50-1.58 [2H, m, $(CH_2)_3CH_2N$] 2.14 (3H, s, CH_3CO) 2.37-2.43 (3H, m, CH_2N and CH_3COCH_2) 2.46-2.52 (1H, m, CH_2N) 3.74 (1H, q, *J* 6.8 Hz, $NCHCH_3$) 7.22-7.27 (1H, m, Ar-H) 7.29-7.36 (4H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 23.58 (CH_2), 24.31 (CH_3), 26.81 (CH_2), 29.86 (CH_3), 29.97 (CH_2), 43.58 (CH_2), 47.58 (CH_2), 58.38 (CH), 126.49 (CH), 126.81 (CH), 128.37 (CH), 145.67 (C), 209.15 (C).

m/z, (CI): 324 [$(M+H)^+$, 100%), 81 (29%). HRMS: 234.1856. $C_{15}H_{24}NO$ requires $(M+H)^+$, 234.1858.

(*S*)-1-(Furan-3′-yl)-6-(1″-phenyleth-1″-ylamino)hexan-1-one 298g



298g

Following solid phase Takeda reaction general method C using resin-bound ester and general cleavage procedure B, gave *(S)-1(-Furan-3′-yl)-6-(1″-phenyleth-1″-ylamino)hexan-1-one* **298g** (38 mg, 43%) as a yellow oil.

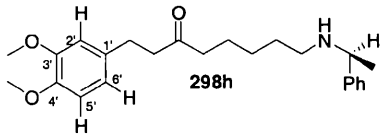
ν_{max} (NaCl)/cm^{-1}: 2929 (CH_2, CH_3), 1677 (C=O), 1562 (NH).

δ_H (400 MHz: $CDCl_3$): 1.23-1.31 [5H, m, $(CH_2)_3CH_2N$ and $NCHCH_3$] 1.34-1.48 [2H, m, $(CH_2)_3CH_2N$] 1.57 –1.65 [2H, m, $(CH_2)_3CH_2N$] 2.25-2.37 (1H, m, CH_2N) 2.40-2.46 (1H, m, CH_2N) 2.60 (2H, t, *J* 7.5 Hz, $COCH_2$) 3.67 (1H, q, *J* 6.5 Hz, $NCHCH_3$) 6.68 (1H, d, *J* 1.3 Hz, **H**-4′) 7.14-7.18 (1H, m, Ar-**H**) 7.21-7.27 (4H, m, Ar-**H**) 7.35 (1H, d, *J* 1.6 Hz, **H**-5′) 7.92 (1H, s, **H**-2′).

δ_C (100 MHz, $CDCl_3$): 24.12 (CH_2), 24.31 (CH_3), 26.95 (CH_2), 30.00 (CH_2), 40.26 (CH_2), 47.58 (CH_2), 58.38 (CH), 108.59 (CH), 126.50 (CH), 126.81 (CH), 128.03 (CH), 144.11 (CH), 145.67 (C), 146.99 (CH), 195.14 (C).

m/z, (EI): 285 ($M^{\bullet+}$, 7%), 270 (35%), 105 (75%), 83 (100%). HRMS: 285.1731. $C_{18}H_{23}NO_2$: requires 285.1729.

(*S*)-1-(3′,4′-Dimethoxyphenyl)-8-(1″-phenylethylamino)octan-3-one 298h



Following solid phase Takeda reaction general method C using resin-bound 3-(3,4-dimethoxy)phenyl)propionic acid and general cleavage procedure B, gave *(S)-1-(3′,4′-Dimethoxyphenyl)-8-(1″-phenylethylamino)octan-3-one* **298h** (0.013 g 11%) as a yellow oil.

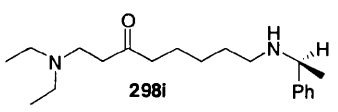
ν_{max} (GG)/cm^{-1}: 2930 (CH_2, CH_3), 1709 (C=O), 1514 (NH).

δ_H (400 MHz: $CDCl_3$): 1.19-1.30 [2H, m, $(CH_2)_3CH_2N$] 1.34 (3H, d, *J* 6.6 Hz, $NCHCH_3$) 1.38-1.48 [2H, m, $(CH_2)_3CH_2N$] 1.49-1.57 [2H, m, $(CH_2)_3CH_2N$] 2.36 [2H, t, *J* 7.4 Hz, $COCH_2(CH_2)_3$] 2.38-2.42 (1H, m, CH_aH_bN) 2.44-2.51 (1H, m, CH_aH_bN) 2.68 [2H, t, *J* 7.5 Hz, $Ar(CH_2)_2CO$] 2.83 [2H, t, *J* 7.5 Hz, $Ar(CH_2)_2CO$] 3.85 (3H, s, OCH_3) 3.86 (3H, s, OCH_3) 6.71 (1H, d, *J* 7.4 Hz, H-5′) 6.71 (1H, d, *J* 3.6 Hz, H-2′) 6.77-6.79 (1H, m, H-6′) 7.21-7.25 (1H, m, Ar-H″) 7.28-7.34 (4H, m, Ar-H″).

δ_C (100 MHz: $CDCl_3$): 23.54 (CH_2), 24.32 (CH_3), 26.87 (CH_2), 29.40 (CH_2), 29.98 (CH_2), 42.92 (CH_2), 44.52 (CH_2), 47.58 (CH_2), 55.79 (CH_3), 55.88 (CH_3), 58.41 (CH), 111.17 (CH), 111.61 (CH), 120.02 (CH), 126.51 (CH), 126.84 (CH), 128.39 (CH), 133.72 (C), 147.27 (C), 148.78 (C), 210.32 (C).

m/z, (EI): 383 ($M^{\bullet+}$, 10%), 368 (25%), 151 (22%), 105 (43%), 83 (100%), 47 (25%). HRMS: 383.2459. $C_{24}H_{33}NO_3$: requires 383.2460.

(*S*)-1-Diethylamino-8-(1′-phenylethylamino)octan-3-one 298i



Following solid phase Takeda reaction general method C using resin-bound 3-(diethylamino)-propionic acid and general cleavage procedure B, gave *1-Diethylamino-8-(1-phenylethylamino)octan-3-one* **298i** (59 mg 56%) as a yellow oil.

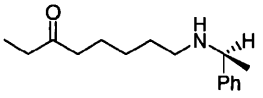
ν_{max} (GG)/cm^{-1}: 2929 (CH_2, CH_3), 1708 (C=O).

δ_H (400 MHz: $CDCl_3$): 1.01 [6H, t, *J* 7.2 Hz, CH_3CH_2N] 1.23-1.31 [2H, m, $(CH_2)_3CH_2N$] 1.35 (3H, d, *J* 6.6 Hz, $NCHCH_3$) 1.40-1.48 [2H, m, $(CH_2)_3CH_2N$] 1.50-1.61 [2H, m, $(CH_2)_3CH_2N$] 2.37-2.43 [3H, m, $N(CH_2)_2COCH_2$ and $CH_aH_bNCHCH_3$] 2.45-2.55 [7H, m, 2 x CH_3CH_2N, $CH_aH_bNCHCH_3$ and NCH_2CH_2CO] 2.73 [2H, t, *J* 7.0 Hz, NCH_2CH_2CO] 3.74 (1H, q, *J* 6.6 Hz, $NCHCH_3$) 7.21-7.25 (1H, m, Ar-**H**) 7.27-7.34 (4H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 11.64 (CH_3), 23.47 (CH_2), 24.31 (CH_3), 26.85 (CH_2), 30.00 (CH_2), 40.35 (CH_2), 43.03 (CH_2), 46.76 (CH_2), 47.28 (CH_2), 47.57 (CH_2), 58.35 (CH), 126.46 (CH), 126.76 (CH), 128.33 (CH), 145.71 (C), 210.52 (C).

m/z, (FAB+NOBA): 319 [$(M+H)^+$, 28%], 246 (20%), 87 (100%). HRMS: 319.2746. $C_{20}H_{35}N_2O$ requires $(M+H)^+$, 319.2749.

(*S*)-8-(1-Phenylethylamino)octan-3-one 298i(b)



This compound was obtained by treatment of (1′S)-1-Diethylamino-8-(1-phenyleth-1-ylamino)octan-3-one **298i** (51 mg, 0.16 mmol) to hydrogenation conditions of $Pd/(OH)_2$ 10% (12 mg) 145 psi, at 40 °C in EtOH (3 mL) with a basic work-up. This gave the unexpected result of *(S)-8-(1-Phenylethylamino-octan-3-one* **298i(b)** as a dark orange oil (23 mg).

ν_{max} (GG)/cm^{-1}: 2930 (CH_2, CH_3), 1714 (C=O), 1452 (CH).

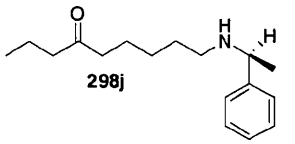
δ_H (400 MHz: $CDCl_3$): 1.04 (3H, t, *J* 7.3 Hz, CH_3CH_2CO) 1.18-1.31 (2H, m, $(CH_2)_3CH_2N$] 1.35 (3H, d, *J* 6.6 Hz, $NCHCH_3$) 1.41-1.51 [2H, m, $(CH_2)_3CH_2N$] 1.52-1.61

[2H, m, $(CH_2)_3CH_2N$] 2.35-2.43 (5H, m, CH_aH_bN and CH_2COCH_2) 2.45-2.54 (1H, m, CH_aH_bN) 3.75 (1H, q, *J* 6.6 Hz, NCH) 7.21-7.25 (1H, m, Ar-H) 7.28-7.35 (4H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 7.79 (CH_3), 23.69 (CH_3), 24.33 (CH_2), 26.98 (CH_2), 29.85 (CH_2), 35.83 (CH_2), 42.21 (CH_2), 47.60 (CH_2), 58.37 (CH), 126.47 (CH), 126.78 (CH), 128.35 (CH), 145.75 (C), 211.78 (C).

m/z, (CI): 248.2 [$(M+H)^+$, 100%]. HRMS: 248.2012. $C_{16}H_{26}NO$ requires $(M+H)^+$, 248.2014.

(*S*)-9-(1-Phenylethylamino)nonan-4-one 298j



298j

Method A

Following solid phase Takeda reaction general method C using resin-bound 3-(diethylamino)-propionic acid and general cleavage procedure B, gave *(S)-9-(1-Phenylethylamino)nonan-4-one* **298j** (62 mg, 72%) as a yellow oil.

Method B

(*S*)-(-)-α-phenylethylamine (1.52 mL, 11.9 mmol) was added to a solution of 9-Iodo-nonan-4-one **320** (11.88 mmol) in dry MeOH (23 mL). This was left stirring for 30 min before triethylamine (1.66 mL, 11.9 mmol) was added and the solution left stirring for 30 h before being refluxed for a further 18 h. At this time the solvent was removed and aqueous HCl (1M) added until the reaction mixture dissolved and was at pH1. This solution was then extracted with ether (x 3), then chloroform (x 3). The aqueous was treated with aqueous NaOH (1M) to pH 12 and then extracted with DCM (x 3). The chloroform layer was neutralised with NaOH solution (1M) and all individual organic extracts were dried separately over sodium sulfate, filtered and concentrated under reduced pressure. The ether layer gave un-reacted 9-Iodo-nonan-4-one (137 mg), the DCM layer gave un-reacted (*S*)-(-)-α-phenylethylamine (836 mg), and the chloroform layer gave *9-('-phenylethylamino-nonan-4-one* **298j** (978 mg, 32%) as a yellow oil. This compound was also prepared in 6% yield using 9-bromo-nonan-4-one (1.16 g, 5.27 mmol) as a starting material in place of 9-Iodononan-4-one.

ν_{max} (GG)/cm^{-1}: 2928 (CH_3, CH_2), 1707 (C=O).

δ_H (400 MHz: $CDCl_3$): 0.81 (3H, t, *J* 7.4 Hz, CH_3CH_2), 1.14-1.20 (2H, m, CH_3CH_2), 1.25 (3H, d, *J* 6.4 Hz, $CHCH_3$), 1.33-1.38 [2H, m, $C(O)CH_2(CH_2)_3$], 1.39-1.54 [4H, m, $C(O)CH_2(CH_2)_3$], 2.24-2.27 [4H, m, $CH_2C(O)CH_2$], 2.28-2.42 (2H, m, CH_2N), 3.65 (1H, q, *J* 6.8, $NCHCH_3$), 7.11-7.16 (1H, m, Ar-**H**), 7.21-7.30 (4H, m, Ar-**H**).

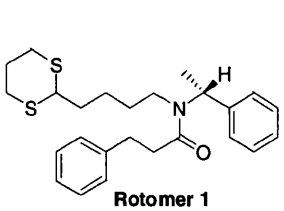
δ_C (100 MHz: $CDCl_3$): 13.68 (CH_3), 17.02 (CH_2), 23.58 (CH_2), 24.16 (CH_3), 26.50 (CH_2), 29.46 (CH_2), 42.38 (CH_2), 44.42 (CH_2), 47.18 (CH_2), 58.16 (CH), 126.27 (CH), 126.56 (CH), 128.13 (CH), 145.28 (C), 210.77 (C).

m/z, (EI): 261 ($M^{\bullet+}$, 22%), 246 [$M^{\bullet+}$-$^{\bullet}CH_3$, 100%], 105 (CH_3CHPh^+, 100%). HRMS: 261.2090. $C_{17}H_{27}NO$ requires 261.2093.

Microanalysis: C, 77.67; H, 10.49; N, 5.36%. $C_{17}H_{27}NO$ requires C, 78.11; H, 10.41; N, 5.36%.

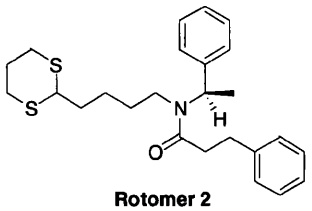
4-([1,3]-dithian-2-yl-butyl)-3-phenyl-N-(1-phenylethyl)propionamide

(*R*)-*N*-4-(1,3-dithian-2-yl-butyl)-3-phenyl-*N*-(1-phenylethyl)propionamide 304



Rotomer 1

304



Rotomer 2

3-Phenylpropionic acid (5.00 g, 33.3 mmol) was treated with thionyl chloride (24.3 mL, 333 mmol) under anhydrous conditions and heated under refluxed for 3h. At this time the thionyl chloride was removed on the rotary evaporator and the acid chloride used directly in the formation of *(R)-N*-4-(1,3-dithian-2-yl-butyl)-3-phenyl-*N*-(1-phenylethyl)propionamide **304**. Triethylamine (2.45 mL, 17.6 mmol) was added to a solution of (*R*)-(1,3-dithian-2-yl-butyl)-N-(1-phenylethyl)amine **285** (2.63 g, 15.6 mmol) stirring dry DCM (10 mL). After 15 min 3-phenylpropionyl chloride was added in dry DCM (5 mL). The reaction was left stirring overnight. Water was added to the reaction upon completion and the mixture extracted with DCM. The combinded organic phases were then washed with water (x 5), NaOH (2M x 2), water (x 2) and brine (x 1). The

organic phases were then dried over sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography (silica) eluting with pet ether / ethyl acetate (2:1) solvent system, gave *(R)-N-{4-(1,3-dithian-2-yl-butyl)-3-phenyl-N-(1-phenyl-ethyl)propionamide* **304** as a thick yellow oil, (2.12 g, 73%). The HNMR is particularly complicated due to the presence of rotamers A.and B in a 3:2 ratio. R_F (SiO_2, 2:1 Pet ether:ethyl acetate): 0.39.

