A Maitland Japp Inspired Synthesis of 2-Spiropiperidines

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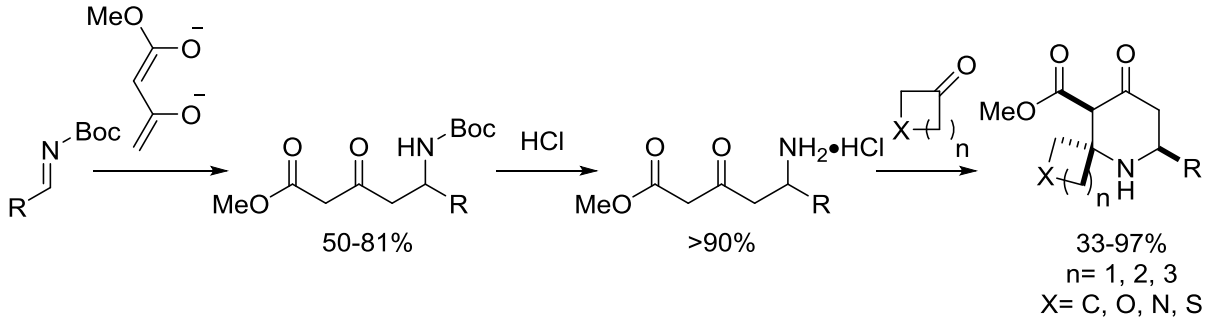
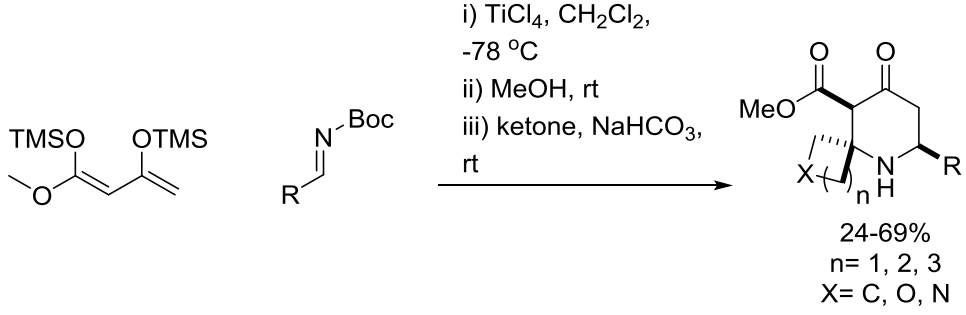
Abstract

With a growing desire to explore three-dimensional chemical space, methods for the synthesis of spirocyclic compounds, more specifically aza-spirocycles, are becoming of great interest to medicinal chemists. The synthesis of 3- and 4-spiropiperidines are well documented, however, there is little precedent for the synthesis of 2-spiropiperidines. The research detailed in this thesis describes the efforts towards the synthesis of 2-spiropiperidines via both a stepwise (Scheme i) and a one-pot procedure (Scheme ii), for use in a fragment drug discovery programme. The scopes of the procedures are demonstrated by the synthesis of a diverse range of 2-spiropiperidines. The 2-spiropiperidines were utilised as scaffolds to construct a small library of lead-like compounds that were analysed by LLAMA and principal moments of inertia analysis. The 2-spiropiperidines were consequently found to be three-dimensional. Methods for the construction of other structurally interesting piperidines are also presented, including bridged piperidines, fused piperidines, and 6-spiropiperidines, though the efforts were unsuccessful.



Scheme i. Stepwise synthesis of 2-spiropiperidines.



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Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.

Some of the research outlined in thesis has been published in the following papers:

A Two-Step Synthesis of 2-Spiropiperidines, S. D. Griggs, N. Thompson, D. T. Tape, M. Fabre and P. A. Clarke, *Chem. Eur. J*., 2017, **23**, 9262-9265.

Synthesis of Highly Substituted 2-Spiropiperidines, S. D. Griggs, N. Thompson, D. T. Tape, M. Fabre and P. A. Clarke, *Org. Biomol. Chem.*, 2018, **16**, 6663-6674.

Strategies for the Synthesis of Spiropiperidines – a review of the Last 10 Years, S. D. Griggs, D. T. Tape and P. A. Clarke, *Org. Biomol. Chem.*, 2018, **16**, 6620-6633

1. Introduction

The identification and generation of high quality lead compounds (compounds that possess pharmaceutical or biological activity that could be therapeutically useful) is imperative in the initial stages of drug discovery. The pharmaceutical industry remains heavily reliant on synthetic methodology to access small, drug-like molecules for drug discovery programmes.[1] Upon the synthesis of libraries of compounds varying in size and complexity, the compounds are then screened to identify new hits. However, the selection and optimisation of the hits are where major difficulties associated with the discovery process lie.[2]

Two of the most commonly used modern methods for the identification and development of drug candidates are high-throughput screening (HTS) and fragment-based drug discovery (FBDD), of which are outlined below.

1.1 High-Throughput Screening

High-throughput screening is one of the more traditional methods adopted in drug discovery. This involves the construction of a large library of compounds, often in the region of 10^6 compounds.[3] These compounds possess 'lead-like' properties, which in the context of HTS, means they have a molecular weight <500 Da with a total number of heavy atoms <30, and a low lipophilicity (AlogP≤4).[4] The large library is then screened across a multitude of targets to find a hit. Optimisation occurs through the elaboration of the initial hit, with further screenings of smaller libraries of analogues undertaken to identify the drug candidate. The HTS process is not fast, and it is currently estimated that it takes 13.5 years to reach approval of the drug from the initial target identification.[5] Hit rates from HTS are often very low, and consequently HTS programmes can be very costly.[6]

Maraviroc **2**, developed by Pfizer, was approved in 2007 as a CCR5 agonist for the treatment of HIV.[7] It was the product of a HTS programme that began in 1997 with the screening of ~500,000 compounds from a Pfizer library.[4] The initial hit was the piperidine 'UK-107,543' **1**, and required the synthesis of over 1,000 analogues to identify the final candidate maraviroc **2** (Figure 1).

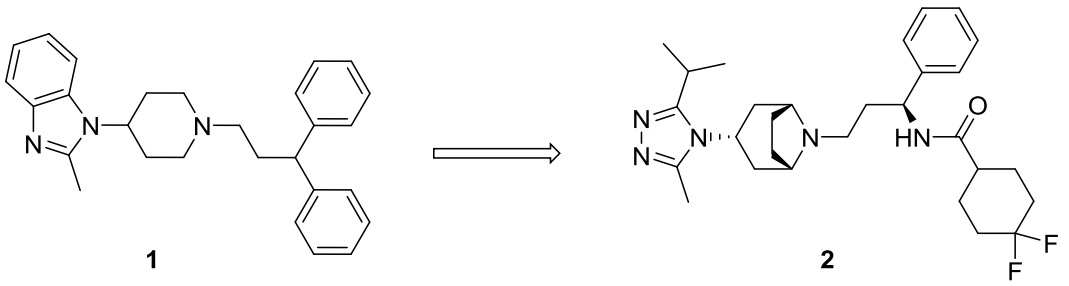


Figure 1. Development of maraviroc **2** from UK-107,543 **1**.

The total number of compounds possessing 'lead-like' properties with the number of heavy atoms (non-hydrogen atoms) less than 30 has been estimated to be in excess of 10^{63}, which is a number far beyond comprehension.[3,8] The vast number of compounds is referred to as the 'virtual collection' because they simply cannot feasibly be synthesised.[8] The suggested number of globally-accessible compounds is estimated to be in the region of 10^8, so even a screen of these compounds would barely touch the surface of diversity space.[9] In a typical HTS screen, approximately 10^6 compounds are screened.[3] As with the globally-accessible compounds, this is a minute number in comparison to the total theoretical number of compounds, and so only a small insignificant area of drug-like chemical space can be sampled. In comparison, it has been estimated that approximately 10^7 different molecules exist with a molecular weight of less than 160 daltons.[10] This number is now far more comprehensible, and a screen of 10^3 or 10^4 compounds means a much greater proportion of drug-like space can be sampled, hence is the reason for the introduction of FBDD programmes.

1.2 Fragment-Based Drug Discovery

The concept of FBDD arose from the synthesis of small fragment molecules, with restrictions imposed such as molecular weight and lipophilicity. Similar to Lipinski's 'rule of five', which assesses the drug-likeness of molecules (molecular weight≤500, AlogP≤5, number of H-bond donors/acceptors≤5),[11] a new set of stipulations have been derived to allow the synthesis of fragment libraries, often following a 'rule of three'.[12] For fragment libraries obeying the 'rule of three', all compounds have molecular weights≤300, AlogP≤3, number of hydrogen bond donors≤3, number of hydrogen bond acceptors≤3.[12] Adding to this criteria, the fragments

should have a number of heavy atoms<20.[13] Obeying the 'rule of three' is advisable as the optimisation studies tend to increase lipophilicity, molecular weight and complexity.[14]

In the construction of fragment libraries, molecules are often synthesised that have handles to allow facile elaboration upon detection of hits.[3] Owing to the small size of the molecules in a fragment library, hits from biological screens often exhibit milli-molar or weak μ-molar affinities to the targets.[15] However, the small molecules then have a greater potential to be optimised to achieve nano-molar affinities.

Adopting a FBDD approach allows the realistic construction of libraries that can exhaust the chemical space that a small molecule can occupy against a target. It was concluded by Hann that simple, small molecules have a greater chance of forming favourable interactions with respective binding sites, compared to larger, more complex molecules typically used in a HTS programme.[16]

The first approved drug to arise from a FBDD programme was vemurafenib **3** (Figure 2) in 2011 by Plexxicon, for the treatment of *BRAF*-mutated metastatic melanoma.[17,18] A library of approximately 20,000 compounds possessing fragment-like properties (low molecular weights, good solubilities, low numbers of hydrogen bond acceptors/donors) were screened against five kinases.[19] From the screen, 238 compounds showed a desirable weak binding to three of the kinases. From these hits, 7-azaindole **4** was selected as it co-crystallised with the target kinase well, and had a weak binding affinity (IC_{50}>200 μM).[19] 7-Azaindole **4** was subsequently grown to aniline **5**, which displayed greater potency (IC_{50}~100 μM). Further optimisation identified *p*-methoxy benzyl **6** (IC_{50} 1.9 μM), sulfonamide **7** (IC_{50} 0.013 μM) and finally the end product vemurafenib **3** (IC_{50} 0.031 μM).[19] Despite the greater potency of sulfonamide **7** over vemurafenib **3**, vemurafenib **3** was the selected candidate because the associated pharmacokinetic properties scaled better in clinical trials.[17]

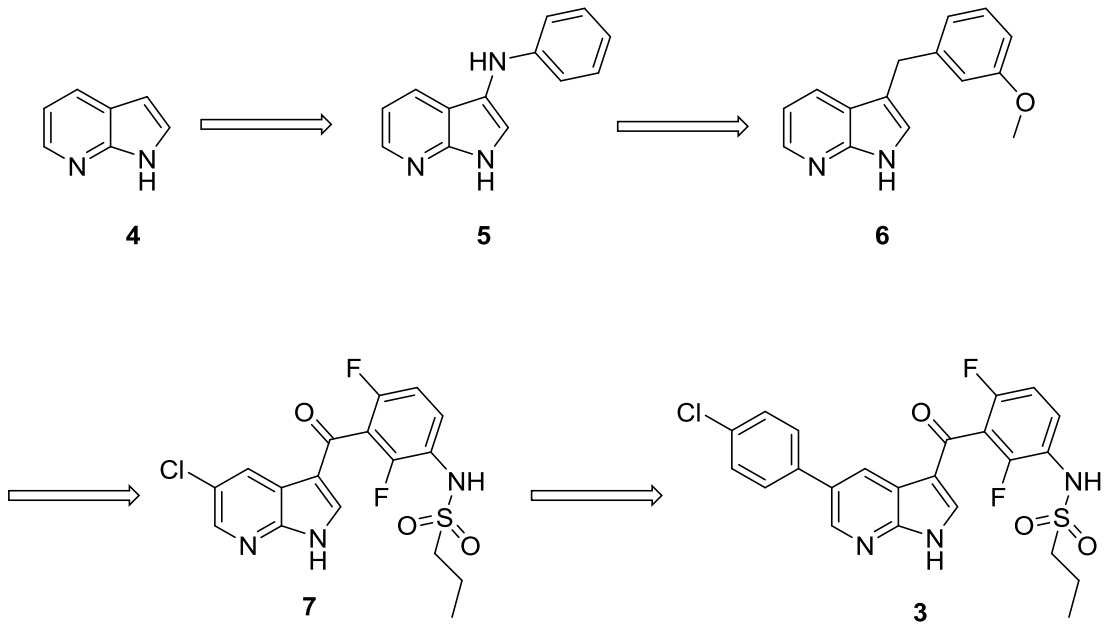


Figure 2. Key steps in the discovery of vemurafenib **3**.

1.3 Methods for Detection

An issue encountered with low binding affinities of the fragment hits means classical biological screening methods may not be sufficient for detection. Ellman demonstrated that screening higher concentrations is possible,[20] however, screening at high concentrations can lead to issues such as false positives/negatives, target denaturation, and toxicity to cells.[21] Because of these disadvantages, biophysical methods such as NMR spectroscopy and X-ray crystallography have been employed.[22] Methods such as mass spectrometry,[23,24] isothermal titration calorimetry,[25] and surface plasmon resonance[21] have also been used for detection.

For analysis by NMR spectroscopy, the most robust method employed involves the use of ^{15}N-labelled protein targets. Upon binding of the compounds to the target proteins, shifts in the ^{1}H-^{15}N HSQC spectrum are detected, and consequently the location of the binding can be identified.[22] Analysis via this method does have its disadvantages, such as the need for significant quantities of pure ^{15}N-labelled protein, and the requirement for a high-field NMR spectrometer.[22] To combat these drawbacks, a method for identification through ^{13}C-labelled proteins was reported by Fesik and coworkers.[26] Isotopically labelling the methyl groups of valine, leucine and isoleucine increased the sensitivity of the technique by nearly 3-fold compared to that of ^{1}H-^{15}N HSQC screening.

The use of X-ray crystallography to identify fragment hits is a very useful technique, as the exact interactions between the fragment and the protein target can be viewed. The technique was employed by Nienaber and coworkers by soaking a crystal of protein with a mixture of fragments for a period of time (1-24 h).[27] The original crystal structure of the protein was then subtracted from the new crystal structure, and differences in the electron density maps allowed the identification of hits. Upon identification of a fragment hit, the fragment-protein interaction can be visualised and used as guidance for the addition of further functionality.[21]

1.4 Methods for Fragment Elaboration

With the identification of weakly binding fragment hits, the next important procedure is the elaboration of the hits. The goal of the elaboration process is to improve the binding affinity by several orders of magnitude, giving rise to a molecule suitable for progressing into clinical trials.[15] The benefits of using NMR spectroscopy and X-ray crystallography for initial detection are that areas for elaboration can be immediately identified, as the binding interactions can be visualised. There are two major strategies for the conversion of fragment hits into lead compounds; fragment growing and fragment linking.[22]

Fragment growing is the most closely related to traditional drug optimisation, in which various substitutions or expansions are made to the initial hit in order to improve binding affinities (Figure 3).[28] The first fragment hit is identified by its weak binding to the desired target (Figure 3, A), and using structural information of how the fragment binds to the target, an improved hit can be rapidly obtained (Figure 3, B). At this stage of the process, the compound may show activity in biological assays.[28] From here, further iterations can be made to the molecule to give higher efficiency interactions with the active site of the target, giving rise to a final drug candidate (Figure 3, C).

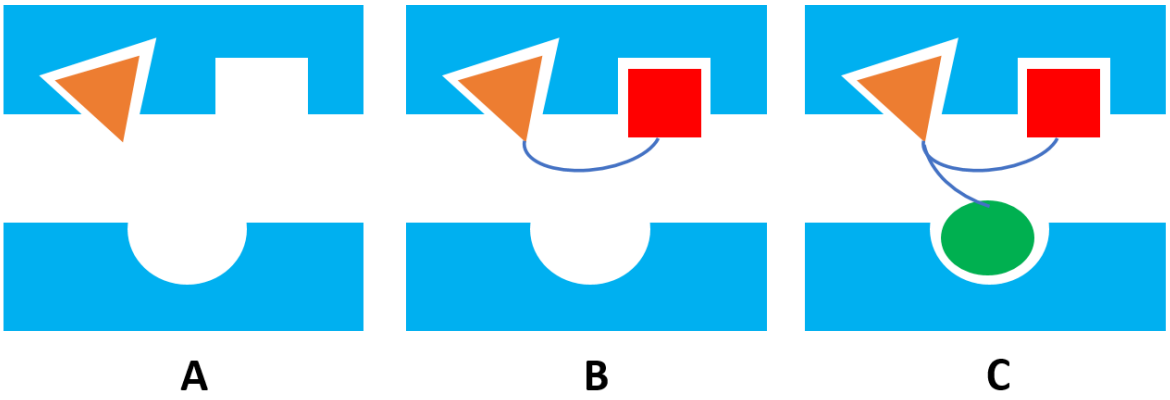


Figure 3. Fragment growing.

Fragment linking works by first identifying multiple fragment hits related to a specific target (Figure 4). Providing they bind to different but nearby sites, the fragments are then chemically linked to give the hybrid lead compound.[29]

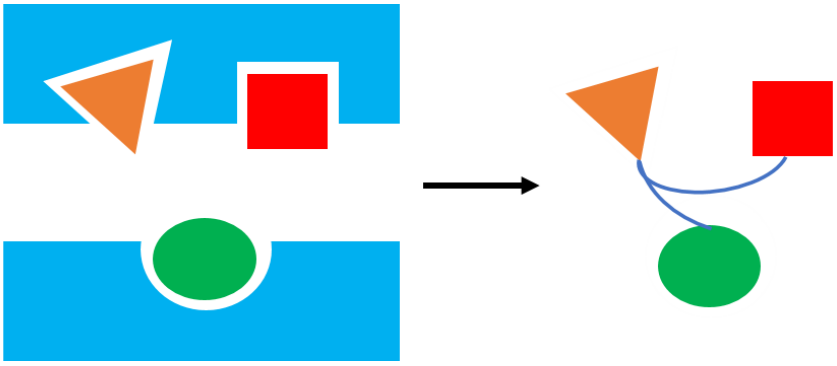


Figure 4. Fragment linking.

A case study by Abell and coworkers towards the discovery of inhibitors of *mycobacterium tuberculosis* pantothenate synthetase, has compared and contrasted the two approaches for fragment elaboration.[30] Interestingly, both approaches for fragment optimisation resulted in the identification of similar compounds with similar potencies. However, the limited number of suitable linkers rendered the fragment linking process as limiting. In contrast, the fragment growing process was shown to allow more freedom for development and optimisation at each stage.[30]

1.5 Shape Analysis

It has been suggested that the presence of too many aromatic rings can have an adverse effect on the potential of a candidate to progress.[31] Despite the possibility for π-π stacking interactions[32] and cation-π interactions,[33] the introduction of multiple aromatic rings increases the lipophilicity of the associated compounds,[31] which has been shown to be a defining property of clinical candidates.[34,35] The majority of FBDD programmes have been centred around the synthesis of sp^2-rich compounds, often with multiple aromatic rings, which ultimately affects the overall three-dimensionality of the molecule. Nature recognises molecules three-dimensionally,[36] and consequently molecules with a high degree of sp and sp^2 character exhibit fewer interactions with the intended targets. There has therefore been a desire to begin probing three-dimensional chemical and biological space.

The synthesis of sp^3-rich, three-dimensional molecules introduces new vectors for elaboration,[15] as well as improving the solubility by disrupting the solid state crystal lattice packing.[37] An increase in sp^3 character should deviate from the planarity associated with sp- and sp^2-rich molecules, as well as increasing molecular complexity.[38,39] To assess the complexity of potential drug candidates, a new descriptor called the fraction of sp^3 (Fsp^3) was coined by Lovering.[38] This is defined by the number of sp^3 hybridised carbons divided by the total carbon count. The rationale arises from saturation allowing the preparation of more complex molecules, without significantly increasing molecular weight.[38] A good example for comparison is dimethylpyridine versus dimethylpiperidine. Dimethylpyridine has a Fsp^3 of 0.29, and has 5 accessible isomers. Comparatively, dimethylpiperidine has a Fsp^3 of 1 and has 34 accessible isomers, which are significantly more complex and exhibit greater three-dimensionality than dimethylpyridine.

The analysis and visualisation of molecular shape is an important tool in the design and characterisation of lead of compounds.[40] The recognition of the large proportion of sp- and sp^2-rich compounds in drug candidates, coupled with the desire to begin to explore three-dimensional chemical space, has led to the increased synthesis of sp^3-rich compounds. Having a high Fsp^3 does not necessarily correlate to a molecule being three-dimensional, and consequently computational methods have been developed to analyse molecular shape.

1.5.1 Principal Moments of Inertia Analysis

Principal moments of inertia (PMI) analysis is a means of portraying the three-dimensional shape of a molecule on a two-dimensional plot. The plot is ternary, and depicts the three extremes of molecular shape.[41] The top left vertex of the plot represents an acetylene equivalent, a species that is *sp* hybridised and possesses a 'rod-like' shape. The bottom vertex of the plot represents a benzene equivalent, a species that is sp^2 hybridised and possesses a planar shape. The top right vertex of the plot represents an adamantane equivalent, a species that is sp^3 hybridised and possesses a cage or sphere-like structure. Therefore, a compound will lie somewhere between the three vertices depending on the degree of which it represents the three classes of morphology.[42]

Different three-dimensional conformers are computationally generated, and the lowest energy conformer is determined. From this, moments of inertia are calculated along the *x*,*y* and *z* axes, to give I_x, I_y, and I_z respectively. Normalised PMI values are calculated by I_x/I_z and I_y/I_z which can then be represented on a two-dimensional plot.[14,43,44] Owing to the normalisation of the values, the results of PMI analysis are irrespective of the size of the molecule.[45]

PMI analysis can be used to profile the three-dimensionality of a large library of compounds with relative ease. The ZINC database is a free to use, online database of commercially available compounds for virtual screening. It currently contains almost one billion commercially available building-blocks, which in turn can be used for library synthesis.[46] Libraries from the ZINC database can be downloaded and analysed by users.

A 'lead-like'[1] library was downloaded from the ZINC database, with restrictions on the properties of the compounds to have molecular weights <350 and AlogP values <3.5. The library consisted of 35,270 randomly selected molecules from the respective ZINC subset deemed to be 'lead-like'. The 35,270 compounds were analysed using the LLAMA software, an open-access, online tool for the analysis of molecular scaffolds.[14,47] Normalised PMI values were obtained and plotted onto a PMI plot (Figure 5).

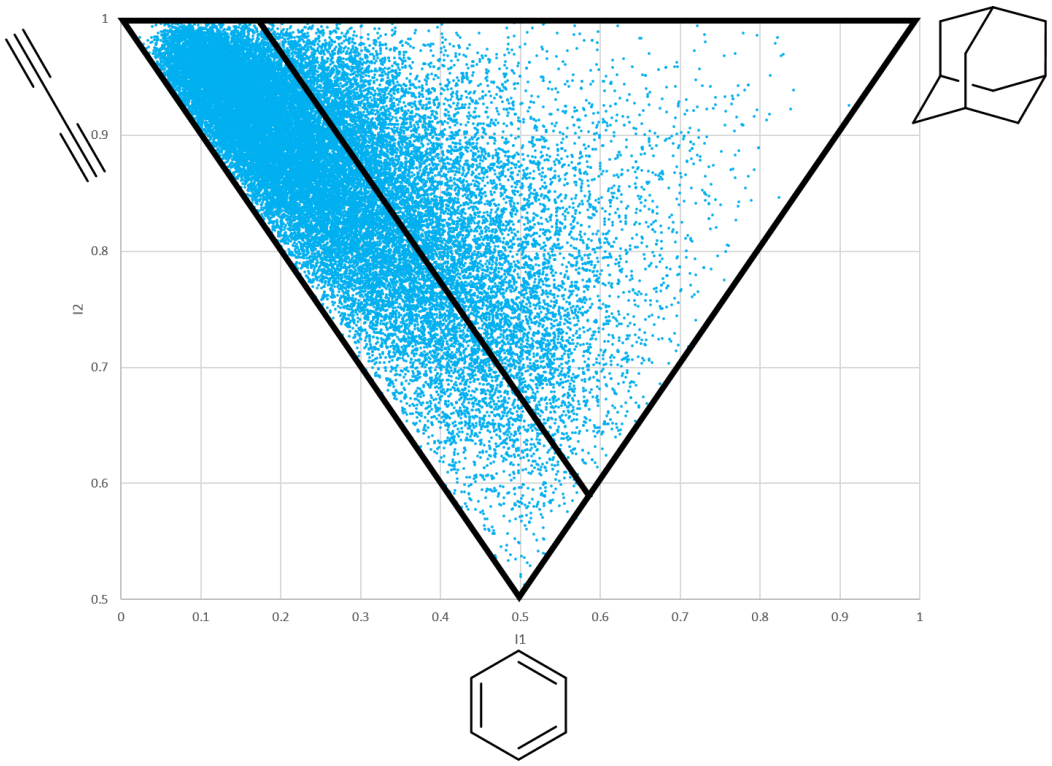


Figure 5. PMI plot of the ZINC 'lead-like' database.

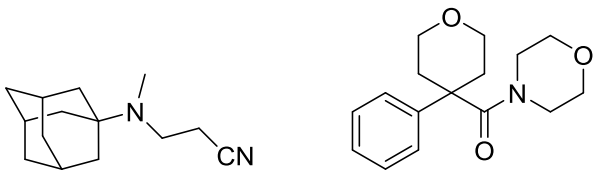
The PMI plot shows that there is not a uniform distribution, and the area of space representing three-dimensional structures is very sparsely populated. In contrast, the area of space representing linear and planar molecules is very densely populated. The extra line on the plot represents a region where, to the left of the line, 75% of the molecules from the ZINC subset reside. This shows that 26,452 'lead-like' compounds are in fact relatively two-dimensional. The PMI plot above is a good representation of why there is a desire to synthesise more sp^3 rich, three-dimensional compounds.

1.5.2 Plane of Best Fit Analysis

Plane of best fit (PBF) has been developed to quantify the three-dimensional character of molecules. The principal of PBF is to give a mean value for the atomic distance of all heavy atoms across the molecule from the plane through all heavy atoms, and a distance in angstroms is obtained. The bigger the distance, the more three-dimensional the molecule is.

In the context of the original precedent by Brown and Blagg, conformations of molecules were generated using CORINA software, with the absence of hydrogen atoms.[40] From these conformations, coordinates were generated and subsequently used to calculate the plane of best fit via a least-squares method. The output of the equation was given as an average of the distances of the heavy atoms from the PBF in angstroms.

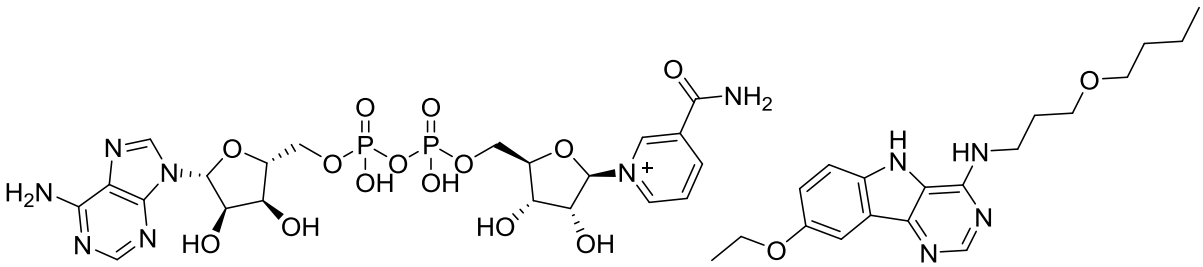
Comparing the adamantane derivative **8** with amide **9** (Figure 6), the former exhibits a PBF score of 0.642 Å, whilst the latter has a PBF score of 0.805 Å.[40] By means of PMI analysis, it would be assumed that the nitrile **8** bearing a spherical adamantane ring would be more three-dimensional than the amide **9** bearing an aromatic ring and a planar amide. However, placing a plane of best fit through the molecules, it can be seen that on average, the heavy atoms of amide **9** lie further from the plane than adamantane derivative **8**. By PBF, amide **9** is more three-dimensional.



8 **9**

Figure 6.Adamantyl derivative **8** and amide **9**.

To demonstrate the utility of PBF, two compounds NAD+ **10** and tricycle **11** (Figure 7) were analysed. The molecules have a similar Fsp^3 of 0.476 and 0.474 respectively, however, NAD+ **10** has a PBF of 1.53 Å and tricycle **11** has a PBF of 0.00475 Å. This highlights the potential flaws in the judgement of three-dimensionality based upon Fsp^3. Comparison of the PBF score with the Fsp^3 of 2465 fragment-like molecules (molecular weight<320, AlogP<3) showed that there was no correlation between the two methods of analysis.[40]



10 **11**

Figure 7. NAD+ **10** and tricycle **11**.

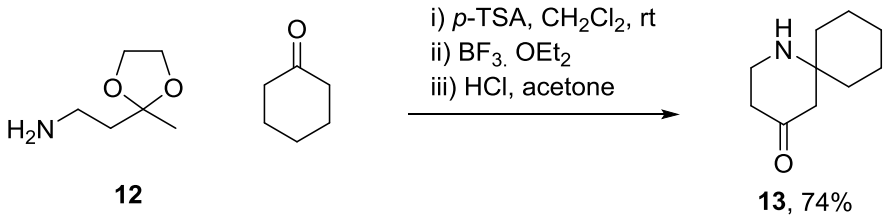
Whilst it should be noted that the Fsp^3 was originally introduced as a measure of molecular complexity, it was recognised that there was a positive correlation between a high Fsp^3 and clinical success.[38] The introduction of PBF analysis has demonstrated that the use of Fsp^3 can be misleading as a sole measure of three-dimensionality. Measurements of Fsp^3 should be accompanied with either PBF or PMI analysis to assess three-dimensionality. Plane of best fit can itself be misleading when comparing molecules of vastly different sizes,[40] however, in the context of small molecule analysis it is a useful method for quantifying three-dimensionality. Analysis by PMI gives normalised co-ordinates so results are irrespective of size, and it provides a visual representation of three-dimensionality on a plot for ease of comparison. Consequently, PMI analysis has been used for analysis of three-dimensionality in this thesis.

1.6 Synthesis of 2-Spiropiperidines

Piperidines are among the most commonly found motifs in drugs, drugs candidates and natural products.[48,49] As a fragment scaffold, they possess a hydrogen bond donor/acceptor for interactions with targets, as well as an amine handle for further functionalisations to be performed. Coupled with the desire to explore three-dimensional space, aza-spirocycles are consequently growing in popularity and frequency in medicinal chemistry as scaffolds and pharmacophores.[48] Aza-spirocycles are conformationally well defined, which allows the elaboration of the spirocycle to occur along a series of well defined vectors. Troin reviewed the synthesis of spirocyclic piperidines as important building blocks in medicinal chemistry in 2009.[48] The review, however, only demonstrates the synthesis of 3- and 4-spiropiperidines, a result of the small amount of literature surrounding the synthesis of 2-spiropiperidines.

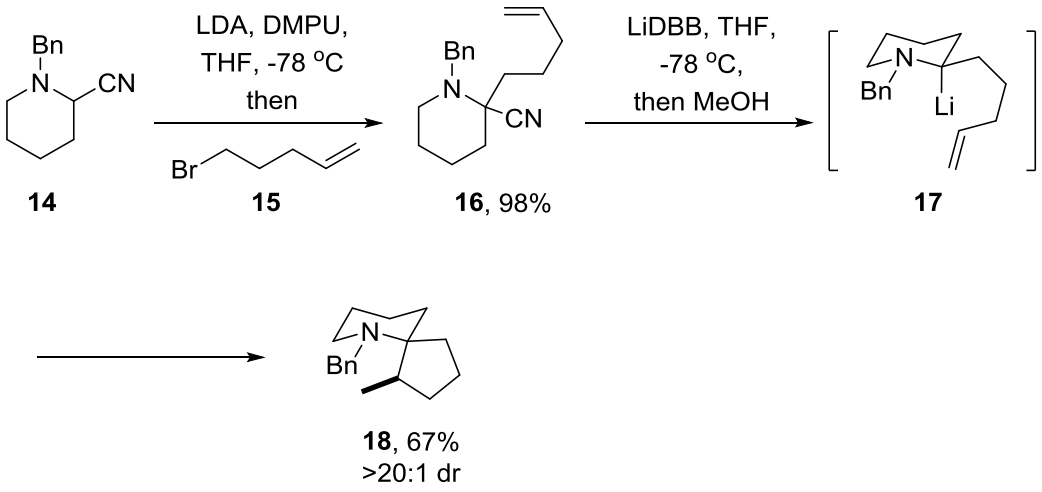
It was therefore determined that an underrepresented yet highly desirable subset of spirocycles to synthesise were 2-spiropiperidines. Examples from the current literature for the synthesis of 2-spiropiperidines from both methodology and natural product synthesis perspectives are presented below. There are few examples that present general methods for the synthesis of 2-spiropiperidines, and the procedures are often solely for the synthesis of specific systems. The development of a general procedure for the synthesis of 2-spiropiperidines was consequently highly appealing.

An intramolecular Mannich reaction was developed by Troin for the synthesis of 2-spiropiperidines.[50] Condensation of amine **12** with cyclohexanone gave an iminium ion, which underwent an intramolecular Mannich reaction to give 2-spiropiperidine **13** in a good 74% yield (Scheme 1). The scope of the spirocyclisation was probed and was shown to proceed with four- to seven-membered aliphatic cyclic ketones, as well as with adamantanone.



Scheme 1. 2-Spiropiperidine synthesis via an intramolecular Mannich reaction.

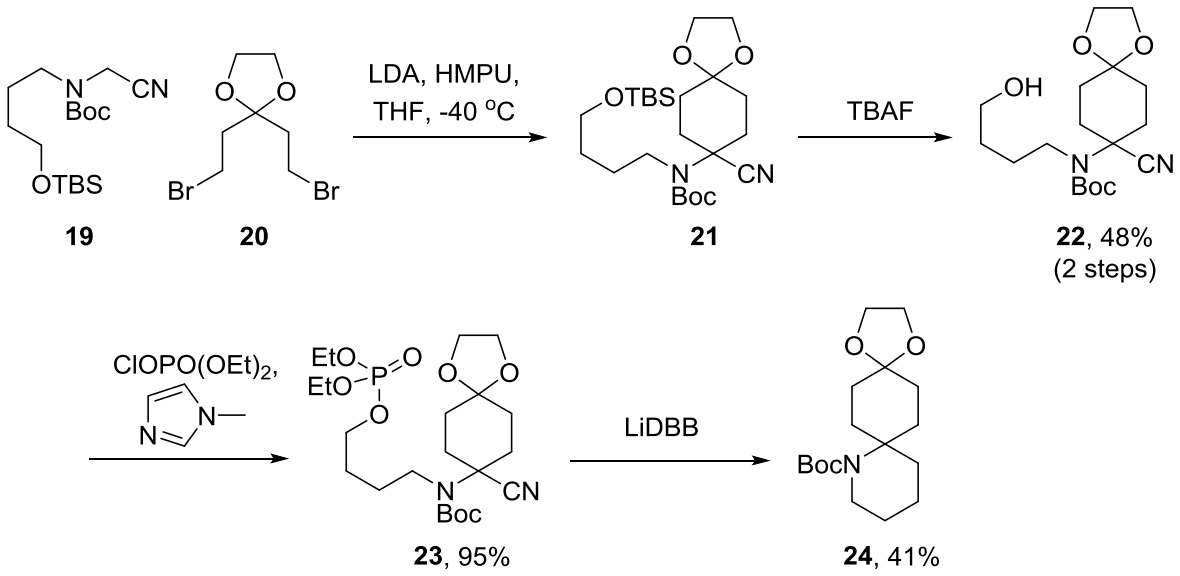
Rychnovsky presented a sequential alkylation of α-amino nitriles followed by a reductive lithiation and cyclisation to give 2-spiropiperidines.[51] Alkylation of α-amino nitrile **14** with alkyl bromide **15** gave the cyclisation precursor **16** in an excellent 98% yield (Scheme 2). Reductive lithiation of α-amino nitrile **16** with lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) gave the lithiated intermediate **17**. Subsequent cyclisation onto the terminal alkene gave 2-spiropiperidine **18** in a good 67% yield with an excellent 20:1 diastereoselectivity. The reaction was demonstrated to introduce differently substituted five and six-membered spirocycles in moderate to good yields.



Scheme 2. Reductive lithiaton/alkylation to furnish 2-spiropiperidines.

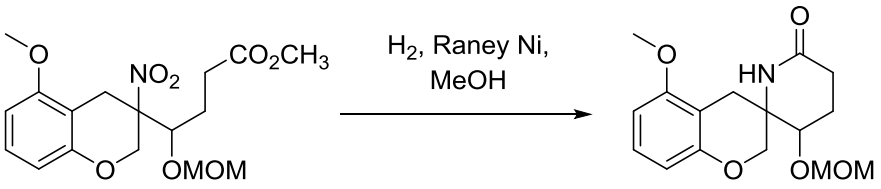
The reductive lithiation-cyclisation reported by Rychnovsky forms the 2-spiropiperidine from a preformed piperidine ring.[51] This approach was later reversed by Rychnovsky, and in 2013 the synthesis of a 2-spiropiperidine from a preformed carbocyclic ring was developed, with

the formation of the piperidine as the key bond forming reaction.[52] Just one example of a 2-spiropiperidine was presented. α-Amino nitrile **19** was envisaged as a trianion synthon for a double alkylation/cyclisation sequence (Scheme 3). *N*-Boc-α-amino nitrile **19** underwent double alkylation with dibromide **20** which installed the tertiary α-amino centre of **21**. The alcohol **22** was then revealed by the treatment of TBS-protected **21** with TBAF. Conversion of the alcohol to a leaving group gave phosphonate **23**, and a subsequent reductive lithiation induced spirocyclisation to 2-spiropiperidine **24**.



Scheme 3. A trianion synthon approach to 2-spiropiperidines.

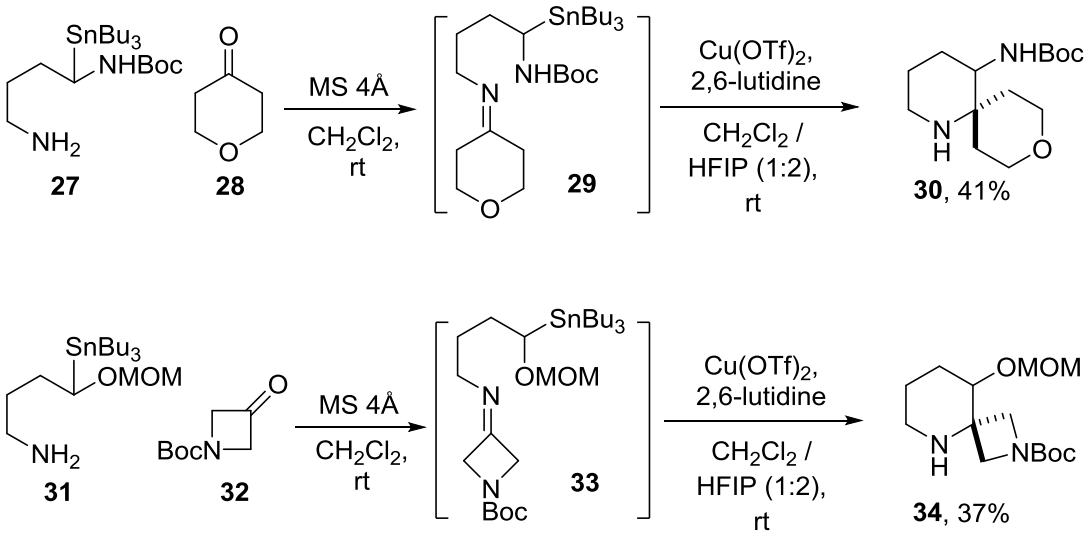
Substituted benzopyrans had been determined as $5HT_{1A}$ receptor ligands as well as potential anxiolytic agents by Guillaumet and coworkers.[53] Cyclisation precursor **25** was synthesised by aldol addition of the nitro benzopyran with the respective aldehyde (Scheme 4). Hydrogenation of the nitro group gave the amine which induced lactamisation to 2-spiro-δ-lactam **26** in a high 80% yield. The lactam was later reduced with BH_3 to furnish the 2-spiropiperidine, and the amine was derivatised to synthesis analogues.