ν_{max} (GG)/cm^{-1}: 2932 (CH), 1633 [$R_2NC(O)R$].

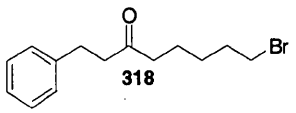
δ_H (400 MHz, $CDCl_3$): 0.93 ($1H^A$, m, CH_2N) 1.13-1.23 [$4H^{A+B}$, m, $SCHCH_2CH_2$], 1.30 [$3H^A$, d, *J* 7.6 Hz, $NCH(CH_3)$], 1.41 ($3H^B$, d, *J* 7.1 Hz, $NCHCH_3$), 1.56-1.60 ($2H^B$, m, CH_2CH_2N), 1.74-1.81 [$1H^{A+B}$, m, $CH_{ax}H_{eq}(CH_2)_2S_2$], 2.00-2.05 [$1H^{A+B}$, m, $CH_{ax}H_{eq}(CH_2)_2S_2$], 2.60 [$2H^A$, t, *J* 7.4 Hz, $CH_2C(O)N$], 2.67 [$2H^B$, t, *J* 7.5 Hz, $CH_2C(O)N$)], 2.71-2.74 ($4H^{A+B}$, m, $CHSCH_2$), 2.77-2.95 ($2H^A$, m, CH_2CH_2N), 2.93-3.00 [$2H^{A+B}$, m, CH_2Ph], 3.14-3.19 ($1H^B$, m, CH_2N) 3.80 ($1H^A$, t, *J* 6.9 Hz, CHS), 3.87 ($1H^B$, t, *J* 6.9 Hz, CHS), 4.99 ($1H^B$, q, *J* 6.9 Hz, NCH), 5.96 ($1H^A$, q, *J* 7.0 Hz, NCH), 7.08-7.26 ($10H^{A+B}$, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 16.63 (CH_3), 18.31 (CH_3), 23.94 (CH_2), 24.30 (CH_2), 25.80 (CH_2), 25.89 (CH_2), 28.34 (CH_2), 30.20 (CH_2), 30.24 (CH_2), 31.56 (CH_2), 31.80 (CH_2), 34.51 (CH_2), 34.82 (CH_2), 35.35 (CH_2), 35.50 (CH_2), 43.08 (CH_2), 43.46 (CH_2), 46.99 (CH), 47.24 (CH), 55.00 (CH), 50.85 (CH), 126.02 (CH), 126.58 (CH), 127.22 (CH), 127.43 (CH), 127.48 (CH), 128.26 (CH), 128.38 (CH), 128.43 (CH), 128.53 (CH), 140.43 (C), 140.88 (C), 171.77 (C), 172.09 (C).

m/z, (EI): 427 ($M^{\bullet+}$, 70%), 105 ($C_6H_5CHCH_3^+$, 100%), 322 [$(CH_2)_3S_2CH(CH_2)_4NC(O)(CH_2)_2Ph^+$, 32%]. HRMS: 427.2003. $C_{25}H_{33}NOS_2$: requires 427.2004.

Microanalysis: C, 69.70; H, 7.74; N, 3.41%. $C_{23}H_{33}NOS_2$ requires C, 70.21; H, 7.77; N, 3.28%.

8-Bromo-1-phenyl-octan-3-one 318



Following a literature procedure[120], phenylethyl bromide (4.17 mL, 30.5 mmol) was added drop-wise, via a pressure equalizing dropping funnel, in dry ether (8 mL) to magnesium turnings (690 mg, 28.4 mmol) under argon. The 3 neck flask also had a water condenser attached. A couple of crystals of iodine were added and the reaction left till there was no more magnesium (1 h). At this point 6-Bromohexane nitrile (5.00 g, 28.4 mmol) was added drop-wise in 20 mL dry ether and the reaction left stirring for 48 h. The reaction was cooled to 0 °C and ice was added to quench, followed by aqueous HCl (1M). The reaction mixture was then extracted with ether (x 5) and the combined organic phases dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting ketone was purified using silica gel column chromatography eluting with hexane and ether (3:1). The impure ketone was then purified further using kugelrorh distillation 170 °C at 0.6 mmHg removing all impurities from the product leaving pure 8-Bromo-1-phenyl-octan-3-one **318**[177] (825 mg, 10%) as orange oil. R_F (SiO_2, 2:1, hexane:diethyl ether): 0.6

ν_{max} (GG)/cm^{-1}: 2935 (CH_3, CH_2), 1711 (C=O), 1452 (C-H).

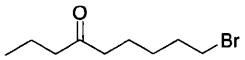
δ_H (400 MHz: $CDCl_3$): 1.19-2.25 [2H, m, $(CH_2)_3CH_2Br$] 1.36-1.43 [2H, m, $(CH_2)_3CH_2Br$] 1.54-1.62 [2H, m, $(CH_2)_3CH_2Br$] 2.40 (2H, t, *J* 7.4 Hz, $CH_2(CH_2)_4Br$ 2.73 [2H, t, *J* 7.6 Hz, $Ph(CH_2)_2$] 2.90 [2H, t, *J* 7.6 Hz, $Ph(CH_2)_2$] 3.90 (2H, t, *J* 6.8 Hz, CH_2CH_2Br) 7.14-7.21 (3H, m, Ar-**H**) 7.26-7.30 (2H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 22.70 (CH_2), 27.64 (CH_2), 29.75 (CH_2), 32.48 (CH_2), 33.60 (CH_2), 42.67 (CH_2), 44.29 (CH_2), 126.09 (CH), 128.50 (CH), 128.47 (CH), 141.03 (C), 209.84 (C).

m/z, (EI): 284 ($M^{\bullet+}$, ^{81}Br, 18%), 282 ($M^{\bullet+}$, ^{79}Br, 20%), 203 [$M^{\bullet+}$-$Br^{\bullet}$, 25%], 179 [$^{+}C(O)(CH_2)_5$, ^{81}Br, 13%], 177 [$^{+}C(O)(CH_2)_5$, ^{79}Br, 15%], 91 ($PhCH_2^{+}$, 5%). HRMS: 282.0619 (100%), 284.0602 (91%). $C_{14}H_{19}{}^{79}BrO$ requires 282.0619, $C_{14}H_{19}{}^{81}BrO$ requires 284.0600.

Microanalysis: C, 60.12; H, 6.82%. $C_{14}H_{19}BrO$ requires C, 59.37; H, 6.76%.

9-Bromononan-4-one 319



319

Following a literature procedure, [120] 6-bromohexane nitrile (3.98 mL, 30 mmol), was added to an n-propylmagnesium chloride (2M) solution in ether (15.0 mL, 30 mmol). This was left stirring at 40 °C for 48 h. The reaction was then cooled to 0 °C and ice was added to quench, followed by aqueous HCl (1M), water was added and the reaction mixture extracted with ether (x 5). The combined organic phases were then dried over magnesium sulfate, filtered and concentrated under reduced pressure. Chromatography (silica), eluting with hexane and EtOAc (3:1) gave 9-Bromo-nonan-4-one **319** [178] in (3.55 g, 54%), as a yellow oil. R_F (SiO_2, 10:1 hexane: diethyl ether): 0.32

ν_{max} (GG)/cm^{-1}: 2928 (CH_3, CH_2), 1709 (C=O).

δ_H (400 MHz: $CDCl_3$): 0.91 (3H, t, *J* 7.2 Hz, C**H**$_3$) 1.39-1.47 (2H, m, $CH_3C\mathbf{H}_2$) 1.53-1.63 [4H, m, $C(O)CH_2(C\mathbf{H}_2)_2$] 1.81-1.90 (2H, m, $C\mathbf{H}_2CH_2Br$) 2.38 [2H, t, *J* 7.6 Hz, $CH_3C\mathbf{H}_2C\mathbf{H}_2C(O)$] 2.42 (2H, t, *J* 7.2 Hz, $CH_3CH_2CH_2C(O)C\mathbf{H}_2$) 3.41 (2H, t, *J* 6.6 Hz, $C\mathbf{H}_2Br$).

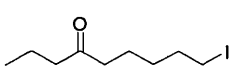
δ_C (100 MHz: $CDCl_3$): 13.74 (CH_3), 17.27 (CH_2), 22.79 (CH_2), 27.71 (CH_2), 32.52 (CH_2), 33.63 (CH_2), 42.41 (CH_2), 44.76 (CH_2), 211.00 (C).

m/z, (CI): 221 [$(M+H)^+$, 100%], 223 [$(M+H)^+$, 98%], 141 [$CH_3(CH_2)_2C(O)(CH_2)_5^{\bullet+}$, 15%]. HRMS: 221.0541 (100%), 223.0522 (90%). $C_9H_{18}{}^{79}BrO$ requires 221.0541, $C_9H_{18}{}^{81}BrO$ 223.0521.

Microanalysis: C, 49.13; H, 7.90%. $C_9H_{17}Br$ requires C, 48.88; H, 7.75%.

Data agrees with literature. [178]

9-Iodononan-4-one 320



320

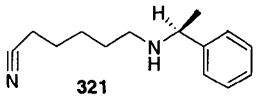
9-Bromononan-4-one **319** (2.63 g, 11.9 mmol) was added to a solution of sodium iodide (2.23 g, 14.9 mmol) in dry acetone (24 mL). The reaction mixture was left stirring for 1 h under argon, then heated under reflux for 30 min. The precipitate was then filtered off and washed with acetone. The acetone layer was then concentrated under reduced pressure to give iodide **320** (3.22 g, quantitative)

δ_H (400 MHz: MeOD): 0.94 (3H, t, *J* 7.4 Hz, $\mathbf{CH_3}$) 1.38-1.47 (2H, m, $CH_3\mathbf{CH_2}$) 1.56-1.64 [4H, m, $C(O)CH_2(\mathbf{CH_2})_2$] 1.80-1.87 (2H, m, $\mathbf{CH_2}CH_2I$) 2.45-2.60 [4H, m, $\mathbf{CH_2}C(O)C\mathbf{H_2}$] 3.26 (2H, t, *J* 6.8 Hz, $\mathbf{CH_2}I$)

δ_C (100 MHz: MeOD): 6.82 (CH_2I), 14.10 (CH_3), 18.27 (CH_2), 23.72 (CH_2), 31.09 (CH_2), 34.58 (CH_2), 43.23 (CH_2), 45.45 (CH_2), 213.82 (C).

Data agrees with literature. [179]

(*S*)-6-(1′-Phenylethylamino)hexanenitrile 321



321

(*S*)-(-)-α-Phenylethylamine (2.56 mL, 20.0 mmol) was added to a stirred solution of 6-bromohexane nitrile (1.33 mL, 10.0 mmol) in dry MeOH (15 mL). This was left stirring under argon overnight. The reaction mixture was concentrated under reduced pressure and aqueous HCl (1M) was added and the mixture was extracted with ether (x 3), then chloroform (x 3). The chloroform layer was washed with NaOH (1M), then water and brine sequentially. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave *6-(1′-Phenylethylamino)hexanenitrile* **321** (1.36 g, 63%) as an oil.

ν_{max} (GG)/cm^{-1}: 2928 (CH_3, CH_2), 2244 (CN).

δ_H (400 MHz: $CDCl_3$): 1.35 (3H, d, *J* 6.4 Hz, $\mathbf{CH_3}$), 1.39-1.53 [4H, m, $(\mathbf{CH_2})_2CH_2N$], 1.63 (2H, quin, *J* 7.2 Hz, $NCCH_2\mathbf{CH_2}$), 2.31 (2H, t, *J* 7.2 Hz, $NCC\mathbf{H_2}$),

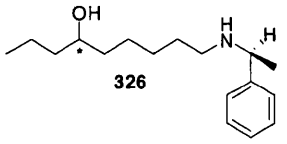
2.38-2.45 (1H, m, C**H**$_2$N), 2.48-2.54 (1H, m, C**H**$_2$N), 3.74 (1H, q, *J* 6.5 Hz, NC**H**CH$_3$), 7.22-7.26 (1H, m, Ar-**H**), 7.301-7.380 (4H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 17.10 (CH_2), 24.41 (CH_3), 25.26 (CH_2), 26.43 (CH_2), 25.68 (CH_2), 29.50 (CH_2), 47.36 (CH_2), 58.44 (CH), 119.74 (C), 126.51 (CH), 126.91 (CH), 128.40 (CH), 145.69 (C).

m/z, (CI): 217 [$(M+H)^+$, 100%], 201 [$NC(CH_2)_5NHCPh^+$, 18%). HRMS: 217.1709. $C_{14}H_{21}N_2$ requires $(M+H)^+$, 217.1705.

9-[1(*S*)-Phenylethylamino]nonan-4(S)-ol and

9-[1(*S*)-Phenylethylamino]nonan-4(R)-ol : mixture of diastereomers 326



326

Method A

(S)-1-Phenyl-8-(1-phenylethylamino)octan-3-one **298j** (100 mg, 0.383 mmol) was dissolved in dry DCM (1 mL) and stirred with TMSCl (0.24 mL, 1.9 mmol) overnight under argon. At which time sodium triacetoxyborohydride (487 mg, 2.30 mmol) was added followed by dry DCM (1 mL) and the reaction left stirring overnight. Water was added to quench the reaction and the mixture was extracted with DCM. The organics were washed with 1M NaOH, water and then brine. The solution was dried over sodium sulfate, filtered and concentrated under reduced pressure. The reaction was incomplete so the residue was dissolved in dry DCM (2 mL) and treated to TMSCl (0.49 mL, 3.8 mmol) followed by sodium triacetoxyborohydride (975 mg, 4.6 mmol) and dry DCM (2 mL). Column chromatography on deactivated alumina eluted with hexane : DCM : MeOH (67:33:2) alcohol *9-(1-Phenyl-ethylamino)-nonan-4-ol* **326** (35 mg, 35%) as a pale yellow oil. R_F (Al_2O_3, 66:32:2 hexane: DCM:MeOH): 0.47

Method B

Sodium borohydride (26 mg, 0.694 mmol) was added to a solution of 1-Phenyl-8-(1-phenylethylamino)octan-3-one **298j** (0.0907 g, 0.347 mmol) in MeOH (0.50 mL) and the reaction left stirring under nitrogen overnight. Water was added to quench the reaction,

followed by aqueous HCl (1M). The reaction mixture was then extracted with chloroform and the organic layer washed with, sodium bicarbonate solution (x 2), water (x 2), brine (x 1) and then dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave *alcohol* **326** (63 mg 69%) as a pale yellow oil.

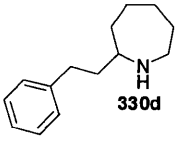
ν_{max} (GG)/cm^{-1}: 3305 (OH), 2926 (CH_2, CH_3), 1492 (Ar).