25 **26**, 80%

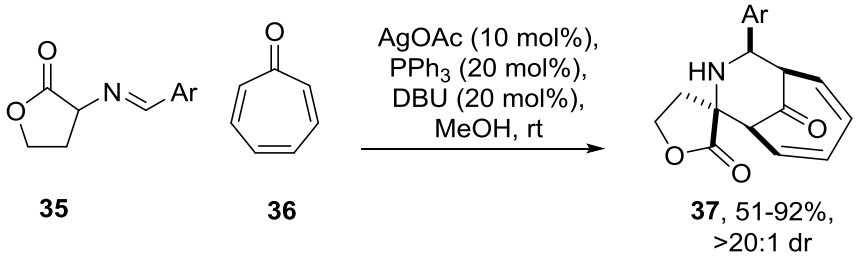
Scheme 4. Reductive amidation to form a 2-spirolactam.

Tin amine protocol (SnAP) reagents have been developed by Bode as precursors to functionalised heterocycles. Heterocyclic systems synthesised using SnAP reagents include piperazines and morpholines,[54,55] thiomorpholines,[56] piperidines and pyrrolidines,[57] and diazepanes.[58,59] The SnAP reagents are commercially available, and treatment of the SnAP reagents with aldehydes or ketones and $Cu(OTf)_2$ gives rise to substituted and spirocyclic heterocycles. Condensation of SnAP reagent **27** with tetrahydro-4*H*-pyranone **28** gave imine **29** (Scheme 5).[57] Upon addition of $Cu(OTf)_2$, homolytic cleavage of the C-Sn bond occurred followed by a radical addition to the imine, giving 2-spiropiperidine **30** in a moderate 41% yield. Utilisation of a different SnAP reagent **31** with azetidinone **32** under the same conditions gave 2-spiropiperidine **34** in a moderate 37% yield (Scheme 5).[57] The robust reaction does not require protection of the piperidine nitrogen, and has been applied to the synthesis of a range of different 2-spiropiperidines. The reaction, however, does require the use of toxic organotin reagents.



Scheme 5. 2-Spiropiperidine synthesis with SnAP reagents.

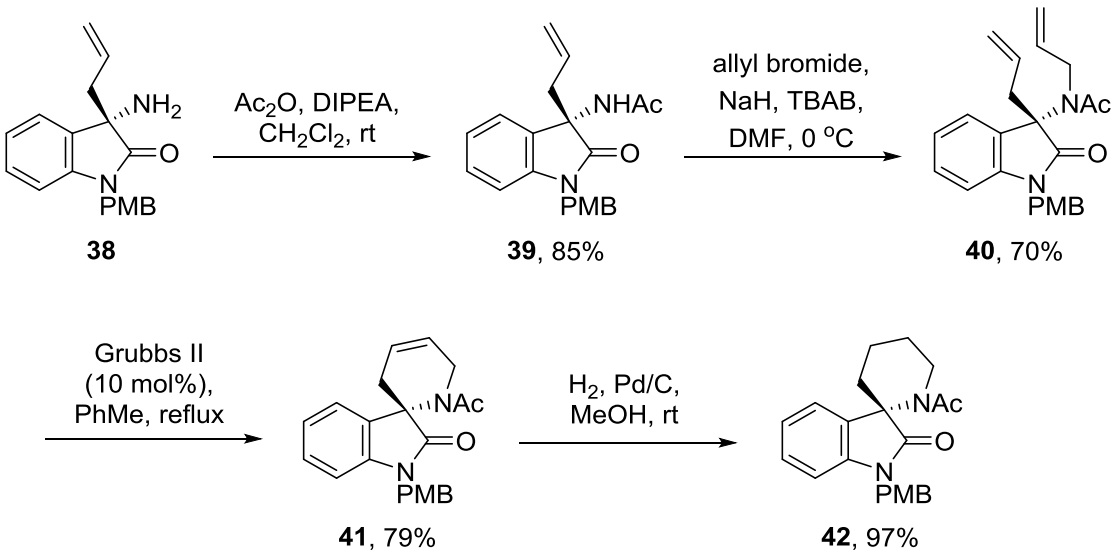
The synthesis of tricyclic, bridged 2-spiropiperidines was developed by Guo and coworkers by means of a silver-catalysed [6+3] cycloaddition. Under mild conditions, the cycloaddition proceeded to give 2-spiropiperidines in moderate to excellent yields with excellent diastereoselectivities.[60] Treatment of precursor **35**, which was derived from homoserine lactone, with AgOAc generated an azomethine ylide which underwent a [6+3] cycloaddition with tropone **36** to give the bridged 2-spiropiperidine **37** (Scheme 6). The scope of the cycloaddition was demonstrated with different aromatic substituents on the piperidine.



Scheme 6. [6+3] Cycloaddition of tropone **36** to azomethine ylides.

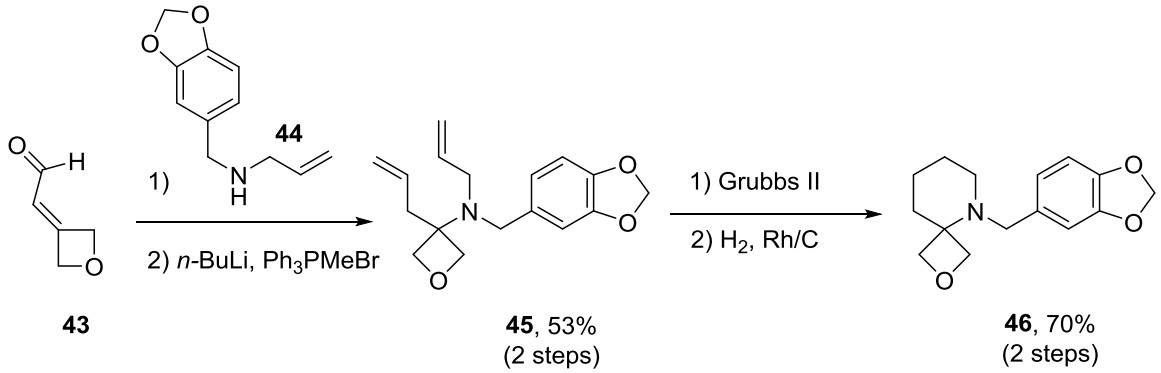
Silvani reported a ring closing metathesis reaction for the synthesis of a spiropiperidine-3,3'-oxindole scaffold as a type II β-turn peptide isostere.[61] The scaffold possessed a 2-spiropiperidine, which was synthesised in five steps from isatine **38** (Scheme 7). Amine **38** was

formed via Grignard addition of allyl bromide into a chiral sulfinimine, followed by amine deprotection with HCl.[62] Acetylation of amine **38** with Ac_2O gave acetamide **39** in a high 85% yield, which was then alkylated with allyl bromide to give diene **40** in a good 70% yield. Ring closing metathesis gave tetrahydropyridine **41** which was subsequently reduced by hydrogenation to give 2-spiropiperidine **42** in an excellent 97% yield.[61]



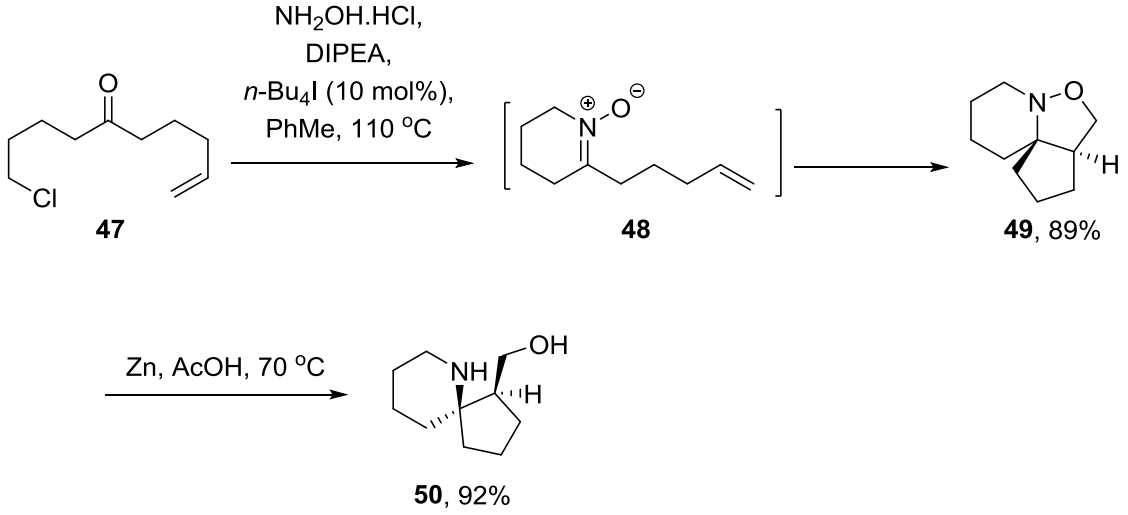
Scheme 7. Synthesis of a 2-spiropiperidine as a type II β-turn peptide isostere.

Carreira also reported the synthesis of a 2-spiropiperidine via a ring closing metathesis.[63] Amine **44** underwent Michael addition into α,β-unsaturated aldehyde **43**, followed by a Wittig methylenation to furnish diene **45** in a moderate 53% yield over 2 steps (Scheme 8). The 2-spiropiperidine **46** was formed by a ring closing metathesis using Grubbs II catalyst, followed by a hydrogenation of the tetrahydropyridine. The simple procedure, however, only presents the synthesis of a spirocyclic oxetane.



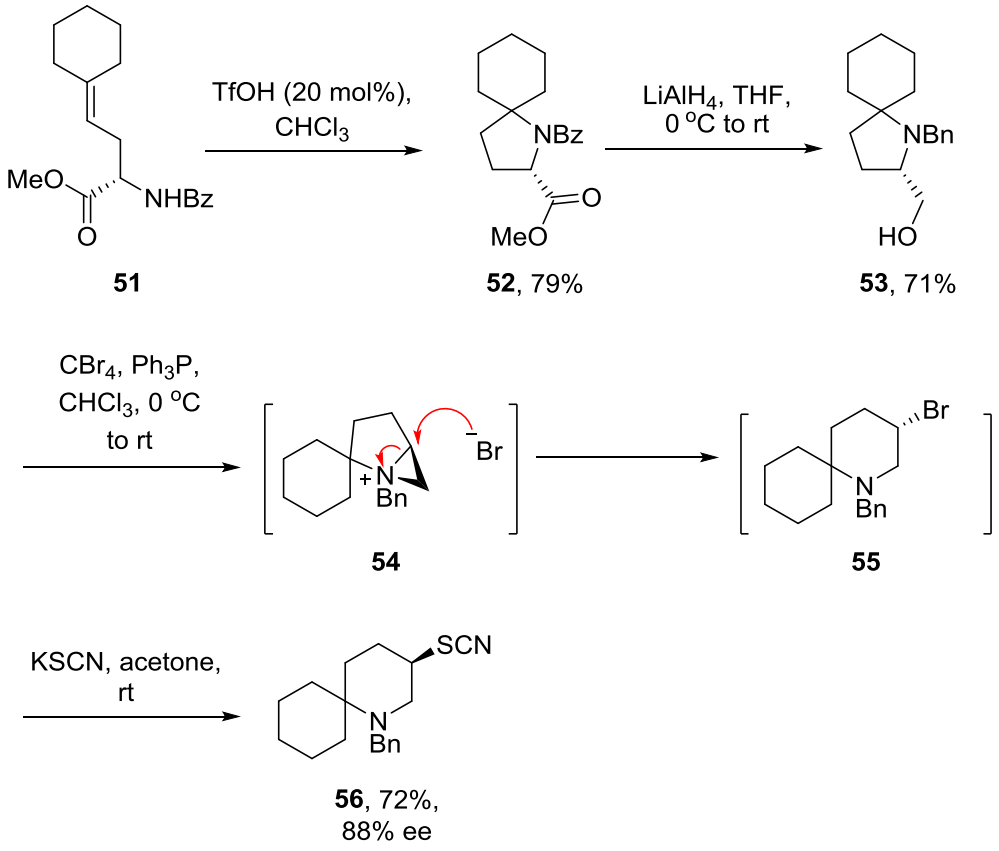
Scheme 8. Ring closing metathesis to access spirocyclic oxetanes.

An intramolecular 1,3-dipolar cycloaddition of nitrones was developed by Coldham for the synthesis of spirocyclic pyrrolidines and piperidines.[64] Displacement of the chloride of ketone **47** with hydroxylamine followed by an intramolecular condensation gave the intermediate nitrone **48** (Scheme 9). At elevated temperatures, nitrone **48** underwent an intramolecular 1,3-dipolar cycloaddition with the terminal olefin to give tricycle **49** in an excellent 89% yield. The *N*-O bond was then reductively cleaved with Zn in AcOH to give 2-spiropiperidine **50**. The 1,3-dipolar cycloaddition was applied to the synthesis of five, six and seven-membered spirocycles in moderate to high yields.



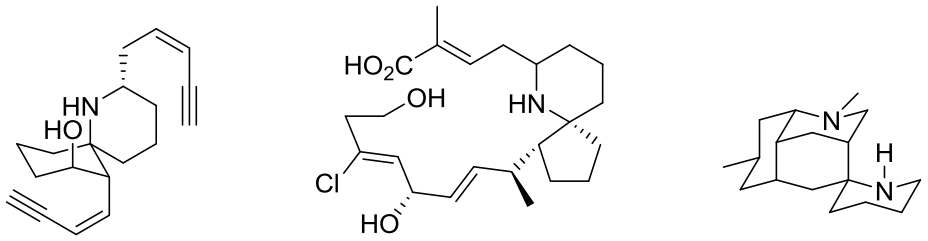
Scheme 9. 1,3-Dipolar cycloaddition followed by reductive cleavage for 2-spiropiperidine synthesis.

A ring expansion of enantiopure 2-spiropyrrolidines was presented by Robinson for the synthesis of 2-spiropiperidines.[65] Enantiopure cyclisation precursor **51** was synthesised via a cross metathesis between *N*-Bz protected allylglycine and methylenecyclohexane (Scheme 10). An acid mediated intramolecular cyclisation of amine **51** with TfOH gave 2-spiropyrrolidine **52** in a good 79% yield. Reaction with $LiAlH_4$ reduced the ester to the primary alcohol **53** as well as reducing the protecting group from a Bz to a Bn. Under Appel reaction conditions, the 2-spiropyrrolidine **53** underwent ring expansion to the 2-spiropiperidine **55**. Seemingly the alcohol was converted to the bromide, which was then displaced by the pyrrolidine nitrogen to form the aziridinium intermediate **54**. Re-addition of the bromide afforded ring opening of the aziridinium intermediate **54** to give 2-spiropiperidine **55**. Due to the instability of the 2-spiropiperidine **55** to silica gel during column chromatography, conversion of the bromide to the thiocyanate analogue gave 2-spiropiperidine **56** in a good 72% yield, though with a slight erosion of %ee (from 100% ee of enantiopure **51**).



Scheme 10. Ring expansion of a 2-spiropyrrolidine.

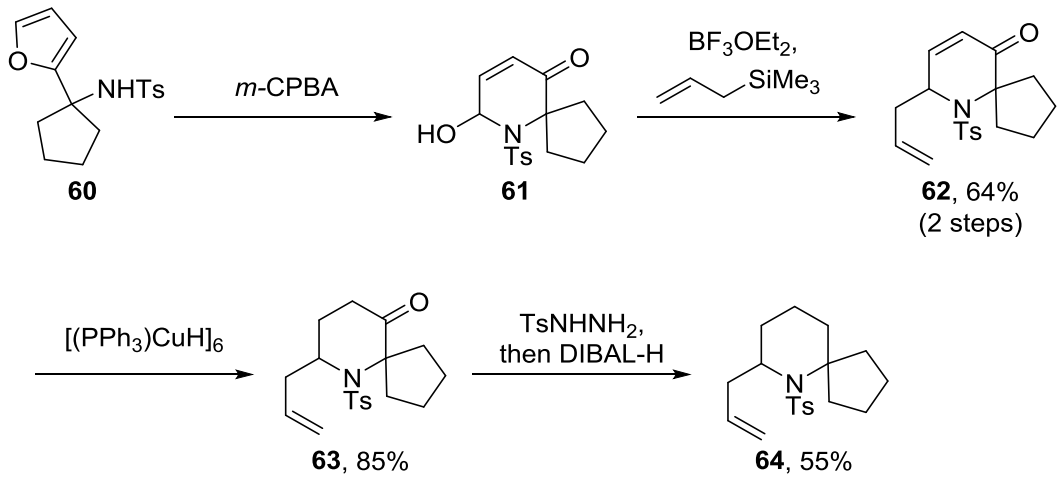
The 2-spiropiperidine motif has been identified in natural products. Histrionicotoxin **57** (Figure 8) was isolated from the skin extracts of frogs,[66] and has been used as an important neurophysiological research tool.[67] Pinnaic acid **58** (Figure 8),[68] and the closely related tauropinnaic acid[68] and halichlorine,[69] were all isolated from marine sponges and have been demonstrated to possess anti-inflammatory properties.[70] Nankakurine A **59** (Figure 8) is a lycopodium alkaloid isolated from a club moss.[71] It has been found to induce secretion of neurotrophic factors from human astrocytoma cells.[72] Methods for the construction of the 2-spiropiperidine core of these natural products will be presented below.



57 **58** **59**

Figure 8. Natural products containing 2-spiropiperidines; histrionicotoxin **57**, pinnaic acid **58** and nankakurine A **59**.

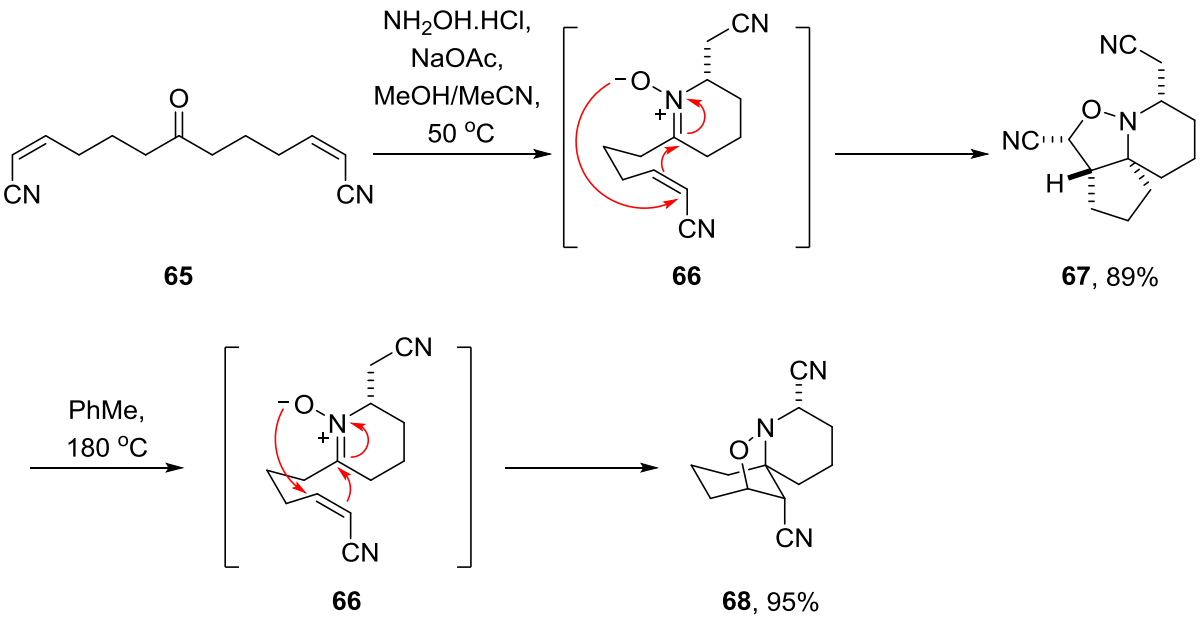
Marquez developed a divergent approach to the polymaxenolide (2-spiropyran containing) and pinnaic acid (2-spiropiperidine containing) cores.[73] Achmatowicz and aza-Achmatowicz rearrangements of α-hydroxy furans and α-amino furans gave 2-spiropyran-3-ones and 2-spiropiperidin-3-ones respectively. Upon oxidation with *m*CPBA, α-amino furan **60** underwent an aza-Achmatowicz rearrangement to give 2-spirotetrahydropyridine **61** (Scheme 11). Subsequent allylation of the hemiaminal under Lewis acidic conditions gave **62** in a good 64% yield over the two steps. A selective 1,4-reduction of 2-spirotetrahydropyridine **62** with Stryker's reagent furnished **63**, which was deoxygenated with tosylhydrazine and DIBAL-H to give 2-spiropiperidine **64** in a moderate 55% yield.



Scheme 11. Aza-Achmatowicz rearrangement of an α-amino furan to a 2-spiropiperidine.

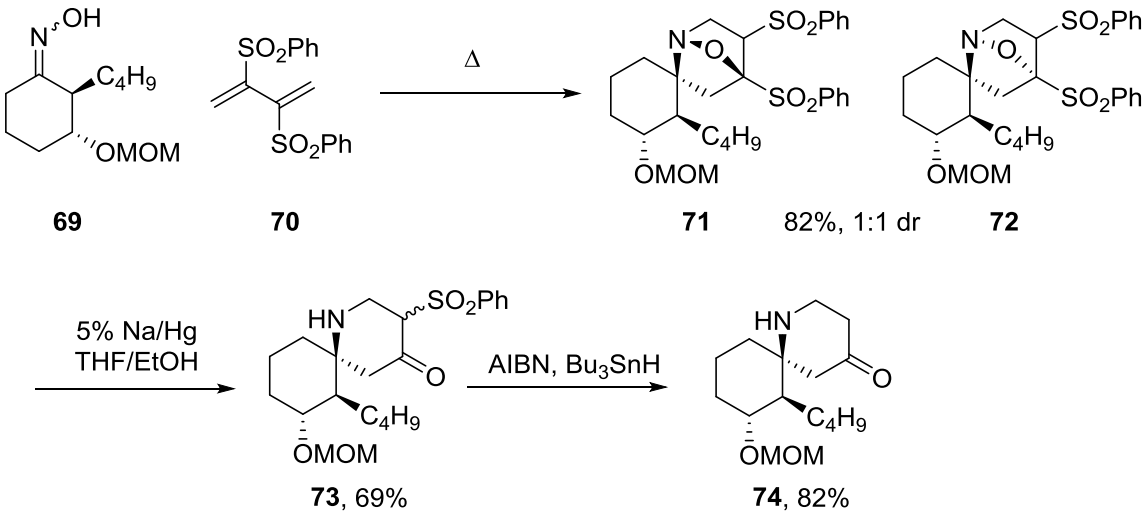
There have been multiple syntheses of histrionicotoxin and related analogues beginning with syntheses by Kishi in 1985 (38 steps)[74] and by Stork in 1990 (18 steps).[75] Since these syntheses, more concise methods have been reported, including the use of cross metathesis,[76] displacement chemistry,[77] ring expansions,[78] and radical cyclisations.[79]

Stockman reported the desymmetrisation of an open chain ketone **65** en route to the synthesis of histrionicotoxin **57** (Scheme 12).[80] Oxime formation by condensation of hydroxylamine with ketone **65** followed by conjugate addition and a 1,4-prototopic shift gave nitrone **66**. At 50 ^{o}C, nitrone **66** underwent an intramolecular [3+2] cycloaddition to form tricycle **67**. It was found that heating tricycle **67** to 180 ^{o}C in a sealed vial induced a retro [3+2] cycloaddition/[3+2] cycloaddition sequence to give the thermodynamic product **68** in an excellent 95% yield. The *N*-*O* bond was later cleaved with superstoichiometric $CrCl_2$ and *n*PrSH to reveal the 2-spiropiperidine core. Ryan demonstrated that the *N*-*O* bond could be cleaved by hydrogenation in a similar synthesis to access the core 2-spiropiperidine of histrionicotoxin **57**.[81]



Scheme 12. 1,3-Dipolar cycloaddition for the synthesis of the core of histrionicotoxin.

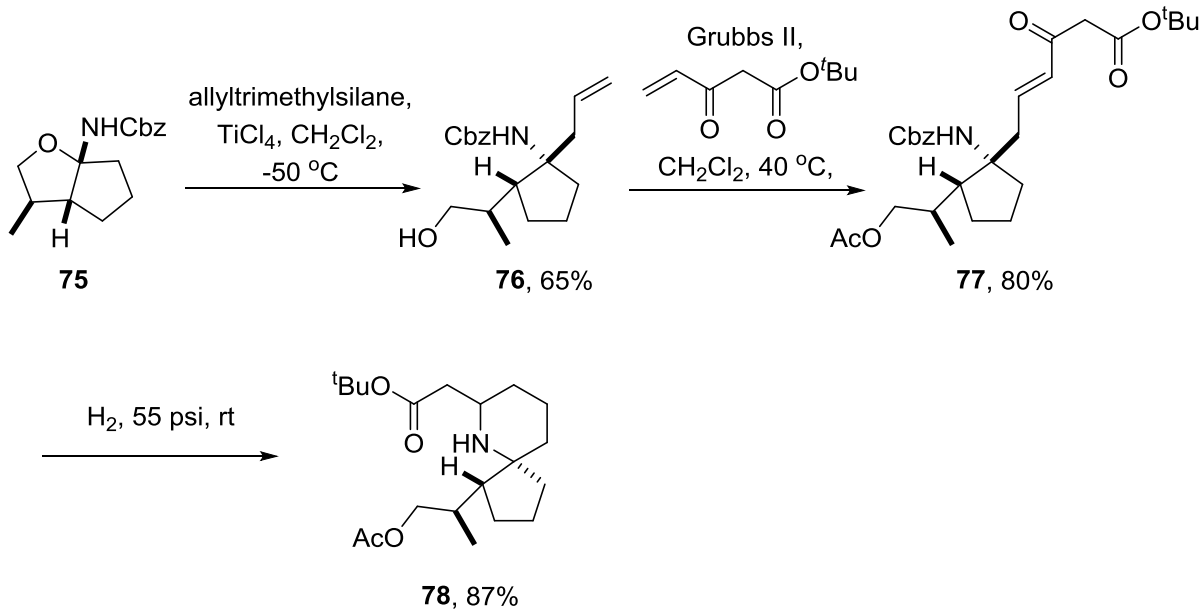
A conjugate addition/dipolar cycloaddition cascade was developed by Padwa for the synthesis of (±)-2,7,8-*epi*-perhydrohistrionicotoxin.[82] The chemistry derives from research developed by Padwa in 1991 for the synthesis of 2-substituted- and 2-spiropiperidines.[83] Oxime **69** underwent conjugate addition with diene **70** to give a nitrone, and subsequent 1,3-dipolar cycloaddition generated 2-spiropiperidines **71** and **72** in a high 82% yield as a 1:1 mixture of diastereomers (Scheme 13). The lack of selectivity was not an issue, as the oxo-bridge was subsequently destroyed via a reductive cleavage with Na/Hg amalgam to give ketone **73** in a good 69% yield. The sulfone was then reduced to the alkane using radical reduction conditions of AIBN/$SnBu_3$ to give 2-spiropiperidine **74**.



Scheme 13. Conjugate addition/dipolar cycloaddition cascade to give a 2-spiropiperidine.

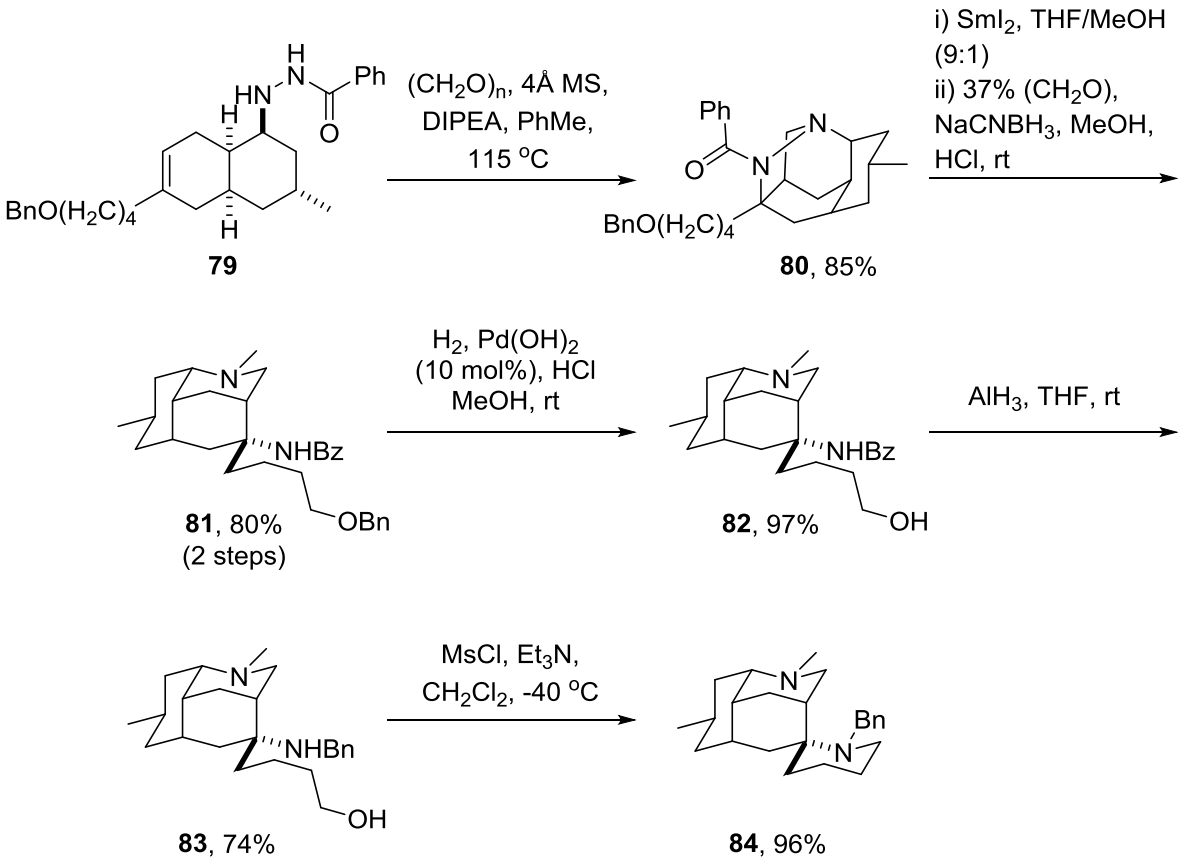
Several syntheses of pinnaic acid have been reported, the first by Danishefsky in 2001, forming the 2-spiropiperidine by an aza-1,6-conjugate addition.[84] Other reported syntheses include accessing the 2-spiropiperidine via a reductive cyclisation,[85,86] aza-1,4 conjugate addition,[87] and radical cylisations.[88] Ring closing metathesis to form the piperidine was reported by Wright[89] via a similar procedure presented by Silvani for the synthesis of an isatine analogue **42**.[61]

A racemic synthesis of pinnaic acid was performed by Heathcock.[70] Allylation of hemiaminal **75** with allyltrimethylsilane and $TiCl_4$ gave terminal alkene **76** (Scheme 14). A cross metathesis of terminal alkene **76** with ethyl 3-oxo-4-pentenoate gave cyclisation precursor **77** in a high 80% yield. Removal of the Cbz group of **77** by hydrogenation revealed the free amine, and subsequent 1,2-addition followed by dehydration and reduction gave 2-spiropiperidine **78** in an excellent 87% yield as a single isomer. Arimoto also reported a hydrogenative cyclisation but from an enantiopure starting material for the enantioselective synthesis of pinnaic acid.[90,91]



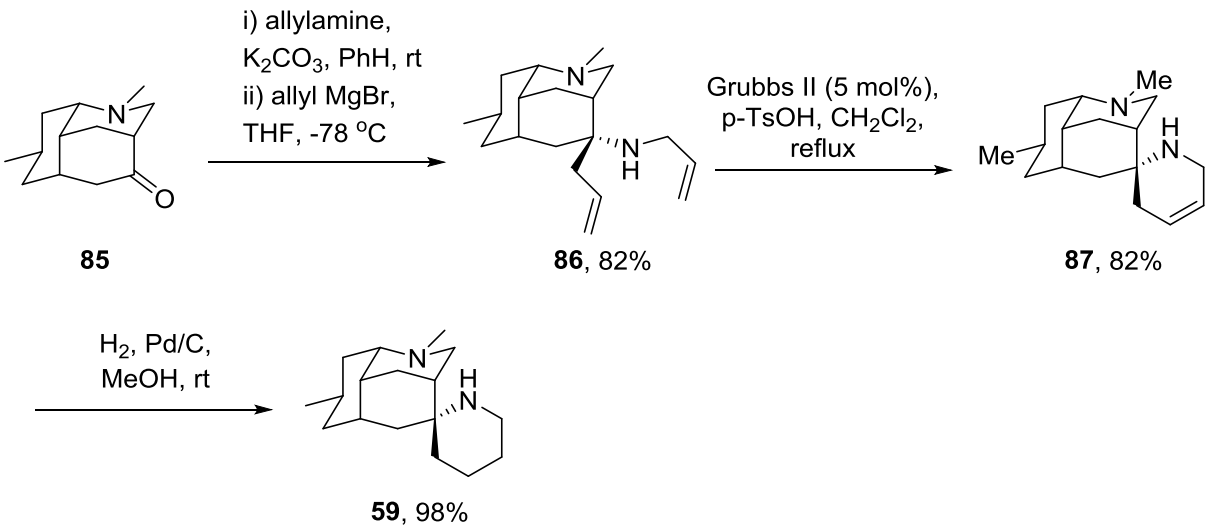
Scheme 14. Hydrogenation/hydrogenolysis sequence to access a 2-spiropiperidine.

Overman presented an enantioselective synthesis of nankakurine A proceeding through an intramolecular azomethine imine cycloaddition with hydrazide **79** to give tetracyclic pyrazolidine **80** in a high 85% yield (Scheme 15).[92,93] The *N*-*N* bond was cleaved with SmI_2, and a selective *in situ* reductive amination gave diamine **81** in a high 80% yield over two steps. Hydrogenolytic cleavage revealed the free alcohol **82**, and subsequent treatment with AlH_3 reduced the amide to give diamino alcohol **83**. A selective *O*-mesylation allowed substitution to occur, furnishing the 2-spiropiperidine **84** in an excellent 96% yield.



Scheme 15. Intramolecular azo-methine imine dipolar cycloaddition to construct the precursor to the 2-spiropiperidine of nankakurine A.

A ring closing metathesis approach was adopted by Waters for the synthesis of nankakurine A,[94] and is reminiscent of the methodology presented by Silvani for the synthesis of the isatine analogue **42**.[61] Sequential alkylation of ketone **85** with allylamine and allyl magnesium bromide gave diene **86** (Scheme 16). Ring closing metathesis with Grubbs II catalyst formed the 2-spirotetrahydropyridine **87**, which was then reduced by hydrogenation to give the natural product nankakurine A **59** in an excellent 98% yield.



Scheme 16. Ring closing metathesis to form the 2-spiropiperidine of nankakurine A.

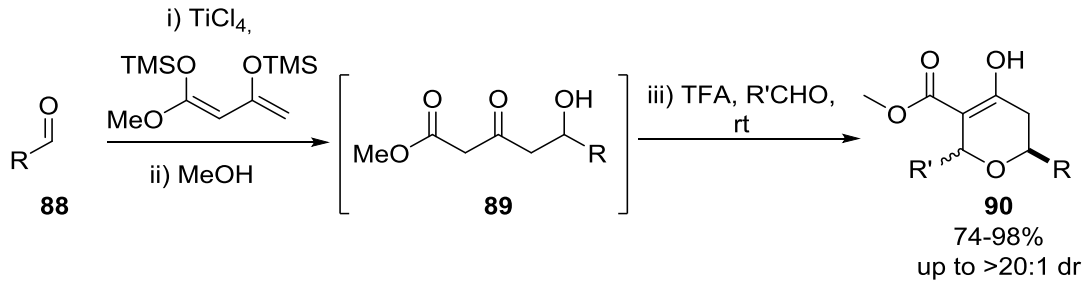
Whilst the presented examples are not extensive, the methodologies for the syntheses of the 2-spiropiperidines highlight the absence of general procedures. Moreover, the methodologies that do present general syntheses give rise to either non-functionalised 2-spiropiperidines, or require the synthesis or use of complex reagents and intermediates. The combination of the limitations means that there is a possibility that the use of 2-spiropiperidines in drug discovery programs has been underutilised.

It was therefore recognised that the development of a general procedure for the synthesis of functionalised 2-spiropiperidines would be productive. This would allow the rapid generation of structurally interesting molecules that could be used for a drug discovery program.

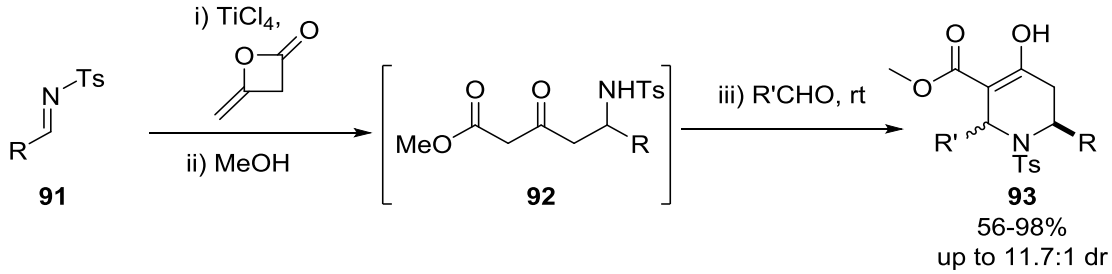
2. Synthesis of 2-Spiropiperidines

2.1 Aza-Maitland Japp

The aza-Maitland Japp reaction was reported by Clarke for the synthesis of highly functionalised piperidines.[95] Adapting previous methodology from within the group for the one-pot synthesis of highly functionalised tetrahydropyrans **90** (Scheme 17),[96] the initial aldehyde equivalent **88** was substituted for a tosyl aldimine **91**, giving rise to a one-pot synthesis of functionalised piperidines **93** (Scheme 18).[95]

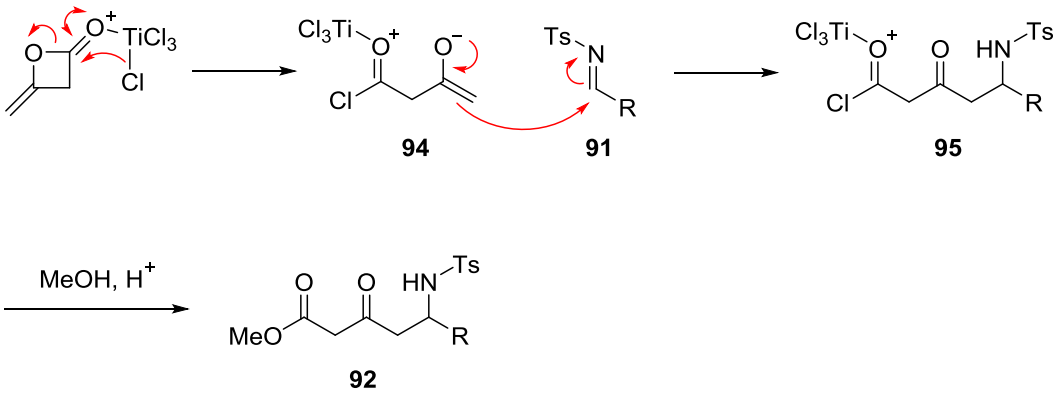


Scheme 17. The Maitland Japp reaction for highly functionalised tetrahydropyrans.



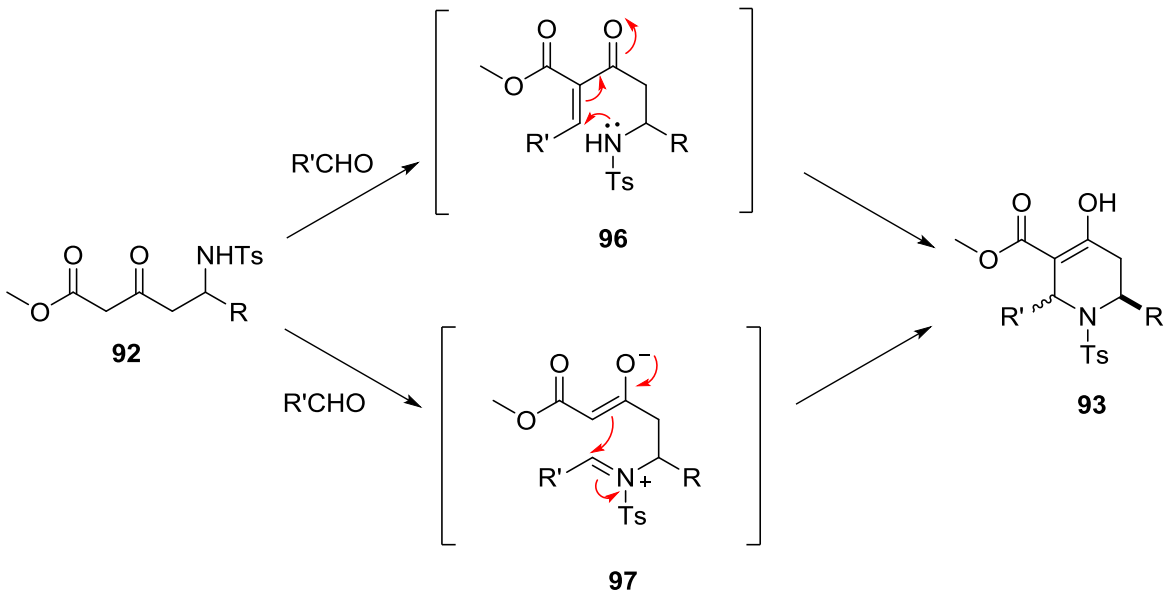
Scheme 18. The aza-Maitland Japp reaction highly functionalised piperidines.

Under the reaction conditions, ring opening of diketene with $TiCl_4$ gave titanium enolate **94**, which underwent Mannich addition to a tosyl aldimine **91** (Scheme 19). Methanolysis and protonation gave the intermediate *N*-tosyl-δ-amino-β-ketoester **92**.



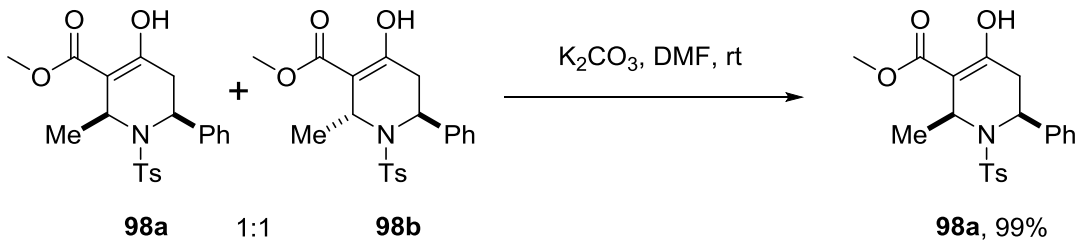
Scheme 19. Formation of the intermediate *N*-tosyl-δ-amino-β-ketoester **92** in the Aza-Maitland Japp reaction.

The reaction was then postulated to proceed via one of two mechanistic pathways (Scheme 20). By either first forming the Knoevenagel adduct **96** with the aldehyde, followed by an aza-Michael addition to give functionalised piperidine **93**, or in an alternate hypothesis, iminium ion **97** was formed with the aldehyde, and a second Mannich addition of the tautomerised β-ketoester gave piperidine **93**.



Scheme 20. Plausible mechanistic pathways for the formation of piperidine **93**.

The one-pot procedure was demonstrated to proceed with a range of aliphatic and aromatic C-2 and C-6 substituents in moderate to excellent yields and diastereoselectivities. Separation of the diastereomers was challenging. However, it was determined that the *trans* diastereomer could be epimerised to the *cis* diastereomer under basic conditions (Scheme 21). Treatment of a mixture of *cis* **98a** and *trans* **98b** diastereomers with K_2CO_3 resulted in the exclusive isolation of the *cis* diastereomer **98a** in an excellent 99% yield.

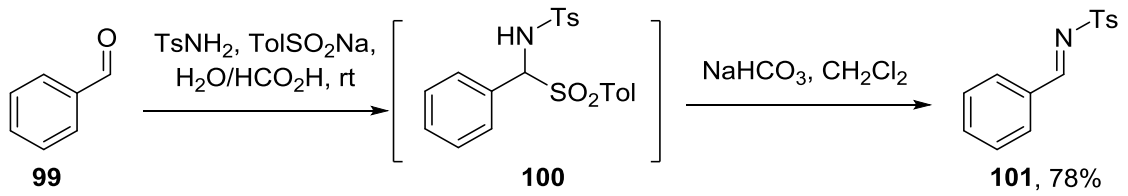


Scheme 21. Epimerisation of diastereomers from the Aza-Maitland Japp reaction.

The aza-Maitland Japp reaction had been shown to proceed with aldehydes and aldimines, however, the use of ketones or ketimines to give rise to spirocyclic piperidines had not been reported. It was therefore desirable to expand the scope of the Aza-Maitland Japp reaction to allow the synthesis of 2-spiropiperidines.

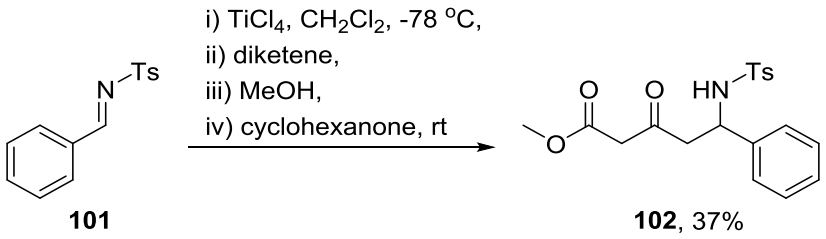
2.2 Cyclisation Studies with a Tosyl Protecting Group

Studies towards the synthesis of 2-spiropiperidines began with replication of the conditions reported for the synthesis of 2,6-substituted piperidines,[95] except the aldehyde equivalent was exchanged for a ketone. *N*-Tosyl aldimine **101** was synthesised via a literature procedure.[97] Benzaldehyde was treated with tosylamide and sodium toluenesulfinate to give the intermediate sulfone **100** (Scheme 22). Sulfone **100** was not isolated, and instead subjected to a basic wash with sat. aq. $NaHCO_3$, which eliminated toluenesulfinic acid to give imine **101** in a good 78% yield. Imine **101** was used for the cyclisation without further purification.



Scheme 22. Synthesis of aldimine **101** from benzaldehyde.

Aldimine **101** was treated with $TiCl_4$, diketene and cyclohexanone under the reported conditions (Scheme 23).[95] Unfortunately, no cyclised product was observed, however, *N*-Tosyl-δ-amino-β-ketoester **102** was isolated from the reaction mixture in a moderate 37% yield. This showed that Mannich addition was occurring, but subsequent Knoevenagel/aza-Michael or iminium/Mannich reactions were not taking place to form the desired 2-spiropiperidine.

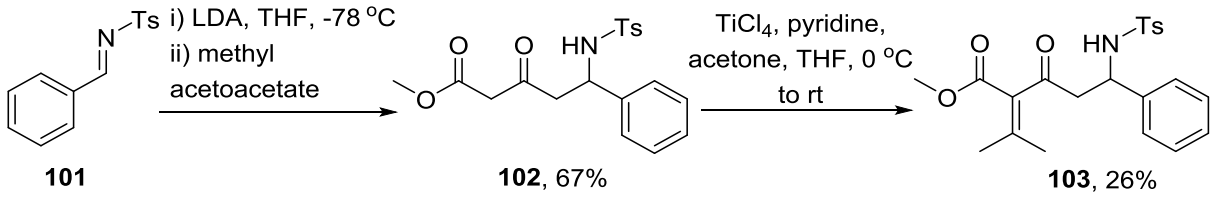


Scheme 23. One-pot conditions for cyclisation with cyclohexanone.

To see if cyclisation could be induced, *N*-tosyl-δ-amino-β-ketoester **102** was treated with different Lewis acids at room temperature in the presence of cyclohexanone. Lewis acids included $TiCl_4$, $YbCl_3$, $AlCl_3$ and $BF_3.OEt_2$, but in all cases only unreacted starting material was isolated from the reaction mixtures.

It was believed that synthesising the piperidine in a stepwise-manner could help elucidate the reaction pathway and understand the reasons for the unsuccessful one-pot procedure. Initial investigations used acetone, as it was the smallest, symmetrical ketone that could be used. This would ultimately not give rise to a 2-spiropiperidine, however, it would provide insight into cyclisations with a ketone. *N*-Tosyl aldimine **101** was treated with the Weiler dianion,[98]

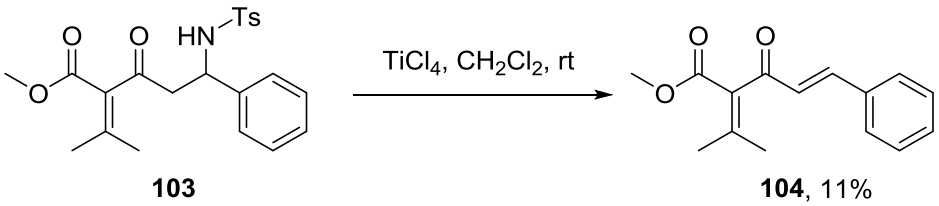
the dianion of methyl acetoacetate, in a procedure highlighted by Bunch for the synthesis of *N*-Boc-δ-amino-β-ketoesters, to give rise to *N*-tosyl-δ-amino-β-ketoester **102** in a good 67% yield (Scheme 24).[99]



Scheme 24. Synthesis of the Knoevenagel adduct **103**.

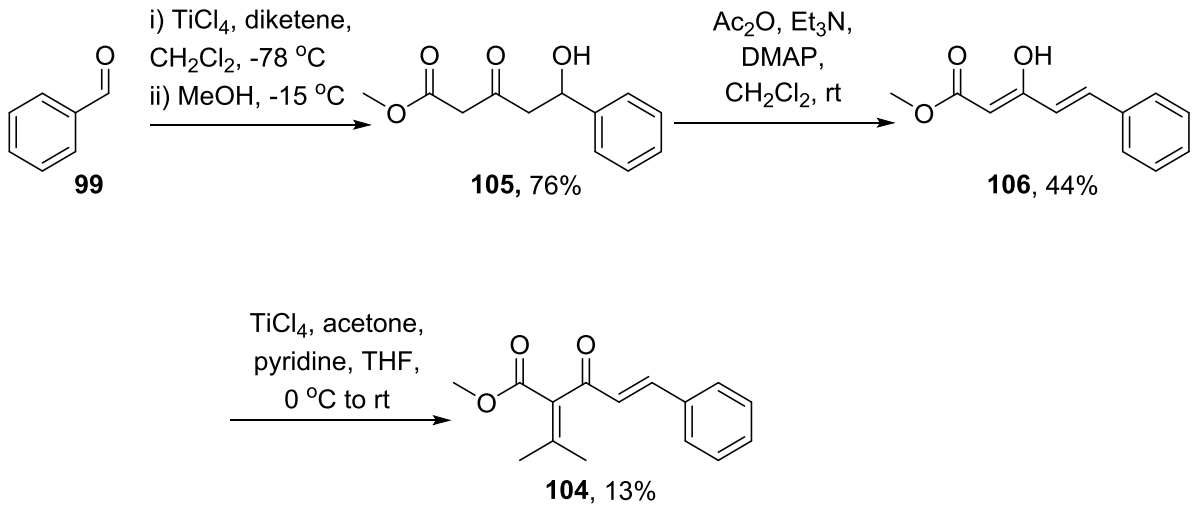
The synthesis of Knoevenagel adduct **103** was found to be challenging. Various methods were trialled for performing the Knoevenagel condensation, including the use of ethylenediamine,[100] $ZnCl_2$,[101] acetic acid,[102] and $TiCl_4$.[103] Only the use of $TiCl_4$ yielded any of the desired Knoevenagel adduct **103**, with the other methods giving no reaction, with starting material being re-isolated in all cases. The Knoevenagel condensation was found to be capricious, and a low 26% yield of isolation of **103** was the best result of multiple attempts.

With the Knoevenagel adduct **103** in hand, the cyclisation was attempted to form the 2,2-dimethyl piperidine. Treatment of Knoevenagel adduct **103** with $TiCl_4$ did not induce cyclisation, instead the elimination of tosylamide was observed to give conjugated enone **104**, along with unreacted starting material (Scheme 25).



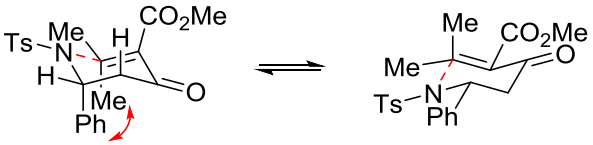
Scheme 25. Elimination of tosylamide to give conjugated enone **104**.

To clarify the identity of enone **104**, an alternate synthesis was devised (Scheme 26). δ-Hydroxy-β-ketoester **105** was synthesised via a literature procedure by way of an aldol addition of diketene to benzaldehyde (Scheme 26).[104] Acetate formation/elimination of the alcohol of δ-hydroxy-β-ketoester **105** with Ac_2O yielded diene **106** in a moderate 44% yield.[105] Presumably the alcohol underwent acylation, but subsequent elimination of acetic acid in the presence of a base gave the conjugated system. This was a fortuitous result, as a Knoevenagel condensation would directly give the desired product enone **104**. Treatment of diene **106** with $TiCl_4$ and acetone[103] gave rise to the desired conjugated enone **104** in a low 13% yield. The data obtained for enone **104** was identical to the data obtained from the previous method.



Scheme 26. Clarification of the structure of enone **104**.

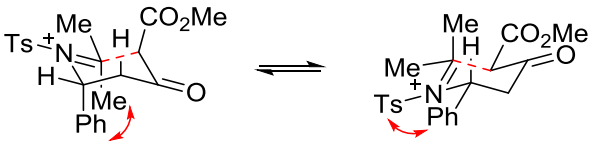
In the proposed reactive intermediate for the cyclisation of the *N*-tosyl-δ-amino-β-ketoester onto the Knoevenagel adduct (Figure 9), an unfavourable 1,3-diaxial interaction between the phenyl group and the axial methyl group is observed (Figure 9, **107**). Upon ring flipping, the destabilising interaction is eliviated, giving a more favoured conformation (Figure 9, **108**).



107 **108**

Figure 9. Proposed reactive intermediates for the Knoevenagel pathway.

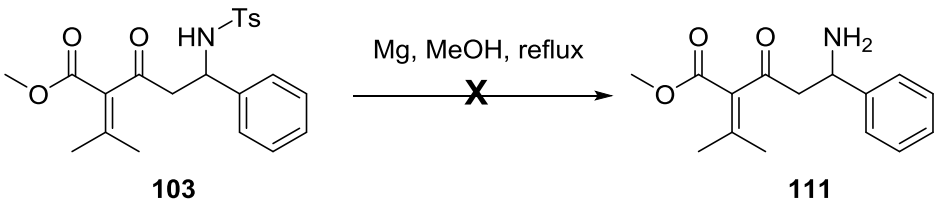
Equally in the proposed reactive intermediates for the Mannich reaction of the enolate onto the iminium ion (Figure 10), a 1,3-diaxial interaction between the phenyl group and the axial methyl substituent is observed (Figure 10, **109**). However, in the ring flipped conformation, an $A_{1,2}$-like strain between the *N*-tosyl group and the phenyl group is observed (Figure 10, **110**). To properly elucidate which pathway is undertaken, a method such as ReactIR could be used to monitor Knoevenagel adduct/iminium formation.



109 **110**

Figure 10. Proposed reactive intermediates for the iminium pathway.

For cyclisation to occur, it was believed that at least one of these destabilising interactions had to be removed. Eradication of the 1,3-diaxial interaction was not possible, otherwise 2-spiropiperidines could not be synthesised via this method. Consequently, it was believed that deprotection of the amine would remove the destabilising $A_{1,2}$-like strain and induce cyclisation. Knoevenagel adduct **103** was treated with magnesium turnings and refluxed in methanol,[106,107] but only decomposition of starting material was observed (Scheme 27).

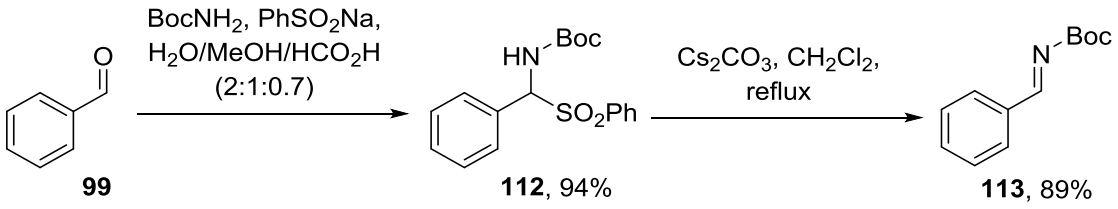


Scheme 27. Attempted deprotection of δ-amino-β-ketoester **103**.

Owing to the low yielding reactions and the low quantities of material of the intermediates, an alternative approach was required. The *N*-protecting group was changed from an *N*-tosyl group to an *N*-Boc group. The Boc group is more labile than a tosyl group, so cyclisation could be attempted on the unprotected amine, yet also makes the imine carbon electrophilic enough for Mannich addition to occur.

2.3 Cyclisation Studies with a Boc Protecting Group

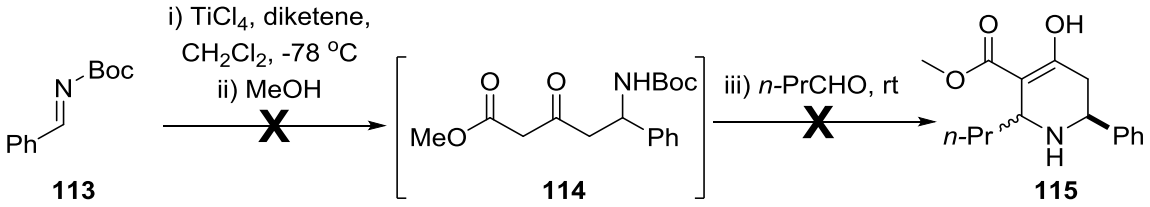
Studies began with the synthesis of *N*-Boc imine **113** in a procedure disclosed by Lam (Scheme 28).[108] Treatment of benzaldehyde with Boc-amide and sodium benzenesulfinate gave rise to sulfone **112**, which was isolated in an excellent 94% yield. Elimination of benzenesulfinic acid was achieved by refluxing **112** in Cs_2CO_3, to give *N*-Boc imine **113** in a high 89% yield.



Scheme 28. Synthesis of *N*-Boc imine **113**.

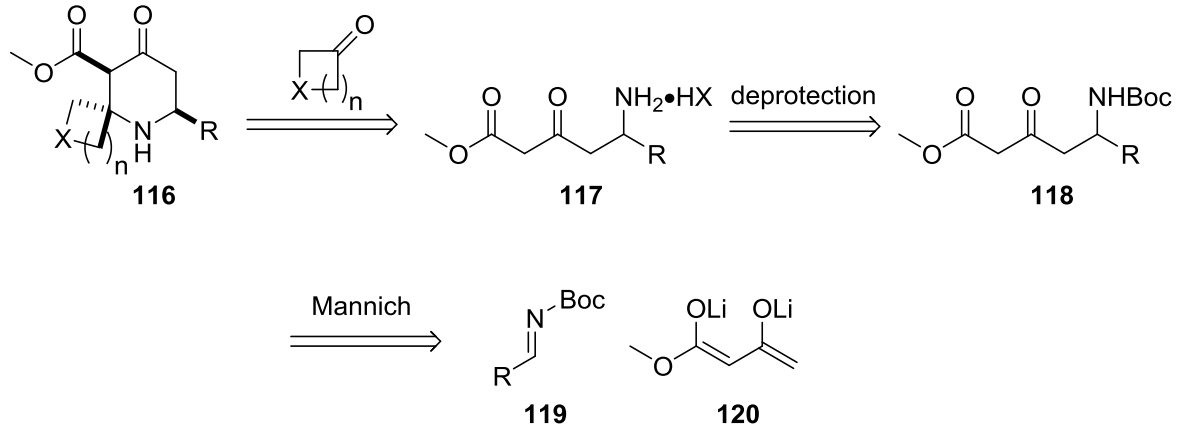
It was believed that subjecting *N*-Boc imine **113** to the original cyclisation conditions reported by Clarke with an aldehyde[95] would result in deprotection and cyclisation (Scheme 29).

However, neither piperidine **115** nor the intermediate δ-amino-β-ketoester **114** was observed, instead a complex mixture of products was obtained.



Scheme 29. One-pot conditions with an *N*-Boc imine.

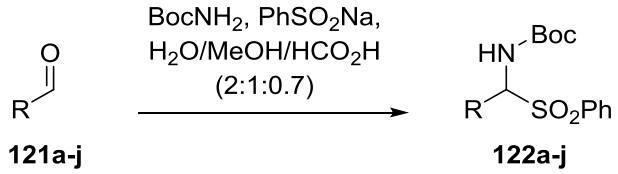
It was therefore decided to investigate, in the first instance, a stepwise approach towards the synthesis of 2-spiropiperidines. It was postulated that 2-spiropiperidine **116** could be formed from a cyclisation of salt **117** with a ketone (Scheme 30). The salt **117** would arise from deprotection of *N*-Boc-δ-amino-β-ketoester **118**, which in turn could be synthesised via a Mannich reaction between an *N*-Boc imine **119** and the Weiler dianion **120**.



Scheme 30. Retrosynthetic plan for the synthesis of 2-spiropiperidines.

Imine precursors **122a-k** were synthesised using the procedure of Lam (Scheme 31),[108] giving a wide range of aliphatic (**122a-c**), aromatic (**122d-f, j**) and heteroaromatic (**122g-i**) sulfones

in moderate to excellent yields.[109] The synthesis was trialled with protected and non-protected indoles, but issues with substrate solubility resulted in no reaction occurring.

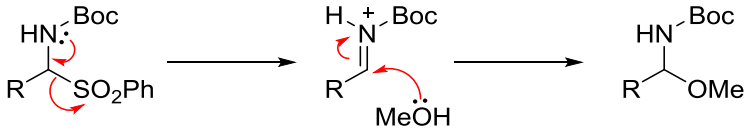


121a-j **122a-j**

122a R = Me, 81%
122b R = ^{i}Pr, 47%
122c R = *n*-Pr, 50%
122d R = Ph, 94%
122e R = 4-F-Ph, 91%
122f R = 4-OMe-Ph, 71%
122g R = 3-pyridyl, 47%
122h R = 2-methyl thiazole, 52%
122i R = *N*-methyl pyrazole, 71%
122j R = 4-CN-Ph, 94%

Scheme 31. Synthesis of *N*-Boc imine precursors **122a-j**.

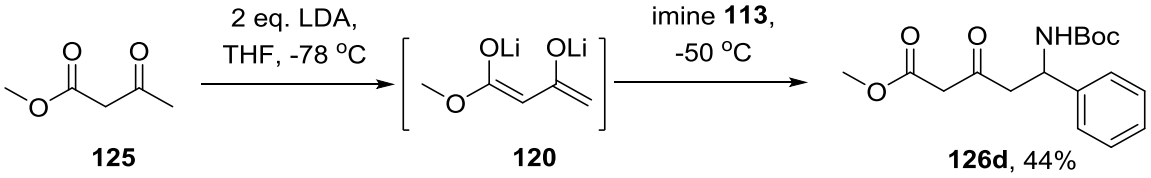
Upon analysis of *N*-Boc-sulfones **122a-k**, the desired mass peak was rarely observed in the compounds' HRMS. Instead, the mass of the methanol adduct **124** was observed. The HRMS samples were run using methanol as a solvent, and the mass observed was the addition of methanol to the imine that was supposedly forming during the HRMS procedure through elimination of benzene sulfinate (Scheme 32).



122 **123** **124**

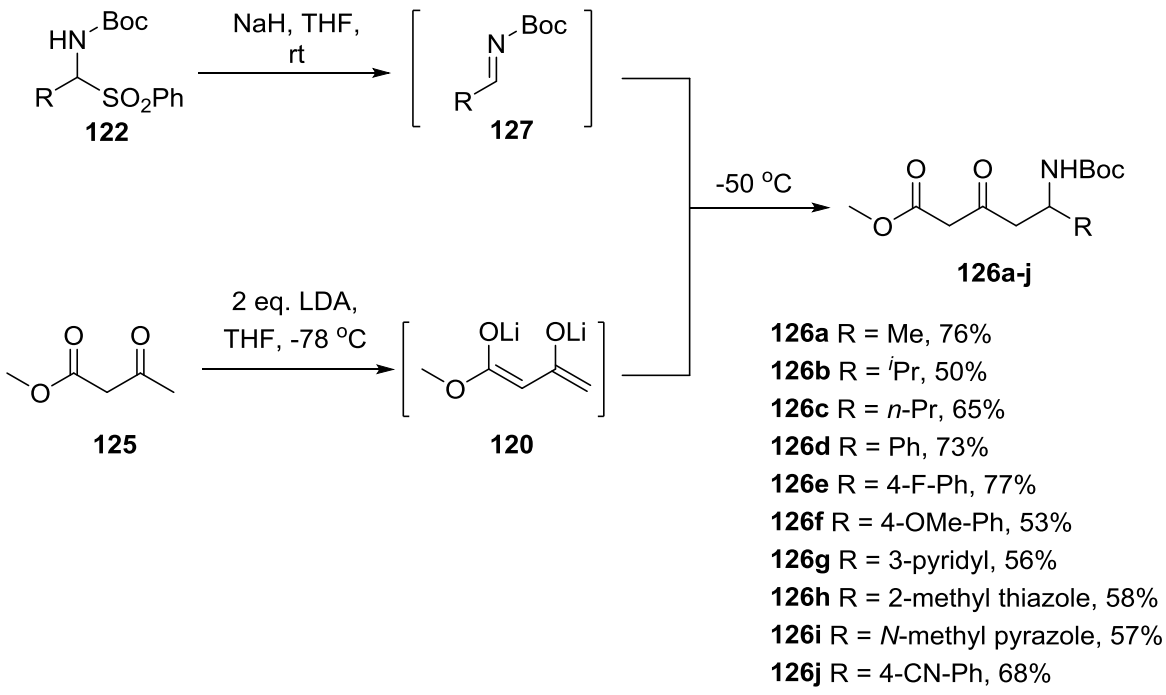
Scheme 32. Elimination of benzene sulfinate in HRMS.

Mannich product **126d** was first synthesised using the procedure of Bunch[99] with imine **113** (Scheme 33). Double deprotonation of methyl acetoacetate **125** with 2 equivalents of LDA generated the Weiler dianion **120**,[98] which, when treated with imine **113**, yielded δ-amino-β-ketoester **126d** in a moderate 44% yield. However, with multiple runs of the reaction, the experimental yield was always significantly lower than previously reported in the literature (44% yield experimental, 80% yield in literature[99]). There were also issues encountered with the isolation of aliphatic *N*-Boc imines, presumably because of their low molecular weights and assumed high volatility and instability. Consequently, it was believed that the formation of *N*-Boc imines should be performed *in situ*.



Scheme 33. Mannich addition of the Weiler dianion to imine **113**.

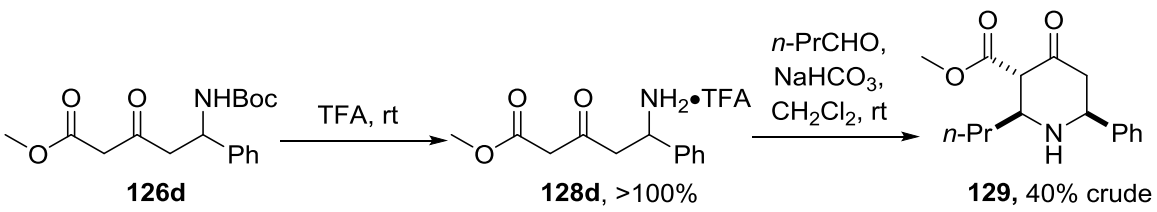
Zwierzak reported the *in situ* formation of aliphatic *N*-Boc imines from similar *N*-Boc sulfones as electrophiles for the synthesis of aminoalkylphosphonates.[110] Using a similar approach, *N*-Boc sulfones **122a-j** were treated with NaH, and after consumption of starting material by TLC, were added to the Weiler dianion **120** (Scheme 34).[109] Through this method, *N*-Boc-δ-amino-β-ketoester **126d** was isolated in a higher 73% yield than that reported above in Scheme 33, and allowed the synthesis of *N*-Boc-δ-amino-β-ketoesters **126a-j** in moderate to high yields. The robustness of the reaction was demonstrated by the synthesis of *N*-Boc-δ-amino-β-ketoesters bearing aliphatic (**126a-c**), aromatic (**126d-f, j**) and heteroaromatic (**126g-i**) substituents. The reaction was also found to be scalable with *N*-Boc-δ-amino-β-ketoesters **126e, g, h** synthesised on a 5 g scale, all with retention of yield.



Scheme 34. Synthesis of δ-amino-β-ketoesters 126a-j from N-Boc sulfones **122a-j**.

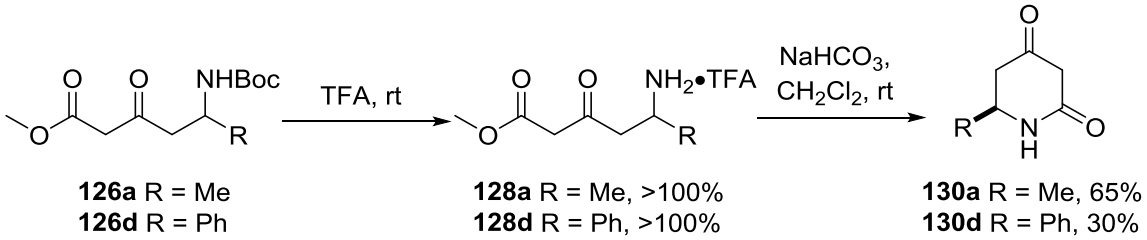
Treatment of *N*-Boc-δ-amino-β-ketoester **126d** with $TiCl_4$ and cyclohexanone unsurprisingly did not induce any desired cyclisation. It was therefore believed that deprotection of the amine had to occur for cyclisation to proceed. Davis reported the formation of 2,6-substituted piperidines by cyclisation of the TFA salt of δ-amino-β-ketoesters with an aldehyde.[111] In a slightly modified approach, deprotection of *N*-Boc-δ-amino-β-ketoester **126d** with neat TFA gave TFA salt **128d** in a quantitative yield (Scheme 35). Subjecting TFA salt **128d** to a biphase of sat. aq. $NaHCO_3$ and CH_2Cl_2 in the presence of butyraldehyde induced cyclisation give 2,6-substituted piperidine **129** in a 40% crude yield.

Piperidine **129** was not purified due to issues with column chromatography, but its formation was confirmed by ^{1}H NMR agreement with the data reported by Clarke.[95] The overall yield of the reaction was difficult to obtain, as not only was column chromatography a challenge, the mass after deprotection was >100%. Consequently, there was not a true representation for the amount of starting TFA salt **128d**. Lyophilisation was used to remove excess TFA from the salt **128d**, but instead of retrieving an anticipated solid, the outcome was a highly viscous oil that was difficult to handle and still had a yield >100%.



Scheme 35. Cyclisation from the TFA salt.

In concurrence with Davis, in the absence of an aldehyde, the free base of salt **128** underwent intramolecular lactamisation to give β-keto-δ-lactam **130** (Scheme 36).[111] Lactam **130** was not observed in the formation of piperidine **129**, suggesting that upon cracking of the salt, reaction with the aldehyde and subsequent cyclisation is faster than intramolecular lactamisation.



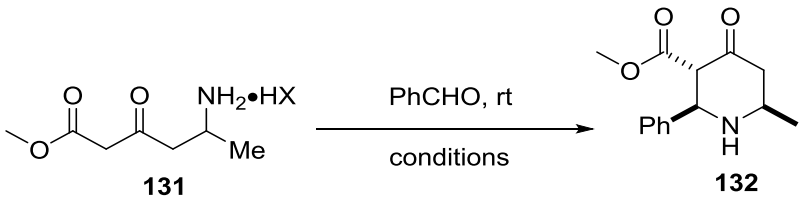
Scheme 36. Cyclisation in the absence of an aldehyde to form a lactam.

Owing to the difficulties associated with TFA salt isolation, the AcOH salt was synthesised instead using neat glacial AcOH. Cyclisations were performed using salt **131** and benzaldehyde to give known piperidine **132**[95] (Scheme 37, Table 1).

Repetition of the conditions reported by Davis[111] (Table 1, Entry 1) gave a low crude yield, and no product was isolated from the silica plug filtration. Reacting in a sat. aq. $NaHCO_3$ biphase with different solvents (Table 1, Entry 2-5) gave low crude yields and low isolated yields with moderate dr. Introducing $NaHCO_3$ as a solid instead of an aqueous solution with varied solvents (Table 1, Entry 6-8) gave much higher crude yields, however, the isolated yields were still low.

Coupled with the accompanying low isolated yields of cyclisation, lyophilisation was deemed too time consuming, so the acetic acid salt was changed to the HCl salt; formed with 4M HCl

in dioxane solution through deprotection of the *N*-Boc-δ-amino-β-ketoester. Unlike the TFA and AcOH salts, the HCl salt was isolated as a stable solid. Treatment of the HCl salt with a basic biphase (Table 1, Entry 9) gave a low isolated yield, as did the use of solid $NaHCO_3$ with THF and Et_2O (Table 1, Entry 10-11). There was however one anomalous result with solid $NaHCO_3$ and CH_2Cl_2 (Table 1, Entry 12), giving a high, reproducible 82% isolated yield and good 6:1 dr. These conditions (5 eq $NaHCO_3$ (s), 5 eq aldehyde, CH_2Cl_2 (0.3 M)) were selected as standard conditions to proceed with our studies towards the synthesis of 2-spiropiperidines.



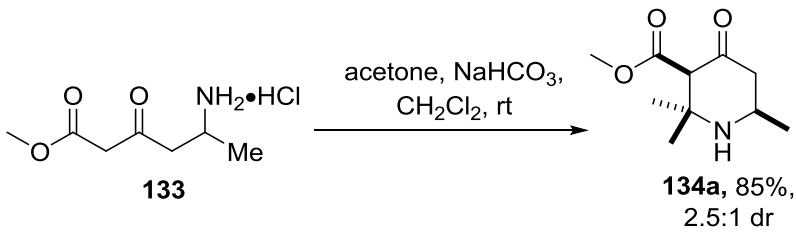
Scheme 37. Cyclisation of different acid salts **131** to give piperidine **132**.

Entry	Salt	Conditions	Solvent	Crude Yield	Isolated Yield[a]	dr[b]
1	AcOH	Sat. aq. $NaHCO_3$ quench	CH_2Cl_2	72%	n/a	5:1
2	AcOH	Sat. aq. $NaHCO_3$ (2.5 eq) biphase	Et_2O	57%	28%	n/a[b]
3	AcOH	Sat. aq. $NaHCO_3$ (2.5 eq) biphase	THF	120%	35%	4:1
4	AcOH	Sat. aq. $NaHCO_3$ (5 eq) biphase	THF	87%	22%	5:1
5	AcOH	Sat. aq. $NaHCO_3$ (5 eq) biphase	THF	68%	40%	6:1
6	AcOH	$NaHCO_3$(s)	Et_2O	199%	36%	5:1
7	AcOH	$NaHCO_3$(s)	THF	148%	43%	5:1
8	AcOH	$NaHCO_3$(s)	THF	165%	20%	3:1
9	HCl	Sat. aq. $NaHCO_3$ (5 eq) biphase	THF	188%	18%	5:1
10	HCl	$NaHCO_3$(s)	THF	106%	46%	5:1
11	HCl	$NaHCO_3$(s)	Et_2O	98%	20%	>20:1
12	HCl	$NaHCO_3$(s)	CH_2Cl_2	199%	82%	6:1

Table 1. Conditions for the cyclisation of different acid salts **131** to give piperidine **132**. [a]Isolated yields after a silica plug filtration. [b]The dr of the cyclisation was derived from the ^{1}H NMR spectrum of the crude reaction mixture.

2.4 Synthesis of 2-Spiropiperidines

For the studies towards 2-spiropiperidines, the use of symmetrical ketones was desirable as the number of possible diastereomers would be just two. Acetone was the chosen ketone for the first cyclisation. Assuming clean and complete conversion, excess acetone would be removed *in vacuo*, so subsequent purification by column chromatography would not be required. Subjection of HCl salt **133** to 5 eq of acetone and 5 eq of $NaHCO_3$ (s) in CH_2Cl_2 gave rise to 2,2,6-substituted piperidine **134a** in high isolated yield and low 2.5:1 dr (Scheme 38), with no further purification required. The reaction was repeated for the use of aromatic (**134b**) and heteroaromatic (**134c**) C-6 substituents (Figure 11), with clean conversion to the respective piperidines observed and high isolated yields.



Scheme 38. Initial cyclisation with a ketone.

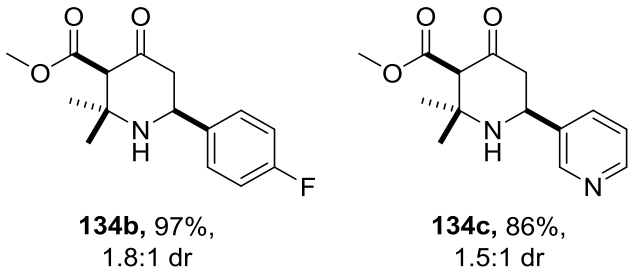
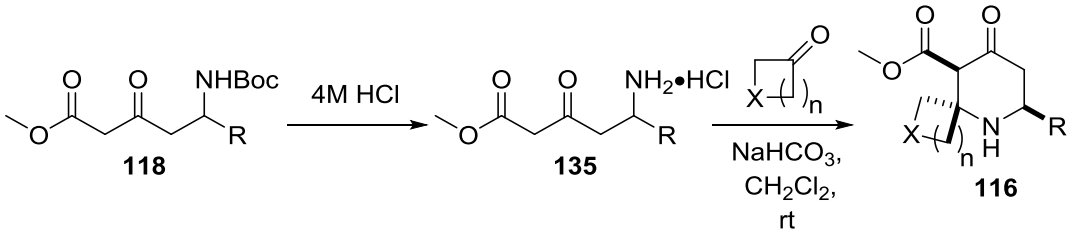


Figure 11. Examples of cyclisation with acetone.

A geminal dimethyl group had been successfully installed at C-2 with acetone, so the next choice of ketone was different sized symmetrical carbocyclic ketones. Following the general procedure for piperidine synthesis (Scheme 39), 2-spiropiperidines were synthesised in good

to high yields (Figure 12). The procedure has been demonstrated with the introduction of cyclohexyl (**135a-c**), cyclopentyl (**136**) and cyclobutyl (**137a-b**) 2-spiropiperidines.



Scheme 39. General procedure for the synthesis of 2-spiropiperidines.

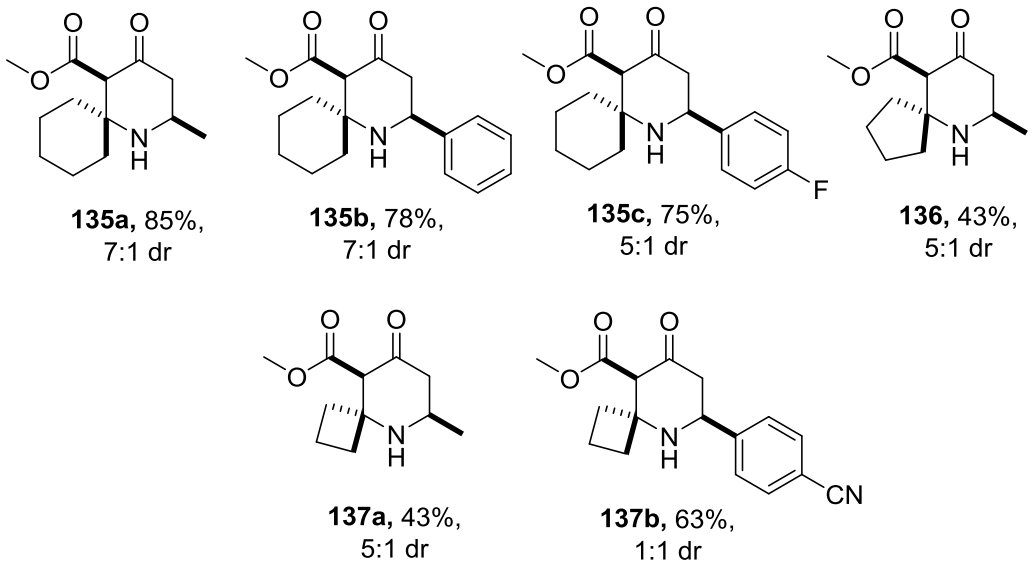


Figure 12. Examples of 2-spiropiperidines bearing carbocyclic spirocycles.