δ_H (400 MHz: $CDCl_3$): 0.83 (3H, t, *J* 6.8 Hz, C**H**$_3$CH$_2$), 1.20-1.25 (2H, m, CH$_3$C**H**$_2$), 1.28 (3H, d, *J* 6.8 Hz, NCHC**H**$_3$), 1.31-1.44 [10H, m, CHOH(C**H**$_2$)$_4$ CH$_3$CH$_2$C**H**$_2$], 2.23-2.39 (1H, m, C**H**$_2$N), 2.41-2.49 (1H, m, C**H**$_2$N), 3.50-3.51 (1H, bs/m, C**H**OH), 3.68 (1H, q, *J* 6.8 Hz, NC**H**CH$_3$), 7.14-7.19 (1H, m, Ar-**H**), 7.20-7.27 (4H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 14.08 (CH_3), 18.78 (CH_2), 24.42 (CH_3), 25.43 (CH_2), 27.29 (CH_2), 30.09 (CH_2), 37.29 (CH_2), 39.61 (CH_2), 47.68 (CH_2), 58.35 (CH), 71.43 (CH), 126.48 (CH), 126.79 (CH), 126.35 (CH), 145.65 (C).

m/z, (EI): 248 ($M^{\bullet+}$-CH_3, 40%), 158 ($M^{\bullet+}$-$CHCH_3Ph$, 8%), 105 [CH_3CHPh^+, 80%] 84 (100%) HRMS: 263.2249. $C_{17}H_{29}NO$ requires 263.2249.

2-Phenethylazepane 330d



330d

(*S*)-1-Phenyl-8-(1-phenylethylamino)octan-3-one **298d** (102 mg, 0.316 mmol) was placed into a glass vessel with EtOH (5 mL) and 20% palladium hydroxide on carbon (25 mg). The glass container was placed inside a bomb and the contents were hydrogenated at 70 psi H_2 and 40 °C overnight. The reaction mixture was filtered through a pipette plugged with cotton wool and celite, washing through with more EtOH and concentrated under reduced pressure. The resultant mixture of starting material and product was separated on deactivated alumina eluting with DCM :MeOH (100:1) to give *2-phenethylazepane* **330d** (21.9 mg, 34%), as a yellow oil. R_F (Al_2O_3, 99:1 DCM:MeOH): 0.06

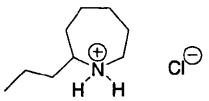
ν_{max} (GG)/cm^{-1}: 2918 (CH_2, CH_3), 1494 (Ar).

δ_H (400 MHz: $CDCl_3$): 1.35-1.44 (1H, m, NCHC**H**$_2$) 1.46-1.56 [1H, m, NCHC**H**$_2$(CH_2)$_4$] 1.57-1.68 [4H, m, NCHCH_2(C**H**$_2$)$_3$] 1.70-1.74 (3H, m, NCHCH_2(C**H**$_2$)$_3$, NC**H**$_2$) 1.78-1.86 (1H, m, NC**H**$_2$) 2.61-2.75 [4H, m, N(C**H**$_2$)$_2$Ph] 3.00-3.05 (1H, m, NC**H**) 7.13-7.22 (3H, m, Ar-**H**), 7.25-7.32 (2H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 25.51 (CH_2), 27.17 (CH_2), 30.72 (CH_2), 32.87 (CH_2), 36.04 (CH_2), 39.23 (CH_2), 47.16 (CH_2), 58.47 (CH), 125.67 (CH), 128.29 (CH), 128.33 (CH), 142.22 (C).

m/z, (CI): 204 [$(M+H)^+$, 100%]. HRMS: 204.1751. $C_{14}H_{22}N$ requires $(M+H)^+$ 204.1752.

2-Propyl-azepanium chloride 330j



330j

(S)-9-(1-Phenylethylamino)nonan-4-one **298j** (74.1 g, 0.284 mmol) in EtOH (5 mL) was put into a glass vessel followed by 20% palladium hydroxide on carbon (36 mg). the vessel was placed in a bomb and the contents were hydrogenated at 90 psi H_2 and 42°C overnight. The reaction mixture was filtered through a pipette plugged with cotton wool and celite, washed through with more EtOH and a few drops of ethereal HCl (2M) was added. The salt was then concentrated under reduced pressure. This gave 2-propylazepanium; chloride **330j** (56.8g, quantitatively), as a peach coloured solid. [180]

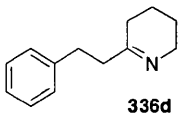
ν_{max} (GG)/cm^{-1}: 2930 (CH_2, CH_3), 2596 (-$^+NH_2$-),1452 (CH).

δ_H (400 MHz: $CDCl_3$): 0.96 (3H, t, *J* 7.2 Hz, C**H**$_3$CH_2), 1.47 (2H, bs, CH_3C**H**$_2$), 1.55-1.77 [6H, m, CH_3CH_2C**H**$_2$, NCHC**H**$_2$, N(CH_2)$_2$C**H**$_2$], 1.90-1.98 [5H, m, N(CH_2)$_3$C**H**$_2$, NC**H**$_2$, N(CH_2)$_2$C**H**$_2$], 2.05 (1H, bs, NC**H**$_2$), 3.21 (2H, bs, N**H**$_2$), 3.28 (1H, bs, NC**H**).

δ_C (100 MHz: $CDCl_3$): 13.72 (CH_3), 19.16 (CH_2), 24.74 (CH_2), 24.91 (CH_2), 26.94 (CH_2), 30.47 (CH_2), 35.82 (CH_2), 44.99 (CH_2), 58.72 (CH).

m/z, (CI): 142 [$(M+H)^+$, 100%]. HRMS: 142.1599. $C_9H_{20}N$ requires 142.1596.

6-Phenethyl-2,3,4,5-tetrahydro-pyridine 336d



336d

Following general solid-phase Takeda reaction C, using *N*-[4,4-Bis(phenylsulfanyl)but-I-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound 3-phenyl propionoic acid **30d** containing 0.328 meq the corresponding enol ether was formed. This was cleaved from resin using general cleavage method D and the 6-phenethyl-2,3,4,5-tetrahydropyridine **336d** isolated (53.1 mg 87%) as a yellow oil.

ν_{max} (NaCl)/cm^{-1}: 2929 (CH_2), 1665 (C=N), 1453 (CH).

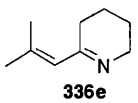
δ_H (400 MHz: $CDCl_3$): 1.56-1.58 [2H, m, $NCCH_2C\mathbf{H}_{eq}H_{ax}$,$NC(CH_2)_2C\mathbf{H}_{eq}H_{ax}$] 1.63-1.69 [2H, m, $NCCH_2CH_{eq}\mathbf{H}_{ax}$,$NC(CH_2)_2CH_{eq}\mathbf{H}_{ax}$] 2.08-2.12 [2H, m, $NCC\mathbf{H}_2(CH_2)_3$] 2.42-2.46 (2H, m, $NCC\mathbf{H}_2CH_2Ph$) 2.84-2.88 (2H, m, $NCH_2C\mathbf{H}_2Ph$) 3.57-3.60 (2H, m, $NC\mathbf{H}_2$) 7.16-7.21 (3H, m, Ar-**H**) 7.28-7.29 (2H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 19.59 (CH_2), 21.93 (CH_2), 29.63 (CH_2), 32.63 (CH_2), 42.45 (CH_2), 49.29 (CH_2), 125.82 (CH), 128.35 (CH), 142.01 (C), 170.12 (C).

m/z, (EI): 187 ($M^{\bullet+}$, 100%), 110 (35%), 91 (75%). HRMS: 187.1362. $C_{13}H_{17}N$ requires 187.1361

Data agrees with literature.[160]

6-(2-Methyl-propenyl)-2,3,4,5-tetrahydro-pyridine 336e



336e

Following general solid-phase Takeda reaction C, using *N*-[3-(1,3-dithian-2-yl)propyl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound (*N*,-*N*,-dimethylamino)acrylic acid **30e** containing 0.328 meq the corresponding enol ether was

formed. This was cleaved from resin by shaking the kan with TFA (4%) and Et_3SiH (1%) in 5 mL DCM for 2 h. At this time the cleavage solution was decanted and the kan washed with DCM (x 3). The organic phases were combined and concentrated under reduced pressure. The HCl salt was formed by addition of saturated ethereal HCl and the salt was washed with diethyl ether. *6-(2-Methyl-propenyl)-2,3,4,5-tetrahydro-pyridine* **336e** was isolated on washing with NaOH (aq, 4M) (62.7 mg, quantitative yield with some impurities present that could not be removed).

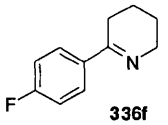
ν_{max} (NaCl)/cm^{-1}: 2916 (CH_2, CH_3), 1637 (C=N)

δ_H (400 MHz: CD_3OD): 1.82-1.96 [6H, m, $(CH_2)_3CH_2N$] 2.09 (3H, s, CH_3) 2.14 (3H, s, CH_3) 3.69 [2H, m, CH_2C=N] 6.20 [1H, s, CH=$C(CH_3)_2$].

δ_C (100 MHz: CD_3OD): 18.08 (CH_2), 20.45 (CH_2), 22.05 (CH_3), 29.22 (CH_3), 45.53 (CH_2), 121.35 (CH), 161.45 (C), 182.50 (C).

m/z, (CI): 138 (M^+, 100%). HRMS: 138.1287. $C_9H_{16}N$ requires 138.1283.

6-(4'-Fluoro-phenyl)-2,3,4,5-tetrahydro-pyridine 336f



336f

Following general solid-phase Takeda reaction C, using *N*-[4,4-bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound 4-flourobenzoic acid **30f** (0.328 meq) gave the corresponding enol ether. This was cleaved from resin and cyclised using general cleavage method D and the 6-(4'-fluoro-phenyl)-2,3,4,5-tetrahydropyridine **336f** isolated in (11.4 mg, 20%) as a yellow oil.

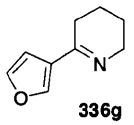
ν_{max} (NaCl)/cm^{-1}: 2924 (CH_2), 1599 (C=N), 1506 (Aromatic ring).

δ_H (400 MHz: $CDCl_3$): 1.64-1.70 [2H, m, $NCH_2(CH_2)_2$], 1.81-1.87 [2H, m, $NCH_2(CH_2)_2$], 2.58-2.62 (2H, m, $NCCH_2$), 3.81-3.83 (2H, m, NCH_2), 7.04 (2H, t, *J* 8.7 Hz, **H**-3' and **H**-4'), 7.76 (2H, dd, *J* 8.6 Hz, 5.6 Hz, **H**-2' and **H**-6').

δ_C (100 MHz: $CDCl_3$): 19.69 (CH_2), 21.77 (CH_2), 26.91 (CH_2), 49.83 (CH_2), 114.99 (d, *J* 22 Hz, CH), 127.74 (d, *J* 8.0 Hz, CH), 136.38 (d, *J* 3.0 Hz, C), 163.68 (d, *J* 247 Hz, C), 164.29 (C).

m/z, (EI): 177 ($M^{\bullet+}$, 100%), 176 (98%), 135 (45%), 121 (98%), 84 (57%). HRMS: 177.0955. $C_{11}H_{12}NF$ requires 177.0954.

6-Furan-3'-yl-2,3,4,5-tetrahydropyridine 336g



336g

Following general solid-phase Takeda reaction C, using *N*-[4,4-bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound 3-furoic acid **30g** (0.311 meq), the corresponding enol ether was formed. This was cleaved from resin and cyclised using general cleavage method D and the *6-furan-3-yl-2,3,4,5-tetrahydro-pyridine* **336g** isolated in (48.9 mg, 70%) as a yellow oil.

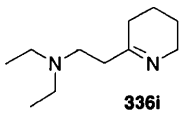
ν_{max} (NaCl)/cm^{-1}: 2933 (CH_2), 1636 (C=N).

δ_H (400 MHz: $CDCl_3$): 1.63-1.69 [2H, m, $NCH_2(CH_2)_2$] 1.76-1.82 [2H, m, $NCH_2(CH_2)_2$] 2.45-2.49 (2H, m, $NCCH_2$) 3.74-3.77 (2H, m, NCH_2) 6.76 (1H, dd, *J* 1.8 Hz, 0.65 Hz, furanyl-**H**-2') 7.39 (1H, t, *J* 1.7 Hz, furanyl-**H**-4') 7.69 (1H, broad s, furanyl-**H**-5').

δ_C (100 MHz: $CDCl_3$): 19.36 (CH_2), 22.10 (CH_2), 27.63 (CH_2), 49.46 (CH_2), 107.92 (CH), 128.64 (C), 141.72 (CH), 143.46 (CH), 160.18 (C).

m/z, (EI): 149 ($M^{\bullet+}$, 45%), 120 (40%), 84 (98%), 49 (100%). HRMS: 149.0840. $C_9H_{11}ON$ requires 149.0841.

N,N-Diethyl-[2-(3,4,5,6-tetrahydro-pyridin-2-yl)-ethyl]-amine 336i



336i

Following general solid-phase Takeda reaction C, using *N*-[4,4-Bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound 3-(diethylamino)-

propionic acid **30i** containing 0.328 meq, the corresponding enol ether was formed. This was cleaved from resin and cyclised using general cleavage method D and the *N,N-diethyl-[2-(3,4,5,6-tetrahydro-pyridin-2'-yl)ethyl]amine* **336i** isolated in 72% yield, 0.0431 g as a yellow oil.

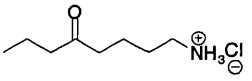
ν_{max} (NaCl)/cm^{-1}: 2932 (CH_2, CH_3), 1713 [(C=O) very weak], 1660 (C=N), 1444 (CH).

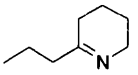
δ_H (400 MHz: $CDCl_3$): 1.03 [6H, t, *J* 7.2 Hz, $N(CH_2C\mathbf{H}_3)_2$], 1.52-1.58 [2H, m, $NCCH_2C\mathbf{H}_{eq}H_{ax}$, $NC(CH_2)_2C\mathbf{H}_{eq}H_{ax}$], 1.62-1.70 [2H, m, $NCCH_2CH_{eq}\mathbf{H}_{ax}$, $NC(CH_2)_2CH_{eq}\mathbf{H}_{ax}$], 2.12-2.18 [2H, m, $NC\mathbf{H}_2(CH_2)_3$], 2.30 (2H, t, *J* 7.9 Hz, $NCC\mathbf{H}_2CH_2Ph$), 2.54 [4H, q, *J* 7.2 Hz, $N(C\mathbf{H}_2CH_3)_2$], 2.69 (2H, t, *J* 8.0 Hz, $NCCH_2C\mathbf{H}_2Ph$), 3.54-3.56 (2H, m, $NC\mathbf{H}_2$).

δ_C (100 MHz: $CDCl_3$): 11.81 (CH_3), 19.57 (CH_2), 21.85 (CH_2), 29.65 (CH_2), 38.14 (CH_2), 46.83 (CH_2), 49.24 (CH_2), 49.66 (CH_2), 169.91 (C).

Unstable under all conditions for mass spectrometry EI, CI and FAB.