The scope of the general procedure for the synthesis of 2-spiropiperidines was expanded for the introduction of heterocyclic spirocycles (Figure 13). Pyrans (**138a-f**), thiopyrans (**139a-b**), piperidines (**140**) and oxetanes (**141**) have been introduced via this method in moderate to high yield. The reaction has also been demonstrated with aliphatic, aromatic and heteroaromatic C-6 substituents. The synthesis of 2-spiropiperidine **138d** was performed on a 1.5 g scale with retention of yield, demonstrating the robustness of the procedure.

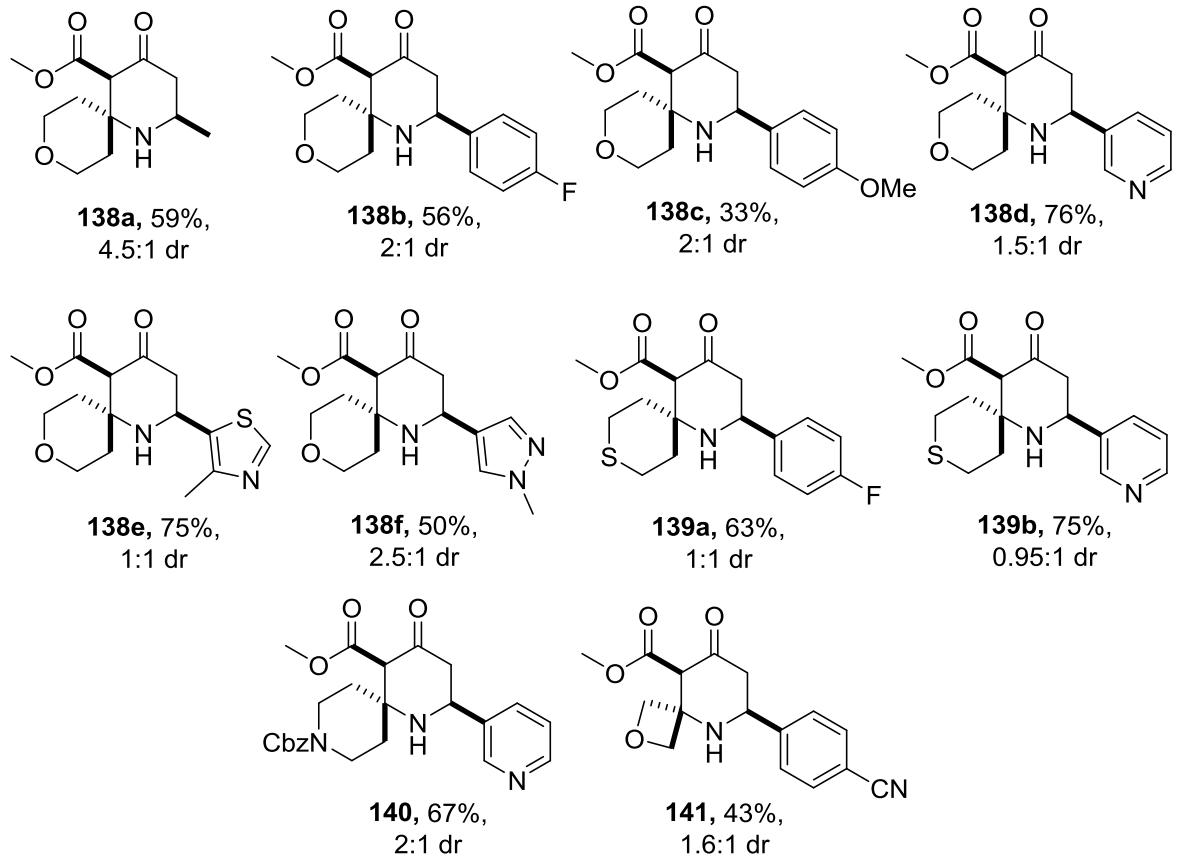


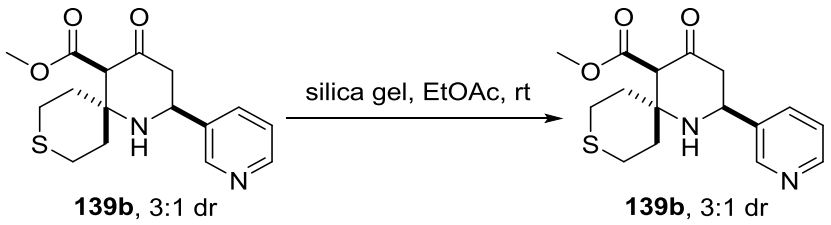
Figure 13. Examples of 2-spiropiperidines bearing a heterocyclic spirocycle.

It had been found that some of the 2-spiropiperidines were water soluble, and during aqueous work-up some product 2-spiropiperidine was lost in the water layer. Consequently, upon completion of the spirocyclisation for all 2-spiropiperidines, the reaction mixture was filtered, concentrated *in vacuo* and loaded directly onto silica gel for column chromatography. 2-Spiropiperidines **135a** and **135b** were exceptions and were purified by aqueous work-up, because of co-elution of cyclohexanone with the 2-spiropiperidine. The use of polar C-6 substituents ultimately made separation of the 2-spiropiperidine from the excess ketone easier. Many of the 2-spiropiperidines were found to be unstable to acidified silica gel during column chromatography, so triethylamine deadened silica gel was required. A plausible mechanism for decomposition would be to go via a retro-Mannich reaction, which would give rise to reactive intermediates susceptible to hydrolysis and other modes of reaction.

Unfortunately, diastereomers could not be separated by column chromatography in all cases. Only the major diastereomer is reported in this thesis. Diastereomers were separable by

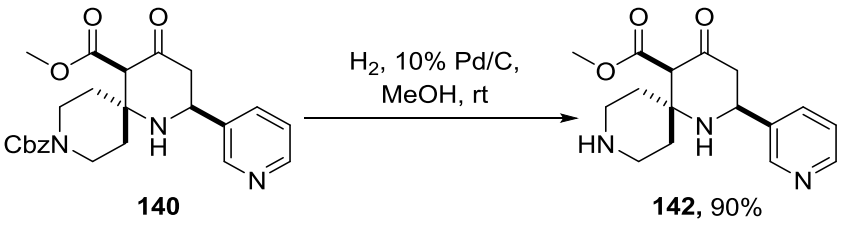
LCMS, but upon submission to purification by mass directed auto-purification (MDAP), no product was retrieved. This unfortunate result was consistent as multiple 2-spiropiperidines were subjected to MDAP for diastereomer separation, but all were unsuccessful and product was lost. Presumably, the 2-spiropiperidines were decomposing on the silica gel column during the chromatography.

Interestingly, the dr of the crude reaction mixture for 2-spiropiperidine **139b** was 0.95:1 in favour of the opposite diastereomer to that formed in the other spirocyclisations. However, after column chromatography on silica gel, the isolated 2-spiropiperidine **139b** had a dr of 3:1. To see if epimerisation was occurring on the column, spirocycle **139b** was stirred in silica gel in the chromatography eluent for 30 mins at room temperature, then filtered (Scheme 40). 2-Spiropiperidines **135a** and **138e** were treated under the same conditions, but in all three cases no change in dr was observed. It was therefore believed that preferential loss of one diastereomer on the column was occurring. Consequently, the isolated yields were lower than that was expected from the ^{1}H NMR spectrum of the crude reaction mixture.



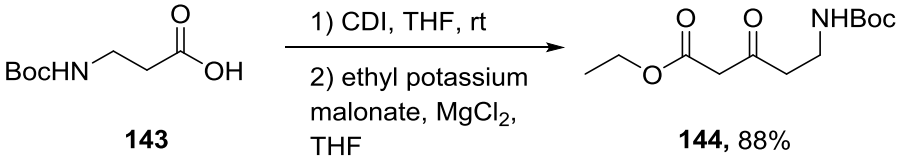
Scheme 40. Epimerisation study of 2-spiropiperidine **139b** on silica gel.

In the case of 2-spiropiperidine **140** rotamers were observed, presumably around the *N-Cbz* bond, which made ^{1}H NMR spectroscopic analysis slightly more challenging than other 2-spiropiperidines. The execution of variable temperature NMR experiments would have aided analysis, but these were not carried out. Instead, the Cbz group was removed via hydrogenation in an excellent 90% yield (Scheme 41). The reaction proceeded cleanly and complete conversion was observed, with the product 2-spiropiperidine **142** not requiring column chromatography. This was fortunate, as the 2-spiropiperidine **142** was very polar and would have required the use of reverse-phase column chromatography.



Scheme 41. Cbz removal by hydrogenation.

All 2-spiropiperidines had been synthesised with substituents at the C-6 position. For the 2-spiropiperidine to be unsubstituted at C-6, the respective unsubstituted *N*-Boc sulfone would need to be synthesised. The *N*-Boc sulfone formed with formaldehyde had been reported,[112] but was not used for our studies. Instead, a small amount of *N*-Boc-δ-amino-δ-ketoester **144** was provided by Dr William Unsworth, synthesised from the β-amino acid **143** (Scheme 42).



Scheme 42. Synthesis of the unsubstituted δ-amino-δ-ketoester **144**.

Subjecting δ-amino-δ-ketoester **144** to the standard spirocyclisation conditions (Scheme 39) of 4 M HCl followed by treatment with a ketone and $NaHCO_3$ gave rise to C-6 unsubstituted 2,2-dimethyl piperidine **145** and 2-spiropiperidine **146** (Figure 14).

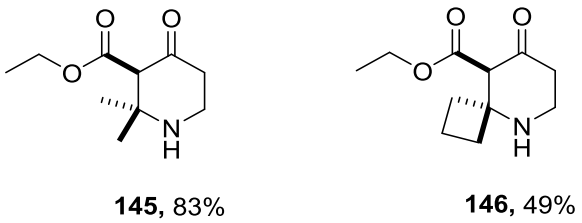


Figure 14. Examples of C-6 unsubstituted piperidines.

2.5 Determination of the Stereochemistry

It had initially been assumed that the stereochemistry of the major diastereomer was replicant of the results reported by Clarke for 2,6-di-substituted piperidines, positioning the C-3 ester and the C-6 substituent in an *anti* relationship.[95] Upon analysis of the ^{1}H NMR, the correct relative stereochemistry of the major diastereomer was confirmed to place the C-3 ester and the C-6 substituent in a *syn* relationship. The ^{1}H NMR spectrum of spirocycle **138a** is shown in Figure 15, with expansions of two key regions of the spectrum shown in Figure 16.

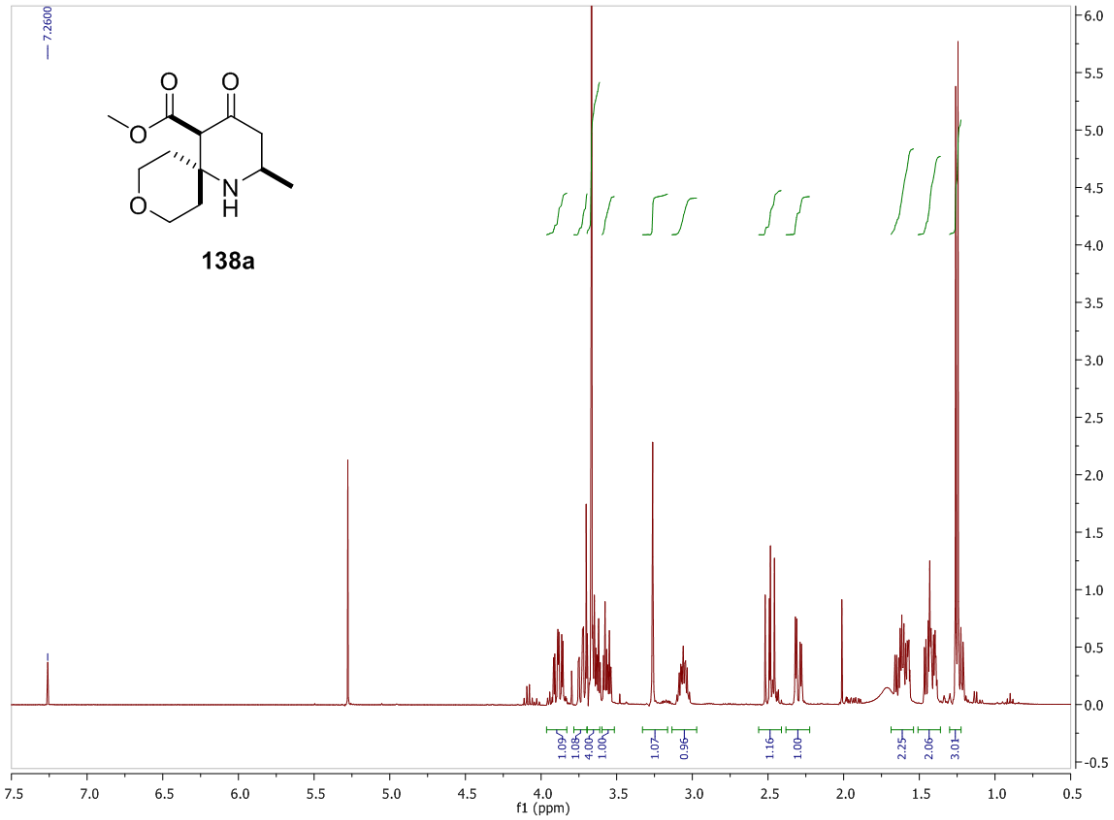
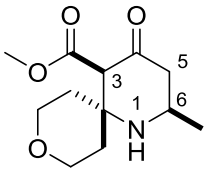


Figure 15. ^{1}H NMR spectrum of spirocycle **138a**.

In the expansion of 3.40-2.90 ppm, two protons H-3 and H-6 (Figure 16, A and B) are observed, and in the expansion of 2.65-2.15 ppm, two protons H-5_{ax} and H-5_{eq} (Figure 16, C and D) are observed.

The doublet at δ 3.26 ppm for H-3 has a ^{4}J coupling of 1.0 Hz indicating a 'W-coupling' (Figure 16, A). The ddd at δ 2.30 ppm also exhibits a ^{4}J coupling of 1.0 Hz, indicating an equatorial

proton at C-5 and thus identifying H-5_{eq} (Figure 16, D). Also in the ddd at δ 2.30 ppm, a ^{2}J geminal coupling to H-5_{ax} of 13.5 Hz is observed, as well as a ^{3}J coupling of 3.7 Hz indicating an axial-equatorial coupling with H-6. The H-5_{ax} was confirmed by the ^{2}J geminal coupling of 13.5 Hz with H-5_{eq}, and the axial-axial ^{3}J coupling of 10.5 Hz with H-6 (Figure 16, C). The dqd at δ 3.06 ppm has a ^{3}J coupling of 3.7 Hz confirming the axial-equatorial coupling with H-5_{eq}, and a ^{3}J coupling of 10.5 Hz confirming the axial-axial coupling with H-5_{ax} (Figure 16, B). With these couplings, it was deduced that the major diastereomer had a *syn* relationship between C-3 and C-6.



138a

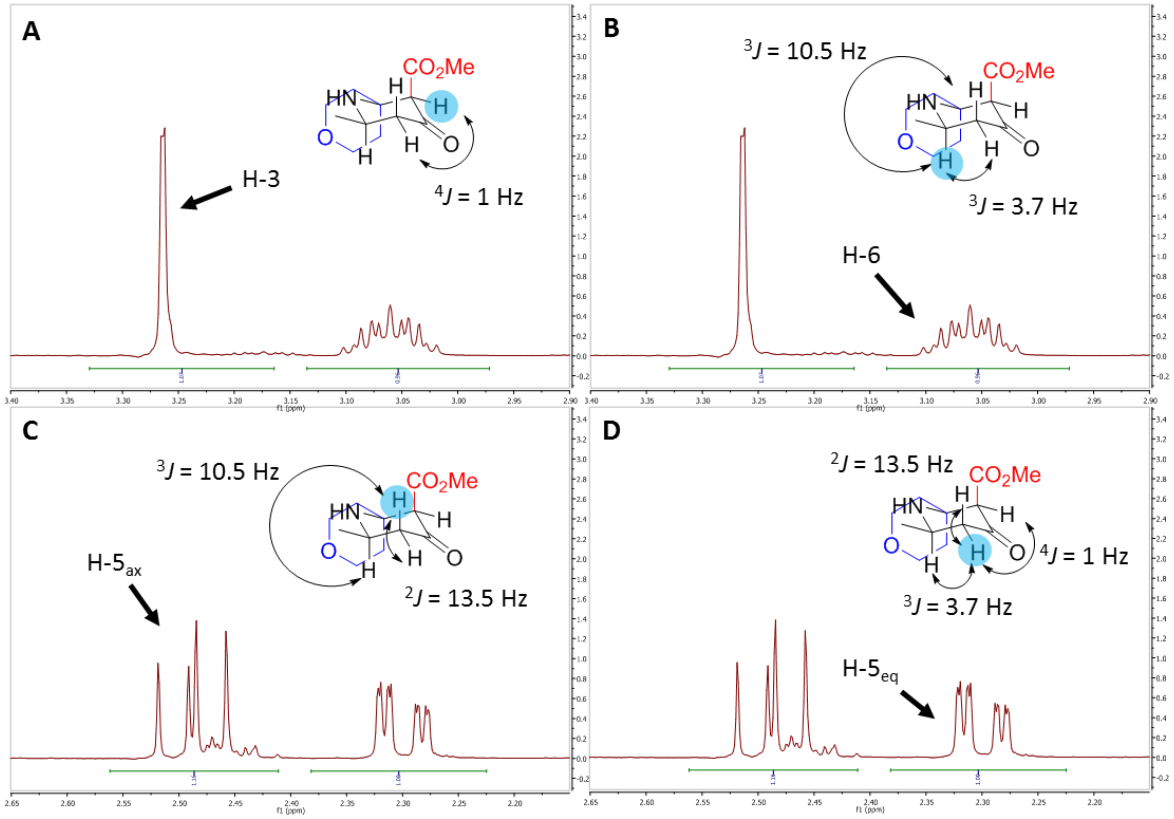


Figure 16. Expansions of the ^{1}H NMR spectrum of spirocycle **138a**.

The relative stereochemistry of the major diastereomer from spirocyclisation was later confirmed with a crystal structure of spirocycle **138b** (Figure 17). Interestingly, the C-3/C-6 *syn* relationship places the ester in a seemingly unfavourable axial configuration. Presumably this is to avoid a destabilising steric interaction with the hydrogens on the adjacent spirocyclic ring. The wide range of diastereomeric ratios obtained from the cyclisation procedure was also believed to be a consequence of the 2-spiropiperidines undergoing a retro-Mannich reaction. It was then believed that during the room temperature reaction, the system was slowly equilibrating, consequently giving a mixture of diastereomers. The electronics of the C-6 substituent also appeared to be a key factor, with the methyl substitutent giving much greater diastereomeric ratios than the aromatic C-6 subsitutents.

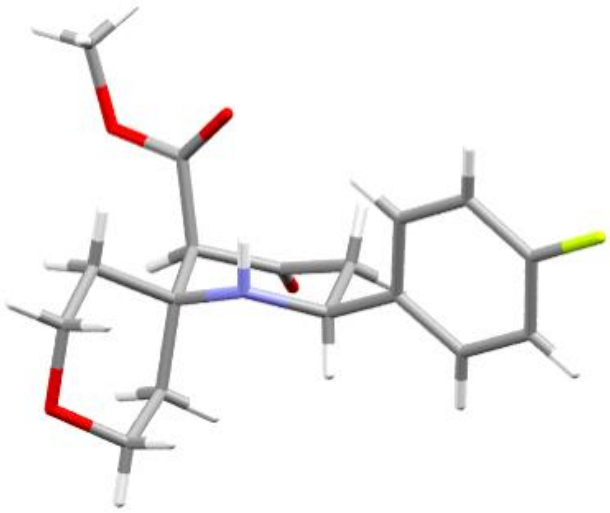


Figure 17. Crystal structure of the major diastereomer of spirocycle **138b**.

2.6 PMI Analysis

A library of novel compounds consisting of 18 2-spiropiperidines and four 2,2-dimethyl piperidines had been constructed via a novel stepwise procedure. It was important to be able to observe the relative three-dimensionality of the 2-spiropiperidines, as an original aim of the project was to synthesise three-dimensional compounds. The 22 compounds were plotted onto a PMI plot using the LLAMA software,[14] with the 75% line from the ZINC database plot still shown for reference (Figure 18). It can be seen that 20 out of 22 2-spiropiperidines

lay on or to the right of the ZINC 75% line, with many examples pushing towards the area of relatively unpopulated three-dimensional chemical space.

Unsurprisingly the 2-spiropiperidines bearing the aliphatic methyl group at C-6 were amongst the most three-dimensional. 2,2-Dimethyl piperidine **134a** (Figure 18, A) was the best performing compound, reaching the spherical region of the PMI plot. The other stand out compound was 2-spiropiperidine **137a** with a cyclobutane ring as the spirocycle (Figure 18, B). Of note is 2-spiropiperidine **135b** with a phenyl ring at C-6 (Figure 18, C), which was more three-dimensional than similar sp^2 C-6 substituents. 2-Spiropiperidine **140** was understandably the worst performer (Figure 18, D), containing an aromatic C-6 substitutent and a Cbz protecting group. The negative impact of the Cbz protecting group was recognised by the performance of the Cbz deprotected 2-spiropiperidine **142** (Figure 18, E).

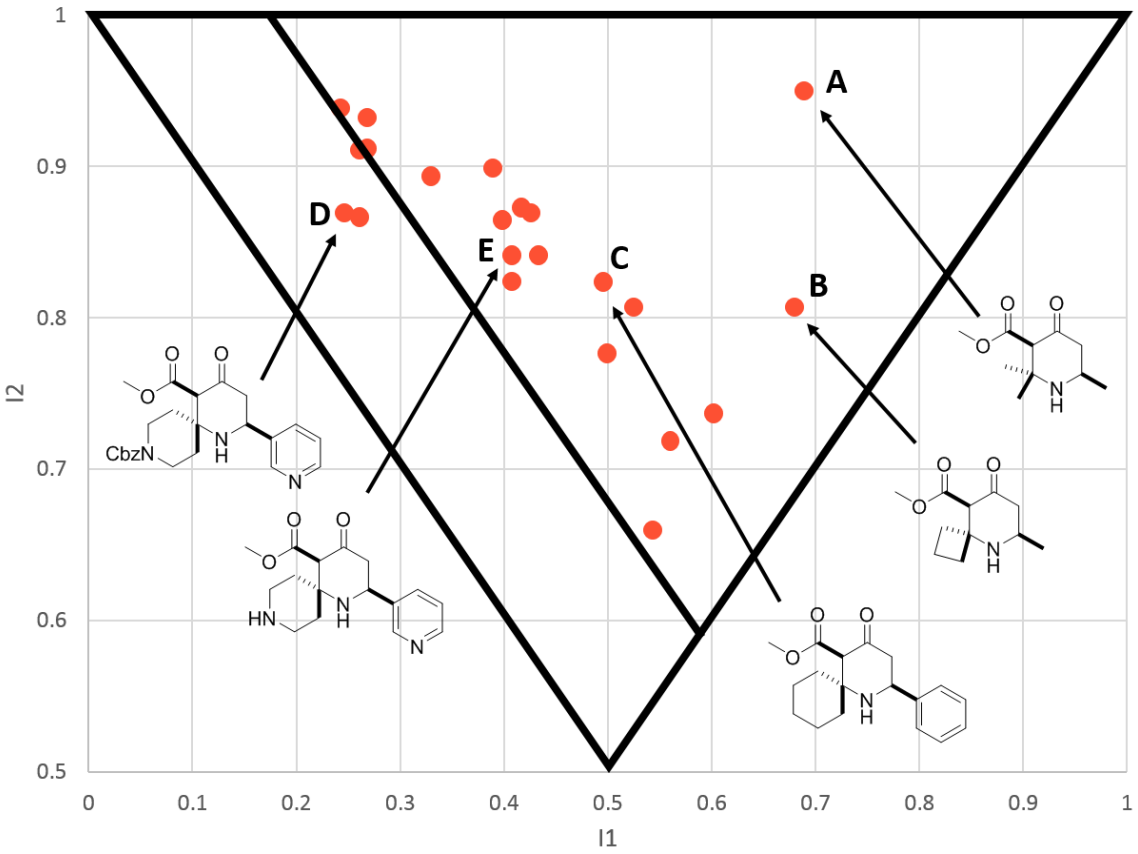


Figure 18. PMI plot for the 2-spiropiperidines.

The outcome of the PMI plot was promising, with the majority of the 2-spiropiperidines occupying the underrepresented region of chemical space. The next aim of the project was to utilise the 2-spiropiperidines as scaffolds for a fragment based drug discovery program. Iterations would be made to the 2-spiropiperidines, so it was interesting to see if the relative three-dimensionality of the functionalised 2-spiropiperidines was retained.

3. Functionalisations

With a robust procedure in place for the synthesis of 2-spiropiperidines, and with the knowledge that they occupy the desired region of chemical space, attention turned to exploring their versatility for elaboration. The 2-spiropiperidines were identified as useful scaffolds for a fragment drug discovery programme. Whilst the C-6 substituents and the spirocycles could be readily varied, the 2-spiropiperidines also possessed three handles that could be used for further functionalisations; an ester, a ketone and an amine (Figure 19).

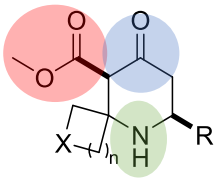


Figure 19. Highlighted handles for 2-spiropiperidine elaboration.

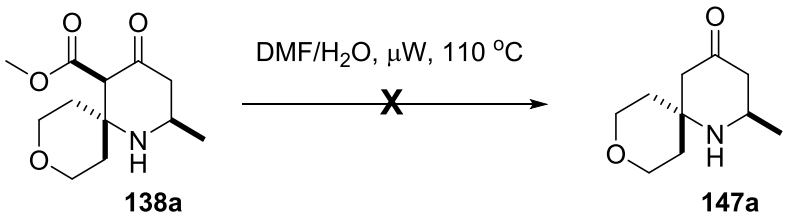
The functionalisations were deemed relevant to improve the lead-likeness of the 2-spiropiperidines. Planned functionalisations included the manipulation of the C-3 ester, which is an undesirable functional group to be present for screening,[113] to give either decarboxylated 2-spiropiperidines or amidated 2-spiropiperidines. Methods for the introduction of fluorine at C-3 and C-4 were trialled to improve hydrophilicity and bioavailability.[114] Derivatisation of the ketone via reductive methods would give a better Fsp^3, which was therefore assumed that the respective three-dimensionality would also improve. Manipulation of the amine or the reduced ketone would introduce new vectors to allow further exploration of the underrepresented region of chemical space.

Consequently, a small library of structurally interesting, medicinally relevant 2-spiropiperidines was constructed with the implication for use in a fragment based drug discovery programme.

3.1 Decarboxylation

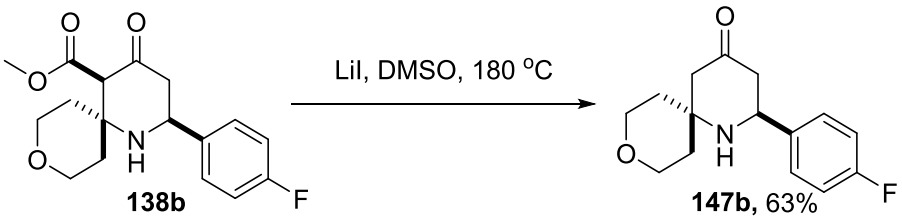
Aliphatic esters have been flagged as an undesirable functional group to be present in clinical candidates.[14,113] The electrophilic ester has the potential to be unintentionally reactive towards proteins and is susceptible to decomposition by solvolysis or hydrolysis. This can consequently lead to false-positives that can plague screening efforts.[115] It was therefore deemed necessary to be able to manipulate the methyl ester of the 2-spiropiperidine.

Investigations began with the decarboxylation of 2-spiropiperidine **138a** through microwave irradiation, using known conditions developed in the group's tetrahydropyran work (Scheme 43).[116] Unfortunately, this led to decomposition of starting material and no decarboxylation was observed from the ^{1}H NMR spectrum of the crude reaction mixture.



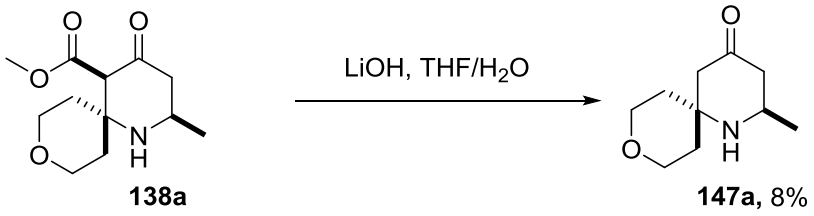
Scheme 43. Decarboxylation using microwaves.

Attention was then turned to conditions for Krapcho decarboxylation of 2-spiropiperidine **138b** using LiI in DMSO at elevated temperatures (Scheme 44).[117,118] As the product was suspected to have a high water solubility, the DMSO was subsequently removed via kugelrohr distillation. Purification by chromatography gave the decarboxylated product **147b** in a pleasing 63% yield.



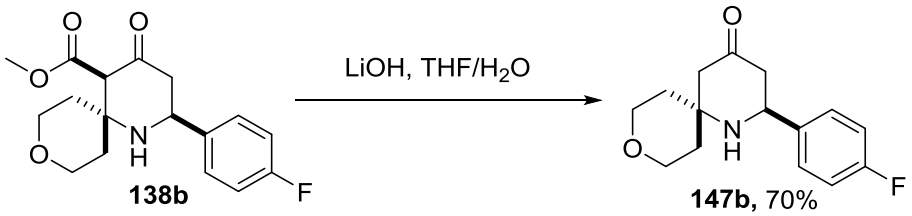
Scheme 44. Decarboxylation with Krapcho conditions.

However, it was quickly determined that the reaction was capricious and the yield for the decarboxylation of 2-spiropiperidine **138b** was found to be irreproducible. Consequently, a new approach for the decarboxylation had to be made. A base-mediated decarboxylation with LiOH in a THF/H_2O biphase was initially trialled with 2-spiropiperidine **138a**,[119] however, the reaction gave a disappointing 8% yield (Scheme 45). It was believed that the product was lost on work-up at the end of the reaction because of the high water solubility of the resultant 2-spiropiperidine.



Scheme 45. Base-mediated decarboxylation of 2-spiropiperidine **138a**.

The partition coefficient (AlogP) of a molecule is a measure of its solubility in a water/*n*-octanol system.[120] A low AlogP value corresponds to a hydrophilic molecule, and conversely a high AlogP value corresponds to a lipophilic molecule. The calculated AlogP value for the decarboxylated 2-spiropiperidine **147a** was determined to be 0.1.[14,47] Compared to the calculated AlogP value of 0.35 for THF which is relatively water miscible, it is understandable why the product may have been lost during the aqueous work-up. Consequently, the C-6 substituent was changed to a 4-fluorophenyl group **138b**, which increased the lipophilicity of the resultant product **147b** with an AlogP value of 1.1.[14,47] Pleasingly the decarboxylated 2-spiropiperidine **147b** was isolated in a 70% yield (Scheme 46).



Scheme 46. Base-mediated decarboxylation of 2-spiropiperidine **138b**.

The new conditions were found to be reproducible as well as higher yielding, and three more examples were synthesized (Figure 20), demonstrating the robustness of the decarboxylation procedure. In all cases, complete decarboxylation occurred with no carboxylic acid formation observed.

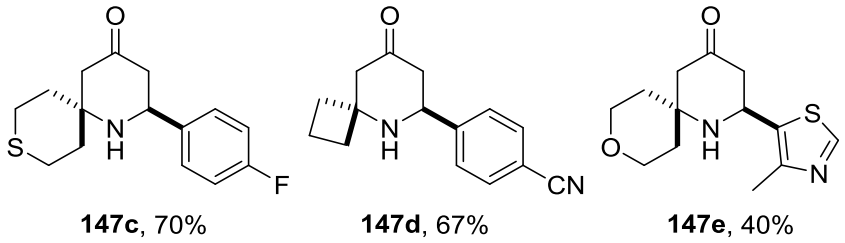
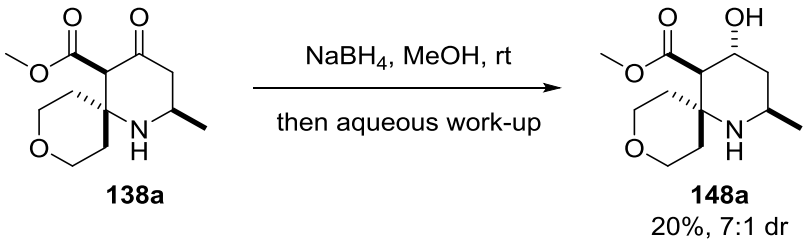


Figure 20. Substrate scope for the base-mediated decarboxylation.

3.2 Ketone Reduction

The ketone was viewed as a reactive handle to functionalise. Reactions such as reductions and additions would introduce a new sp^3 centre. This in turn would introduce new vectors to explore three-dimensional chemical space and consequently give rise to molecules with greater three-dimensionality.

Reduction of ketone **138a** to the alcohol **148a** with $NaBH_4$ delivered a disappointing 20% yield of alcohol **148a** after work-up and column chromatography (Scheme 47). It was believed that the low yield was a consequence of an aqueous work-up. It had already been determined that the 2-spiropiperidines were relatively water soluble, and the work-up procedure also involved an acidic wash giving potential for salt formation. It was therefore unsurprising to observe low crude and isolated yields.



Scheme 47. Ketone reduction with $NaBH_4$ and aqueous work-up.

Despite the low yield of reduction, crystallographic data was obtained. The crystal structure confirmed the relative stereochemistry of alcohol **148a**, placing the alcohol *anti* to the C-3 ester. Despite showing the enantiomer, the crystal confirms the relative stereochemistry originally deduced. It is interesting to note the crystal structure is a salt with a Cl^-:HCO_3^- ratio of 88:12. The HCl salt must arise either as a consequence of the acidic work-up, or the presence of HCl in a potentially dated bottle of $CDCl_3$, however the carbonate salt would have to be a consequence of the original spirocyclisation. This could explain the difficulties associated with the purification of the 2-spiropiperidines and their high water solubility, though further investigation was required.

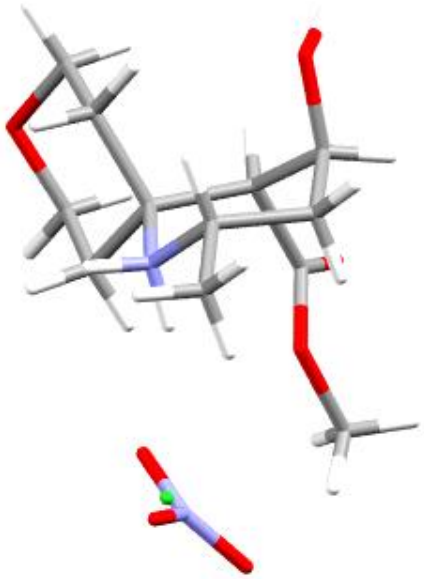
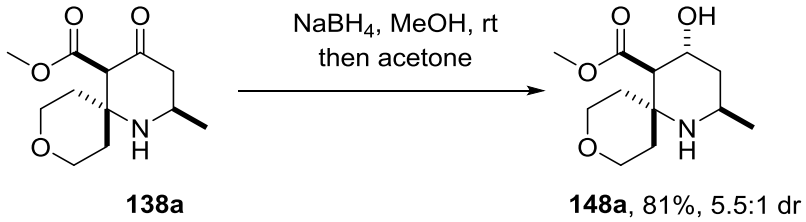


Figure 21. Crystal structure of alcohol **148a**.

It was therefore deemed necessary to avoid an aqueous work-up after the reduction of the ketone. Upon quenching the excess $NaBH_4$ with acetone, the reaction mixture was concentrated *in vacuo* and purified by column chromatography to give **148a** in a high 81% yield (Scheme 48).



Scheme 48. Ketone reduction without aqueous work-up.

This method proved successful, and the much-improved yield demonstrated the importance of avoiding aqueous work-ups for this chemistry. Through this method, aliphatic, aromatic and heteroaromatic C-6 substituents furnished alcohols **148a-d** in good to high yields with good selectivities (Figure 22). The diastereomeric ratio of products of **148c** could not be determined from both the crude ^{1}H NMR spectrum and the purified ^{1}H NMR spectrum.

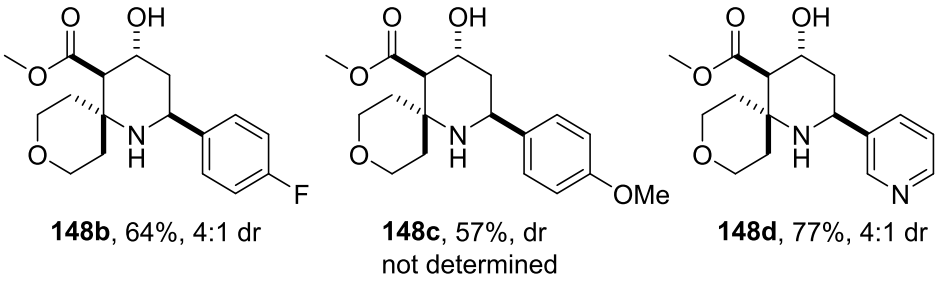
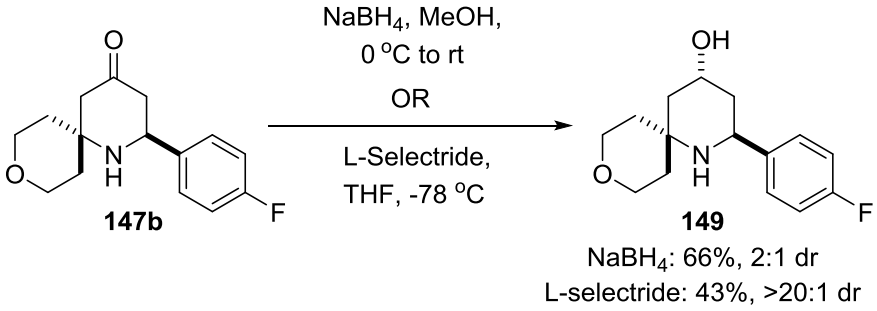


Figure 22. Substrate scope for ketone reduction.

The reduction of decarboxylated 2-spiropiperidine **147b** was also achieved (Scheme 49). Both $NaBH_4$ and L-Selectride were used for the reduction, and both delivered the same major diastereomer. Analysis of the crystal structure of alcohol **149** (Figure 23) showed that axial delivery of the hydride would involve an unfavourable steric interaction with the spirocycle.

With $NaBH_4$, a small reducing agent, a 2:1 ratio of diastereomers was observed, showing that axial delivery of the hydride was still occurring. Unsurprisingly, with the bulky L-Selectride, greater selectivity of >20:1 was observed for equatorial hydride delivery.



Scheme 49. Reduction of ketone **147b** with different reducing agents.

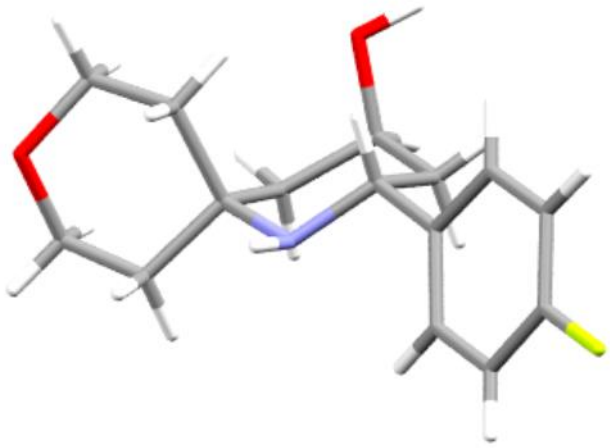


Figure 23. Crystal structure of alcohol **149**.