6-Propyl-2,3,4,5-tetrahydro-pyridine 336j





336j

Following general solid-phase Takeda reaction procedure, using *N*-[4,4-bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound butyric acid **30j** containing 0.328 meq, the corresponding enol ether was formed. This was cleaved from resin using TFA (4%) and Et_3SiH (1%) in DCM (5 mL) by shaking for 2 h with the kan containing resin-bound enol ether. The cleavage mixture was decanted and the kan washed (x 3) with DCM, than all the washings combined and concentrated under reduced pressure. The residue was washed with hexane to remove triphenylmethane. Addition of saturated ethereal HCl and a few drops of EtOAc to solvate TFA salt, followed by decanting of the solution left the precipitated HCl salt. This was then dried under high vacuum and characterised (43.8 mg, 74%). Conversion into the imine **336j** was carried out by addition of NaOH (4 M) followed by $CDCl_3$ and the organic layer dried with sodium

sulfate after the aqueous was removed. The characterisation data given is that of Louis Adriaenssens who carried out the synthesis of this compound after partial deuterium exchange at the positions indicated occurred in my sample.

5-Oxo-octyl-ammonium chloride: Evidence of D/H exchange 434

ν_{max} (NaCl)/cm^{-1} in CD_3OD: 2964 (CH_2, CH_3) and (-NH_3^+), 1690 (C=O).

δ_H (400 MHz: DMSO): 0.94 (3H, t, *J* 7.4 Hz, $\mathbf{CH_3}CH_2$), 1.67 (2H, sextet, *J* 7.5, $\mathbf{CH_2}CH_2NH_3$), 1.70-1.83 [4H, m, $CH_3\mathbf{CH_2}CH_2C(O)$, $C(O)CH_2\mathbf{CH_2}$], 2.68 [2H, t, *J* 7.6 Hz, $CH_3CH_2\mathbf{CH_2}C(O)$], 2.77 [2H, t, *J* 6.0 Hz, $C(O)\mathbf{CH_2}(CH_2)_3$], 3.56 (2H, m, $\mathbf{CH_2}NH_3$), 3.70 (3H, bs, $N\mathbf{H_3}$)

δ_C (100 MHz: DMSO): 13.31 (CH_3), 16.48 (CH_2), 18.89 (CH_2), 18.95 (CH_2), 28.87 (CH_2), 38.45 (CH_2), 43.57 (CH_2), 190.48 (C).

m/z, (CI): 126 [$(M+H)^+$-H_2O, 100%], 97 (12%), 71 (18%). HRMS: 126.1284. $C_8H_{16}N$ requires [$(M+H)^+$-H_2O] 126.1283.

6-Propyl-2,3,4,5-tetrahydro-pyridine 336j

ν_{max} (NaCl)/cm^{-1}: 2927 (CH_2, CH_3), 1660 (C=N), 1459 (CH).

δ_H (400 MHz: $CDCl_3$): 0.91 [3H, t, *J* 7.4 Hz, $NC(CH_2)_2\mathbf{CH_3}$] 1.52-1.60 [4H, m, $NCCH_2(\mathbf{CH_2})_2$] 1.62-1.68 (2H, m, $NCC\mathbf{H_2}CH_2CH_3$), 2.08-2.13 (4H, m, $NCC\mathbf{H_2}$)* 3.52-3.55 (2H, m, $NC\mathbf{H_2}$).

δ_C (100 MHz: $CDCl_3$): 13.90 (CH_3), 19.58 (CH_2), 19.77 (CH_2)**, 21.91 (CH_2), 28.94 (CH_2)*, 43.06 (CH_2)*, 49.11 (CH_2), 171.06 (C).

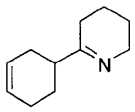
m/z, (CI): 126 [$(M+H)^+$, 100%], 71 (10%). HRMS: 126.1282. $C_8H_{16}N$ requires 126.1283.

*= positions where D/H exchange has occurred.

**= positions that D/H exchange affects in the NMR.

Data unlabelled agrees with literature. [141]

6-Cyclohex-3-enyl-2,3,4,5-tetrahydro-pyridine 336k



336k

Following general solid-phase Takeda reaction C, using *N*-[4,4-bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound 3-cyclohexene-1-carboxylic acid **30k** containing 0.310 meq, the corresponding enol ether was formed. This was cleaved from resin and cyclised using general cleavage method D and the *6-Cyclohex-3-enyl-2,3,4,5-tetrahydro-pyridine* **336k** isolated in (38.8 mg 77%) as a yellow oil.

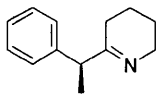
ν_{max} (NaCl)/cm^{-1}: 2929 (CH_2), 1662 (C=N) (C=C).

δ_H (400 MHz: $CDCl_3$): 1.47-1.59 [3H, m, $NC(CH_2)_2C\mathbf{H}_2$, $NCCH_2C\mathbf{H}_{eq}H_{ax}$] 1.64-1.70 [2H, m, $NCCH_2CH_{eq}\mathbf{H}_{ax}$, $NCCHC\mathbf{H}_{eq}H_{ax}$] 1.85-1.89 (1H, m, $NCCHCH_{eq}\mathbf{H}_{ax}$) 2.07-2.18 (6H, m, $NCC\mathbf{H}_2$, $NCCHCH_2C\mathbf{H}_2$, $NCCHC\mathbf{H}_2CHCH$) 2.25-2.32 (1H, m, NCC**H**) 3.56-3.59 (2H, m, $NC\mathbf{H}_2$) 5.66-5.73 (2H, m, $NCCHCH_2C\mathbf{H}C\mathbf{H}$).

δ_C (100 MHz: $CDCl_3$): 19.63 (CH_2), 22.08 (CH_2), 25.55 (CH_2), 26.32 (CH_2), 27.29 (CH_2), 28.87 (CH_2), 44.51 (CH), 49.21 (CH_2), 126.30 (CH), 126.66 (CH), 173.85 (C).

m/z, (CI): 164 [$(M+H)^+$, 100%], 163 (10%). HRMS: 164.1428. $C_{11}H_{18}N$ requires $(M+H)^+$, 164.1439.

6-((*S*)-1-Phenyl-ethyl)-2,3,4,5-tetrahydro-pyridine 336m



336m

Following general solid-phase Takeda reaction C, using *N*-[4,4-bis(phenylsulfanyl)but-1-yl]-*N*-tritylamine **429** (523 mg, 0.984 mmol) and a kan of resin-bound (R)-(-)-2-phenyl propionic acid **30m** containing 0.328 meq, the corresponding enol ether was formed. This

was cleaved from resin and cyclised using general cleavage method D and the 6-((*S*)-1-Phenyl-ethyl)-2,3,4,5-tetrahydro-pyridine **336m** isolated (28.2 mg, 46%) as a yellow oil.

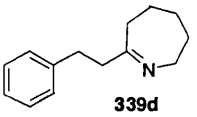
ν_{max} (NaCl)/cm^{-1}: 2929 (CH_2, CH_3), 1662 (C=N), 1448 (CH).

δ_H (400 MHz: $CDCl_3$): 1.40 (3H, d, *J* 7.1 Hz, C**H**$_3$) 1.51-1.58 (4H, m, NCC**H**$_2$C**H**$_2$) 1.87-1.92 (1H, m, NCH$_2$C**H**$_{eq}$H$_{ax}$) 1.93-2.05 (1H, m, NCH$_2$CH$_{eq}$**H**$_{ax}$) 3.51 [1H, q, *J* 7.1 Hz, NCC**H**(CH)$_3$] 3.61-3.70 (2H, m, NC**H**$_2$) 7.20-7.32 (5H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 18.56 (CH_3), 19.58 (CH_2), 22.06 (CH_2), 27.58 (CH_2), 49.39 (CH_2), 49.86 (CH), 126.39 (CH), 127.57 (CH), 128.46 (CH), 143.75 (C), 172.44 (C).

m/z, (CI): 188 [(M+H)$^+$, 100%], 100 (20%). HRMS: 188.1436. $C_{13}H_{18}N$ requires (M+H)$^+$, 188.1439.

7-Phenethyl-3,4,5,6-tetrahydro-2*H*-azepine 339d



339d

7-Phenethyl-3,4,5,6-tetrahydro-2*H*-azepine **339d** was obtained as a yellow oil (40 mg, 60%) *via* solid phase Takeda reaction general method C, using titanocene dichloride (980 mg, 3.94 mmol), magnesium (105 mg, 4.33 mmol), triethyl phosphite (1.35 mL, 7.87 mmol), 4-([1,3]dithian-2-yl-butyl-tritylamine (0.427 g, 0.984 mmol) and one kan of resin-bound 3-phenyl propionic acid **30d** (0.328 meq). The resultant enol ether was cleaved using general cleavage method C. The trifluoroacetic acid salt obtained from resin was dissolved in aqueous HCl (1 M) and washed with ether. The aqueous phase was then basified with NaOH (4 M) and extracted with DCM (x 3). The DCM washings were combined washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to give (39.7 mg, 60%) of 7-Phenethyl-3,4,5,6-tetrahydro-2*H*-azepine **339d** as a yellow oil.

ν_{max} (NaCl)/cm^{-1}: 2922 (CH_2, CH_3), 1663 (C=N).

δ_H (400 MHz: $CDCl_3$): 1.41-1.47 [2H, m, (C**H**$_2$)$_3$CH$_2$N], 1.51-1.57 [2H, m, (C**H**$_2$)$_3$CH$_2$N], 1.76-1.81 [2H, m, (C**H**$_2$)$_3$CH$_2$N], 2.38-2.40 (2H, m, C**H**$_2$CN), 2.56-2.60

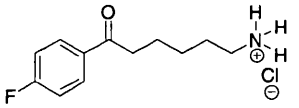
(2H, m, CH_2CH_2Ph), 2.84-2.88 (2H, m, CH_2CH_2Ph), 3.59-3.62 (2H, m, CH_2N), 7.20-7.23 (1H, m, Ar-**H**), 7.26-7.29 (4H, m, Ar-**H**).

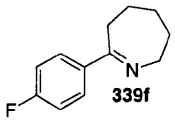
δ_C (100 MHz: $CDCl_3$): 23.38 (CH_2), 26.39 (CH_2), 31.53 (CH_2), 32.40 (CH_2), 33.62 (CH_2), 44.28 (CH_2), 51.84 (CH_2), 125.82 (CH), 128.34 (CH), 128.40 (CH),141.88 (C), 177.94 (C).

m/z, (EI): 201 ($M^{\bullet+}$, 30%), 83 (100%), 47 (21%). HRMS: 201.1518. $C_{14}H_{19}N$ requires 201.1517.

Data agrees with literature. [160]

7-(4'-Fluorophenyl)-3,4,5,6-tetrahydro-2*H*-azepine 339f





339f

Following general solid-phase Takeda reaction C, using N-[5,5-bis(phenylsulfanyl)pent-1-y]tritylamine **417** (535 mg, 0.984 mmol) and a kan of resin-bound 4-fluorobenzoic acid **30f** (0.328 meq), the corresponding enol ether was formed. This was cleaved from resin by shaking the kan containing the resin-bound enol ether with TFA (4%) and Et_3SiH (1%) in DCM (5 mL) for 2 h. The cleavage solution was then decanted, the kan washed with DCM and saturated ethereal HCl added to the combined organic phases to form the HCl salt. The solvent was then removed under reduced pressure and the residue washed with hexane to remove triphenylmethane to give the HCl salt, *6-(4'-fluorophenyl)-6-oxohexylammonium chloride* **418f**; (43.2 mg, 51%) as a grey solid; was the characterised before NaOH (4 M) was added to it followed by DCM. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give *7-(4'-fluorophenyl)-3,4,5,6-tetrahydro-2H-azepine* **339f** (15.2 g 24%), as an orange oil. To ensure complete conversion to the imine the compound was placed under argon and heated at 65 °C for 4 h. At this the yield and NMR experiments were taken, which indicated alone was present.

6-(4'-Fluorophenyl)-6-oxohexylammonium chloride 418f

ν_{max} (KBr)/cm^{-1}: 2945 (CH_2, CH_3), 1678 (C=O), 1595 (aromatic-H).

δ_H (400 MHz: CD_3OD): 1.45-1.53 [2H, m, $NCH_2(CH_2)_3$], 1.70-1.80 (4H, m, $NCH_2(CH_2)_3$], 2.96 [2H, t, *J* 7.5 Hz, $(CO)CH_2$], 3.07 (2H, t, *J* 7.1 Hz, NCH_2), 7.22 (2H, t, *J* 8.7 Hz, **H**-3' and **H**-5'), 8.06-8.09 (2H, m, **H**-2' and **H**-6').

δ_C (100 MHz: CD_3OD): 24.66 (CH_2), 27.03 (CH_2), 28.45 (CH_2), 39.01 (CH_2,) 40.66 (CH_2), 116.66 (d, *J* 22 Hz, CH), 132.11 (d, *J* 9.0 Hz, CH), 134.88 (d, *J* 3.0 Hz, C), 167.19 (d, *J* 251 Hz, C), 200.61 (C).

m/z, (CI): 210 (M^+, 100%), 192 [(M^+-H_2O), 50%].

7-(4'-Fluorophenyl)-3,4,5,6-tetrahydro-2*H*-azepine 339f

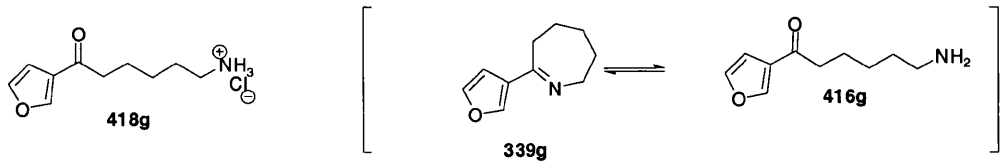
ν_{max} (NaCl) cm^{-1}: 2925 (CH_2, CH_3), 1632 (C=N).

δ_H (400 MHz: $CDCl_3$): 1.56-1.66 [4H, m, $NCH_2(CH_2)_3$], 1.85-1.91 [2H, m, $NCH_2(CH_2)_3$], 2.82-2.88 (2H, m, $NCCH_2$), 3.81-3.86 (2H, m, NCH_2), 7.02-7.07 (2H, m, **H**-3' and **H**-5'), 7.67-7.72 (2H, m, **H**-2' and **H**-6').

δ_C (100 MHz: $CDCl_3$): 23.56 (CH_2), 25.98 (CH_2), 30.86 (CH_2), 31.43 (CH_2), 52.41 (CH_2), 115.05 (d, *J* 21 Hz, CH), 128.50 (d, *J* 8.0 Hz, CH), 137.55 (d, *J* 3.0 Hz, C), 163.60 (d, *J* 247 Hz, C).

m/z, (EI): 191 ($M^{\bullet+}$, 10%), 83 (100%). HRMS: 191.1113. $C_{12}H_{14}NF$ requires 191.1110.

7-(Furan-3'-yl)-3,4,5,6-tetrahydro-2*H*-azepine 339g



Following general solid-phase Takeda reaction C, using N-[5,5-bis(phenylsulfanyl)pent-1-yl]tritylamine **417** (535 mg, 0.984 mmol) and a kan of resin-bound 3-furoic acid **30g** (0.311 meq), the corresponding enol ether was formed. This was cleaved from resin by shaking the kan containing the resin-bound enol ether with TFA (4%) and Et_3SiH (1%) in DCM (5 mL) for 2 h. The cleavage solution was then decanted, the kan washed with DCM and saturated ethereal HCl added to the combined organic phases to form the HCl salt.