3.3 Amidation

The C-3 ester provided an extra vector to explore three-dimensional chemical space, so the subsequent removal by decarboxylation was not ideal. Manipulation of the ester group to an amide was therefore deemed an appropriate transformation. Amide bonds play a crucial role in life as they are the backbone of proteins, and are also found in a large number of pharmacologically active compounds.[121] According to a survey of drug candidates, 67%

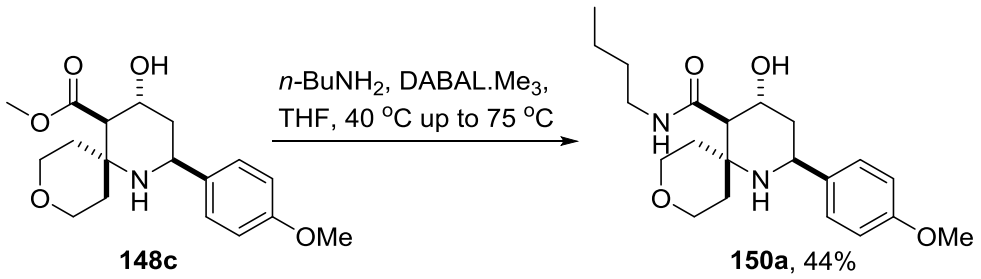
possess at least one amide bond.[122] Typical procedures for amide couplings via the carboxylic acid were not viable as hydrolysis of the ester resulted in decarboxylation. It was therefore concluded that a procedure for direct amidation of the ester was required.

Investigations began with methods for activation of the ester, first by a lanthanum triflate catalysed amidation in solvent-free conditions.[123] The procedure demonstrates the direct amidation of ethyl esters with primary and secondary amines, including the amidation of an unprotected piperidinyl ethyl ester. However, when the conditions were applied to the 2-spiropiperidines, no reactivity was observed and unreacted starting material was re-isolated.

Aluminium trichloride was utilised to directly amidate quinolone ethyl esters in a procedure by Schwaebe.[124] Quinolone esters exhibit a β-ketoester system like the 2-spiropiperidine scaffolds, and it was believed that similar amidation results would be observed. Unfortunately, no reactivity was observed when the 2-spiropiperidine scaffolds were treated under the same conditions. The industrially favoured guanidine derived 1,5,7-triazabicyclodecene (TBD), which has also been shown to efficiently directly amidate esters,[125] also yielded no reaction.

With no success in the activation of the ester, a method for increasing the nucleophilicity of the amine by deprotonation was trialled. The DABCO-trimethylaluminium complex (DABAL.Me_3) developed by Woodward has been reported to directly amidate esters including β-ketoester systems.[126] However, as with previous at attempts at the direct amidation, upon treatment of the 2-spiroperidines to the conditions of Woodward, no amidation was observed.

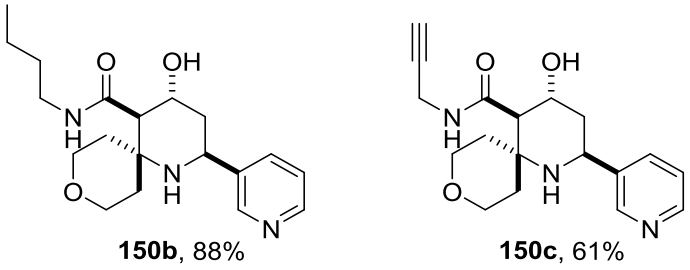
It was believed that the lack of reactivity arose from the steric hindrance of the ester and the presence of the β-ketoester system. Upon reduction of the ketone, 2-spiropiperidine **148c** was treated with TBD and butylamine, however still no reactivity was observed. This was an unsurprising result as the reaction required the formation of a hindered intermediate on an already hindered system. The complex DABAL.Me_3 was revisited, and in the presence of butylamine with 2-spiropiperidine **148c**, amide formation was achieved to give amide **150a** in a moderate 44% yield (Scheme 50).



148c **150a**, 44%

Scheme 50. Procedure for amidations with DABAL.Me_3.

Using this method, two further amidations were performed on 2-spiropiperidine **148d** (Figure 24). The use of propargylamine to give amide **150c** introduces a new handle to the scaffold. This could be utilised for a palladium-mediated coupling such as a Sonogashira coupling[127] or it could be used for Click (azide-alkyne) chemistry.[128]

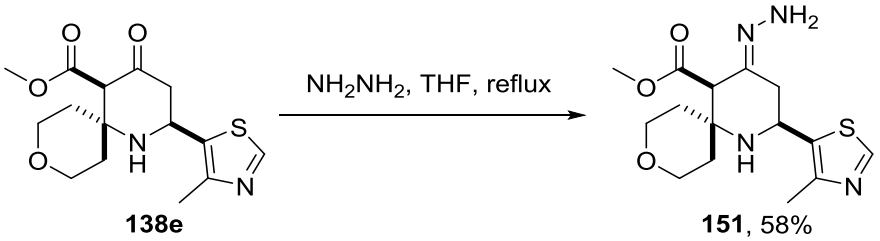


150b, 88% **150c**, 61%

Figure 24. Examples of amidation on 2-spiropiperidine **148d**.

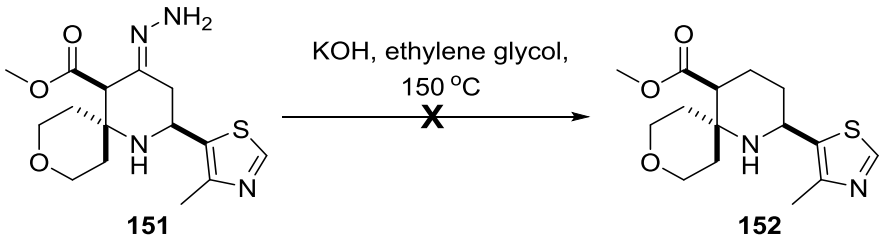
3.4 Hydrazone Formation

Retaining focus on the ester handle, formation of a hydrazide was an appealing transformation. Whilst installing an amide bond which is known to be desirable, it also introduces an amine, which is an extra hydrogen bond donor/acceptor and can be used for further manipulation. Following literature precedent,[129] 2-spiropiperidine **138e** was refluxed with hydrazine in THF, however, no hydrazide formation was observed (Scheme 51). Instead, the hydrazine reacted with the ketone, giving the resultant hydrazone **151**.



Scheme 51. Hydrazone formation.

The formation of the hydrazone **151** over the hydrazide was not regarded as a disappointing outcome, as the hydrazone could be used for further functionalisation. Hydrazone **151** was heated in KOH under Wolff-Kishner reduction conditions to reduce to the alkane **152**, but unfortunately this resulted in complete decomposition of starting material (Scheme 52).[130]



Scheme 52. Attempted Wolff-Kishner reduction of hydrazone **151**.

The utility of the hydrazone **151** could be further probed by converting to the vinyl halide[130] or by performing addition reactions such as allylation,[131] however neither transformation was attempted in the substrate scope.

3.5 *N*-Functionalisation

Having had early success manipulating the ketone and ester handles, the reactivity of the amine was next probed. Without substitution, the amine can act as a hydrogen bond donor for interactions with other molecules. However, manipulation of the amine can introduce new vectors to further explore the underrepresented region of chemical space.

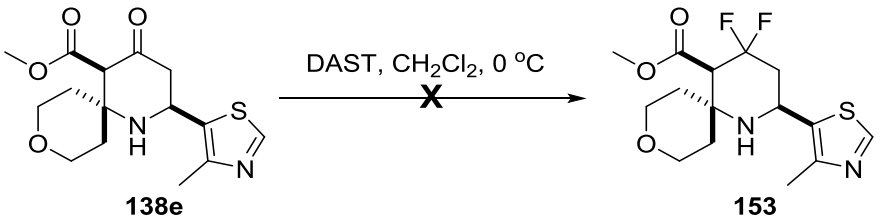
2-Spiropiperidine **138a** was first subjected to conditions for carbamate formation. Treatment of the 2-spiropiperidine with Boc_2O and DMAP for *N*-Boc formation,[132] and methyl chloroformate and K_2CO_3 for methyl carbamate synthesis[133] resulted in no carbamate formation in both cases. Acetylation by treatment of the 2-spiropiperidine with acetyl chloride and triethylamine[134] was also unsuccessful. Formation of a sulfonamide by tosylation with triethylamine and tosyl chloride,[135] and by mesylation with triethylamine and mesyl chloride[136] also yielded no desired product.

It was disappointing that none of the reactions showed any conversion to the respective products. The piperidine nitrogen is sterically encumbered by the adjacent C-2 spirocycle and C-6 substituent, making it difficult to react to form a planar bond in the cases of the reactions trialled. The lack of reactivity may also be associated with the results obtained from the reduction of the ketone, showing that the 2-spiropiperidine may be existing as a salt. Further investigations were required to determine whether the 2-spiropiperidines exist a salt, and for time constraints, further functionalization attempts of the piperidine nitrogen were consequently stopped.

3.6 Fluorination

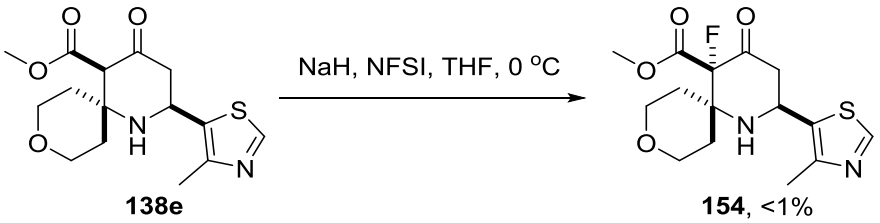
The desire for the incorporation of fluorine into organic molecules is growing in medicinal chemistry.[137] Metabolic stability of the molecule is increased by the replacement of an oxidisable C-H bond with a C-F bond, and the binding affinity of the respective molecule has been shown to increase.[114] The incorporation of fluorine also increases hydrophilicity and improves bioavailability.[114] Therefore attempts were made to incorporate fluorine into the 2-spiropiperidine scaffolds. This proved to be a challenging transformation.

Introduction of a geminal difluoride group through treatment of 2-spiropiperidine **138e** with diethylaminosulfur trifluoride (DAST) was unsuccessful, and did not yield fluorinated piperidine **153** (Scheme 53).[138] It was believed the DAST reagent was too harsh, as only decomposition of 2-spiropiperidine **138e** was observed. Upon decarboxylation and treatment with DAST, fluorinated 2-spiropiperidine was still not formed.



Scheme 53. DAST fluorination to access a geminal difluoro-alkane.

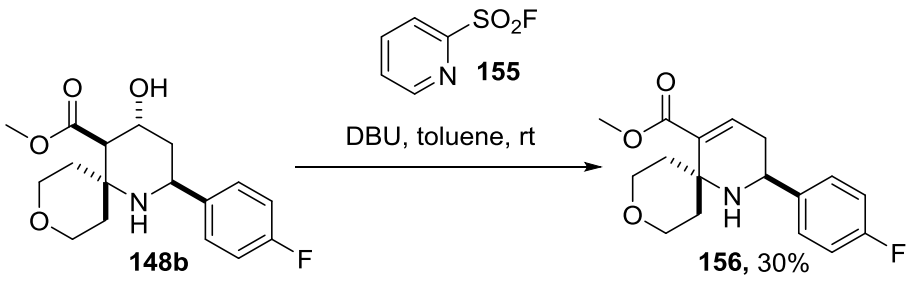
It was postulated that the acidic C-3 position could be manipulated through deprotonation with NaH and treatment with *N*-fluorobenzenesulfonimide (NFSI);[139] a mild electrophilic fluorinating agent. Upon submission of 2-spiropiperidine **138e** to NaH and NFSI, C-3 fluorination was observed by LCMS and crude NMR spectroscopy to give fluoride **154** (Scheme 54). The crude residue was purified by mass directed autopurification (MDAP), however, the yield of recovery was too low to obtain characterisation. The reaction was found to be capricious and repetition of the reaction was unsuccessful, which was believed to be a consequence of the steric hindrance at C-3. In similar tetrahydropyran systems, it was found that only addition to small electrophiles like MeI and allyl bromide resulted in C-3 functionalisation.[116]



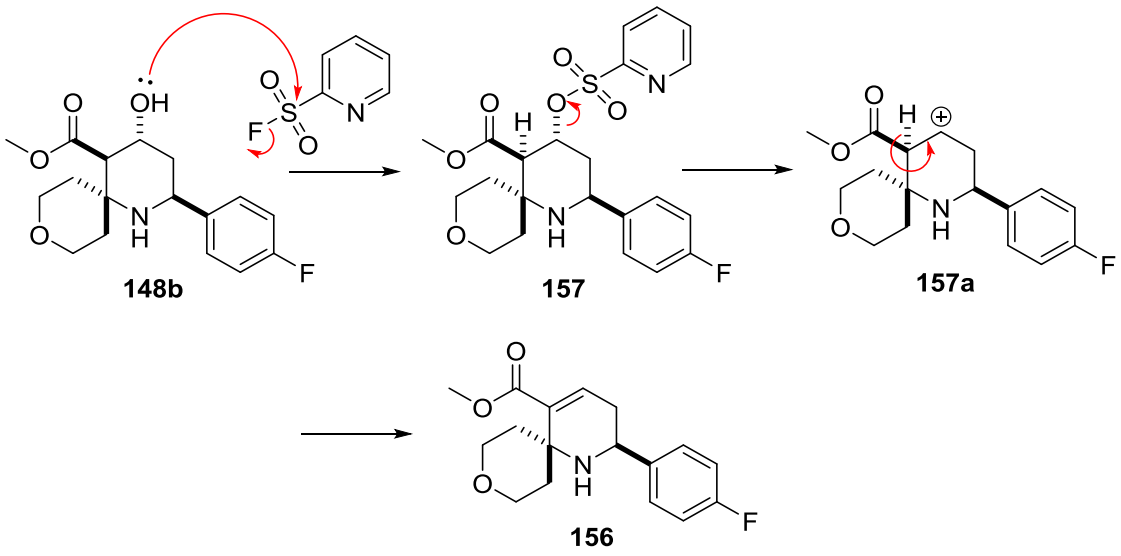
Scheme 54. Electrophilic fluorination with NFSI at C-3.

Manipulation of the 2-spiropiperidine with the β-ketoester was proving challenging, so the fluorination strategy was altered to proceed through the alcohol. Displacement of the alcohol with a fluoride would give rise to a 4-fluoro-2-spiropiperidine. Alcohol **148b** was subjected to three different fluorinating agents. With DAST[140] and XtalFluor-E (the BF_4^- salt of DAST),[141] as the sources of fluorine, no reactivity was observed and starting alcohol **148b** was re-isolated. With PyFluor **155**,[142] no fluorination occurred as with the other two reagents, however, α,β-

unsaturated ester **156** was isolated from the reaction (Scheme 55). Presumably, reactive intermediate **157** undergoes elimination to form the more stable α,β-unsaturated ester **156** (Scheme 56).

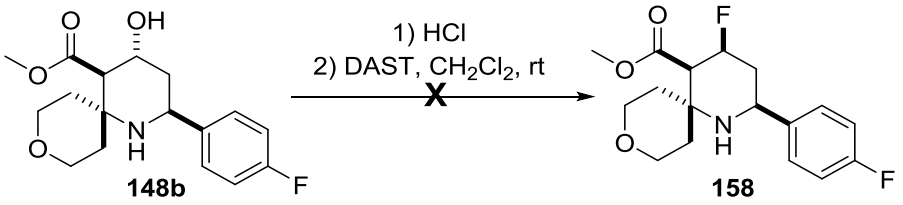


Scheme 55. Alcohol elimination with PyFluor.



Scheme 56. Plausible mechanism for alcohol elimination.

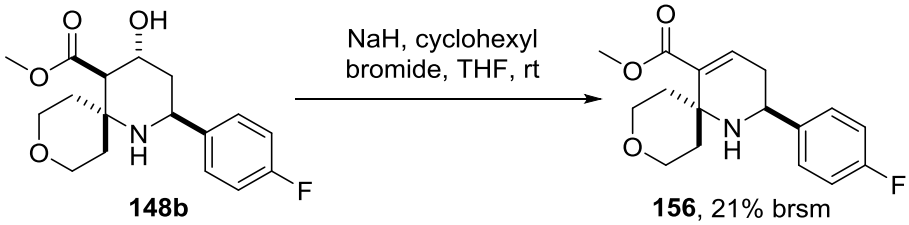
Believing the piperidine nitrogen could also be hindering the fluorination by reacting with fluorinating agent, alcohol **148b** was treated with HCl to form the salt. Treatment of the salt of alcohol **148b** to DAST, once again, resulted in decomposition of starting material, and no fluorinated product **158** (Scheme 57). The disappointing results ceased any further attempts at fluorination of the 2-spiropiperidine scaffolds.



Scheme 57. Formation of the HCl salt prior to DAST addition.

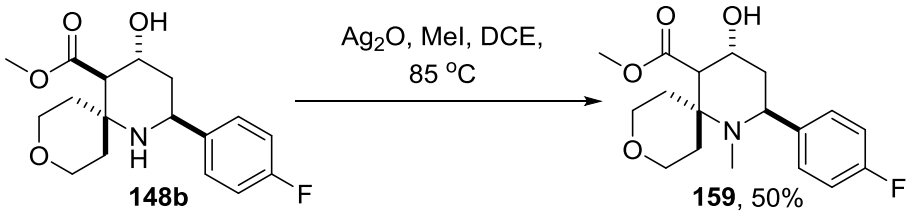
3.7 *O*-Alkylation

With the desire to explore three-dimensional space along a new vector, etherification of the alcohol was the next functionalisation to be trialled. Alkylation of alcohol **148b** was envisaged to proceed via a Williamson ether synthesis,[143] by deprotonation of the alcohol with NaH and displacement with cyclohexyl bromide (Scheme 58). However, no alkylated product was observed, instead α,β-unsaturated ester **156** was isolated in low yield. Presumably, etherification was occurring, and the subsequent alkoxide eliminated to form the favourable α,β-unsaturated ester **156** and cyclohexanol. To achieve *O*-alkylation it was believed that a decarboxylation was required, but this was not attempted.



Scheme 58. Alcohol elimination by etherification.

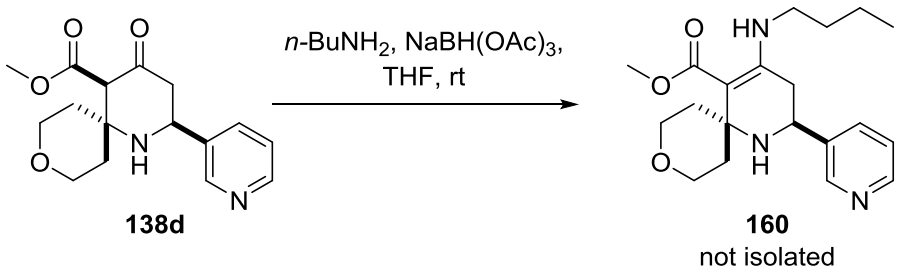
Alcohol **148b** was treated with silver oxide and iodomethane at 85 °C in a sealed vial in the dark (Scheme 59).[144] Interestingly, this led to *N*-methylation and not *O*-methylation, furnishing **159** in 50% yield. This was first time reactivity at the piperidine nitrogen had been observed, showing the methyl group is a small enough electrophile to be attacked by the congested piperidine nitrogen.



Scheme 59. *N*-Methylation with silver oxide and iodomethane.

3.8 Reductive Amination

With similar intentions to the *O*-alkylation, performing a reductive amination of the 2-spiropiperidines would allow for elaboration along a new vector to explore three-dimensional space. The transformation converts an sp^2 centre to an sp^3 centre which increases the three-dimensionality of the 2-spiropiperidine. It also introduces an amine to the 2-spiropiperidine, which is a hydrogen bond donor/acceptor and can increase solubility. Treatment of 2-spiropiperidine **138d** with butylamine and sodium triacetoxyborohydride did not provide the desired amine product, instead formation of enamine **160** was observed (Scheme 60).[145]

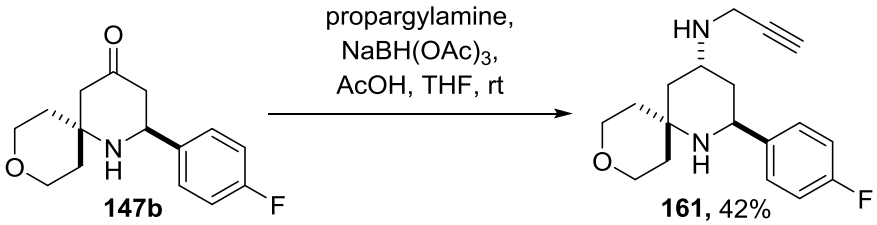


Scheme 60. Enamine formation under conditions for reductive amination.

Formation of the iminium must be occurring, but subsequent tautomerisation to the conjugated enamine must be faster than reduction with sodium triacetoxyborohydride. Supporting evidence for the formation of enamine **160** was obtained from LCMS and NMR spectroscopy of the crude reaction mixture, but was not isolated. Column chromatography of the crude reaction mixture returned no desired product nor any starting 2-spiropiperidine **138d** that may have resulted from hydrolysis. After repeating the reductive amination reaction procedure, the crude reaction mixture was treated with $NaBH_4$, but still no desired

amine product was observed. There are reported methods for the reduction of enamines in the literature such as hydrogentation with platinum[146] or rhodium,[147] and by microwave irradiation with alcohols[148] but these were not trialled.

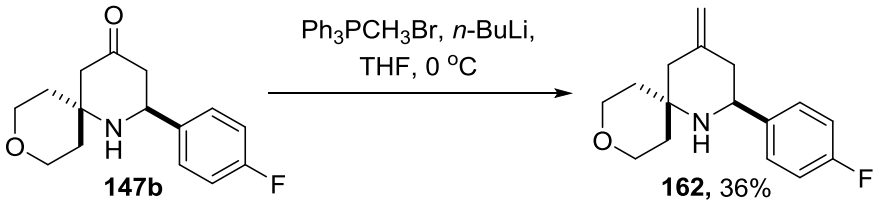
To avoid tautomerisation, the β-ketoester system of 2-spiropiperidine **138b** was removed through decarboxylation to give ketone **147b**. Ketone **147b** was then treated with propargylamine and sodium triacetoxyborohdyride, furnishing amine **161** as a single diastereomer in a moderate 42% yield (Scheme 61).



Scheme 61. Reductive amination on 2-spiropiperidine **147b**.

3.9 Methylenation

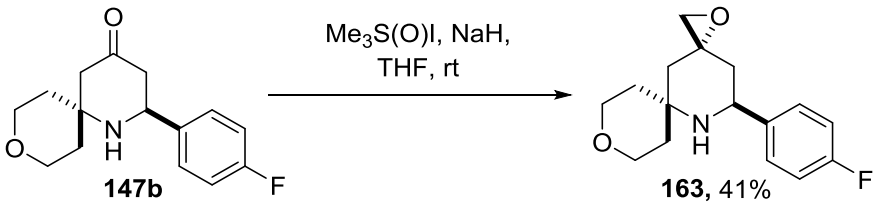
Olefination of the ketone was regarded a logical transformation, owing to the large literature precedent for the Wittig reaction.[149,150,151] Introduction of an olefin would, depending on the substrate chosen, give rise to at least one new functional group, and also increase the lipophilicity of the resultant 2-spiropiperidine. A simple olefination was desired, and introduction of a methylene group would give rise to just one product and not generate *E*/*Z* stereoisomers. The ylide was generated *in situ* through the deprotonation of methyl triphenylphosphonium bromide with *n*-BuLi, and subsequent treatment with 2-spiropiperidine **147b** gave the olefinated 2-spiropiperidine **162** in a moderate 36% yield (Scheme 62).[152]



Scheme 62. Wittig methylenation of 2-spiropiperidine **147b**.

3.10 Epoxidation

Having achieved success with a methylenation and a reductive amination of the ketone, it was postulated performing a Corey-Chaykovsky epoxidation with a sulfoxonium ylide. Treatment of ketone **147b** with the trimethylsulfoxonium ylide, formed by deprotonation of trimethylsulfoxonium iodide with NaH, furnished epoxide **163** as a single diastereomer in a moderate 41% yield (Scheme 63).[153] The success of the reaction was pleasing as it generated a structurally interesting 2,4-*bis*-spiropiperidine.



Scheme 63. Corey-Chaykovsky epoxidation of 2-spiropiperidine **147b**.

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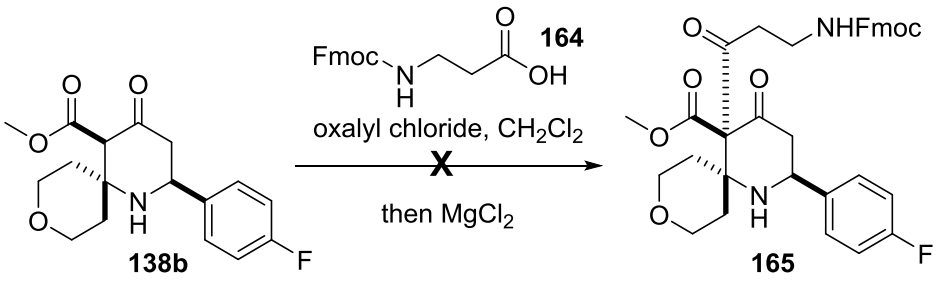
3.11 Other Functionalisations

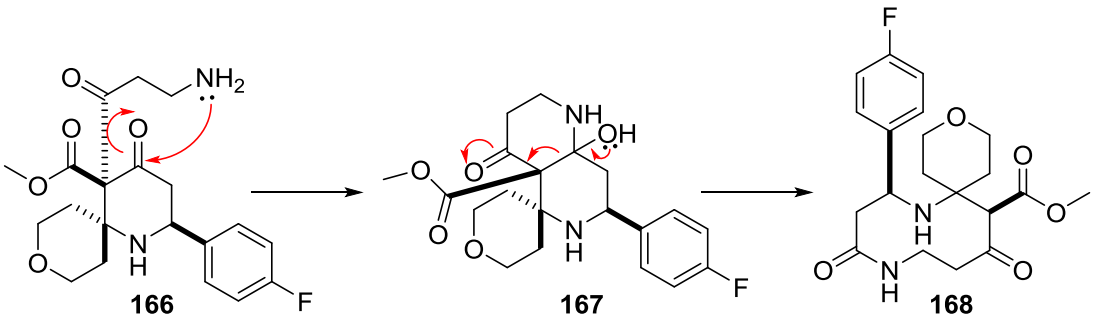
Having successfully synthesised a small library of functionalised 2-spiropiperidines (17 compounds), there was still material left from the scaffold synthesis to trial some speculative chemistry. Unsworth had recently published methods for successive ring expansions to form macrocycles utilising β-ketoesters.[154] Addition of the enolate formed at C-3 of 2-spiropiperidine **138b** into the acid chloride of Fmoc-β-Ala-OH **164** to form macrocyclisation

precursor **165** was unsuccessful (Scheme 64). It is believed that this is yet again a consequence of the sterically encumbered C-3 position.



Scheme 64. Step one for 2-spiropiperidine macrocyclization.

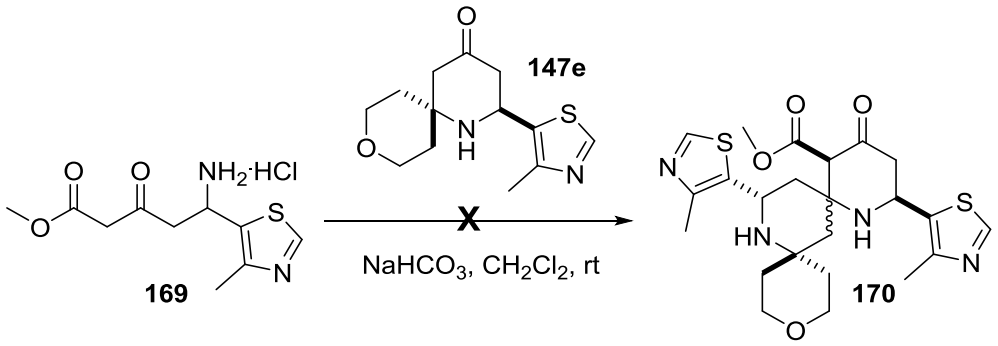
Had the installation of Fmoc-β-Ala-OH been successful, deprotection of the amine with piperidine would have induced formation of aminal **167** and subsequent macrocyclisation to macrocyclic 2-spiropiperidine **168** (Scheme 65).



Scheme 65. Mechanism for 2-spiropiperidine macrocyclisation.

The cyclisation step for the two-step synthesis of 2-spiropiperidines required treatment of the HCl salt of a δ-amino-β-ketoester with a ketone. Decarboxylation of the 2-spiropiperidines gave rise to ketones, which we believed could be used in the cyclisation step for 2-spiropiperidine synthesis. HCl salt **169** was subjected to the original spirocyclisation conditions with ketone **147e**, in the hope of forming a structurally interesting 2,4-*bis* spiropiperidine **170** (Scheme 66). The molar equivalents of ketone **147e** was reduced from 5 to 1, a consequence of the limited amount of ketone **147e** in hand. Unfortunately, the ^{1}H NMR

spectrum of the crude reaction mixture showed just unreacted ketone **147e**, despite HRMS finding the desired mass of 2-spiropiperidine **170**. 2-Spiropiperidine **170** was not isolated.



Scheme 66. Spirocyclisation using 2-spiropiperidine **147e** as the ketone.

3.12 LLAMA Analysis

Having constructed a small library of 2-spiropiperidines utilising a diverse range of chemistry to introduce new functional groups, the lead-likeness and the relative three-dimensionality of the 2-spiropiperidines was of interest. The 18 functionalised 2-spiropiperidines were analysed through LLAMA to gauge their lead-likeness and three-dimensionality.

3.12.1 Lead-Likeness

It has been determined that the lipophilicity of a molecule is a defining characteristic for its potential success as a drug candidate.[34] In order to facilitate delivery of a drug candidate to the desired pharmacological target as well as participate in subsequent interactions, aqueous solubility is a necessity.[155] If the molecule is too hydrophobic, it has the ability to interact with other biological environments and consequently have potentially undesired toxic effects.[1,156] It has therefore been determined that a low lipophilicity is required for lead compounds prior to lead optimization. It has also been deduced that during the lead optimisation process, an increase in both molecular weight and lipophilicity is observed, as extra complexity and size are added to the molecules.[157] Tentative limits are therefore installed to deduce whether a compound can be described as 'lead-like', based on its molecular weight and lipophilicity.

Whilst not all drugs are administered orally, these guidelines that describe molecules as 'lead-like' represents the best starting points to allow maximum flexibility through optimisation.[1]

Churcher described an area of chemical space in which lead compounds reside, in which there is a potential for the development into a drug candidate.[1] This area of chemical space, coined as 'lead-like space', defines compounds as having AlogP values in the range of -1 to +3 and a molecular weight in the range of 200-350 (14-26 non-hydrogen atoms) (Figure 25). The orange oval described as optimal drug-like space gives a broad representation of the properties of oral drug candidates (Figure 25), and typically as molecular weight increases, the associated lipophilicity also increases.

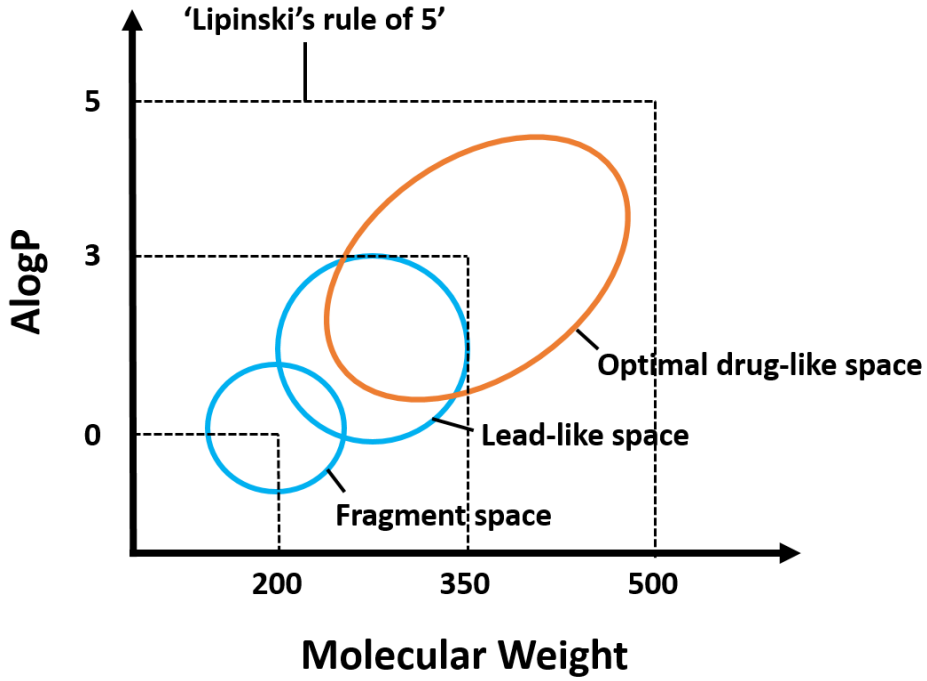
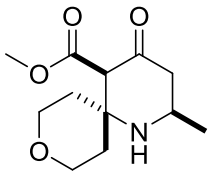


Figure 25. Molecular weight vs AlogP for identification of 'lead-like' space.

Whilst a compound may exhibit the desirable properties to describe it as 'lead-like', it may also possess certain properties and functionalities that impose a negative impact on its overall 'lead-likeness'. Consequently, a 'lead-likeness' penalty was introduced by Marsden and Nelson.[14] The penalty is an integer value calculated by analysing the key properties of the molecule; the AlogP value, the heavy atom count, the number of aromatic rings, and the

number of undesirable functional groups. The AlogP value should ideally be between -1 and +3,[1] the heavy atom count should be between 17-24,[1] the number of aromatic rings present should not exceed two,[38] and there should be no reactive functional groups that can interfere with potential bindings.[14,113] Penalty points are awarded based upon how far outside the ideal space the molecule lies, and the further away from the ideal space, the larger the penalty. The largest penalty that can be imposed is for the presence of a bad functional group. The closer the penalty to zero, the greater the 'lead-likeness' of a compound. Using the LLAMA online software, an example of the calculation of the penalty is described for 2-spiropiperidine **138a** (Figure 26).[47] Both the heavy atom count and the AlogP value fit within the desired guidelines, however, the lack of an aromatic group and a presence of a methyl ester (undesirable functional group, as defined by LLAMA) gives 2-spiropiperidine **138a** a 'lead-likeness' score of six. 2-Spiropiperidine **138a** is therefore not described as 'lead-like'.

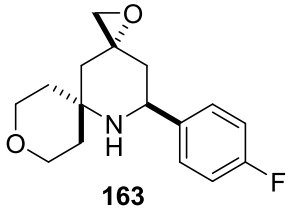


138a

Property	Value	Penalty
Heavy atom count	17	0
AlogP	0.1	0
No. of aromatics	0	1
Bad functional groups	1	5
		6

Figure 26. Calculation of the 'lead-likeness' score of 2-spiropiperidine **138a**.

The 'lead-likeness' of the functionalised 2-spiropiperidines were analysed using the LLAMA online software.[47] An example calculation of the lead-likeness of 2-spiropiperidine **163** is described below (Figure 27). As well as satisfying the guidelines for the heavy atom count and AlogP value, 2-spiropiperidine **163** also has an aromatic ring, and has been decarboxylated so the bad functional group has been removed. As a result, 2-spiropiperidine **163** has a 'lead-likeness' score of zero, deeming the compound to be 'lead-like'.



163

Property	Value	Penalty
Heavy atom count	20	0
AlogP	1.75	0
No. of aromatics	1	0
Bad functional groups	0	0
		0

Figure 27. Calculation of the 'lead-likeness' score of 2-spiropiperidine **163**.

LLAMA analysis of the functionalised 2-spiropiperidines has shown that over half of the compounds have an excellent 'lead-likeness' score of zero (Figure 28).[47] The higher-scoring amides **150a** and **150b** have earnt their penalty from the number of heavy atoms, exceeding the desired number for a 'lead-like' compound. The remaining 2-spiropiperidines all have 'lead-likeness' scores of five and six. This is because of the presence of the ester group, and in the case of 2-spiropiperidine **148a**, the lack of an aromatic group. Removal or manipulation of the ester group of the 2-spiropiperidines would consequently improve the 'lead-likeness' of all compounds.

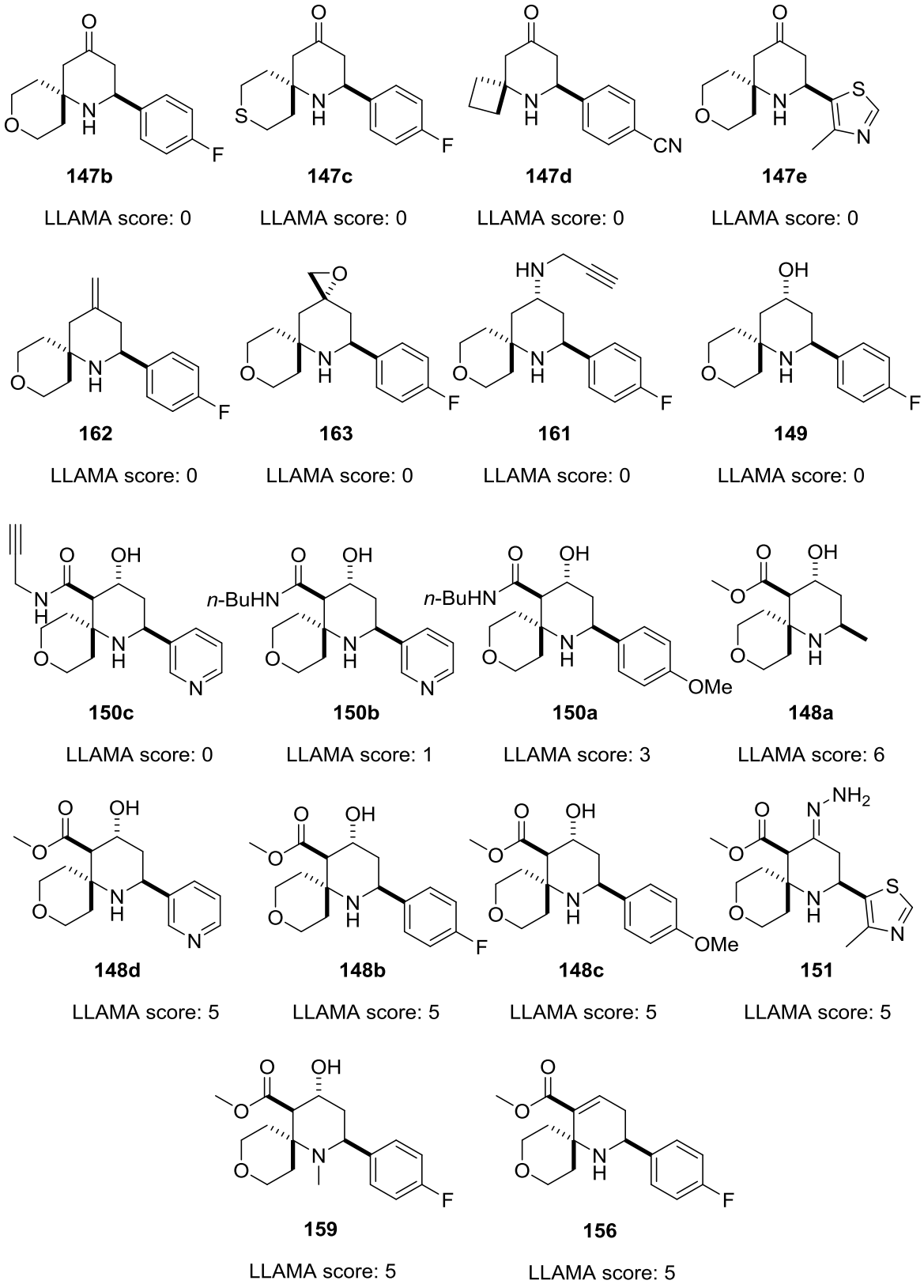


Figure 28. LLAMA analysis of the functionalised 2-spiropiperidines.

3.12.2 PMI Analysis

Having assessed the 'lead-likeness' of the 2-spiropiperidines, the 18 functionalised 2-spiropiperidines were next plotted onto a PMI plot using the LLAMA software, with the 75% line from the ZINC database plot still shown for reference (Figure 29).[47,14]

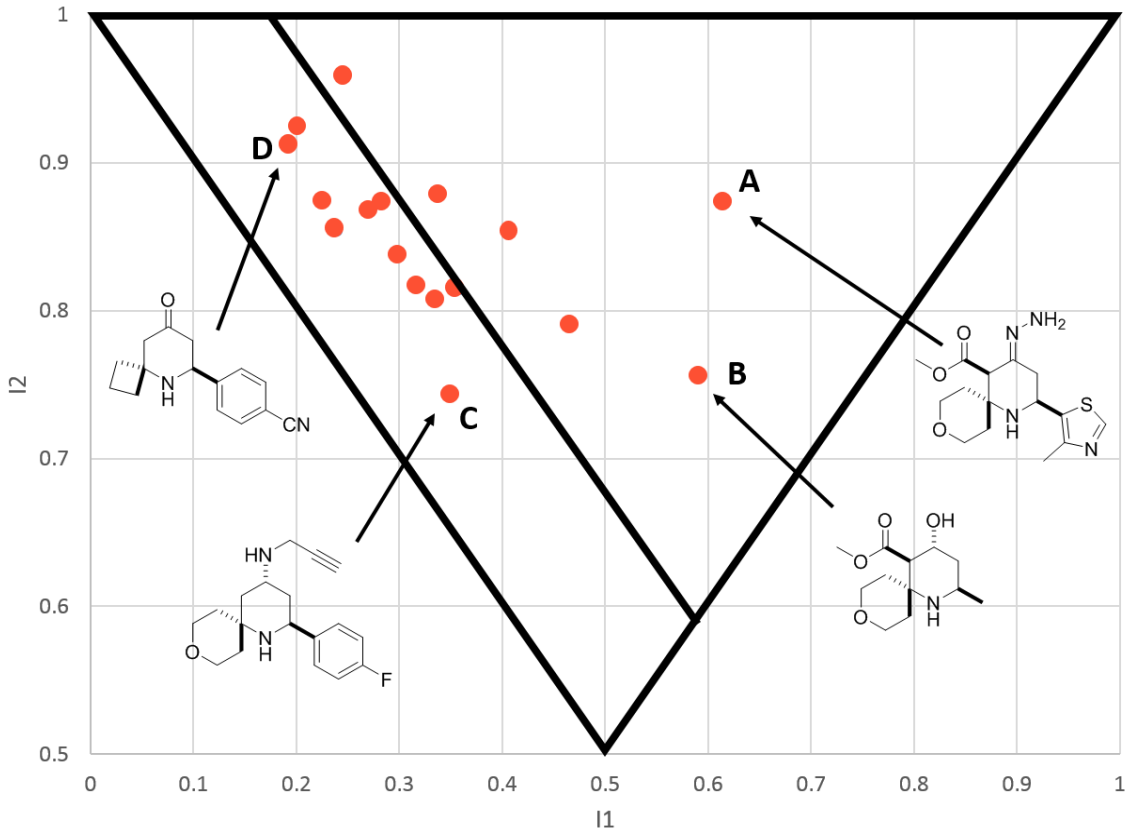


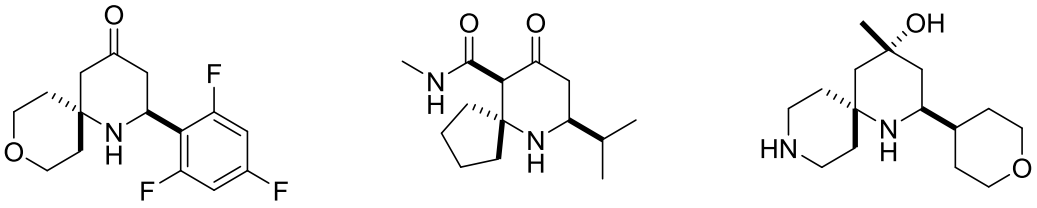
Figure 29. PMI plot for the functionalized 2-spiropiperidines.

It can be seen that a greater proportion of the functionalised 2-spiropiperidines lie to the left of the ZINC 75% line than the respective 2-spiropiperidine scaffolds. This is a consequence of numerous factors. All of the examples were performed on 2-spiropiperidines with aromatic C-6 substituents (except the reduction of **138a**), which consequently adds planarity to the structure. Approximately one half of the structures underwent decarboxylation, which in turn removed the C-3 tether, which was a vector to point into and explore three-dimensional

space. Adding to this, the introduction of alkenes and alkynes reduces the fsp^3 in the molecules and ultimately reduces three-dimensionality.

Interestingly, the most three-dimensional structure was hydrazone **151** (Figure 29, A), presumably a consequence of the hydrazone functional group, with the amine providing an extra vector for elaboration and exploration. It also exhibits a plane of best fit of 1.468 Å, compared to approximately 1-1.2 Å for the other functionalised 2-spiropiperidines.[47,14] The other three-dimensional 2-spiropiperidine was alcohol **148a** (Figure 29, B). The reduction was performed on an aliphatic C-6 substituent (methyl group), the C-3 ester remained, and the sp^2 ketone was reduced to an sp^3 alcohol. Understandably, two of the most two-dimensional was 2-spiropiperidine **161** (Figure 29, C) and **147d** (Figure 29, D). Amine **161** exhibits all three of the negative impacting factors described above; an aromatic C-6 substituent, C-3 decarboxylation, and introduction of an alkyne. Ketone **147d** possesses similar properties but contains a linear nitrile on the aromatic ring.

The synthesis of a library of functionalised 2-spiropiperidines that exhibit greater three-dimensionality can be achieved by careful design of substrate, reaction and reagent. Aliphatic and substituted aromatic C-6 substituents on the parent 2-spiropiperidine scaffold aid in giving three-dimensionality to the functionalised 2-spiropiperidine. Reactions that remove substituents such as the C-3 ester or the C-4 ketone increases two-dimensionality, so functional group interconvention is preferential. Choice of the coupling reagent is also essential, as the introduction of alkynes, alkenes and aromatics will reduce three-dimensionality. Examples of functionalised 2-spiropiperidines that all lie to the right of the 75% ZINC line on the PMI plot that have been designed with the above rules are demonstrated below (Figure 30, **164**, **165** and **166**).



164
LLAMA score: 0

165
LLAMA score: 1

166
LLAMA score: 1

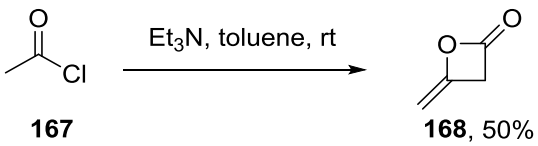
Figure 30. Designed functionalised three-dimensional 2-spiropiperidines.

4. One-Pot Synthesis of 2-Spiropiperidines

4.1 Preliminary Studies

A stepwise procedure for the synthesis of 2-spiropiperidines had been successfully developed, and it was next deemed desirable to synthesise 2-spiropiperidines in one-pot.

In preliminary studies, diketene **168** was used to be consistent with the previous one-pot piperidine synthesis reported from within the group.[95] Due to its commercial unavailability, diketene **168** had to be prepared through treatment of acetyl chloride **167** with triethylamine (Scheme 67).[158,159] Under the reaction conditions, ketene was formed which spontaneously dimerised to diketene **168**. Aqueous work-up of the reaction mixture would result in hydrolysis of diketene **168**, so the solvent choice was crucial. Diketene **168** has a high volatility, so would be used as a solution in subsequent reactions. Toluene was chosen as the solvent due to the insolubility of the by-product triethylamine hydrochloride. The preferred solvent would have been Et_2O, however, the subsequent reaction would require the use of $TiCl_4$ which is incompatible with Et_2O.[160] Upon filtration of triethylamine hydrochloride, diketene **168** was retrieved as a 4.91 wt% solution in a moderate 50% yield (Scheme 67), and was prepared freshly for each reaction. The formation of diketene was confirmed by ^{1}H NMR spectroscopy.

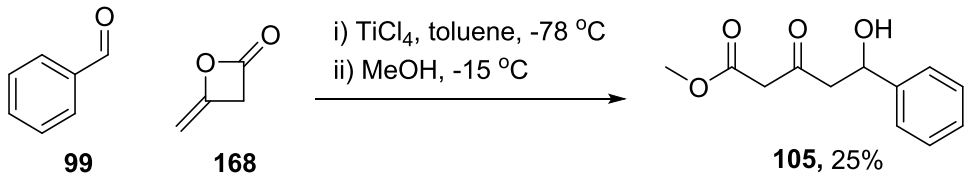


167 **168**, 50%

Scheme 67. Diketene synthesis.

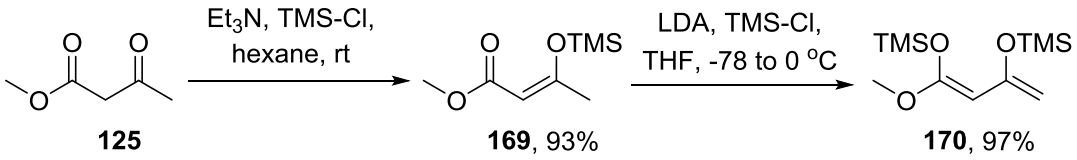
To test the synthetic tractability of the diketene solution, a trial aldol addition with benzaldehyde was undertaken using literature conditions,[104] with the exception that toluene was used instead of CH_2Cl_2 (Scheme 68). The desired δ-hydroxy-β-ketoester **105** was isolated in a low 25% yield. Whilst it was pleasing to observe reactivity, the low yield was

disappointing. Unfortunately, further results were inconsistent and irreproducible, so the use of diketene **168** for the one-pot investigations was halted.



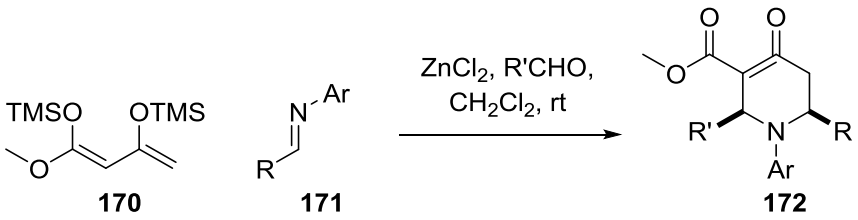
Scheme 68. Aldol addition of diketene onto benzaldehyde.

Chan's diene **170**,[161] the *bis*-silyl enol ether of methyl acetoacetate, has been described for use in asymmetric Mukaiyama-aldol reactions.[162,163,164] Mukaiyama-Mannich reactions have also been described with Chan's diene[165] as well as related silyl ketene acetals.[166,167] It was envisaged to perform the one-pot procedure via a Mukaiyama-Mannich reaction with Chan's diene. Chan's diene **170** was synthesised according to literature precedent from methyl acetoacetate **125** (Scheme 69).[168] Deprotonation of methyl acetoacetate with triethylamine generated the enol ether, which was trapped with TMS-chloride to give silyl enol ether **169** in an excellent 93% yield. The second deprotonation required the use of LDA, and subsequent trapping with TMS-chloride gave the *bis*-silyl enol ether, Chan's diene **170**, in an excellent 97% yield. The reaction was performed on a 12 g scale, which yielded 22 g of Chan's diene **170**.



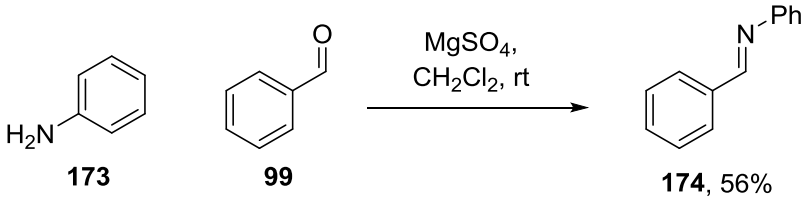
Scheme 69. Synthesis of Chan's diene **170**.

Unpublished results from within the group demonstrated the synthesis of *N*-phenyl and *N*-PMP protected 2,6-piperidines **172** from the respective *N*-protected imines **171** and aldehydes with Chan's diene **170** and $ZnCl_2$ (Scheme 70).[169] It was postulated that a similar approach could be made to access 2-spiropiperidines.



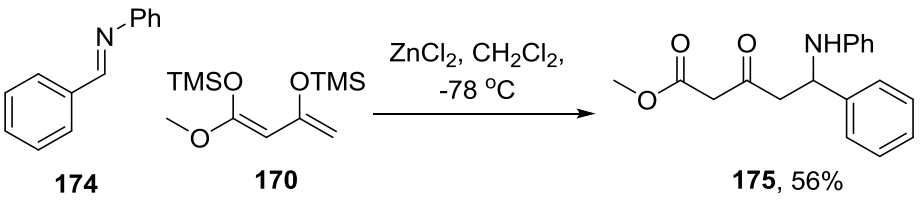
Scheme 70. Zinc chloride mediated synthesis of piperidines.

Condensation of aniline **173** with benzaldehyde **99**, using $MgSO_4$ as a dehydrating agent gave *N*-phenyl imine **174** in a moderate 56% yield (Scheme 71).[170] With Chan's diene **170** and *N*-phenyl imine **174** in hand, a stepwise approach towards the piperidine **172** was investigated.



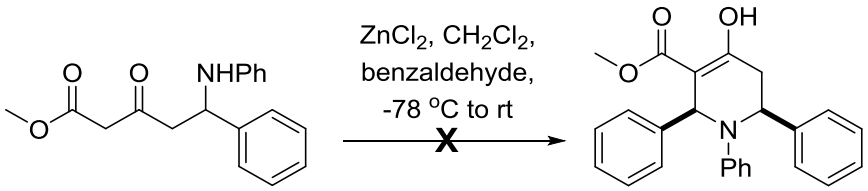
Scheme 71. Synthesis of N-phenyl imine **174**.

In the presence of $ZnCl_2$, a Mukaiyama-Mannich reaction between *N*-phenyl imine **174** and Chan's diene **170** gave the desired δ-amino-β-ketoester **175** in a moderate 56% yield (Scheme 72). The reaction did not go to completion, explaining the relatively lower than expected yield. Extra Chan's diene and $ZnCl_2$ were added to the reaction, but still unreacted imine remained. Enough δ-amino-β-ketoester **175** had been formed, however, to trial the cyclisation, so Mannich reaction optimisation was not carried out at this stage.



Scheme 72. Zinc chloride mediated Mukaiyama-Mannich reaction of N-Ph imine **174** with Chan's diene.

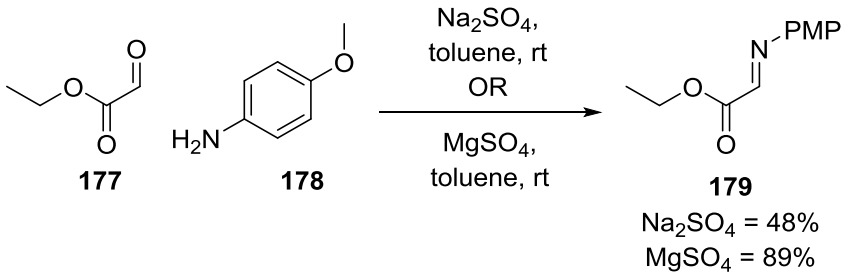
Upon re-subjecting δ-amino-β-ketoester **175** to the Mukaiyama-Mannich reaction conditions in the presence of benzaldehyde, no reaction was observed and δ-amino-β-ketoester **175** was re-isolated from the crude reaction mixture (Scheme 73). It was reported that the introduction of two molar equivalents of TFA would induce cyclisation,[169] but still none of the desired piperidine **176** was formed.



175 **176**

Scheme 73. Cyclisation with δ-amino-β-ketoester **175**.

With unpromising results using *N*-phenyl imine **174**, similar procedures were trialled with *N*-PMP glyoxal imine **179**, as the *N*-PMP glyoxal imine is more electrophilic than the *N*-phenyl imine. Condensation of ethyl glyoxylate **177** with *p*-anisidine **178** using Na_2SO_4 as a dehydrating agent gave *N*-PMP imine **179** in a moderate 48% yield (Scheme 74).[171] Upon changing the dehydrating agent to $MgSO_4$, the yields improved to give an excellent 89% yield.



177 **178** **179**

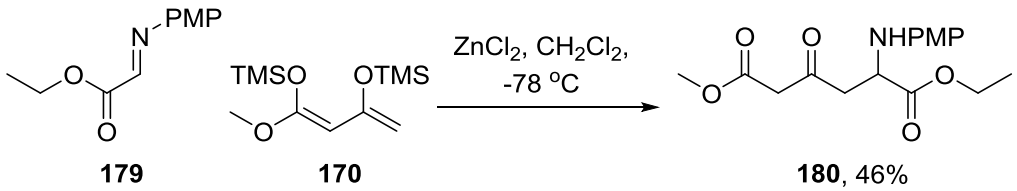
Na_2SO_4 = 48%

$MgSO_4$ = 89%

Scheme 74. Synthesis of N-PMP imine **179**.

To begin the investigations towards the zinc-mediated cyclisations, *N*-PMP imine **179** was treated with Chan's diene **170** and $ZnCl_2$ to form the δ-amino-β-ketoester **180** (Scheme 75). The reaction proceeded to give δ-amino-β-ketoester **180** in a moderate 46% yield, though

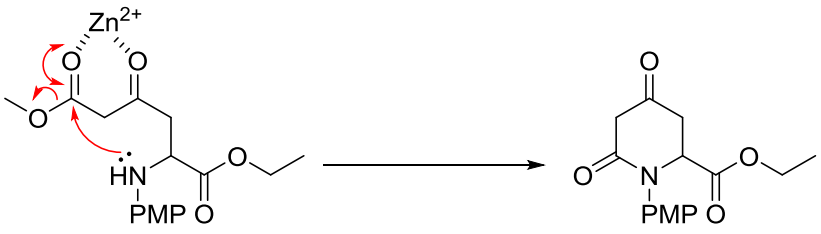
complete consumption of *N*-PMP imine **179** was observed by TLC and ^{1}H NMR spectroscopy of the crude reaction mixture.



179 **170** **180**, 46%

Scheme 75. Zinc-mediated Mukaiyama-Mannich reaction of N-PMP imine **179** with Chan's diene.

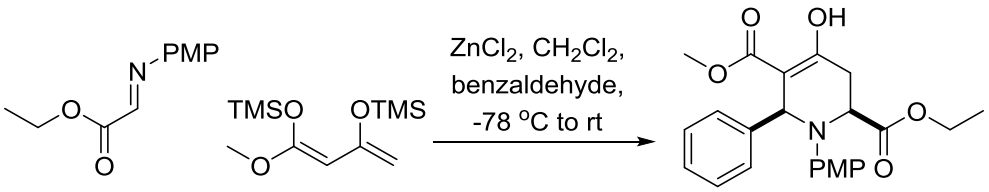
The Mukaiyama-Mannich reaction was found to be capricious, as inconsistent yields of isolated product were obtained. However, it was found that β-keto-δ-lactam **181** was forming under the reaction conditions, with lactamisaton occurring by addition of the electron rich amine into the zinc-activated ester (Scheme 76). The formation of β-keto-δ-lactam **181** was not detected by the TLC of the reaction mixture, so lactamisation must be occurring during aqueous work-up and column chromatography. The ratios of formation of δ-amino-β-ketoester **180** to β-keto-δ-lactam **181** were inconsistent and could not be controlled. It was therefore decided to take two separate approaches; the first was to not isolate the δ-amino-β-ketoester **180** and to add an aldehyde/ketone to the reaction mixture to induce cyclisation to the piperidine *in situ*, and the second was to use the *tert*-butyl ester of Chan's diene for the Mannich reaction to avoid lactamisation.



180 **181**

Scheme 76. Formation of lactam **181** from δ-amino-β-ketoester **180**.

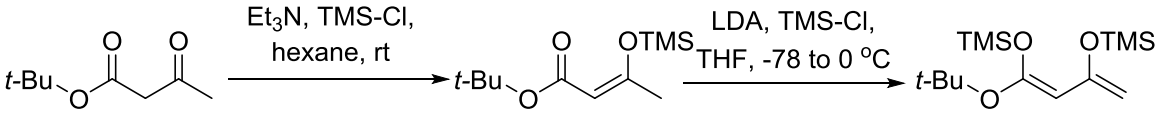
The *N*-PMP imine **179** was treated with Chan's diene **170** in the presence of $ZnCl_2$ and, before detection of β-keto-δ-lactam **181** by TLC, benzaldehyde was added to induce cyclisation (Scheme 77).[169] Pleasingly, piperidine **182** was isolated from the reaction mixture, though as an inseparable mixture of diastereomers in a moderate 47% yield, however, no formation of β-keto-δ-lactam **181** observed. With the use of cyclohexanone, no cyclisation to the 2-spiropiperidine was observed.



179 **170** **182**, 47%, 2.5:1 dr

Scheme 77. One-pot cyclisation to form *N*-PMP piperidines.

In parallel with the efforts towards the one pot synthesis with *N*-PMP imine **179** and Chan's diene **170**, investigations towards the stepwise cyclisation using the *tert*-butyl variant of Chan's diene **170** were undertaken. *tert*-Butyl Chan's diene **185** was synthesised from *tert*-butyl acetoacetate **183** using the same procedure as reported for the synthesis of Chan's diene **170** (Scheme 78).

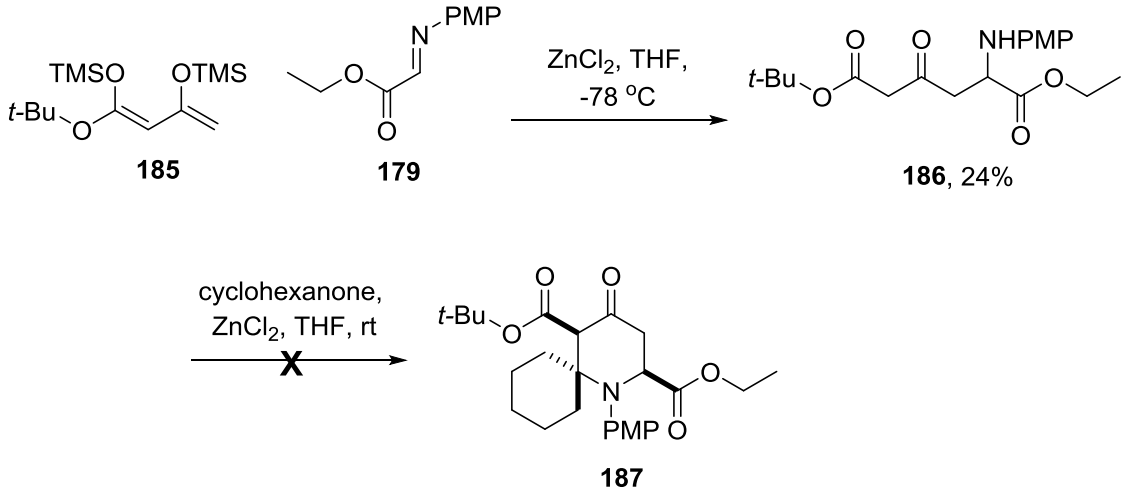


183 **184**, 98% **185**, 94%

Scheme 78. Synthesis of *tert*-butyl Chan's diene **185**.

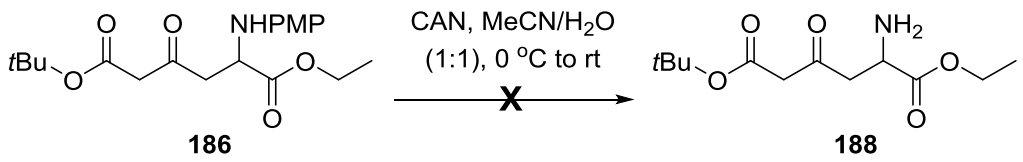
Under the previously reported Mukaiyama-Mannich reaction conditions with *tert*-butyl Chan's diene **185** and *N*-PMP imine **179** in the presence of $ZnCl_2$, δ-amino-β-ketoester **186** was synthesised in a low 24% yield (Scheme 79). As expected, no lactamisation to the respective β-keto-δ-lactam was observed. Submission of δ-amino-β-ketoester **186** to the

reaction conditions in the presence of cyclohexanone gave no desired 2-spiropiperidine **187**. Unreacted δ-amino-β-ketoester **186** was reisolated from the crude reaction mixture. Repeating the reaction conditions with isobutyraldehyde yielded similar results, so it was believed the PMP group was hindering cyclisation.



Scheme 79. Attempted 2-spiropiperidine synthesis with *tert*-butyl Chan's diene.

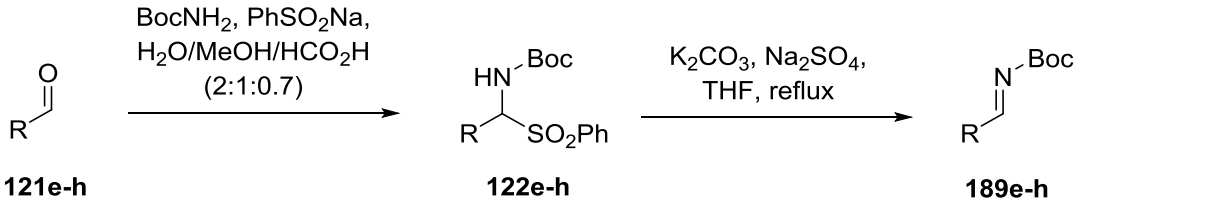
Ceric ammonium nitrate (CAN) has been reported to oxidatively cleave the *N*-PMP bond, and the procedure was applied to the deprotection of δ-amino-β-ketoester **186** (Scheme 80).[172] Unfortunately, only decomposition of the starting material was observed, with no deprotected δ-amino-β-ketoester **188** or the subsequent lactamised product found in the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 80. Deprotection of *N*-PMP-δ-amino-β-ketoester **186**.

4.2 Synthesis of 2-Spiropiperidines

With disappointing results for the use of *N*-phenyl and *N*-PMP imines towards the one-pot synthesis of 2-spiropiperidines, it was decided to return to *N*-Boc imines **189**. Refluxing *N*-Boc sulfones **122e-k** in a suspension of K_2CO_3 and Na_2SO_4 in THF, followed by filtration and careful concentration gave *N*-Boc imines **189e-k** in excellent yields (Scheme 81).[173]



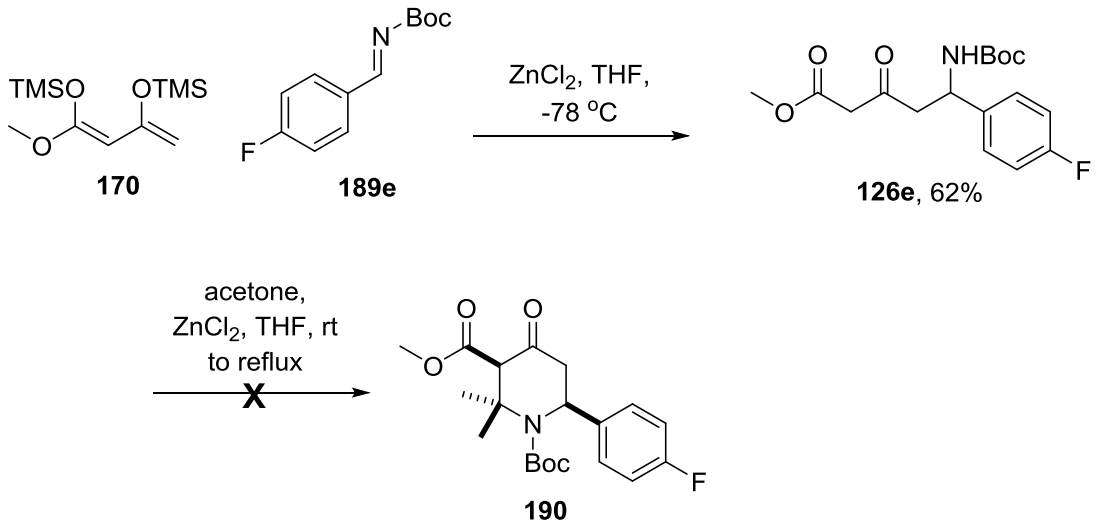
121e-h **122e-h** **189e-h**

122e R = 4-F-Ph, 91%
122f R = 4-OMe-Ph, 71%
122g R = 3-pyridyl, 47%
122h R = 2-methyl thiazole, 52%
122i R = *N*-methyl pyrazole, 71%
122j R = 4-CN-Ph, 94%
122k R = 4-CF_3-Ph, 72%

189e R = 4-F-Ph, 93%
189f R = 4-OMe-Ph, 90%
189g R = 3-pyridyl, 100%
189h R = 2-methyl thiazole, 99%
189i R = *N*-methyl pyrazole, 95%
189j R = 4-CN-Ph, 100%
189k R = 4-CF_3-Ph, 99%

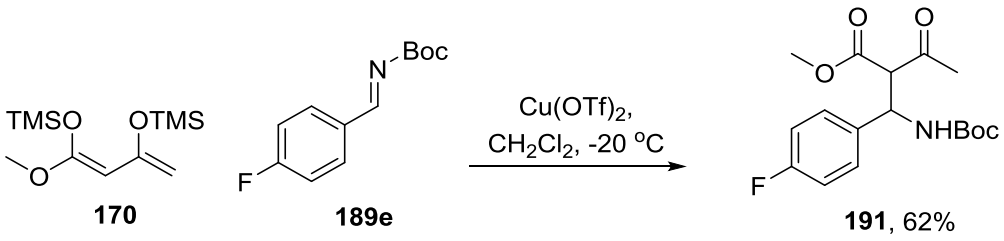
Scheme 81. Synthesis of *N*-Boc imines.

Treatment of *N*-Boc imine **189e** with Chan's diene in the presence of $ZnCl_2$ gave δ-amino-β-ketoester **126e** in a good 62% yield (Scheme 82). However, upon treatment of δ-amino-β-ketoester **126e** with acetone and $ZnCl_2$, no cyclisation to piperidine **190** was observed. Even under reflux, δ-amino-β-ketoester **126e** was recovered unchanged.



Scheme 82. Zinc-mediated cyclisation with *N*-Boc δ-amino-β-ketoester **126e**.

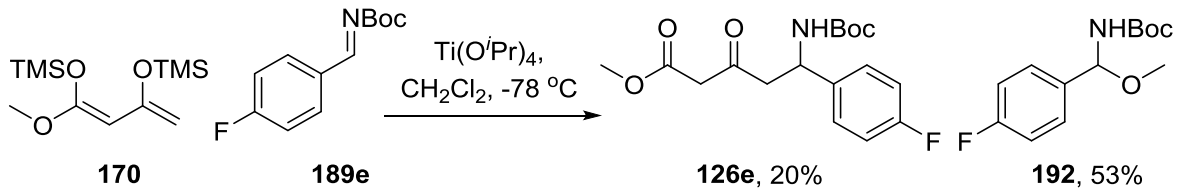
The utility of $ZnCl_2$ as the Lewis acid for the one-pot synthesis was proving unsuccessful, so different Lewis acids were investigated. Investigations began with $Cu(OTf)_2$, which had been demonstrated to catalyse the addition of silyl enol ethers to *N*-acyl imines.[174] Addition of *N*-Boc imine **189e** to a solution of Chan's diene **170** and $Cu(OTf)_2$ did not yield the desired δ-amino-β-ketoester **126e**. Interestingly, β-amino-β'-ketoester **191** was isolated from the reaction mixture in a 62% yield, arising from addition of the less reactive position of Chan's diene **170** (Scheme 83).



Scheme 83. $Cu(OTf)_2$-mediated addition of Chan's diene to *N*-Boc imine **189e**.

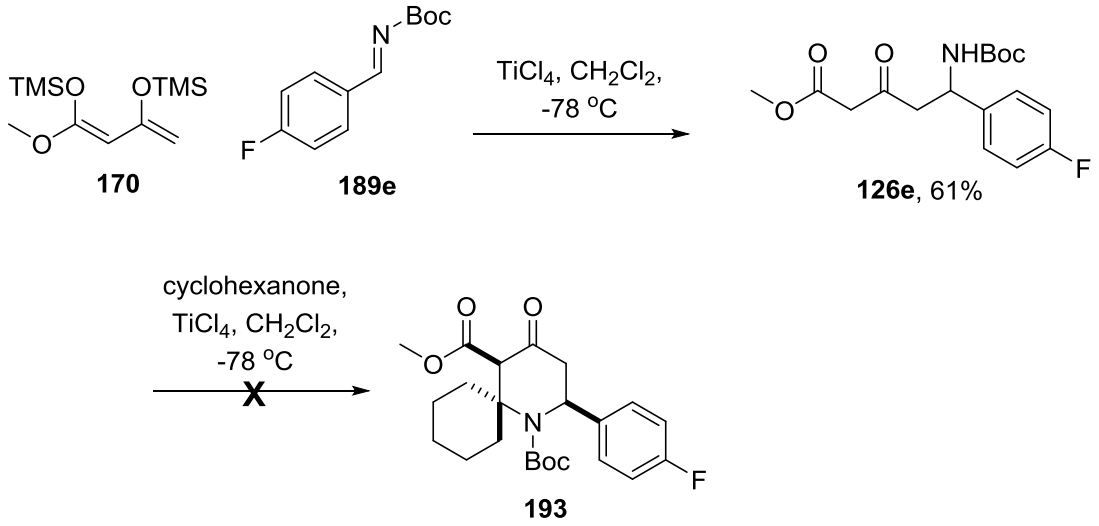
The next Lewis acid of choice was $Ti(O^iPr)_4$ as it had been shown to promote Mannich reactions with Chan's diene.[162] Addition of Chan's diene **170** to *N*-Boc imine **189e** at -78 °C with $Ti(O^iPr)_4$ gave the desired δ-amino-β-ketoester **126e** in a low 20% yield (Scheme 84). Also

isolated from the reaction mixture was amine **192**. Presumably amine **192** is formed by the addition of methanol to unreacted *N*-Boc imine **189e** when the reaction is quenched with methanolic citric acid. The formation of amine **192** was surprising as the TLC of the reaction mixture showed complete consumption of the *N*-Boc imine **189e**.



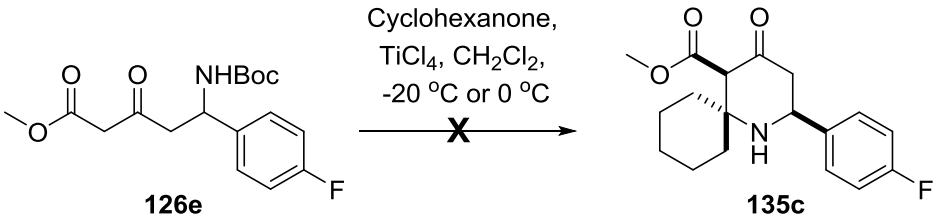
Scheme 84. Ti(OiPr)$_4$-mediated addition of Chan's diene to N-Boc imine **189e**.

It was deemed that Ti(O^{i}Pr)$_4$ was too slow reacting towards the addition of Chan's diene **170** to *N*-Boc imine **189e**, so attention returned to the use of the more reactive $TiCl_4$. Pleasingly, δ-amino-β-ketoester **126e** was isolated in a good 61% yield (Scheme 85). Upon treatment of δ-amino-β-ketoester **126e** with cyclohexanone with $TiCl_4$ at -78 °C, no reaction was observed and starting material was re-isolated.



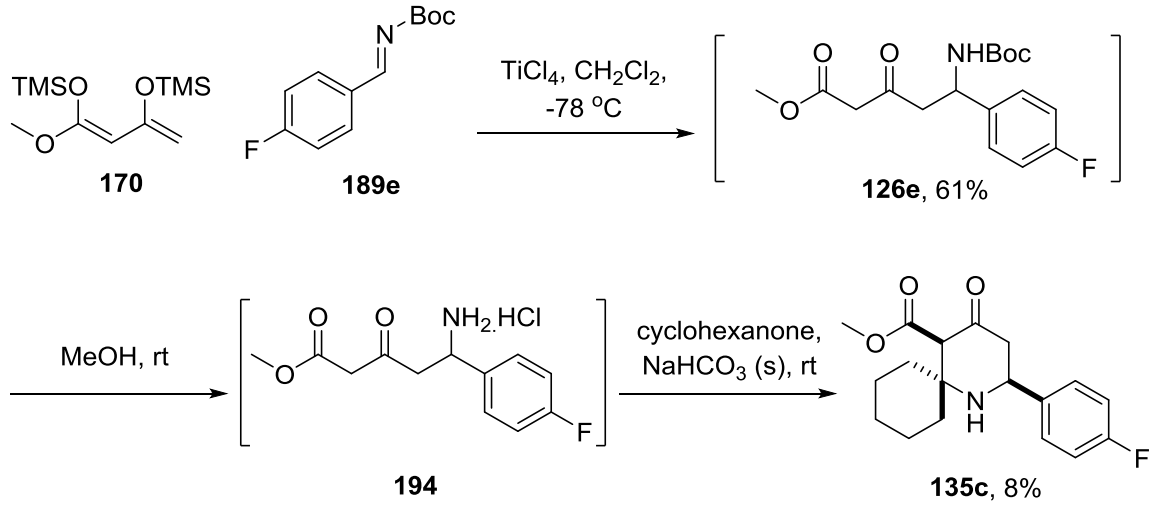
Scheme 85. $TiCl_4$-mediated addition of Chan's diene to *N*-Boc imine **189e** and subsequent cyclisation.

It was believed that the Boc group was still hindering cyclisation to the desired 2-spiropiperidine, so one-pot conditions for the cyclisation would require *in situ* deprotection. It was postulated that at elevated temperatures the $TiCl_4$ could affect deprotection. Stability studies of *N*-Boc-δ-amino-β-ketoester **126e** were undertaken by stirring *N*-Boc-δ-amino-β-ketoester **126e** with $TiCl_4$ in CH_2Cl_2. At -78 ^oC and -40 ^oC, no change to starting material was observed over a period of 1h. However, at -20 ^oC, starting material slowly began to be consumed by TLC, with the baseline spot on the TLC plate becoming more visible, which was consistent with expected deprotection. Assuming deprotectection had occurred, cyclohexanone was then introduced to the reaction. This yielded no 2-spiropiperidine and instead a complex mixture of products was observed by ^1H NMR spectroscopy of the crude reaction mixture (Scheme 86). The same procedure was repeated except at 0 ^oC, and yet again a complex mixture of products was obtained (Scheme 86).



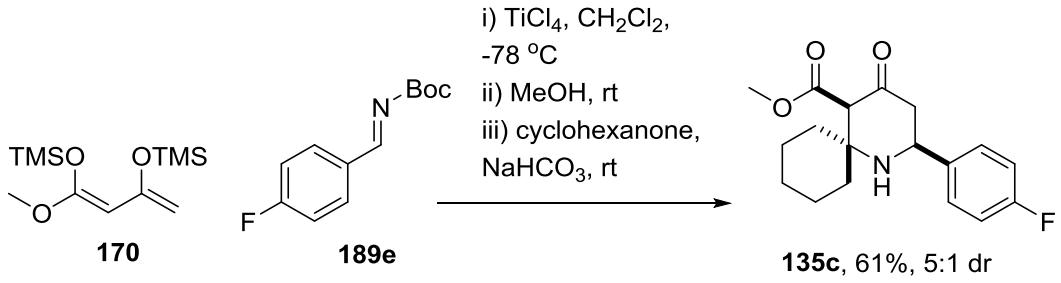
Scheme 86. Attempted $TiCl_4$-mediated cyclisation.

It was concluded that an additive would be required to affect efficient deprotection. The introduction of MeOH would initiate methanolysis of $TiCl_4$, generating $Ti(OMe)_4$ and four molar equivalents of HCl. In the stepwise procedure 15 molar equivalents of HCl was required for efficient deprotection, so the amount of $TiCl_4$ used in the reaction was increased to 4 molar equivalents, which would in turn generate 16 molar equivalents of HCl. Upon formation of δ-amino-β-ketoester **126e** by TLC, MeOH was added and the reaction was warmed to room temperature, which resulted in effective deprotection of *N*-Boc-δ-amino-β-ketoester **126e** (Scheme 87). As with the stepwise procedure, cyclohexanone and $NaHCO_3$ (s) were then added and the reaction was stirred overnight. Pleasingly, 2-spiropiperidine **135c** was formed under the reaction conditions, although in a low 8% yield after column chromatography.