The solvent was then removed under reduced pressure and the residue washed with hexane to remove triphenylmethane to give the HCl salt, 6-(furan-3'-yl)-6-oxohexylammonium chloride **418g** (30.3 mg; 45%), as a grey solid; which was the characterised before NaOH (4 M) was added to it followed by DCM. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. To ensure complete conversion to the imine the compound was placed under argon and heated at 65 °C for 20 min. ^{1}HNMR spectroscopy showed incomplete conversion to the imine. Heating the NMR sample under argon for 40 min was tried but again incomplete conversion was attained. Finally the mixture was re-treated to a NaOH (4M) wash, the organic layer ($CDCl_3$) dried over sodium sulfate and the organic layer passed through potassium carbonate but again a mixture of *ketone* **416g** and *imine* **339g** were obtained.

6-(Furan-3'-yl)-6-oxohexylammonium chloride 418g

ν_{max} (NaCl)/cm^{-1}: 3367 (-NH_3^+), 1671 (C=O).

δ_H (400 MHz: CD_3OD): 1.32-1.69 [2H, m $NCH_2(CH_2)_3$], 1.56-1.69 [4H, m, $NCH_2(CH_2)_3$], 2.77 [2H, t, *J* 7.2 Hz, (CO)CH_2], 2.84 (2H, t, *J* 7.6, NCH_2), 6.67-6.67 (1H, m, **H**-5'), 7.50 (1H, t, *J* 1.7 Hz, **H**-4'), 8.26 (1H, s, **H**-6').

δ_C (100 MHz: CD_3OD): 24.77 (CH_2), 26.98 (CH_2), 28.41 (CH_2), 40.59 (CH_2), 40.64 (CH_2), 109.21 (CH), 128.89 (C), 145.97 (CH), 149.99 (CH), 197.49 (C).

m/z, (EI): 163 ($M^{\bullet+}$-H_2O, 4%), 83 (100%), 47 (23%). HRMS: 163.0995. $C_{10}H_{13}NO$ requires ($M^{\bullet+}$-H_2O) 163.0997.

Evidence of imine: 7-(Furan-3'-yl)-3,4,5,6-tetrahydro-2*H*-azepine 339g

ν_{max} (NaCl)/cm^{-1}: 2925 (CH_2, CH_3), 1629 (C=N).

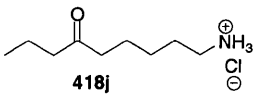
δ_H (400 MHz: $CDCl_3$): 3.76-3.78 (2H, m, NCH_2), 6.78-6.79 (1H, dd, *J* 0.8 and 1.8 Hz, **H**-5'), 7.41 (1H, t, *J* 1.7 Hz, **H**-4'), 7.71 (1H, s, **H**-6').

δ_C (100 MHz: $CDCl_3$): 23.69 (CH_2), 26.25 (CH_2), 31.35 (CH_2), 31.92(CH_2), 52.01 (CH_2), 108.66 (CH), 129.32 (C), 142.53 (CH), 144.00 (CH), 167.85 (C).

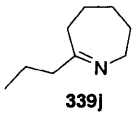
m/z, (EI): 163 ($M^{\bullet+}$, 85%), 135 (100%), 120 (75%), 107 (72%), 94 (84%).

HRMS: 163.0998. $C_{10}H_{13}NO$ requires 163.0997.

7-Propyl-3,4,5,6-tetrahydro-2*H*-azepine 339j



418j



339j

Following general solid-phase Takeda reaction C, using *N*-[5,5-bis(phenylsulfanyl)pent-1-yl]-*N*-tritylamine **417** (535 mg, 0.984 mmol) and a kan of resin-bound butyric acid **30j** containing 0.328 meq, the corresponding enol ether was formed. This was cleaved from resin by shaking the kan containing the resin-bound enol ether with TFA (4%) and Et_3SiH (1%) in DCM (5 mL) for 2 h. At this time the cleavage mixture was decanted and the kan washed with DCM (x 3) the organic phases combined and ethereal HCl added. The solvent was removed under reduced pressure and the resultant salt washed with hexane to remove triphenylmethane. This gave *6-Oxononylammonium chloride* **418j** (27.9 mg, 48%) as a white solid 48% yield. This was converted to 7-propyl-3,4,5,6-tetrahydro-2*H*-azepine **339j** by addition of NaOH (4 M) followed by extraction with DCM. The organic phase was dried over sodium sulfate, filtered and carefully concentrated under reduced pressure, with $CDCl_3$ added when the bulk of the DCM had been removed. This was concentrated under reduced pressure again to remove remaining DCM and the process repeated 3 times. This gave a sample for HNMR spectroscopy that indicated partial conversion to the imine (2:1 amino ketone to imine). The NMR sample was then decanted into a dry flask, flushed with argon, and heated to 60 °C for 20 min. At this point a NMR spectra were taken showing complete conversion to the imine. No yield was taken due to the compounds volatility.

6-Oxo-nonyl-ammonium chloride

ν_{max} (NaCl in CD_3OD)/cm^{-1}: 2934 (CH_2, CH_3), 2557 ($-NH_3^+$), 1704 (C=O).

δ_H (400 MHz: CD_3OD): 0.91 (3H, t, *J* 7.4 Hz, CH_3CH_2) 1.34-1.41 (2H, m, CH_3CH_2) 1.52-1.61 [4H, m, $(CH_2)_3CH_2N$] 1.63-1.71 [2H, m, $(CH_2)_3CH_2N$] 2.44 [2H, t, *J* 7.3 Hz, $CH_2(CO)CH_2$] 2.50 [2H, t, *J* 7.2 Hz, $CH_2(CO)CH_2$] 2.92 (2H, t, *J* 7.6 Hz, CH_2N).

δ_C (100 MHz: CD_3OD): 14.07 (CH_3), 18.26 (CH_2), 24.13 (CH_2), 26.99 (CH_2), 28.40 (CH_2), 40.62 (CH_2), 43.03 (CH_2), 45.48 (CH_2), 213.68 (C).

m/z, (CI): 140 (M^+-H_2O, 100%). HRMS: 140.1439 $C_9H_{18}N$ (M^+-H_2O) requires 140.1441.

7-Propyl-3,4,5,6-tetrahydro-2*H*-azepine 339j

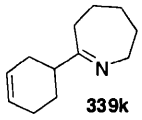
ν_{max} (NaCl)/cm^{-1}: 2925 (CH_2, CH_3), 1656 (C=N).

δ_H (400 MHz, $CDCl_3$): 0.94 (3H, t, *J* 7.4 Hz, CH_3CH_2), 1.40-1.46 (2H, m, CH_3CH_2), 1.50-1.64 [4H, m, $NCH_2(CH_2)_3$], 1.75-1.81 [2H, m, $NCH_2(CH_2)_3$], 2.23 (2H, t, *J* 7.6 Hz, $NCCH_2CH_2CH_3$), 2.34-2.37 (2H, m, $NCCH_2$), 3.56-3.58 (2H, m, NCH_2).

δ_C (100 MHz, $CDCl_3$): 13.96 (CH_3), 19.47 (CH_2), 23.49 (CH_2), 26.48 (CH_2), 31.58 (CH_2), 29.97 (CH_2), 44.91 (CH_2), 51.77 (CH_2), 178.76 (C=N).

m/z, (EI): 139 ($M^{\bullet+}$, 23%), 124 (40%), 111 (100%), 83 (70%). HRMS: 139.1360. $C_9H_{17}N$ requires 139.1361.

7-[Cyclohex-3'-en-1-yl]-3,4,5,6-tetrahydro-2*H*-azepine 339k



339k

Following general solid-phase Takeda reaction C, using N-{5,5-bis(phenylsulfanyl)pent-1-yl}tritylamine **417** (535 mg, 0.984 mmol) and a kan of resin-bound 3-cylcohexene-1-carboxylic acid **30k** (0.328 meq), the corresponding enol ether was formed. This was cleaved from resin and cyclised using general cleavage method D and a ^{1}HNMR and ^{13}CNMR spectra obtained. This indicated that partial conversion to the imine had taken place (2:1 imine to amino ketone) so the NMR sample was concentrated under reduced pressure and re-subjected to a base wash with NaOH (4 M). This gave *7-[cyclohex-3'-en-1-yl]-3,4,5,6-tetrahydro-2H-azepine* **339k**, (15.9 mg, 27%) as a yellow oil.

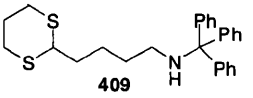
ν_{max} (NaCl)/cm^{-1}: 2924 (CH_2, CH_3), 1681 (C=N), 1448 (CH).

δ_H (400 MHz: $CDCl_3$): 1.40-1.48 [2H, m, $NCH_2(CH_2)_3$], 1.50-1.56 [3H, m, $NCH_2(CH_2)_3$], 1.75-1.81 [2H, m, $NCH_2(CH_2)_3$, $NCCHCH_{eq}H_{ax}CH_2$], 1.88-1.91 (1H, m, $NCCHCH_{eq}H_{ax}CH_2$), 2.10-2.12 (4H, m, $NCCHCH_2CH_2$, $NCCHCH_2CHCH$), 2.37-2.40 (3H, m, $NCCHCH_2$, $NCCH_2$), 3.59-3.61 (2H, m, NCH_2), 5.57-5.73 (2H, m, CH=CH).

δ_C (100 MHz: $CDCl_3$): 23.95 (CH_2), 25.36 (CH_2), 25.83 (CH_2), 26.42 (CH_2), 28.31 (CH_2), 31.43 (CH_2), 31.55 (CH_2), 46.16 (CH), 51.75 (CH_2), 126.12 (CH), 126.63 (CH), 181.18 (C).

m/z, (CI): 178 [$(M+H)^+$, 100%], 177 (20%). HRMS: 178.1595. $C_{12}H_{20}N$ requires $(M+H)^+$ 178.1596.

N-[*4*-(1,3-Dithian-2-yl)-butyl]-*N*-tritylamine 409



409

Method A

Pyridine sulphur trioxide (5.83 g, 36.6 mmol) was added to a solution of 4-(1,3-dithian-2-yl)butanol **282** (1.85 g, 9.64 mmol), triethylamine (9.0 mL, 64 mmol), and DMSO (6.8 mL, 96 mmol) in DCM (30 mL) and the solution stirred overnight. The reaction was quenched with water (20 mL) followed by aqueous sodium hydrogen carbonate solution and the aqueous layer extracted with DCM (3 x 100 mL). The organic phases were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. This gave 4-(1,3-dithian-2-yl)butyraldehyde, **283** (2.72 g, 97%), which was used without further purification. δ_H (400 MHz: $CDCl_3$): 1.76-1.97 [5H, m, $CHSCH_2CH_{ax}H_{eq}$, $(CH_2)_2CH_2CHO$], 2.09-2.15 (1H, m, $CHSCH_2CH_{ax}H_{eq}$), 2.48 [2H, t, *J* 6.6 Hz, $(CH_2)_2CH_2CHO$], 2.81-2.92 (4H, m, $CHSCH_2$), 4.05 (2H, t, *J* 6.6 Hz, CHS) 9.77 (1H, s, CHO). A portion of the crude aldehyde (1.13 g) was subjected to reductive amination conditions. Tritylamine (1.03 g, 3.97 mmol) was added to a solution of aldehyde (1.13 g) in dry MeOH (38 mL). Powdered 4 Å molecular sieves were added (200 mg) and the mixture was heated under reflux overnight. After this time sodium cyanoborohydride (613 mg, 9.75 mmol) was added and the reaction left stirring for 4h. Water 30 mL) was added to quench the reaction and the methanol was removed on a rotary evaporator. Ethyl acetate was added to and the layers separated. The aqueous layer was extracted with ethyl acetate (x3). The combined organics were washed with water, brine then dried over sodium sulfate, filtered and concentrated under reduced pressure. Column

chromatography (SiO_2), hexane:DCM (2:1) gave a solid, which was then recrystallised in hot methanol to give *N-[4-(1,3-dithian-2-yl)-butyl]-N-tritylamine* **409** as prisms (521 mg, 18% yield). An X-ray crystal structure was obtained to confirm the structure, please see appendix **1a**.

Method B

4-(1,3-Dithian-2-yl)butyraldehyde oxime **410** (31.7 g 132 mmol) in THF (650 mL), was treated with $LiAlH_4$ (25.1 g, 661 mmol) portion-wise at 0 °C. The reaction was stirred overnight. Water was added to quench the reaction, followed by NaOH (4 M) solution and the salts were filtered off. The aqueous phase was extracted with EtOAc (x 3) and the combined organics washed with brine and dried over sodium sulfate. The organic phase was then filtered and concentrated under reduced pressure to give crude 4-(1,3-dithian-2-yl-butyl)amine **411** (12.1 g). which was used directly in the next step. Product signals: δ_H (400 MHz: $CDCl_3$): 1.43-1.50 [2H, m, $(CH_2)_3CH_2N$], 1.51-1.62 [2H, m, $(CH_2)_3CH_2N$], 1.74-1.80 [3H, m, $(CH_2)_3CH_2N$ and $CH_{ax}H_{eq}(CH_2)_2S_2$], 1.81-1.92 [1H, m, $CH_{ax}H_{eq}(CH_2)_2S_2$], 2.70 (2H, t, *J* 6.9 Hz, CH_2N), 2.80-2.92 [4H, m, $(SCH_2)_2$], 4.06 [1H, t, *J* 6.8 Hz, $CH(SCH_2)_2$]. Trityl chloride (19.0 g, 68.3 mmol) was added to a solution of 4-(1,3-dithian-2-yl-butyl)amine (11.9 g, 62.1 mmol) in pyridine (200 mL). This was left stirring under argon overnight. At this time the pyridine solvent was removed on rotary evaporator and ethyl acetate added. The organics were then washed with aqueous copper sulfate solution (0.5 M, x 3), brine, dried over sodium sulfate, filtered and concentrated under vacuum. The resultant red/brown solid was subjected to column chromatography on deactivated alumina (5% water added) eluted with hexane:DCM (2:1) to give *amine* **409** as prisms (4.68 g, 20% yield over 4 steps from 4-(1,3-dithian-2-yl)butanol **282**.

m.p. 115-117 °C.

ν_{max} (KBr)/cm^{-1}: 3439 s (NH), 2933 s (CH_3, CH_2).

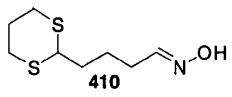
δ_H (400 MHz: $CDCl_3$): 1.50-1.52 [4H, m, $(CH_2)_3CH_2N$], 1.68-1.73 (2H, m, CH_2CHS_2), 1.77-1.90 [1H, m, $CH_{ax}H_{eq}(CH_2)_2S_2$], 2.05-2.13 (3H, m, CH_2N and $CHSCH_2CH_{ax}H_{eq}$), 2.76-2.88 (4H, m, $CHSCH_2$), 4.01 (1H, t, *J* 6.8 Hz, CHS), 7.15-7.19 (3H, m, Ar-H), 7.23-7.33 (6H, Ar-H), 7.46-7.48 (6H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 24.48 (CH_2), 26.00 (CH_2), 30.48 (CH_2), 35.45 (CH_2), 43.31 (CH_2), 47.58 (CH), 70.81 (C), 126.14 (CH), 127.74 (CH), 128.60 (CH), 146.22 (C).

m/z, (FAB+/NOBA): 434 [$(M+H)^+$, 10%], 356 (55%), 243 (100%), 190 (68%), 165 (48%), 105 (10%). HRMS: 434.1975. $C_{27}H_{32}NS_2$: requires $(M+H)^+$ 434.1976.