Scheme 87. Initial one-pot cyclisation results.

Despite the low yield, this was the first successful example of a one-pot procedure for the synthesis of a 2-spiropiperidine. It was believed the low yield was a consequence of the work-up procedure, which involved a quench with sat. aq. $NaHCO_3$ and resulted in the formation of an emulsion that was difficult to handle. Upon completion of the reaction, the quench was changed to 1.59 M citric acid in MeOH as used in the one-pot synthesis of 2,6-piperidines,[95] followed by the addition of water. Vigorous stirring of the biphasic mixture gave clear separation, making the aqueous work-up much easier. After column chromatography, 2-spiropiperidine **135c** was isolated in a good 61% yield (Scheme 88). This was very pleasing, as the overall yield for the synthesis of 2-spiropiperidine **135c** in the two-step procedure was 58%.



Scheme 88. One-pot procedure for the improved yield of 2-spiropiperidine **135c**.

The reaction was found to be reproducible, so having developed conditions for spirocyclisation, the scope of the reaction was explored (Figure 31). Owing to the difficulty of isolating aliphatic *N*-Boc imines, the reaction was performed with aromatic and heteroaromatic *N*-Boc imines **189e-k**. With the exception of 2-spiropiperidine **136b**, the yield of spirocyclisation for the one-pot procedure was better than the two-step procedure. 2-Spiropiperidine **138e** was also synthesised on a 1.5 g scale in a 43% yield, showing that the reaction is also scalable. Purification of the 2-spiropiperidines from the one-pot procedure was found to be challenging. Unlike the relatively clean crude reaction mixtures obtained from the two-step procedure, the one-pot procedure required purification of a complex mixture of products. Despite these challenges, 2-spiropiperidines were isolated in moderate to good yields (Figure 31).

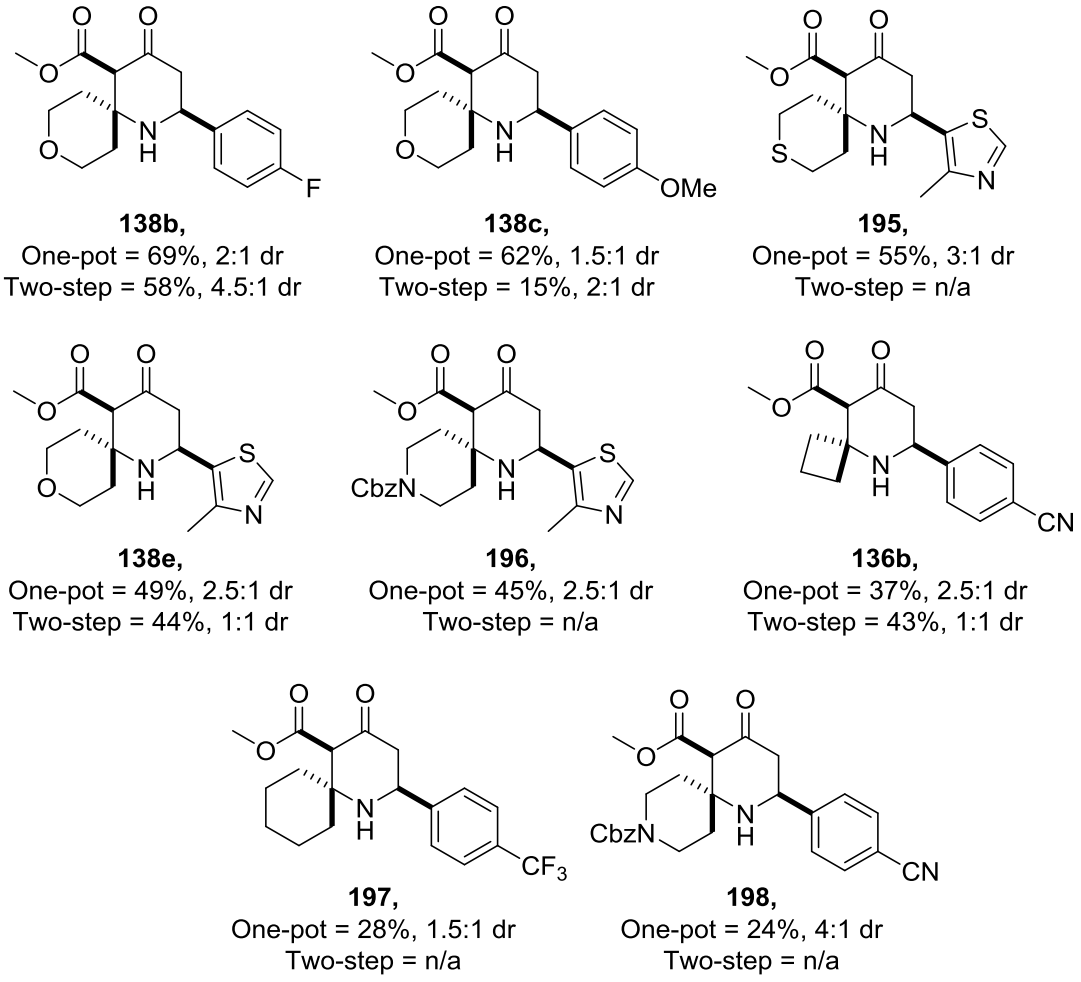
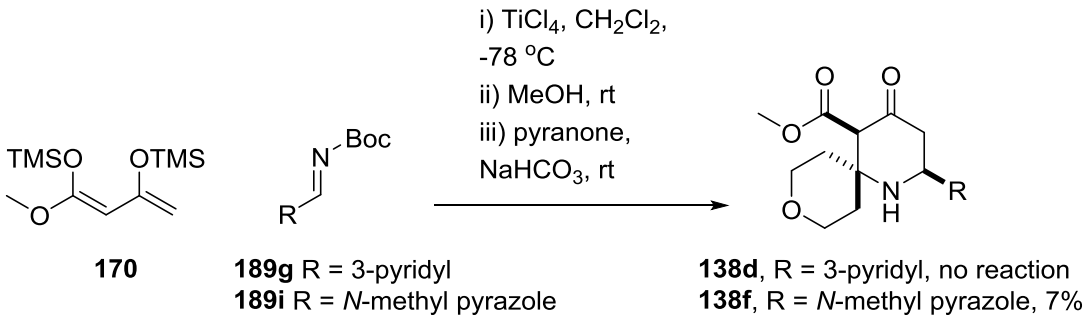


Figure 31. 2-Spiropiperidines synthesised using the one-pot procedure.

Interestingly, in some cases the dr of the one-pot procedure was better than the two-step procedure, and in others it was the opposite. With the reactions run at the same temperature, and the possibility of retro-Mannich reactions to occur under the reaction conditions, it was clear that there was not much control over the outcome of the reactions. An increase in reaction temperatures to induce retro-Mannich reactions and generate the thermodynamic product may be a method to increase diastereoselectivity.

The one-pot procedure had its limitations, and imines **189g** and **189i** performed badly under these conditions. The benefit of using the pyridine and pyrazole derivatives in the two-step reaction was that the 2-spiropiperidines were easy to separate from the respective crude reaction mixtures, because of their higher polarities. However, in the one-pot procedure, 2-spiropiperidine **138f** was isolated in a low 7% yield, and 2-spiropiperidine **138d** was not formed at all (Scheme 89).



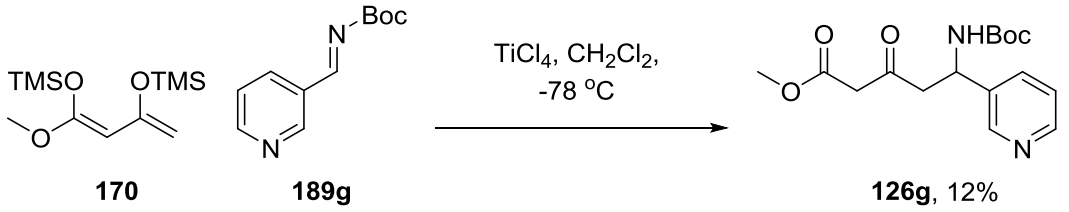
170

189g R = 3-pyridyl
189i R = *N*-methyl pyrazole

138d, R = 3-pyridyl, no reaction
138f, R = *N*-methyl pyrazole, 7%

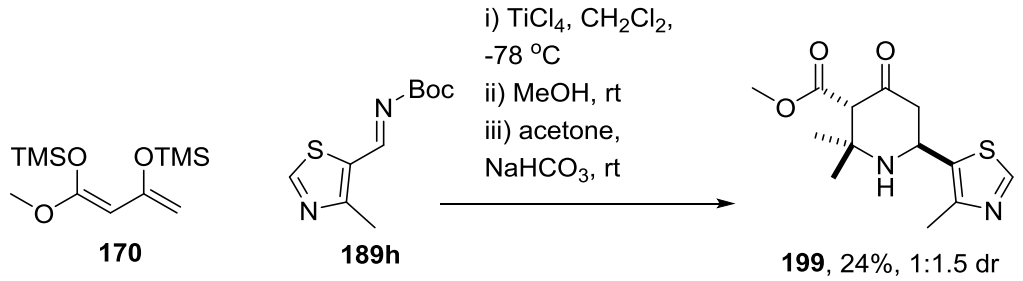
Scheme 89. Limitations of the one-pot procedure.

Presumably, the $TiCl_4$ was co-ordinating to the nitrogen of the aromatic group of the imine, and consequently hindering reactivity towards Mukaiyama-Mannich addition of Chan's diene **170**. To test this hypothesis, the Mukaiyama-Mannich was performed with Chan's diene **170** and *N*-Boc imine **189e** (Scheme 90). δ-Amino-β-ketoester **126g** was isolated in a low 12% yield, and confirmed that a pyridine is a poor substrate for the one-pot procedure.



Scheme 90. Mukaiyama-Mannich addition of Chan's diene to *N*-Boc imine **189g**.

Interestingly, when *N*-Boc imine **189h** was treated under the one-pot reaction conditions, there was a reversed selectivity to give 2-spiropiperidine **199** with a 1:1.5 dr (Scheme 91). This was the first example of an isolation of a 2-spiropiperidine where the C-3 and C-6 substituents exhibited an *anti*-relationship as the major product. As discussed previously, the electronics of the C-6 substituent may be key for the possibility of a retro-Mannich reaction occurring under the reaction conditions. The thiazole C-6 substituent gave no selectivity in the two-step procedure, yet gave a 1:1.5 dr in the one-pot procedure. Consequently, the *anti* product may be the thermodynamic product, which was slowly forming under the reaction conditions. An increase in the reaction temperature may increase the dr of the reaction.



Scheme 91. First example of a 2-spiropiperidine with C-3 and C-6 substituents exhibiting an *anti*-relationship.

As with the previous identification of the major diastereomer of cyclisation, the 2-spiropiperidine *anti* diastereomer **199** was confirmed through analysis of the ^{1}H NMR spectrum. The expansion of the ^{1}H NMR spectrum between 4 ppm and 2.3 ppm is shown below (Figure 32). The H-3 proton was observed as a singlet, meaning no 'W-coupling' was occurring with H-5_{eq}. The H-5_{eq} proton was now observed as a dd indicating only a coupling to

H-6 and a geminal coupling with H-5_{ax}. There was also a shift in the ppm of the H-5_{eq} proton from δ 2.97 ppm for the **199** minor product to δ 2.40 ppm for the **199** major product. There was also an enhancement of the H-5_{ax} proton at 2.59 ppm.

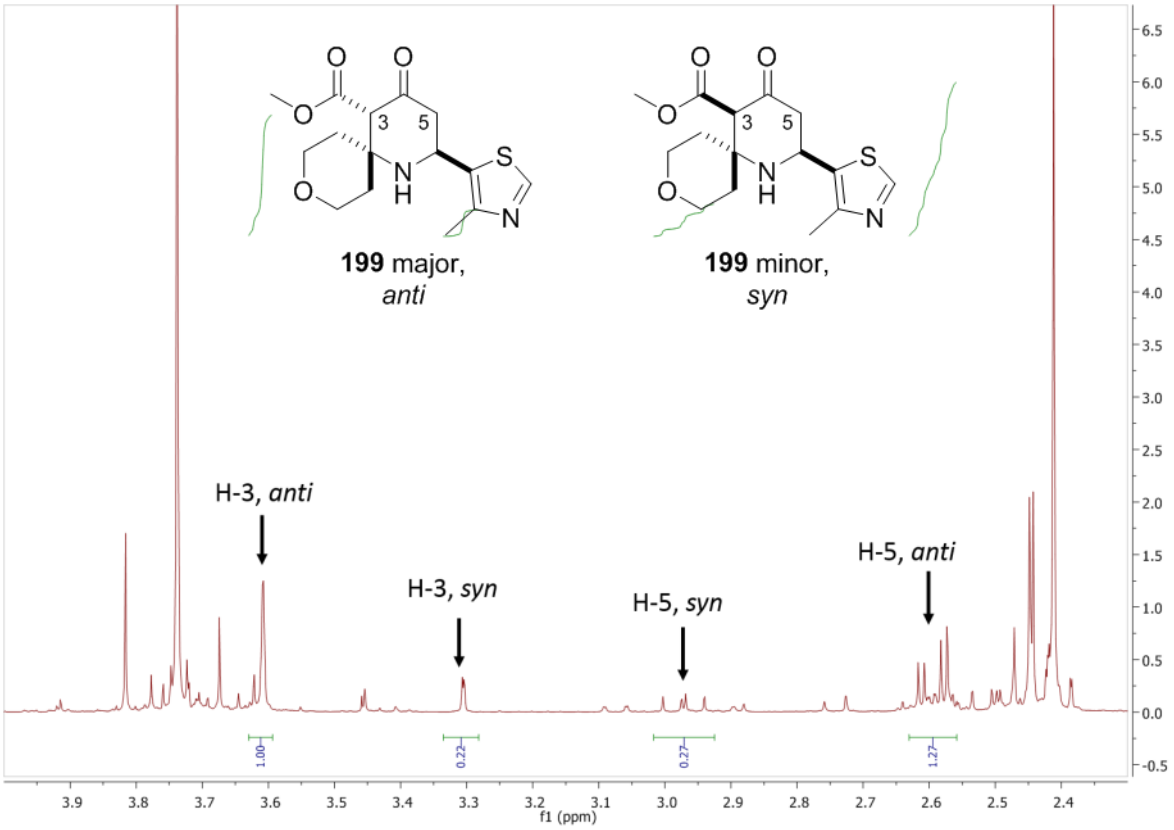
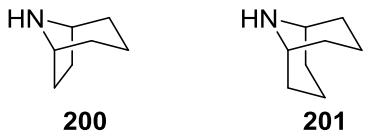


Figure 32. Expansion of the ^{1}H NMR for 2-spiropiperidine **199**.

5. Towards Other Functionalised Piperidines

5.1 Bridged Piperidines

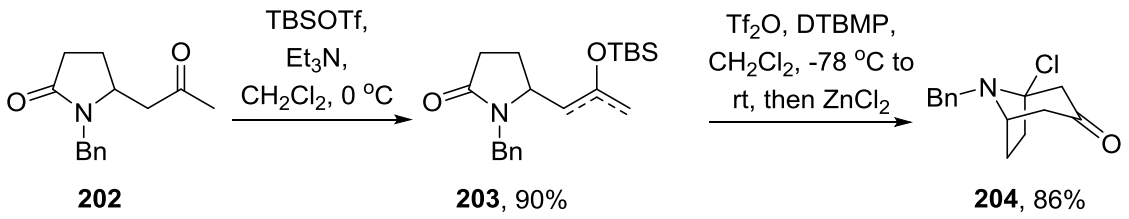
Initial aims of the project involved the synthesis and elaboration of 2-spiropiperidines, however, bridged piperidines were also deemed compounds of interest. Piperidines bridged between the C-2 and C-6 positions include molecules such as tropanes ([3.2.1] bicycles, **200**) and 9-azabicyclo[3.3.1]nonanes ([3.3.1] bicycles **201**) (Figure 33). Natural products containing tropanes include the well-known recreational drug cocaine,[175] and hyoscyamine used for treatment of Parkinson's disease.[176] 9-Azabicyclo[3.3.1]nonanes have also found use in medicinal chemistry as sigma-2 receptors[177] and serotonin receptors.[178]



200 **201**

Figure 33. Bridged piperidines.

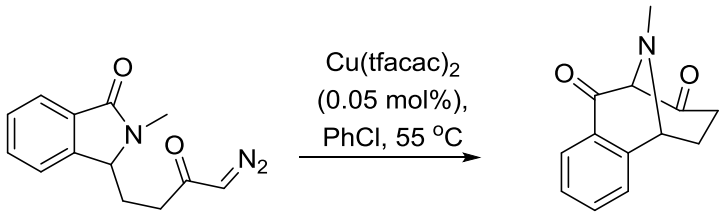
The synthesis of tropanes and 9-azabicyclo[3.3.1]nonanes have been reported to proceed from preformed piperidine rings, as well as forming the piperidine ring as the key bridge forming transformation. Huang demonstrated the synthesis of tropanes from γ-lactams **202**.[179] Treatment of γ-lactam **202** with TBSOTf gave silyl enol ether **203** in an excellent 90% yield (Scheme 92). Formation of the iminium triflate with Tf_2O/2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) followed by an intramolecular cyclisation generated the tropane ring, and the subsequent iminium ion was quenched with a halogen source to give tropane **204** in a high 86% yield. The scope of the reaction was demonstrated by the synthesis of 9-azabicyclo[3.3.1]nonanes as well, by the use of a δ-lactam.



202 **203**, 90% **204**, 86%

Scheme 92. Tropane synthesis by synthesis of the piperidine ring.

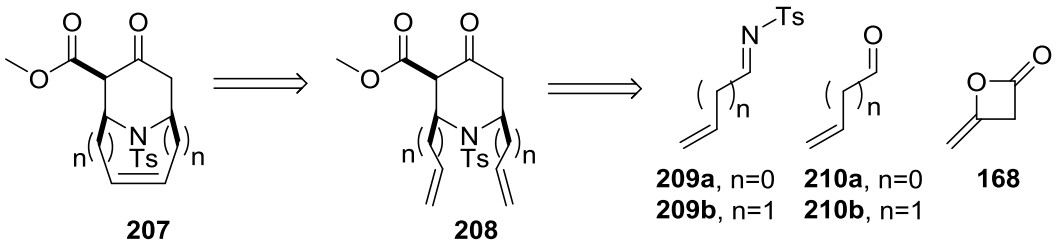
Harada and coworkers reported the synthesis of tropanes and 9-azabicyclo[3.3.1]nonanes via a carbenoid insertion to an amide bond with a low copper catalyst loading.[180] Upon treatment of isoindolinone **205** with $Cu(tfacac)_2$, the carbene generated inserted into the amide bond, forming the bridged amine **206** in a good 67% yield (Scheme 93). An example has also been presented by Harada for the synthesis of a non-aromatic tropane.



205 **206**, 67%

Scheme 93. 9-Azabicyclo[3.3.1]nonane synthesis by amide insertion.

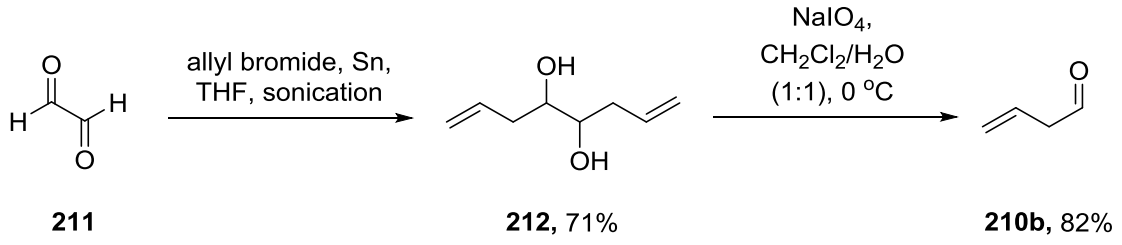
With expertise in the synthesis of piperidines, it was believed that the methods published from within the group could give rise to bridged piperidines.[181,182,95,109] If successful, these methods would provide a novel approach towards the synthesis of tropanes, 9-azabicyclo[3.3.1]nonanes and other bridged piperidines. Investigations began with a retrosynthetic analysis utilising the one-pot procedure reported by Clarke,[95] using aldimines and aldehydes with alkene-terminated chains (Scheme 94). The desired bridged piperidine **207** would arise from a ring closing metathesis of 2,6-substituted piperidine **207**. To keep the new ring size respectably small, only aldimines **209a-b** and aldehydes **210a-b** derived from acrolein and but-3-enal were used for the investigations. Depending on the combination used, bicyclic systems of [3.2.1], [3.3.1] and [4.3.1] could be accessed.



Scheme 94. Retrosynthetic plan for bridged piperidines.

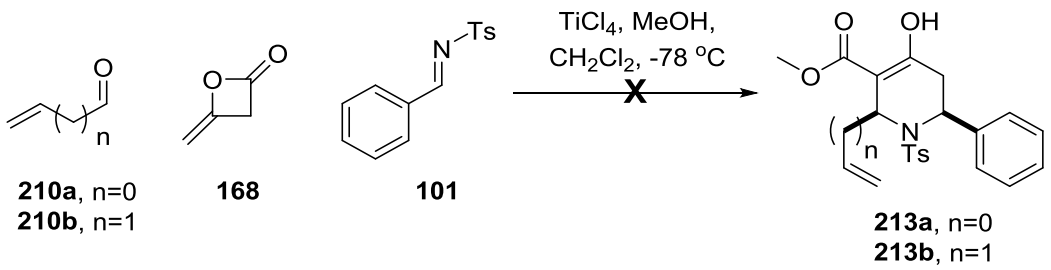
In preliminary studies the use of diketene was used as the primary nucleophilic species, so diketene had to be re-synthesised.[158,159] Unlike the previous synthesis that gave diketene as a solution in toluene, Et_2O was used as the reaction solvent, and the ethereal solution of diketene was carefully concentrated via nitrogen blow-down. Despite the extra care taken, large amounts of the highly volatile diketene was still lost giving diketene in 33% yield. As with the previous synthesis of diketene, the diketene was freshly prepared before use in each reaction.

To attempt the one-pot synthesis of **208**, access to the respective aldehydes **210** and aldimines **209** was required. Acrolein was commercially available, however, but-3-enal had to be synthesised. Using literature procedures, the Barbier addition of allyl bromide to glyoxal **211** gave diol **212** in a good 71% yield,[183] which subsequently underwent oxidative cleavage with $NaIO_4$ to give but-3-enal **210b** in a high 82% yield as a solution in CH_2Cl_2 (Scheme 95).[184]



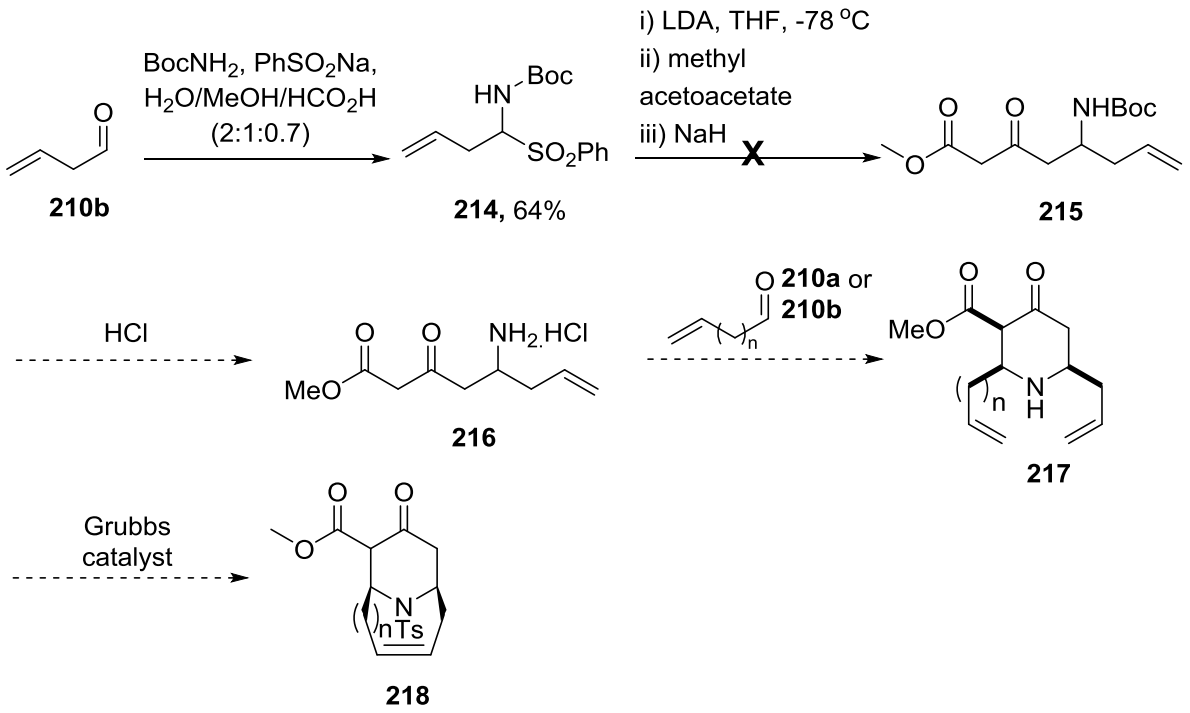
Scheme 95. Synthesis of but-3-enal from glyoxal.

On first attempts, the *N*-tosyl aldimines of acrolein and but-3-enal could not be synthesised. Unsure of the stability and reactivity of the synthesised diketene **168**, a trial reaction using *N*-tosyl aldimine **101** in the one-pot procedure was run (Scheme 96).[95] Disappointingly, with both acrolein **210a** and but-3-enal **210b**, the reaction yielded a complex mixture of products, with no desired piperidine **213a** or **213b** observed in the LCMS or ^{1}H NMR spectrum of the crude reaction mixtures. The product of initial Mannich addition was not observed either, indicating the diketene may have decomposed. The reaction may also have failed as the source of $TiCl_4$ was an old bottle of a 1 M solution of $TiCl_4$. Competing reactions such as conjugate addition and polymerisation may also be occurring under $TiCl_4$. Equally, the one-pot procedure proceeding by addition into acrolein or but-3-enal may not be favourable.



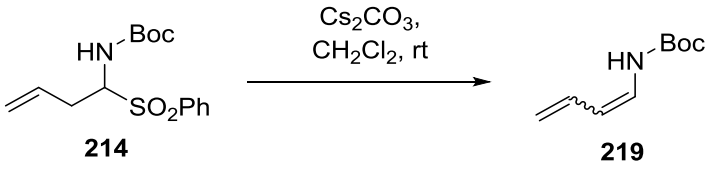
Scheme 96. One-pot procedure for piperidine synthesis with synthesised diketene.

With difficulties in achieving success with the one-pot procedure, attention was turned to synthesising the bridged piperidines by applying the recently developed stepwise procedure for 2-spiropiperidines (Scheme 97). *N*-Boc sulfone **214** was synthesised using the standard procedure for sulfone synthesis,[108] however, the synthesis of δ-amino-β-ketoester **215** was unsuccessful after multiple attempts.



Scheme 97. Stepwise procedure for the synthesis of bridged piperidines.

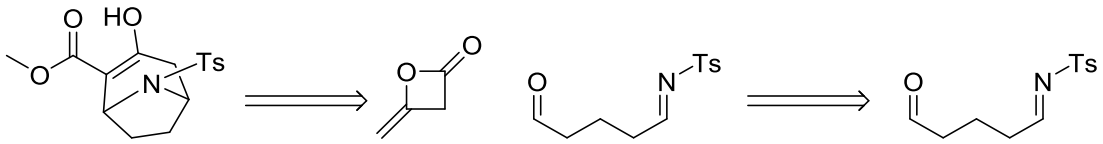
Uncertain as to why the Mannich reaction was unsuccessful, efforts were made to liberate and isolate the respective imine. *N*-Boc sulfone **214** was treated with Cs_2CO_3, and upon consumption of starting material, the mixture was filtered and concentrated *in vacuo* (Scheme 98). The isolated species was identified as enamine **219** (Scheme 98), and its presence was observed in the ^{1}H NMR spectrum of the crude reaction mixture of the unsuccessful Mannich reactions. The formation of the enamine **219** was understandable, as upon formation of the imine, tautomerisation to the enamine **219** brings the system into conjugation with the alkene making it more stable. Existing as the enamine, it is no longer a reactive electrophile and so explains the lack of reactivity for the Mannich reaction. The enamine **219** was stable to column chromatography, and was isolated as an inseparable mixture of *E*/*Z* stereoisomers.



214 **219**

Scheme 98. Confirmation of conjugated enamine **219**.

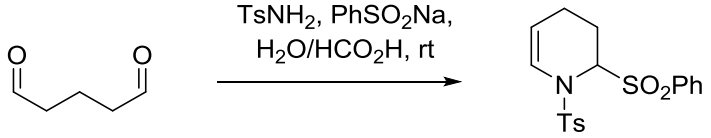
The formation of enamine **219**, coupled with an inability to form the *N*-Boc sulfone from acrolein, effectively ended the efforts towards a stepwise procedure. In a final attempt to form a bridged piperidine **220**, intramolecular delivery of the aldehyde was envisaged, requiring the synthesis of imine **221**, which would arise from the imine precursor *N*-tosyl sulfone **222** (Scheme 99).



220 **168** **221** **222**

Scheme 99. Retrosynthetic plan for intramolecular delivery of the aldehyde equivalent.

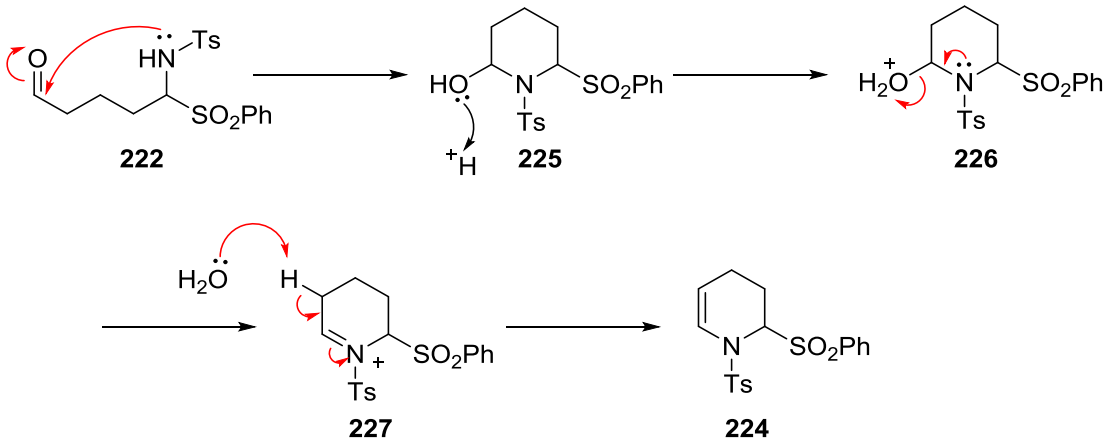
Glutyraldehyde **223** was subjected to standard conditions for *N*-tosyl sulfone formation, and a white solid was isolated as expected from the reaction (Scheme 100).[97] However, the ^{1}H NMR spectrum did not show formation of the desired *N*-tosyl sulfone **222**, nor the expected double addition product. Analysis of ^{1}H NMR spectrum suggested the formation of enamine **224**, which was confirmed by 2D NMR spectroscopy and HRMS.



223 **224**, 64%

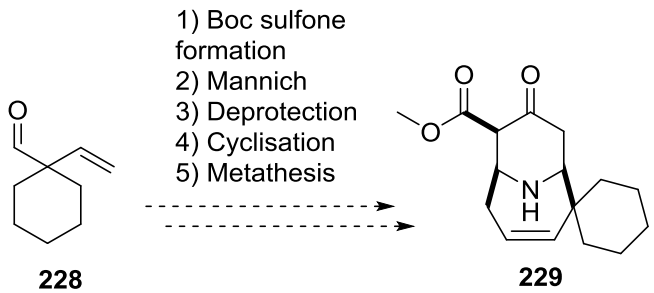
Scheme 100. Synthesis of enamine **224** from glutyraldehyde.

A plausible mechanism for the formation of enamine **224** proceeded via the desired *N*-tosyl sulfone **222** (Scheme 101). Aminal formation followed by dehydration gave imine **227** which subsequently tautomerised to enamine **224.**



Scheme 101. Plausible mechanism for the formation of enamine **224**.

Owing to time constraints, the synthesis of bridged piperidines was no longer pursued. A potential method to access bridged piperidines could be to use an alkene that cannot tautomerise into conjugation, such as pent-4-enal. This however, would ultimately lead to a bridged system with a larger ring size than may be desired. If but-3-enal was used, the 2-position would need to be 'blocked' by having a quaternary carbon, in order to avoid imine-enamine tautomerisation. Though lengthy, this stepwise procedure would then give rise to spirocyclic bridged piperidines (Scheme 102).



Scheme 102. Stepwise synthesis of spirocyclic bridged piperidines.

5.2 Fused Piperidines

Another class of desirable compounds were 2-spiropiperidines with fused rings. Examples of natural product containing piperidines with fused rings include indolizidine 209B **230**[185] and pumiliotoxins A and B **231**[186] (Figure 34), isolated from poison frogs.

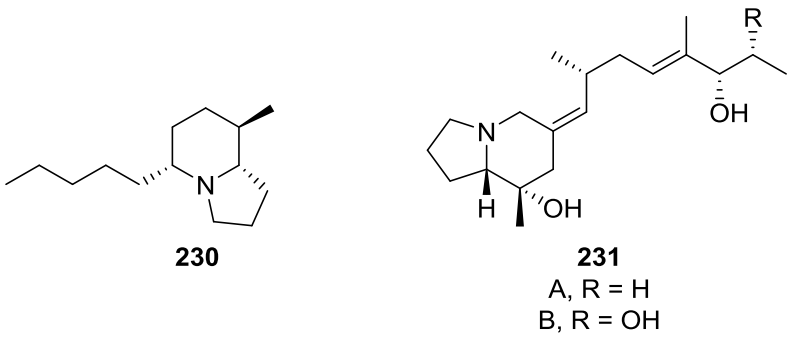
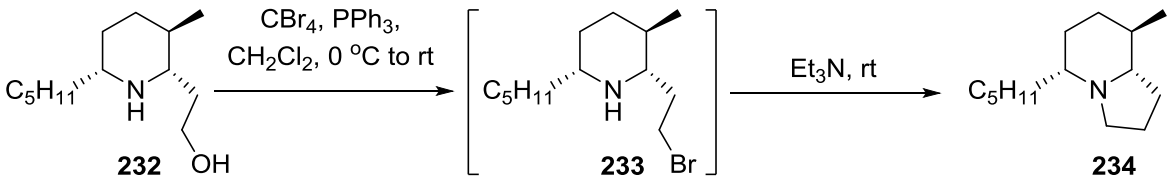


Figure 34. Natural products containing fused piperidine rings.

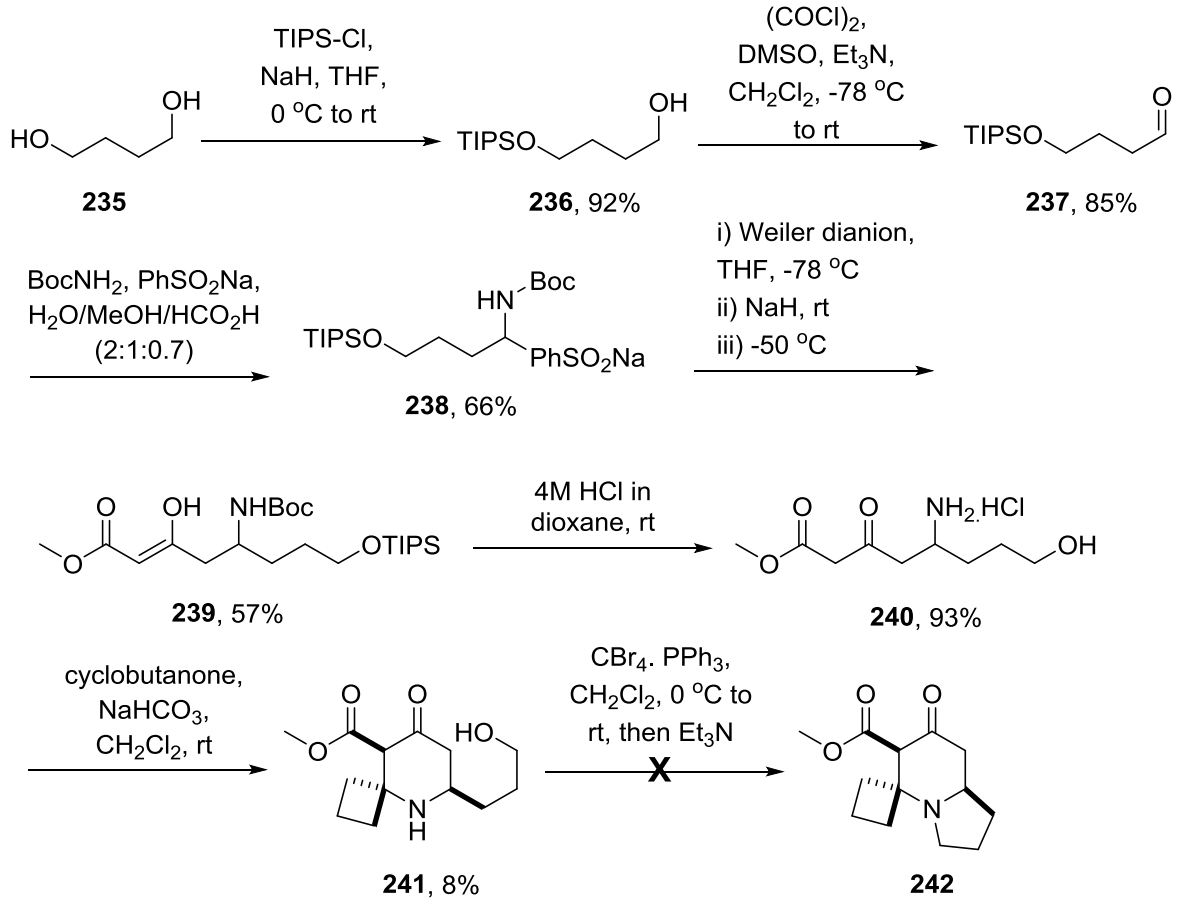
The pumiliotoxins have been synthesised by a variety of methods,[187] however the reported syntheses of indolizidine 209B has been found to proceed via the same procedure.[188,189,190] Treatment of alcohol **232** under Appel conditions converted to the bromide **233**, which was subsequently displaced by the piperidine nitrogen upon addition of Et_3N to give the fused piperidine **234** (Scheme 103).[188]



Scheme 103. Indolizidine synthesis by bromide displacement.

It was postulated that extension of the two-step procedure for the synthesis of 2-spiropiperidines systems similar to that of alcohol **232** would give access to fused ring systems. Aldehyde **237** was synthesised in excellent yield over two steps from 1,4-butanediol

235; first by TIPS protection to alcohol **236**[191] followed by Swern oxidation to aldehyde **237**[192] (Scheme 104). The imine precursor *N*-Boc sulfone **238** was synthesised via the procedure of Lam[108] in a good 66% yield, and subsequent Mannich reaction[109] with the Weiler dianion[98] gave the *N*-Boc-δ-amino-β-ketoester **239** in a moderate 57% yield. Deprotection of the amine also resulted in fortuitous TIPS deprotection to give **240** in an excellent 93% yield. Using the reported conditions for spirocyclisation, HCl salt **240** was treated with cyclobutanone to give 2-spiropiperidine **241** in a disappointingly low 8% yield after column chromatography. It was believed that product was lost during column chromatography, as the high yielding crude reaction showed a relatively clean ^{1}H NMR spectrum. Finally, upon subjection of 2-spiropiperidine **241** to the conditions presented by Davis for indolizidine synthesis,[188] no reaction was observed by TLC or by ^{1}H NMR spectrum of the crude reaction mixture. The mass peak of product indolizidine **242** was observed by HRMS, but was not isolated. Due to time constraints, the synthesis of indolizidine **242** could not be reattempted.



Scheme 104. Indolizidine synthesis via the two-step procedure for 2-spiropiperidines.