Microanalysis: C, 74.54; H, 7.19; N, 3.41%. $C_{27}H_{31}NS_2$ requires C, 74.78; H, 7.21; N, 3.23%

4-(1,3-Dithian-2-yl)butyraldehyde oxime 410



410

A solution of crude the 4-(1,3-dithian-2-yl)butyraldehyde **283** (2.50 g) in ethanol (73 mL) was added to a stirred solution of hydroxylamine hydrochloride (1.00 g, 14.5 mmol) and sodium acetate (1.94 g, 23.7 mmol) in water (7 mL) and the reaction mixture was heated under reflux overnight. The reaction mixture was then concentrated under vacuum and water and chloroform added. The aqueous layer was extracted with chloroform (x 3) and the combined organic phases washed with water and brine, dried over sodium sulfate, filtered and concentrated under vacuum. Recrystallisation from hot diethyl ether gave *4-(1,3-Dithian-2-yl)butyraldehyde oxime* **410** as a beige flaky solid (1.37 g 40% yield over 2 steps from 4-(1,3-dithian-2-yl)butanol **282**) as a mixture of geometrical isomers.

m.p. 100-102 °C.

ν_{max} (KBr)/cm^{-1}: 3200 (OH) 2925 (CH_2, CH_3) 1662 (C=N).

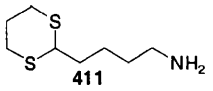
δ_H (400 MHz: $CDCl_3$): 1.69-1.77 (2H, m, C**H**$_2$CH$_2$CHN), 1.79-1.85 [2H, m, C**H**$_2$(CH$_2$)$_2$CHN], 1.86-1.92 (1H, m, CHSCH$_2$C**H**$_{ax}$H$_{eq}$), 2.10-2.15 (1H, m, CHSCH$_2$CH$_{ax}$**H**$_{eq}$), 2.39-2.44 (2H, m, C**H**$_2$CHN), 2.81-2.93 [4H, m, CH(SC**H**$_2$)$_2$], 4.07 [1H, t, *J* 6.7 Hz, C**H**(SCH$_2$)$_2$], 6.72 (1H, t, *J* 5.5 Hz, C**H**N), 7.23 (1H, s, O**H**).

Major isomer; δ_C (100 MHz: $CDCl_3$): 23.14 (CH_2), 24.39 (CH_2), 25.92 (CH_2), 30.38 (CH_2), 34.97 (CH_2), 47.04 (CH), 152.23 (CH). Extra peaks due to minor isomer: 23.52 (CH_2), 28.96 (CH_2), 34.67 (CH_2), 151.57 (CH).

m/z, (CI) : 206 [$(M+H)^+$, 100%], 188 (35%), 148 (32%). HRMS: 206.0674. $C_8H_{16}NOS_2$: requires 206.0673.

Microanalysis: C, 46.66; H, 7.27; N, 6.56%. $C_8H_{15}NOS_2$ requires C, 46.82; H, 7.37; N, 6.83%.

4-(1,3-Dithian-2-yl)butylamine 411



411

Method A

Following a procedure adapted from Molinski and co-workers[181] 4-(1,3-dithian-2-yl)butyraldehyde oxime **410** (200 mg, 0.975 mmol) was dissolved in dry THF (10 mL) under argon. The solution was cooled to 0 °C and lithium aluminium hydride (185 mg, 4.88 mmol) was added portion-wise to the solution, taking care not to add too much at once to avoid a large exotherm. This was left stirring overnight and then was quenched by careful addition of water followed by aqueous NaOH (4M). The aqueous phase was extracted with ethyl acetate (x 3). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. This gave *amine* **411** as an orange oil (121 mg 65%) but further purification was not possible.

Method B

Following a procedure adapted from Demir *et al* [163] sodium borohydride (134 mg, 3.54 mmol) was added to a stirred solution of 4-(1,3-dithian-2-yl)butyraldehyde oxime **410** (100 mg, 0.495 mmol) and molybdenum trioxide (153 mg, 1.06 mmol) in methanol (7 mL). A water bath was used to cool the exotherm and the reaction was left stirring overnight. The reaction mixture was then filtered through celite and washed with methanol. The solvent was removed, under vacuum, and aqueous KOH (20% solution) was added. This was extracted by DCM (x 3). The aqueous layer was saturated with sodium chloride and re-extracted with DCM. The combined organics were washed with water, then brine, dried over sodium sulfate, filtered and concentrated under vacuum. This gave *amine* **411** as a yellow oil (60 mg 64%). Further purification was not possible.

Product signals: δ_H (400 MHz: $CDCl_3$): 1.43-1.50 [2H, m, , $(CH_2)_3CH_2N$] 1.51-1.62 [2H, m, $(CH_2)_3CH_2N$] 1.74-1.80 [3H, m, $(CH_2)_3CH_2N$ and $CHSCH_2CH_{ax}H_{eq}$] 1.81-1.92

(1H, m, $CHSCH_2CH_{ax}\mathbf{H}_{eq}$) 2.70 (2H, t, *J* 6.9 Hz, $C\mathbf{H}_2N$) 2.80-2.92 (4H, m, $CHSC\mathbf{H}_2$) 4.06 (1H, t, *J* 6.8 Hz, C**H**S).

Tritylamine 413

413

Following the procedure of Chadwick and co-workers Ammonia gas was condensed (600 mL) using a cold finger and dry ice. Tritylchloride (30.0 g, 107 mmol) was added and the reaction stirred at –55 °C for 6 h. At this time the ammonia was allowed to evaporate and resulting white solid stirred with diethyl ether. The resulting solution was filtered and washed with 10% aqueous sodium sulphate solution, filtered and concentrated under reduced pressure. This gave tritylamine **413** as a crystalline solid (26.5 g, 95%).

mp: 100 °C, literature: 103 °C[165]

ν_{max} (KBr)/cm^{-1}: 3364 ($-NH_2$), 3298 ($-NH_2$).

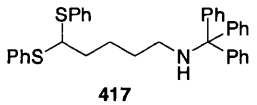
δ_H (400 MHz: $CDCl_3$): 2.31 (2H, s, $N\mathbf{H}_3$), 7.18-7.30 (15H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 66.19 (C), 126.55 (CH),127.86 (CH), 128.09 (CH), 148.58 (C).

m/z, (EI): 259 ($M^{\bullet+}$, 8%), 182 (100%), 104 (65%). HRMS: 259.1360. $C_{19}H_{17}N$ requires 259.1361.

Microanalysis: C, 87.77; H, 6.57; N, 5.42%. $C_{19}H_{17}N$ requires C, 87.99; H, 6.61; N, 5.40%.

N-[5,5-Bis(phenylsulfanyl)pentyl]tritylamine 417



417

Pyridine sulphur trioxide (49.4 g, 310 mmol) was added to a solution of 4,4-Bis(phenylsulfanyl)pentanol **276** (81.7 mmol), triethylamine (75 mL, 539 mmol), and DMSO (58 mL, 810 mmol) in DCM (270 mL) and the solution stirred overnight. The

reaction was quenched with water followed by aqueous sodium hydrogen carbonate solution and the aqueous layer extracted with DCM (x 3). The organics were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. This gave crude 4,4-Bis(phenylsulfanyl)pentaldehyde **277** as a dark orange oil (30.64 g), which was used without further purification. δ_H (400 MHz, $CDCl_3$): 1.83-1.89 [2H, m, $CH(CH_2)_2$], 1.91-1.98 [2H, m, $CH(CH_2)_2$], 2.41 (2H, td, *J* 7.1 Hz and 1.4 Hz, CH_2CHO), 4.38 (1H, t, *J* 6.4 Hz, CHS_2), 7.28-7.35 (6H, m, Ar-**H**), 7.44-7.47 (4H, m, Ar-**H**), 9.71 (1H, t, *J* 1.5 Hz, C**H**O). Tritylamine (25.0 g, 96.4 mmol) was added to a solution containing a third of the crude aldehyde (10.11 g, 81.7 mmol) in MeOH (475 mL). Powdered 4′ molecular sieves were added (1.6 g) and the mixture was heated under reflux overnight. After this time sodium cyanoborohydride (7.75 g, 123 mmol) was added and the reaction left stirring for 4 h. Water was added and the methanol was removed under reduced pressure. Ethyl acetate was added to dissolve the organic phases and the aqueous layer was extracted with ethyl acetate (x 3). The combined organics were washed with water, brine then dried over sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography (Al_2O_3 deactivated), eluting with hexane - DCM (2:1), gave a thick oil, which crystallised on standing. The crystals were washed with hexane to give *N-[5,5-bis(phenylsulfanyl)pentyl]tritylamine* **417** as prisms (14.98 g, 34%). An X-ray crystal structure was obtained to confirm the structure, please see appendix **1b**.

m.p: 60-62 °C.

ν_{max} (KBr)/cm^{-1}: 3056 (NH), 2927 (CH_2, CH_3), 1581 (Ar-H).

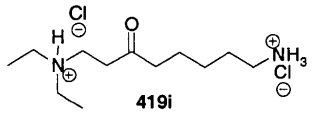
δ_H (400 MHz: $CDCl_3$): 1.40-1.47 [2H, m, $NCH_2(CH_2)_2$], 1.54-1.66 [2H, m, $NCH_2(CH_2)_2$], 1.78-1.83 (2H, m, $SCHCH_2$), 2.08 (2H, t, *J* 7.0 Hz, NCH_2), 4.37 (1H, t, *J* 6.7 Hz, C**H**S), 7.14-7.18 (3H, m, Ar-**H**), 7.21-7.31 (12H, m, Ar-**H**), 7.39-7.44 (10H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 24.80 (CH_2), 30.25 (CH_2), 35.77 (CH_2), 43.26 (CH_2), 58.33 (CH), 70.80 (C), 126.14 (CH), 127.60 (CH), 127.72 (CH), 128.36 (CH), 128.84 (CH), 132.65 (CH), 134.24 (C), 146.19 (C).

m/z, (FAB+/NOBA): 546 [$(M+H^+)$, 8%], 468 (16%), 302 (25%), 243 (100%), 165 (45). HRMS: 546.2294. $C_{36}H_{36}NS_2$ requires $(M+H)^+$, 546.2289.

Microanalysis: C, 79.17; H, 6.44; N, 2.56%. $C_{36}H_{35}NS_2$ requires C, 79.22; H, 6.46; N, 2.57%.

8-(*N,N*-Diethylamino)-6-oxooctylamine bishydrochloride salt 419i



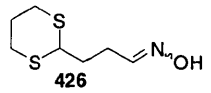
Following general solid-phase Takeda reaction C, using N-{5,5-bis(phenylsulfanyl)pent-1-yl}tritylamine **417** (535 mg, 0.984 mmol) and a kan of resin-bound 3-(*N,N*-diethylamino)propionic acid **30i** (0.328 meq), the corresponding enol ether was formed. This was cleaved from resin by shaking the kan containing the resin-bound enol ether with TFA (4%) and Et_3SiH (1%) in DCM (5 mL) for 2 h. The cleavage solution was then decanted, the kan washed with DCM and the solvent removed under reduced pressure. The residue was washed with hexane to remove triphenyl methane and DCM and saturated ethereal HCl added to form the HCl salt. The solvent was then removed under reduced pressure leaving *8-Diethylamino-6-oxooctylamine bishydrochloride* salt **419i** as an orange oil, (51.7 mg, 55%).

ν_{max} (NaCl in CD_3OD)/cm^{-1}: 2946 (CH_2, CH_3) and (-NH_3^+), 1712 (C=O).

δ_H (400 MHz: CD_3OD): 1.35 [6H, t, *J* 7.2 Hz, ($CH_3CH_2)_2N$], 1.40-1.46 [2H, m, $NCH_2(CH_2)_3$], 1.61-1.74 [4H, m, $NCH_2(CH_2)_3$], 2.62 [2H, t, *J* 7.2 Hz, $(CH_3CH_2)_2NCH_2$], 2.95 [2H, t, *J* 7.6 Hz, $NCH_2CH_2(CO)CH_2$], 3.07 [2H, t, *J* 6.7 Hz, $(CH_3CH_2)_2NCH_2CH_2(CO)$], 3.24 [4H, q, *J* 7.2 Hz, $(CH_3CH_2)_2N$], 3.40 (2H, t, *J* 6.7 Hz, $CH_2NH_3^+$).

δ_C (100 MHz: CD_3OD): 9.33 (CH_3), 23.82 (CH_2), 26.88 (CH_2), 28.29 (CH_2), 37.43 (CH_2), 40.74(CH_2), 43.00 (CH_2), 47.77 (CH_2), 208.67 (C).

3-(1,3-Dithian-2-yl)propionaldehyde oxime 426



3-(1,3-Dithian-2-yl)propionaldehyde **198** was prepared from 3-(1,3-dithian-2-yl)propan-1-ol **197** (15.2 g, 85 mmol) in DCM (280 mL) under modified Swern oxidation conditions detailed previously, using pyridine sulphur trioxide (51.4 g, 323 mmol), triethylamine (78.0 mL, 561 mmol) and DMSO (60.0 mL, 850 mmol). The resultant aldehyde **198** was taken on without further purification. δ_H (400 MHz: $CDCl_3$): 1.82-1.96 (1H, m, $CHSCH_2CH_{ax}H_{eq}$), 2.08-2.16 (3H, m, $CHSCH_2CH_{ax}H_{eq}$ and $CHCH_2CH_2CHO$), 2.72 (2H, td, *J* 7.2 Hz, 1.0, CH_2CHO), 2.84-2.87 (4H, m, $CHSCH_2$), 4.05 (1H, t, *J* 7.0 Hz, CHS), 9.81 (1H, s, CHO). 3-(1,3-Dithian-2-yl)-propionaldehyde in EtOH (425 mL) was added to a stirred solution of hydroxylamine hydrochloride and NaOAc in water (45 mL). The reaction was heated under reflux overnight. The solvent was then removed under reduced pressure and water and EtOAc added. The aqueous layer was then extracted (x 3) with EtOAc and the combined organics washed with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure. The resultant orange oil was treated to recrystallisaion using hot diethyl ether, giving the E isomer pure as a white powder, this was characterised and the supernatant combined and retreated to the crystallisation conditions. This gave *3-(1,3-Dithian-2-yl)propionaldehyde oxime* **426** as a beige powder with the major *E* isomer crystallising out first. The supernatant contained a mixture *E* and *Z* isomers with ratio 3:1, *E* to *Z*. The combined yield of E and E/Z mixtures gave 6.53 g, 40% yield over 2 steps. E isomer Characterisation:

m.p. 92-94 °C.

ν_{max} (KBr)/cm^{-1}: 3207 (OH), 2902 (CH_2, CH_3), 1663 (C=N), 1321 (OH).

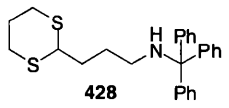
δ_H (400 MHz: $CDCl_3$): 1.83-1.93 [1H, m, $CHSCH_2CH_{ax}H_{eq}$], 1.96-2.01 (2H, m, $CHCH_2CH_2CHN$), 2.09-2.17 (1H, m, $CHSCH_2CH_{ax}H_{eq}$), 2.58-2.64 (2H, m, $CHCH_2CH_2CHN$), 2.82-2.89 (4H, m, SCH_2), 4.04 (1H, t, *J* 7.0 Hz, CHS_2), 6.76 (1H, t, *J* 5.4 Hz, CHNOH), 8.16 (1H, s, OH).

δ_C (100 MHz: $CDCl_3$): 22.47 (CH_2), 25.82 (CH_2), 30.22 (CH_2), 31.79 (CH_2), 46.84 (CH), 151.39 (CH).

m/z, (CI): 192 [$(M+H)^+$, 100%], 174 (43%). HRMS: 192.0514. $C_7H_{14}NOS_2$ requires $(M+H)^+$, 192.0517.

Data agrees with literature.[117]

N-[3-(1,3-Dithian-2-yl)propyl]-*N*-tritylamine 428



428

$LiAlH_4$ (5.20 g, 136 mmol) was added to a solution of 3-(1,3-dithian-2-yl}propionaldehyde oxime **426** (6.53 g, 34 mmol) in THF (340 mL) at 0 °C. This was left stirring overnight. Water was carefully added to quench followed by NaOH (4 M). The mixture was then extracted with EtOAc (x 4) and the combined organic phases washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. This gave 3-(1,3-dithian-2-yl)propylamine **427** as a pale yellow oil (3.06 g, 51%). This was taken directly on without further purification. δ_H (400 MHz, $CDCl_3$): 1.63-1.70 [2H, m, $(CH_2)_2CH_2NH_2$], 1.79-1.92 [3H, m, $(CH_2)_2CH_2NH_2$, $CHSCH_2CH_{ax}H_{eq}$], 2.10-2.15 (1H, m, $CHSCH_2CH_{ax}H_{eq}$), 2.74 (2H, t, *J* 7.0, CH_2NH_2), 2.79-2.92 (4H, m, SCH_2), 4.06 (1H, t, *J* 6.8, CHS_2). DMAP (90 mg, 0.689 mmol), Et_3N (4.30 mL, 30.3 mmol) and trityl chloride (5.29 g, 19.0 mmol) were stirred in DCM (8 mL). This solution was added to the crude 3-(1,3-dithian-2-yl)propylamine (3.06 g, 17.2 mmol) crude stirring in DCM (17 mL). The reaction was left stirring under argon overnight. Water was added to quench and the aqueous layer extracted with EtOAc (x 3). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography was carried out on deactivated alumina eluting with hexane-DCM (2:1) to give a gum which was triturated with hot diethyl ether and hexane to give *N-[3-(1,3-dithian-2-yl)propyl]tritylamine* **428** as a solid (3.77 g, 26% over two steps from oxime **426**).

m.p. 104-106 °C.

ν_{max} (KBr)/cm^{-1}: 3436 (NH), 3019 (CH), 2934 (CH_2), 1489 (-NH-),1465 (CH).

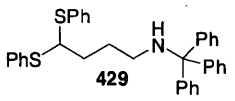
δ_H (400 MHz: $CDCl_3$): 1.66-1.73 [2H, m, $(CH_2)_2CH_2N$], 1.81-1.91 [3H, m, $(CH_2)_2CH_2N$, $CHSCH_2CH_{ax}H_{eq}$], 2.06-2.11 (1H, m, $CHSCH_2CH_{ax}H_{eq}$), 2.14 (2H, t, *J* 6.7 Hz, NCH_2), 2.78-2.86 (4H, m, SCH_2), 4.01 (1H, t, *J* 6.9 Hz, CHS), 7.16-7.20 (3H, m, Ar-H), 7.25-7.33 (6H, m, Ar-H), 7.45-7.48 (6H, m, Ar-H).

δ_C (100 MHz: $CDCl_3$): 26.02 (CH_2), 27.78 (CH_2), 30.45 (CH_2), 33.23 (CH_2), 42.89 (CH_2), 47.53 (CH), 70.82 (C), 126.18 (CH), 127.76 (CH), 128.61 (CH), 146.14 (C).

m/z, (CI): 420 [(M+H)$^+$, 2%], 243 (100%), 178 (48%), 167 (30%). HRMS: 420.1823. $C_{26}H_{30}NS_2$ requires (M+H)$^+$ 420.1820.

Microanalysis: C, 74.20; H, 6.97; N, 3.41%. $C_{26}H_{29}NS_2$ requires C, 74.42; H, 6.97; N, 3.38%.

N-[4,4-Bis(phenylsulfanyl)butyl]-*N*-tritylamine 429



429

Pyridine sulphur trioxide (61.8 g, 388 mmol) was added to a solution of 4,4-Bis(phenylsulfanyl)butanol **182** (29.7 g, 102 mmol), triethylamine (94 mL, 674 mmol), and DMSO (72 mL, 1020 mmol) in DCM (340 mL) and the solution stirred overnight. The reaction was quenched with water followed by aqueous sodium hydrogen carbonate solution and the aqueous layer extracted with DCM. The organics were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. This, gave crude 4,4-Bis(phenylsulfanyl)butyraldehyde **183**, containing large quantities of thiophenol, DMSO and triethylamine salts, as a dark orange oil (46.7 g >100%), which was used without further purification. Product signals: δ_H (400 MHz: $CDCl_3$): 2.17 (2H, dt, *J* 13.9 Hz, 7.0 Hz, C**H**$_2$CH$_2$CHO), 2.81 (2H, t, *J* 7.1 Hz CH$_2$C**H**O) 4.77-4.79 (1H, m, C**H**S), 7.25-7.38 (>8H, m, Ar-**H**), 7.44-7.48 (>2H, m, Ar-**H**). A proportion (64%) of this mixture was taken on to the reductive amination step. Tritylamine (77.1 g, 297 mmol) was added to a solution containing a third of the crude aldehyde (65 mmol) in dry MeOH (380 mL). Powdered 4 angstrom molecular sieves were added (1.5 g) and the mixture was heated under reflux overnight. After this time sodium cyanoborohydride (6.2 g, 98.7 mmol) was added and the reaction left stirring for 4 h. Water was added and the methanol was removed under vacuum. Ethyl acetate was added to dissolve the organic phases and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic phases were washed with water, brine then dried over sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography, (2:1 hexane to DCM, SiO_2) gave a solid, which then recrystallised in methanol to give *N-[4,4-Bis(phenylsulfanyl)butyl]-N-tritylamine* **429** as needles 10.6 g 31% yield. R_F(SiO_2, hexane:DCM, 2:1) 0.54. An X-ray crystal structure was obtained to confirm the structure, please see appendix **1c**.

m.p. 98-100 °C.

ν_{max} (KBr)/cm^{-1}: 3053, 2934 (CH_2, CH_3), 2856 (CH), 1467 (CH).

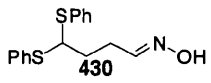
δ_H (400 MHz: $CDCl_3$): 1.42 (1H, s, N**H**), 1.75-1.82 (2H, m, CH_2CH_2N), 1.90-1.95 (2H, m, $CH_2CH_2CH_2N$), 2.10 (2H, t, *J* 6.5 Hz, CH_2N), 4.38 (1H, t, *J* 6.62 Hz, $CHCH_2$), 7.16-7.21 (3H, m, Ar-**H**), 7.24-7.33 (12H, m, Ar-**H**), 7.38-7.52 (10H, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 28.12 (CH_2), 33.44 (CH_2), 42.74 (CH_2), 58.34 (CH), 70.78 (C), 126.17 (CH), 127.71 (CH), 127.75 (CH), 128.56 (CH), 128.87 (CH), 132.86 (CH), 134.06 (C), 146.07 (C).

m/z, (FAB+ NOBA): 532 [$(M+H)^+$, 8%], 288 (20%), 243 (100%), 166 (15%). HRMS: 532.2139. $C_{35}H_{34}NS_2$: requires $(M+H)^+$, 532.2133.

Microanalysis: C, 79.15; H, 6.13; N, 2.69%. $C_{35}H_{33}NS_2$ requires C, 79.05; H, 6.25; N, 2.63%.

4,4-Bis(phenylsulfanyl)butyraldehyde oxime 430



Pyridine sulfur trioxide (21.2 g, 133 mmol) was added to a solution of 4,4-bis(phenylsulfanyl)butan-1-ol **182** (10.2 g 35 mmol), triethylamine (32 mL, 231 mmol), and DMSO (25 mL, 350 mmol) in DCM (110 mL) and the solution stirred overnight. The reaction was quenched with water followed by aqueous sodium hydrogen carbonate solution and the aqueous layer extracted with DCM. The organics were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. A proton NMR was taken, and this showed pyridine present so the compound was dissolved in DCM and washed once with 1 M aq HCl, then with water followed by brine and then dried over sodium sulfate. The compound was then filtered and concentrated under reduced pressure. This gave 4,4-bis(phenylsulfanyl)butyraldehyde **183** (8.25 g, 81%) which was taken on without further purification. Following an analogous procedure by Ikeda *et al*[164], a portion of the crude aldehyde (4.00 g) was then taken up in ethanol (75 mL). This was added to a stirred solution of sodium acetate and hydroxylamine hydrochloride in water (7.5 mL). It should be noted that the solubility of

the aldehyde is very low in ethanol. The mixture was heated under reflux overnight. Following concentration of the reaction mixture on rotary evaporator, water and chloroform were added and the aqueous layer extracted (x 3). The combined organic phases were then washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Column chromatography (SiO_2)with gradient elution of DCM, then DCM-MeOH (95:5) and finally MeOD gave *4,4-Bis(phenylsulfanyl)butyraldehyde oxime* **430** as a yellow oil (1.53 g 36%) as a (1:1) mixture of *E* and *Z* geometrical isomers. This was sufficiently pure for the next step.

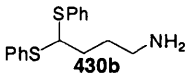
ν_{max} (NaCl)/cm^{-1}: 3255 (OH), 2915 (CH_2), 1654 (C=N-),1438 (CH).

δ_H (400 MHz: $CDCl_3$): 1.97-2.08 ($2H^{E+Z}$, m, C**H**$_2$CH$_2$CHN), 2.53 ($2H^{Z}$, dt, *J* 5.7 Hz, 7.5 Hz, C**H**$_2$CHN), 2.7 ($2H^{E}$, dt, *J* 5.5 Hz, 7.7 Hz, C**H**$_2$CHN), 4.37 [$1H^{E/Z}$, t, *J* 6.7 Hz, C**H**(SPh)$_2$], 4.42 [$1H^{E/Z}$, t, *J* 6.7 Hz, C**H**(SPh)$_2$], 6.67 ($1H^{E}$, t, *J* 5.5, C**H**N), 7.28-7.33 ($6H^{E+Z}$, m, Ar-**H**), 7.39 ($1H^{Z}$, t, *J* 5.7 Hz, C**H**N), 7.46-7.49 ($4H^{E+Z}$, m, Ar-**H**).

δ_C (100 MHz: $CDCl_3$): 22.87 (CH_2), 27.05 (CH_2), 32.02 (CH_2), 32.24 (CH_2), 57.58 (CH), 58.03 (CH), 127.95 (CH), 129.07 (CH), 132.96 (CH), 133.69 (C), 150.78 (CH), 151.23 (CH).

m/z, (EI): 303 ($M^{\bullet+}$, 5%), 194 [($M^{\bullet+}$-PhS$^{\bullet}$), 100%], 149 (35%), 109 (PhS $^{\bullet+}$, 32%), 71 (42%). HRMS: 303.0750. $C_{16}H_{17}NOS_2$: requires 303.0752.

4,4-Bis(phenylsulfanyl)butylamine 430b



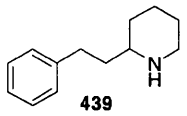
430b

Following a procedure designed for an analogous compound by Molinski, T. F. and co-workers [181] 4,4-bis(phenylsulfanyl)butyraldehyde oxime **430** (1.50 g, 4.95 mmol) was dissolved in dry THF (50 mL) and placed under argon. The solution was cooled to 0 °C and lithium aluminium hydride (770 mg, 19.8 mmol) was added portion-wise to the solution, taking care not to add too much at once to avoid a large exotherm. This was left stirring overnight. The reaction was quenched by careful addition of water followed by addition of aqueous NaOH (4 M). The aqueous phase was then extracted with ethyl acetate (x 3). The combined organics were washed with brine, dried over sodium sulfate, filtered

and concentrated under vacuum to give the *amine* **430b** as an orange oil (1.33 g 93%), further purification was not possible.

Product signals δ_H (400 MHz: $CDCl_3$): 1.73-1.82 [2H,m, $(CH_2)_2CH_2N$], 1.86-1.91 [2H, m, $(CH_2)_2CH_2N$], 2.68 (2H, t, *J* 6.8 Hz, CH_2N), 4.41 [1H, t, *J* 6.5 Hz, $(PhS)_2CHCH_2$], 7.24-7.33 (6H, m, Ar-**H**), 7.44-7.47 (4H, m, Ar-**H**).

2-Phenethylpiperidine 439



439

$LiAlH_4$ (264 mg, 38.0 mmol) was added to a solution of 6-phenethyl-2,3,4,5-tetrahydro-pyridine **336d** (0.328 mmol) freshly cleaved from resin using general cleavage method D, in THF (3 mL), portion-wise at 0 °C under argon. This was left stirring for 5 h 30 min. At this time water was added, followed by NaOH (4 M) and the mixture extracted with DCM (x 3). The combined organic phases were washed with brine, dried over sodium sulphate, and filtered. Ethereal HCl 2M (1 mL) was added and the solution concentrated under reduced pressure. The resultant solvent was treated to hot diethyl ether to remove triphenyl methanol. The salt was dissolved in chloroform and washed with NaOH (1 M) and brine, dried over sodium sulphate, filtered and concentrated under reduced pressure, to give 2-phenethylpiperidine **439** (17.8 mg, 29%) as a pale yellow oil. [182]

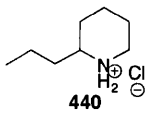
ν_{max} (GG)/cm^{-1}: 2930 (CH_2).

δ_H (400 MHz: $CDCl_3$): 1.07-1.17 [1H, m, $NCH_2(CH_2)_2$], 1.26-1.46 [3H, m, $NCH_2(CH_2)_2$], 1.57-1.72 [4H, m, $NCH(CH_2)_2Ph$], 1.77-1.81 (1H, m, NC**H**), 2.46-2.53 (1H, m, NCH_2), 2.59-2.74 [3H, m, NCH_2, $NCHCH_2(CH_2)_3$], 3.09-3.06 (1H, m, N**H**).

δ_C (100 MHz: $CDCl_3$): 24.80 (CH_2), 26.61 (CH_2), 32.29 (CH_2), 32.30 (CH_2), 39.18 (CH_2), 47.15 (CH_2), 56.45 (CH), 125.71 (CH), 128.33 (CH), 142.35 (C).

m/z, (CI): 190 [$(M+H)^+$, 100%]. HRMS: 190.1595. $C_{13}H_{20}N$ requires $(M+H)^+$ 190.1596.

2-Propylpiperidinium chloride 440



440

6-Propyl-2,3,4,5-tetrahydropyridine **336j** (0.328 mmol) freshly cleaved from resin using general cleavage method D, was dissolved in THF (3 mL) and treated with $LiAlH_4$ at 0 °C. This was left stirring under argon overnight. At this point water was added drop-wise, followed by NaOH (4 M). The mixture was then extracted with DCM (x 4). The combined organics were washed with brine, dried over sodium sulphate and filtered. Saturated ethereal HCl was added and the product concentrated under reduced pressure. The resultant salt was purified by washing with acetone to give 2-propylpiperidinium chloride **440** (4.8 mg, 9%) as a solid.

ν_{max} (GG)/cm^{-1}: 2934 (CH_2CH_3), 2515 (NH_2^+).

δ_H (400 MHz: $CDCl_3$): 0.95 (3H, t, *J* 7.3 Hz, CH_3CH_2) 1.38-1.53 (3H, m, CH_3CH_2, CH_3CH_2CHN)1.59-1.84 (3H, m, CH_3CH_2CHN, $NCHCH_2$) 1.89-2.03 [4H, m, $NCH_2(CH_2)_2$] 2.77-2.86 (1H, m, NCH_2) 2.93 (1H, m, NCH_2) 3.44-3.49 (1H, m, $NCHCH_2$) 9.21 (1H, s, NH) 9.52 (1H, s, NH).

δ_C (100 MHz: $CDCl_3$): 13.74 (CH_3), 18.61 (CH_2), 22.26 (CH_2), 22.45 (CH_2), 28.20 (CH_2), 35.35 (CH_2), 44.74 (CH_2), 57.21 (CH).

m/z, (CI): 128 (M^+, 100%), 71 (26%). HRMS: 128.1437. $C_8H_{18}N$ requires 128.1439.

Data agrees with literature. [183]

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Appendices

Crystal Structures

Data for all three structures were collected at 100K on a Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems low temperature device, and using graphite-monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). The data were integrated using DENZO,[i] and an absorption correction based on the multi-scan method of Blessing[ii] was applied. The structures were solved using SIR92,[iii] and refined using full matrix least squares on all data using CRYSTALS.[iv] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms except those bound to nitrogen were placed in geometrically calculated positions and refined as riding groups. Hydrogen atoms bound to nitrogen atoms were placed on the difference map and refined isotropically. SX018 solved in a non-centrosymmetric space group, and SX019 solved in a chiral space group; the absolute structure for each of these compounds was determined unambiguously by the refinement of a Flack parameter.[v]

For CIF file containing structure data please see accompanying CD.

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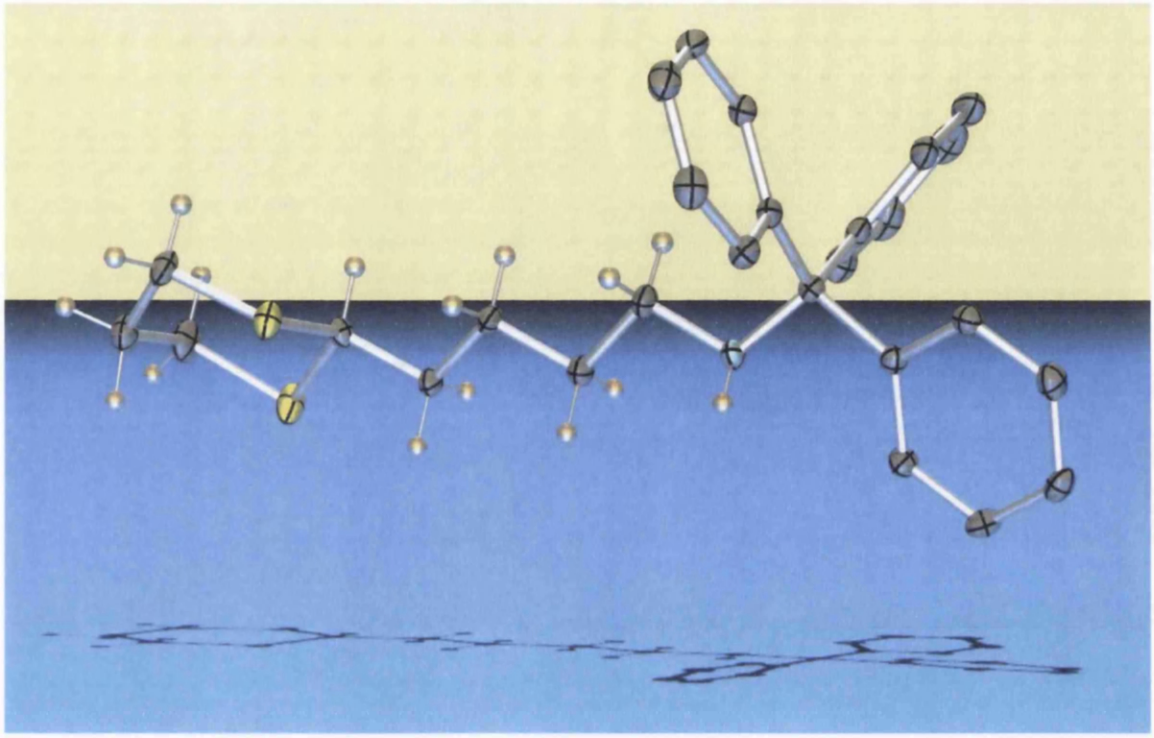
v) Flack, H. D. (1983). Acta Cryst. A39, 876-881.[1]

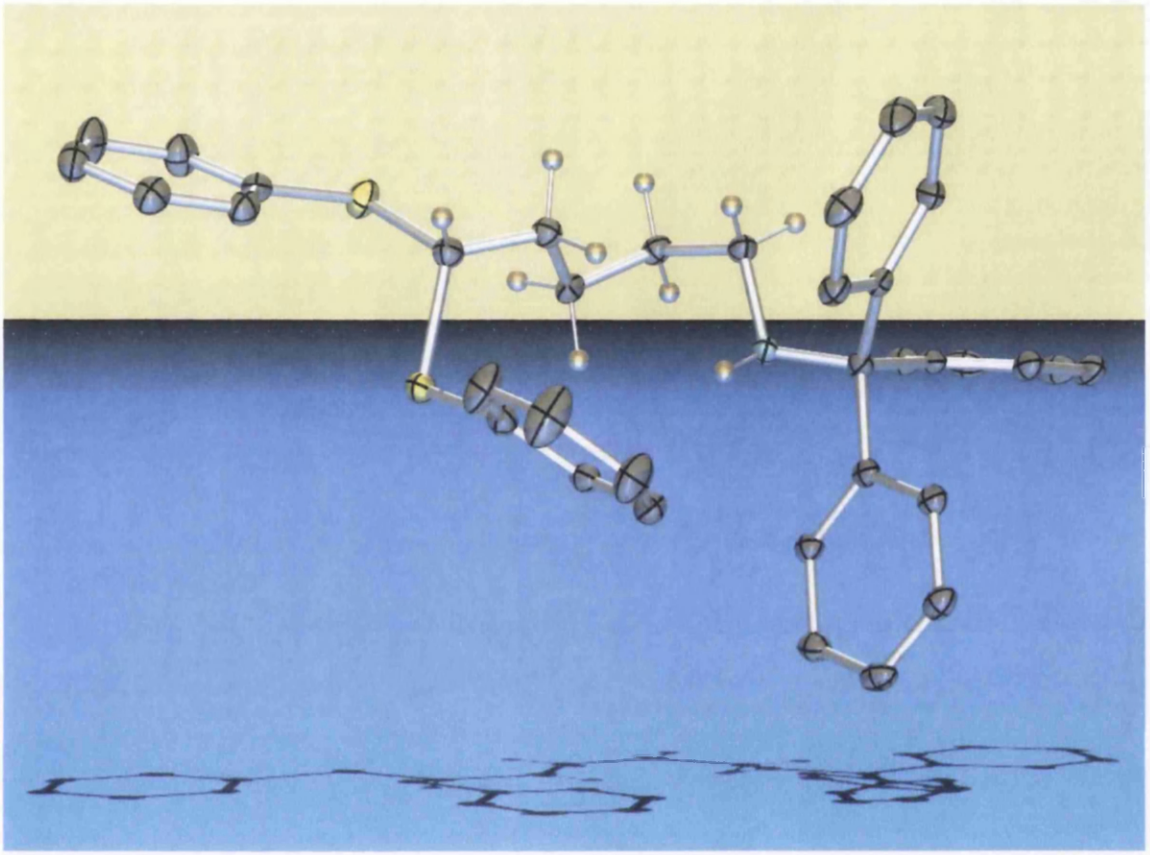
Appendix 1a: Crystal Structure

Crystal Structure of *N*-[*4*-(1,3-Dithian-2-yl)butyl]-*N*-tritylamine 409



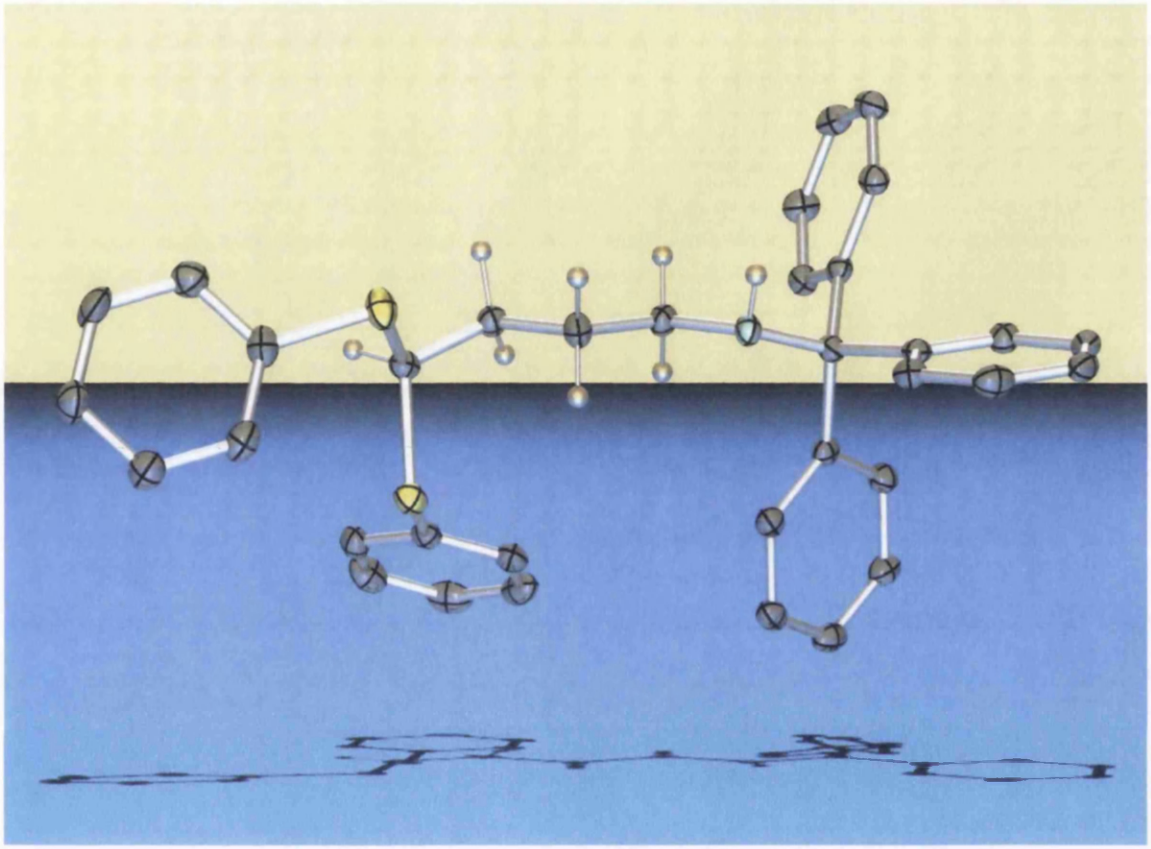
Appendix 1b: Crystal Structure

Crystal Structure of *N*-[5,5-Bis(phenylsulfanyl)pentyl]tritylamine 417

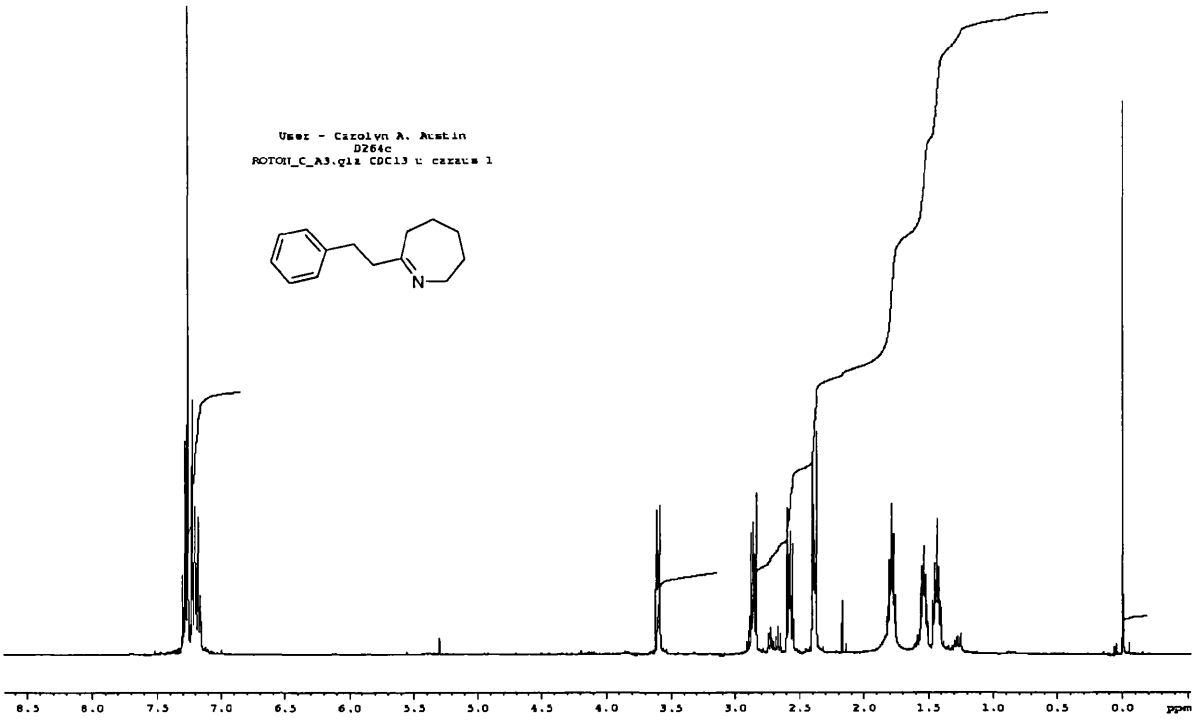


Appendix 1c: Crystal Structure

Crystal Structure of *N*-[4,4-Bis(phenylsulfanyl)butyl]-*N*-tritylamine 429



Appendix 2a: Sample ^{1}HNMR



Appendix 2b: Sample ^{1}HNMR