6. Conclusions

The first general synthesis of highly functionalised 2-spiropiperidines has been presented via a simple, robust, stepwise procedure. Preliminary results using *N*-Tosyl aldimines were unsuccessful, however the use of *N*-Boc imines ultimately furnished the desired 2-spiropiperidines. The scope of the stepwise procedure was demonstrated by the synthesis of a range of aromatic- and aliphatic-substituted 2-spiropiperidines bearing carbocyclic and heterocyclic spirocycles. The cyclisation reaction proceeded in moderate to excellent yields, with moderate to good diastereoselectivities.

A small library of functionalised 2-spiropiperidines was constructed, by performing a range of reactions on the ester, ketone and amine handles. The manipulations were driven by the desire to introduce medicinally relevant properties, and in the case of the methyl ester, to remove undesirable functionality. Successful reactions included decarboxylation, reduction, amidation, alkylations, and epoxidation. Unfortunately, fluorination of the 2-spiropiperidines was unsuccessful and requires further work.

The three-dimensionality of the 2-spiropiperidines was analysed by PMI analysis. It was determined that the 2-spiropiperidine scaffolds occupy the underrepresented region of chemical space. Whilst the functionalised 2-spiropiperidines were less three-dimensional than the respective scaffolds, they still occupied the desired region of chemical space. LLAMA analysis of the functionalised 2-spiropiperidines also rendered them as 'lead-like', concluding that the 2-spiropiperidines have potential to be medicinally relevant.

The procedure for the synthesis of 2-spiropiperidines was developed to a one-pot procedure using *N*-Boc imines and Chan's diene with $TiCl_4$. An *in situ* deprotection of the δ-amino-β-ketoester allowed cyclisation to proceed, furnishing the 2-spiropiperidines in moderate to good yields and moderate to good diastereoselectivities.

The synthesis of other structurally interesting piperidines was trialled. The synthesis of bridged piperidines using but-3-enal resulted in unwanted tautomerisation, and a procedure to allow intramolecular delivery of the second aldehyde was also unsuccessful. Initial results for the stepwise synthesis of fused piperidines was also unsuccessful, however, the procedure

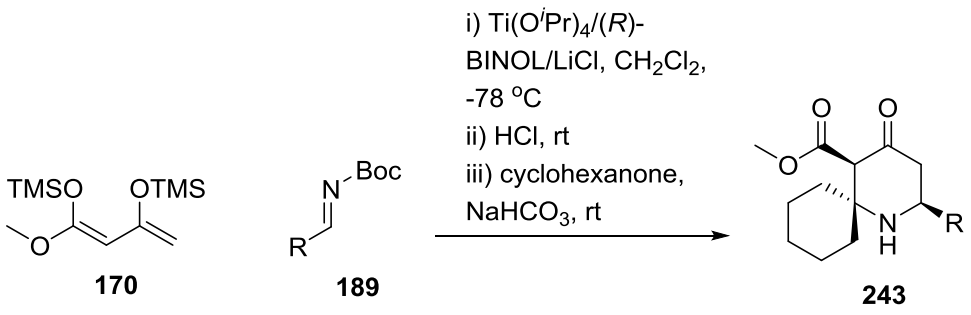
to access the cyclisation precursor was straightforward, and so the subsequent cyclisation to the fused piperidine can be trialled with a range of bases.

7. Future Work

7.1 Towards an Asymmetric Synthesis

With a one-pot procedure in place, it would now be possible to devise an asymmetric synthesis of 2-spiropiperidines. It is desirable to perform the reaction in one-pot, so the use of titanium-based catalysts is preferred, despite the precedent for Mukaiyama addition of Chan's diene to electrophiles.[162,193] Asymmetric Mukaiyama-aldol reactions have been reported for the addition of silyl enol ethers,[194] and Chan's diene[164] with Ti(BINOL) and BINOL derived[195] complexes. Asymmetric Mukaiyama-Mannich reactions have been reported with silyl ketene acetals[196,197] with Ti(BINOL) complexes, and it is believed the scope can be extended for the use with Chan's diene **170**.

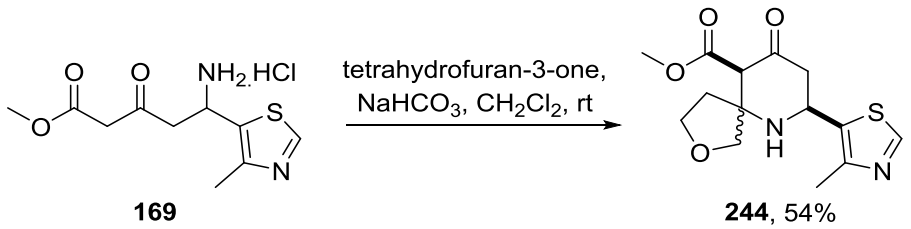
For the synthesis to proceed, HCl may need to be introduced via a different method after Mannich addition of Chan's diene **170**. Clarke reported the use of $Ti(O^iPr)_4$/BINOL/LiCl mixtures for the Mannich addition,[164] which clearly would not generate HCl upon addition of MeOH. Methanolic HCl may be an option to investigate. A hypothetical one-pot procedure has been presented with Chan's diene **170** and an *N*-Boc imine **189** (Scheme 105), though the initial Mannich reaction to generate the δ-amino-β-ketoester would need to be investigated first.



Scheme 105. Plausible asymmetric synthesis of 2-spiropiperidines.

7.2 Non-Symmetrical 2-Spiropiperidines

The method for the synthesis of 2-spiropiperidines had only been applied to symmetrical ketones for ease with analysis. The use of a non-symmetrical ketone would generate additional diastereomers making analysis more challenging. Treatment of HCl salt **169** with tetrahydrofuran-3-one gave 2-spiropiperidine **244** in a moderate 54% yield (Scheme 106).



169 **244**, 54%

Scheme 106. Synthesis of a non-symmetrical 2-spiropiperidine.

The reported 54% yield for the cyclisation with tetrahydrofuran-3-one was the yield for all diastereomers, with no separation achieved by column chromatography. Interpretation of the ^{1}H and ^{13}C NMR spectra was consequently challenging, with multiple overlapping peaks observed in the ^{1}H NMR spectrum, as shown in the expansion between δ 4.60 ppm and δ 2.30 ppm (Figure 35). Identification of the major diastereomer was not possible. A key feature of the ^{1}H NMR spectrum that could be clearly identified was the H-5_{ax} proton double-doublet for the C-3/C-6 *syn* 2-spiropiperidines at δ 2.97 ppm and δ 2.89 ppm (Figure 35). The other clear feature for the C-3/C-6 *syn* 2-spiropiperidines was the H-3 doublets at δ 3.47 ppm and δ 3.40 ppm. These confirmed the formation of 2-spiropiperidine **244**, and the desired mass peak was found in HRMS. Believing the diastereomers could be separated, MDAP was attempted on 2-spiropiperidine **244**, but no product was retrieved from the purification process. Preparative HPLC may be required to achieve separation of the diastereomers.

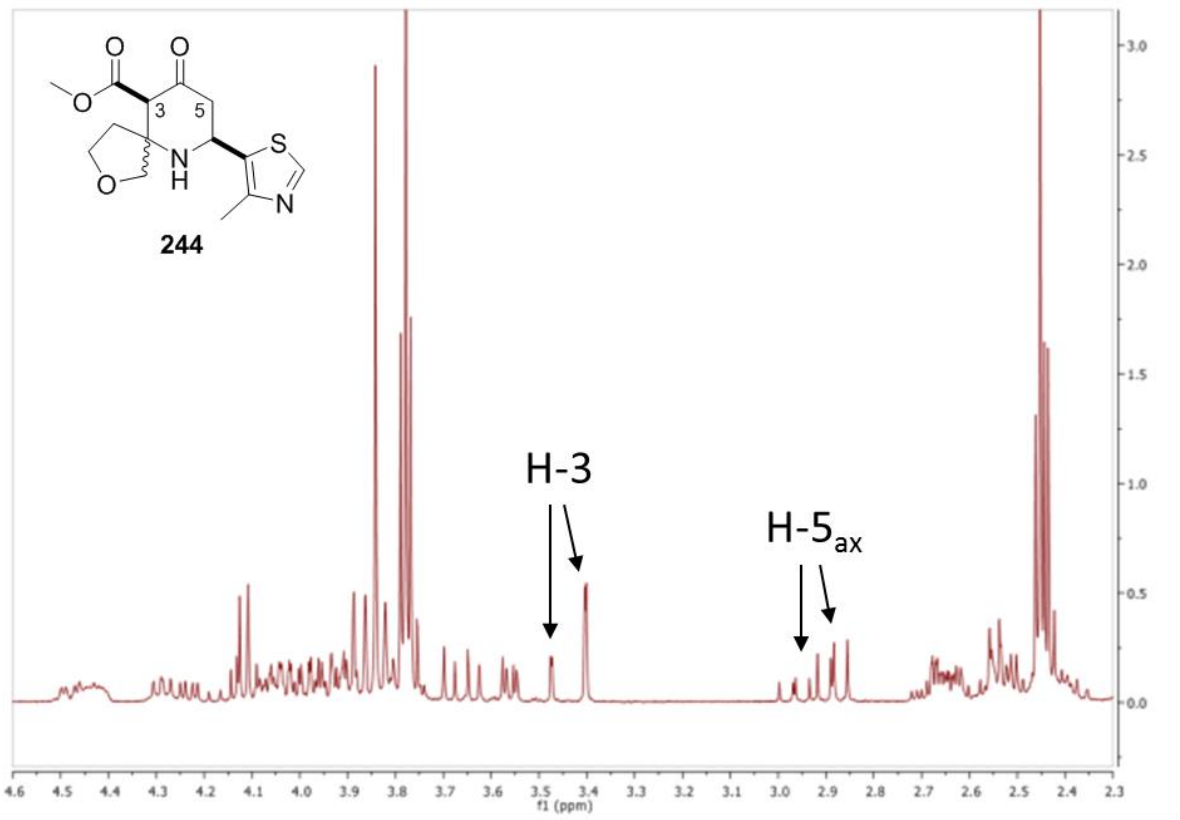
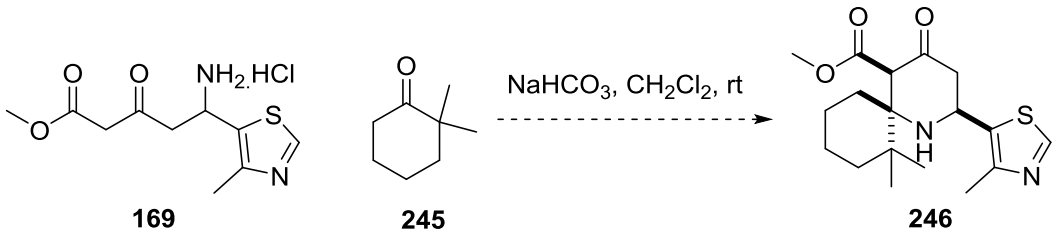


Figure 35. Expansion of the ^{1}H NMR of 2-spiropiperidine **244**.

Conditions for a more selective cyclisation will need to be devised. Use of 2,2-dimethylcyclohexanone **245** could bias the selectivity and eradicate the formation of two diastereomers by avoiding the large steric clash between the geminal-dimethyl group and the C-3 ester (Scheme 107).



Scheme 107. Synthesis of a non-symmetrical 2-spiropiperidine with 2,2-dimethylcyclohexanone.

The original spirocyclisation allowed the introduction of piperidine rings as the spirocycle, for example 2-spiropiperidine **142**. It would also be desirable to install piperidine rings as the spirocycle at the 2- (**247**) and 3- (**248**) positions (Figure 36). Spirocycle **248** could be synthesised from the respective non-symmetrical piperidin-3-one, however similar problems encountered with 2-spiropiperidine **244** may occur, so a large bulky protecting could bias selectivity and make purification easier.

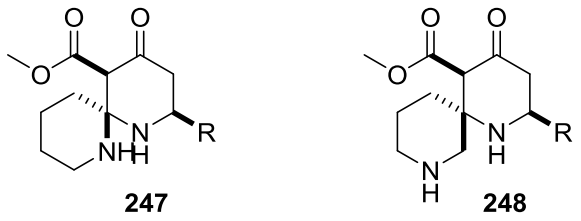
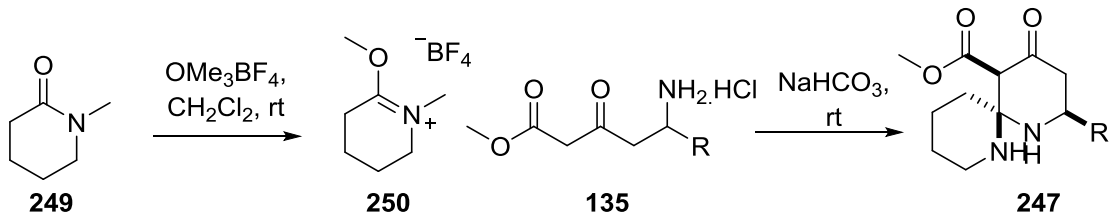


Figure 36. Example 2-spiropiperidines with piperidine spirocycles.

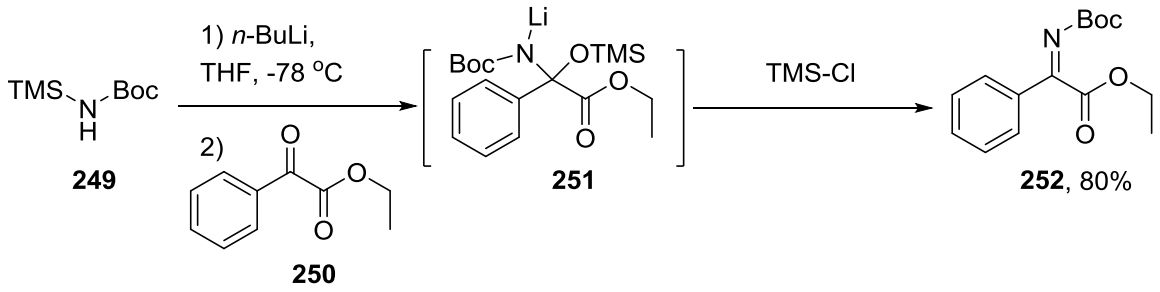
The synthesis of 2-spiropiperidine **247** would require a slightly different approach, as the respective ketone is actually a lactam. Consequently, no reactivity would be observed under the cyclisation conditions. It is believed that a species such as iminium **250** would need to be synthesised. *O*-Methylation of *N*-methyl-δ-valerolactam **249** with Meerwein's salt gives imine **250**,[198] which could be treated under the two-step spirocyclisation reaction conditions to give rise to 2-spiropiperidine **247** (Scheme 108).



Scheme 108. Plausible synthesis of 2-spiropiperidine **247**.

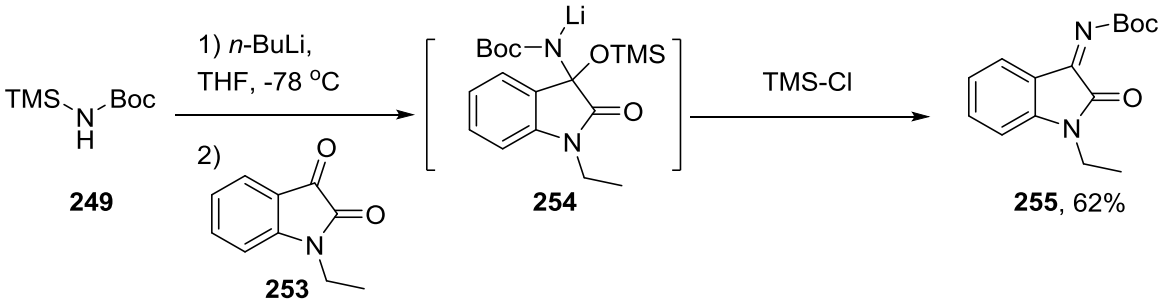
7.3 6-Spiropiperidines

Having devised a stepwise procedure for the synthesis of 2-spiropiperidines, the synthesis of 6-spiropiperidines was also desirable. To use the reported 2-step procedure, this would require the synthesis of an *N*-Boc ketimine. The synthesis of *N*-Boc ketimines has been reported, but only on specific systems such as benzylic ketones. Maruoka reported the synthesis of non-symmetrical *N*-Boc α-ketimino esters (Scheme 109).[199] Treatment of *N*-TMS Boc amide **249** with *n*-BuLi, followed by addition into ethyl benzoyl formate **250** gave tetrahedral intermediate **251**, which subsequently collapsed upon addition of TMS-chloride to give *N*-Boc α-ketimino ester **252**. The reaction has been demonstrated with different benzylic systems and varied aliphatic esters.



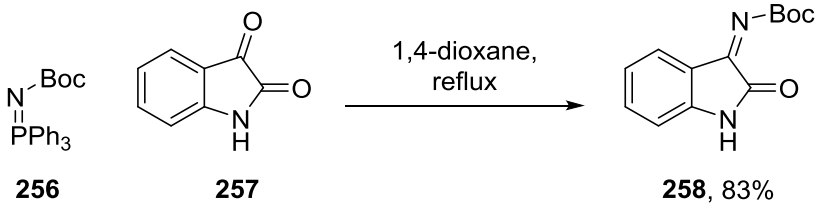
Scheme 109. Synthesis of *N*-Boc α-ketimino esters.

The most common handle for *N*-Boc ketimine synthesis is an isatin, with varied degrees of substitution. Using the same conditions as Maruoka,[199] Nakamura and coworkers demonstrated the application of the chemistry to substituted isatins **253** (Scheme 110).[200] Utility of *N*-Boc ketimine **255** would provide access to a non-symmetrical 6-spiropiperidine.



Scheme 110. Maruoka's synthesis of *N*-Boc ketimines applied to isatins.

An Aza-Wittig reaction[201] was performed on isatin **257** with *N*-Boc-imino-triphenylphosphorane **256** as demonstrated by Pedro[202] and Wang[203] (Scheme 111). *N*-Boc ketimines have been described to be substituted around the aromatic ring, as well as on the isatin nitrogen. Wang also described the addition of a 1,3-dicarbonyl to the *N*-Boc ketimine,[203] showing hindered systems can be formed.

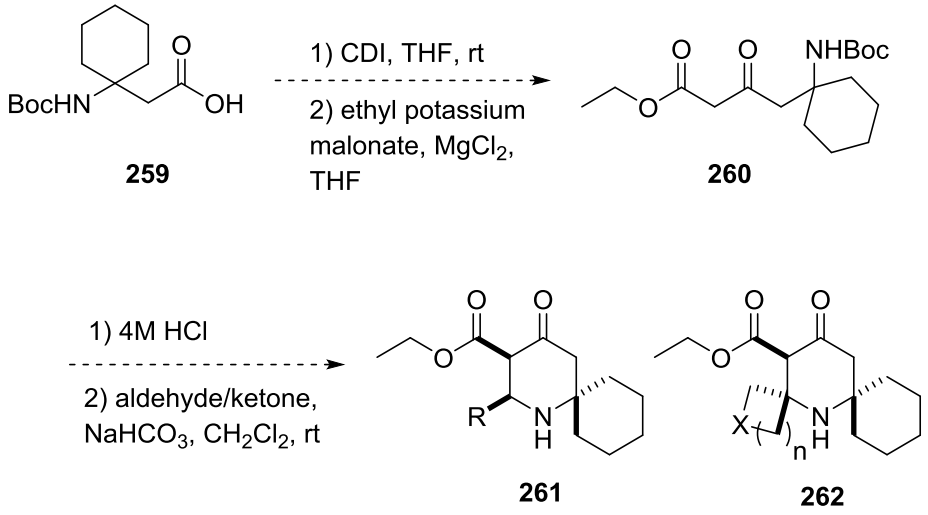


Scheme 111. Aza-Wittig reaction for the synthesis of *N*-Boc ketimines.

Unsurprisingly, when conditions were repeated on cyclohexanone, no reaction occurred. The formation of reported *N*-Boc ketimines have all been performed on highly electron withdrawn systems. This would explain the lack of literature precedent for the formation of simple, cyclic, symmetrical *N*-Boc ketimines.

In the two-step synthesis of 2-spiropiperidines, a procedure was presented for the synthesis of 2-spiropiperidines without a C-6 substituent (Scheme 42). It was believed that this procedure could be adapted to allow the synthesis of 6-spiropiperidines. The synthesis of the β-amino acid precursor has been described by Rai,[204] and subsequent Boc-protection would give rise to carboxylic acid **259** (Scheme 112). Treatment of carboxylic acid **259** with CDI

followed by ethyl potassium malonate[205] would give δ-amino-δ-ketoester **260**, which would undergo the two-step cyclisation procedure reported to give rise to 6-spiropiperidines **261** or 2,6-*bis*-spiropiperidines **262**. Initial attempts at the formation of carboxylic acid **259** were unsuccessful, and due to time constraints, the method was not pursued.



259 **260** **261** **262**

Scheme 112. Plausible synthesis for 6-spiropiperidines or 2,6-bis-spiropiperidines.

8. Experimental

8.1 General Experimental

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Unless otherwise noted the dry solvent used was purified by PureSolv alumina columns from Innovative Technologies. Melting points were determined using a Stuart SMP3 apparatus. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400, a Jeol 500 Avance III HD 500 or a Jeol AV500 at ambient temperature. Coupling constants (*J*) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Thin layer chromatography was performed on aluminium-backed plates coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate or basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Sigma-Aldrich.

8.2 Methods and Characterisation of Compounds

General Procedure A - Synthesis of benzenesulfonyl carbamic esters pg. 124

General Procedure B - Synthesis of *N*-Boc-δ-amino-β-ketoesters pg. 130

General Procedure C - Synthesis of 2-spiropiperidines from *N*-Boc-δ-amino-β-ketoesters pg. 140

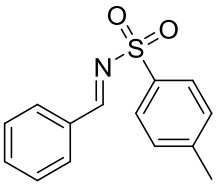
General Procedure D – Decarboxylation of the 2-spiropiperidines pg. 154

General Procedure E – Ketone reduction of the 2-spiropiperidines pg. 157

General Procedure F – Direct amidation of the 2-spiropiperidines pg. 161

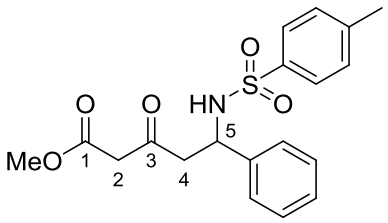
General Procedure G - Synthesis of *N*-Boc-imines pg. 176

General Procedure H - One-Pot cyclisation pg. 181



_N_-Benzylidene-4-methyl-benzenesulfonamide (101)

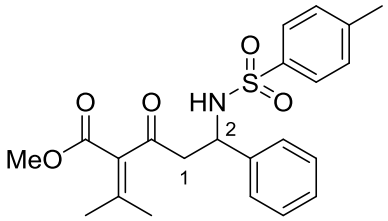
To a solution of benzaldehyde (400 mg, 3.77 mmol) in water/formic acid (1:1, 22 mL), was added tosylamide (645 mg, 3.77 mg), and *p*-toluene sulfinic acid sodium salt (672 mg, 3.77 mmol) at rt. The mixture was stirred overnight at rt. The precipitate was filtered, washed with water (2 x 5 mL), and hexane (10 mL). The solid was dissolved in CH_2Cl_2 (30 mL), and was stirred in sat.aq. $NaHCO_3$ (20 mL) for 1 hour at rt. The layers were separated and the aqueous was extracted with CH_2Cl_2 (20 mL). Organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (484 mg, 2.15 mmol, 78% yield) as a white solid. Mp 115-117 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 9.02 (1H, s, CH), 7.93-7.76 (4H, m, Ar*H*), 7.63-7.58 (1H, m, Ar*H*), 7.48 (2H, t, *J* = 7.6 Hz, Ar*H*), 7.34 (2H, d, *J* = 8.0 Hz, Ar*H*), 2.43 (3H, s, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4 (CH), 144.8 (C), 139.2 (C), 135.2 (C), 131.5 (CH), 129.8 (CH), 129.2 (CH), 128.2 (CH), 126.6 (CH), 21.7 (CH_3) ppm; HRMS (ESI) 260.0748 ($M + H^+$. $C_{14}H_{14}NO_2S$ requires 260.0740); IR (ATR): ν_{max} 3071, 1595, 1572, 1449, 1315, 1304, 1154, 1085 cm^{-1}.



Methyl 3-oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoate (102)

To a solution of diisopropylamine (824 µL, 5.89 mmol) in THF (10 mL) at -78 ^oC was added *n*-BuLi (2.41 mL, 5.79 mmol) dropwise. The mixture was warmed to 0 ^oC for 15 mins, then re-cooled to -78 ^oC. A solution of methyl acetoacetate (312 µL, 2.90 mmol) in THF (2 mL) was added *via* syringe pump over 20 mins. The mixture was warmed to -50 ^oC, and a solution of **101** (250 mg, 0.965 mmol) in THF (2 mL) was added fast. The reaction was stirred for 40 mins, then quenched with sat. aq. NH_4Cl (4 mL). The mixture was warmed to rt, and layers were

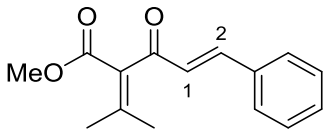
separated. The aqueous was extracted with EtOAc (2 x 20 mL). Organics were combined, washed with water (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (10-30% EtOAc/hexane) to give the title compound (242 mg, 0.647 mmol, 67% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (2H, m, Ar*H*), 7.20-7.11 (5H, m, Ar*H*), 7.09-7.04 (2H, m, Ar*H*), 5.69 (1H, d, *J* = 7.2 Hz, NH), 4.73 (1H, dt, *J* = 7.2, 6.3 Hz, H-5), 3.65 (3H, s, OCH_3), 3.36 (1H, d, *J* = 15.5 Hz, H-2), 3.31 (1H, d, *J* = 15.5 Hz, H-2), 3.17 (1H, dd, *J* = 17.4, 6.3 Hz, H-4), 3.01 (1H, dd, *J* = 17.4, 6.3 Hz, H-4), 2.36 (3H, s, CH_3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.6 (C=O), 167.3 (C=O), 143.5 (C), 139.5 (C), 137.1 (C), 129.6 (CH), 128.7 (CH), 127.9 (CH), 127.3 (CH), 126.7 (CH), 54.0 (CH), 52.5 (CH_3), 49.5 (CH_2), 49.3 (CH_2), 21.6 (CH_3) ppm; HRMS (ESI) 398.1024 (M + Na^+.$C_{19}H_{21}NNaO_5S$ requires 398.1033); IR (ATR): ν_{max} 3277, 2953, 1740 (C=O), 1713 (C=O), 1321, 1154 cm^{-1}.



Methyl 2-isopropylidene-3-oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoate (103)

To a 0.5 M solution of $TiCl_4$ in THF (2 mL, 1.07 mmol) at 0 ^{o}C was added a solution of **102** (400 mg, 1.07 mmol), acetone (156 µL, 2.13 mmol), and pyridine (345 µL, 4.26 mmol) in THF (2 mL). The reaction was stirred overnight at rt. The reaction mixture was partitioned between water (10 mL) and EtOAc (30 mL). The aqueous was extracted with EtOAc (2 x 15 mL). Organics were combined, washed with $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/hexane) to give the title compound (115 mg, 0.277 mmol, 26% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (2H, m, Ar*H*), 7.19-7.12 (5H, m, Ar*H*), 7.11-7.05 (2H, m, Ar*H*), 5.71 (1H, d, *J* = 7.0 Hz, NH), 4.74 (1H, dt, *J* = 7.0, 6.2 Hz, H-2), 3.60 (3H, s, OCH_3), 3.12 (1H, dd, *J* = 17.5, 5.9 Hz, H-1), 2.96 (1H, dd, *J* = 17.5, 6.2 Hz), 2.36 (3H, s, ArCH_3), 2.05 (3H, s, CCH_3), 1.65 (3H, s, CCH_3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 201.1 (C=O), 165.5 (C=O), 156.1 (C), 143.3 (C), 139.8 (C), 137.4 (C), 130.9 (C), 129.5 (CH), 128.5 (CH), 127.7 (CH), 127.3 (CH),

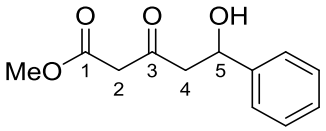
126.8 (CH), 54.3 (CH), 51.9 (CH_3), 49.4 (CH_2), 23.5 (CH_3), 23.1 (CH_3), 21.6 (CH_3) ppm; HRMS (ESI) 438.1338 (M + Na^+. $C_{22}H_{25}NNaO_5S$ requires 438.1346); IR (ATR): ν_{max} 3278, 2952, 1726 (C=O), 1694 (C=O), 1156 cm^{-1}.



2-Isopropylidene-3-oxo-5-phenyl-pent-4-enoic acid methyl ester (104)

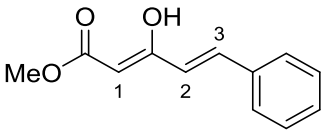
Method A: To a solution of **103** (85 mg, 0.205 mmol) in CH_2Cl_2 (2 mL) at rt was added $TiCl_4$ (112 µL, 1.03 mmol). The mixture was stirred overnight at rt. Water (5 mL) was carefully added, followed by dilution with CH_2Cl_2 (10 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (10 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (5.4 mg, 0.0223 mmol, 11% yield) as a yellow oil.

Method B: To a 0.5 M solution of $TiCl_4$ in THF (1.5 mL, 0.735 mmol) at 0 ^oC was added a solution of **106** (150 mg, 0.735 mmol), acetone (108 µL, 1.47 mmol), and pyridine (240 µL, 2.94 mmol) in THF (1 mL). The reaction was stirred overnight at rt. The reaction mixture was partitioned between water (5 mL) and EtOAc (30 mL). The aqueous was extracted with EtOAc (2 x 15 mL). Organics were combined, washed with $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/hexane) to give the title compound (23 mg, 0.0942 mmol, 13% yield) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.49 (2H, m, Ar*H*), 7.42 – 7.35 (3H, m, Ar*H*), 7.42 (1H, d, *J* = 16.2 Hz, H-1), 6.80 (1H, d, *J* = 16.2 Hz, H-2), 3.69 (3H, s, OCH_3), 2.26 (3H, s, CH_3), 1.87 (3H, s, CH_3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 195.5 (C=O), 165.5 (C=O), 154.8 (C), 145.6 (CH), 134.5 (C), 130.9 (C), 129.5 (CH), 129.1 (CH), 128.6 (CH), 127.6 (CH), 51.9 (CH_3), 24.2 (CH_3), 22.5 (CH_3) ppm; HRMS (ESI) 267.0992 (M + Na^+. $C_{16}H_{16}NaO_3$ requires 267.0992); IR (ATR): ν_{max} 3063, 2912, 1708 (C=O), 1641 (C=O), 1620, 1596, 1435, 1301, 1238, 1217, 1201, 1097, 1033 cm^{-1}.



Methyl 5-hydroxy-3-oxo-5-phenyl-pentanoate (105)

A 3 M solution of $TiCl_4$ in CH_2Cl_2 (3.60 mL, 10.8 mmol) was added dropwise to a solution of diketene (2.79 mL, 18.1 mmol) and benzaldehyde (0.96 mL, 9.43 mmol) in CH_2Cl_2 (45 mL) at -78 ^oC. The mixture was stirred for 5 mins, followed by the addition MeOH (12 mL). The reaction was stirred at -16 ^oC for 50 mins. The mixture was poured onto ice cooled 0.44 M K_2CO_3 solution (65 mL). EtOAc (120 mL) was added and the layers were separated. The aqueous was extracted with EtOAc (3 x 50 mL). Organics were combined, washed with $NaHCO_3$ (150 mL), and brine (150 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15-20% EtOAc/hexane) to give the title compound (1.60 g, 7.22 mmol, 76% yield) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.32 (4H, m, Ar*H*), 7.32 – 7.27 (1H, m, Ar*H*), 5.19 (1H, dd, *J* = 9.3, 3.1 Hz, H-5), 3.74 (3H, s, CH_3), 3.50 (2H, s, H-2), 3.01 (1H, dd, *J* = 17.4, 9.3 Hz, H-4), 2.91 (1H, dd, *J* = 17.4, 3.1 Hz, H-4). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 202.8 (C=O), 167.4 (C=O), 142.6 (C), 128.7 (CH), 127.9 (CH), 125.7 (CH), 69.9 (CH), 52.6 (CH_3), 51.7 (CH_2), 49.8 (CH_2) ppm; HRMS (ESI) 245.0776 (M + Na^+. $C_{12}H_{24}NaO_4$ requires 245.0784). ^1H NMR data was in agreement with literature.[96]



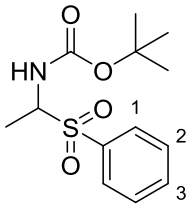
3-Hydroxy-5-phenyl-penta-2,4-dienoic acid methyl ester (106)

To a solution of **105** (500 mg, 2.25 mmol) in CH_2Cl_2 (3 mL) was added acetic anhydride (223 µL, 2.36 mmol), Et_3N (470 µL, 3.38 mmol) and DMAP (cat.). The reaction was stirred for 2h at rt. MeOH (400 µL) was added, and the mixture stirred for 15 mins. The mixture was diluted with CH_2Cl_2 (8 mL) and partitioned with 0.1 M HCl (10 mL). Organics were combined, washed with water (10 mL), $CuSO_4$ (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5%

EtOAc/hexane) to give the title compound (201 mg, 0.905 mmol, 44% yield) as a white solid. Mp 93-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.9 (1H, s, OH), 7.51-7.47 (2H, m, Ar*H*), 7.44 (1H, d, *J* = 16.0 Hz, H-3), 7.39-7.31 (3H, m, Ar*H*), 6.44 (1H, dd, *J* = 16.0, 1.5 Hz, H-2), 5.18 (1H, s, H-1), 3.77 (3H, s OCH_3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.4 (C=O), 169.4 (C), 137.1 (C), 135.4 (C), 129.5 (CH), 128.9 (CH), 127.7 (CH), 121.9 (CH), 91.7 (CH), 51.5 (CH_3) ppm; HRMS (ESI) 227.0695 (M + Na^+. $C_{14}H_{16}NNaO_5$ requires 227.0679); IR (ATR): ν_{max} 3027, 2953, 1634 (C=O), 1590, 1445, 1202 cm^{-1}.

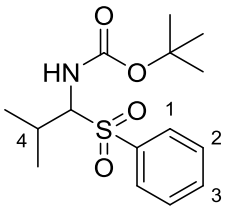
General Procedure A - Synthesis of benzenesulfonyl carbamic esters

To a solution of aldehyde (53.6 mmol) in water, methanol and formic acid (2:1:0.7, 142 mL) was added *tert*-butyl carbamate (35.7 mmol) and benzenesulfinic acid sodium salt (71.4 mmol). The mixture was stirred at room temperature for 3 days. The precipitate was filtered and washed with water (150 mL) and hexane (300 mL), and used without further purification.



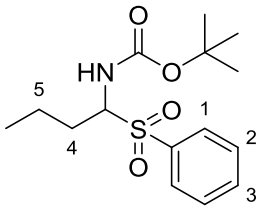
(1-Benzenesulfonyl-ethyl)-carbamic acid *tert*-butyl ester (122a)

Following **general procedure A** with acetaldehyde (3 mL, 53.6 mmol), *tert*-butyl carbamate (4.18 g, 35.7 mmol) and benzenesulfinic acid sodium salt (11.7 g, 71.4 mmol) gave the title compound (8.27 g, 29.0 mmol, 81% yield) as a white solid. Mp 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* = 7.5 Hz, H-1), 7.63 (1H, t, *J* = 7.5 Hz, H-3), 7.54 (2H, dd, *J* = 7.5, 7.5 Hz, H-2), 5.08 (1H, d, *J* = 10.5 Hz, N-H), 4.99 (1H, dq, *J* = 10.5, 7.0 Hz, CH), 1.62 (3H, d, *J* = 7.0 Hz, CH_3), 1.20 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5 (C=O), 136.7 (C), 134.0 (CH), 129.5 (CH), 129.2 (CH), 80.9 (C), 66.9 (CH), 28.1 (CH_3), 13.0 (CH_3) ppm; HRMS (ESI) 308.0918 (M + Na^+. $C_{13}H_{19}NNaO_4S$ requires 308.0927); IR (ATR): ν_{max} 3337, 2973, 1691 (C=O), 1518, 1313, 1145 cm^{-1}.



(1-Benzenesulfonyl-2-methyl-propyl)-carbamic acid *tert*-butyl ester (122b)

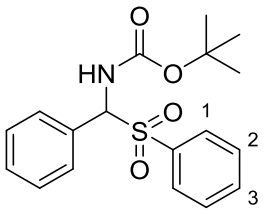
Following **general procedure A** with isobutyraldehyde (4.67 mL, 51.3 mmol), *tert*-butyl carbamate (4.00 g, 34.2 mmol) and benzenesulfinic acid sodium salt (11.2 g, 68.4 mmol) gave the title compound (4.93 g, 4.25 mmol, 47% yield) as a white solid. Mp 116-117.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.86 (2H, m, H-1), 7.64-7.58 (1H, m, H-3), 7.55-7.49 (2H, m, H-3), 5.14 (1H, d, *J* = 11.0 Hz, N-H), 4.84 (1H, dd, *J* = 11.0, 3.5 Hz, CH), 2.82-2.73 (1H, m, H-4), 1.22 (9H, s, $(CH_3)_3$), 1.14 (3H, d, *J* = 7.0 Hz, CH_3), 1.07 (3H, d, *J* = 7.0 Hz, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2 (C=O), 138.2 (C), 133.8 (CH), 129.2 (CH), 129.1 (CH), 80.9 (C), 74.4 (CH), 28.1 (CH_2), 26.8 (CH), 20.8 (CH_3), 17.0 (CH_3) ppm; HRMS (ESI) 226.1404 (M + Na^+. $C_{10}H_{21}NNaO_3$ requires 226.1414 for the methanol adduct); IR (ATR): ν_{max} 3356, 3232, 3142, 2965, 1704 (C=O), 1364, 1307, 1141, 1082 cm^{-1}.



(1-Benzenesulfonyl-butyl)-carbamic acid *tert*-butyl ester (122c)

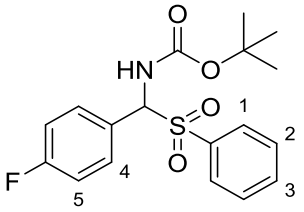
Following **general procedure A** with butyraldehyde (1.15 mL, 12.8 mmol), *tert*-butyl carbamate (1.00 g, 8.54 mmol) and benzenesulfinic acid sodium salt (2.80 g, 17.1 mmol) gave the title compound (1.33 g, 4.25 mmol, 50% yield) as a white solid. Mp 117-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.86 (2H, m, H-1), 7.62-7.56 (1H, m, H-3), 7.54-7.47 (2H, m, H-2), 7.48-7.39 (2H, m, H-4), 7.09 (2H, t, *J* = 8.5 Hz, H-5), 5.07 (1H, d, *J* = 11.0 Hz, N-H), 4.84 (1H, d, *J* = 11.0 Hz, CH), 2.24-2.13 (1H, m, H-4), 1.79-1.65 (1H, m, H-4), 1.62-1.48 (1H, m, H-5), 1.46-1.35 (1H, m, H-5), 1.24 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (C=O), 137.1 (C), 133.9 (CH), 129.4 (CH), 129.1 (CH), 80.8 (C), 70.7 (CH), 28.3 (CH_2), 28.1 (CH_3), 18.8 (CH_2),

13.6 (CH_3) ppm; HRMS (ESI) 336.1243 (M + Na^+. $C_{15}H_{23}NNaO_4S$ requires 336.1240); IR (ATR): ν_{max} 3286, 2960, 2874, 1690 (C=O), 1526, 1310, 1246, 1144, 1083 cm^{-1}.



(Benzenesulfonyl-phenyl-methyl)-carbamic acid *tert*-butyl ester (122d)

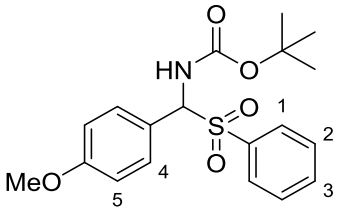
Following **general procedure A** with benzaldehyde (1.52 mL, 15 mmol), *tert*-butyl carbamate (1.17 g, 10 mmol), and benzenesulfinic acid sodium salt (3.28 g, 20 mmol) gave the title compound (3.26 g, 9.42 mmol, 94% yield) as a white solid. Mp 158-161 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, *J* = 7.5 Hz, H-1), 7.64 (1H, t, *J* = 7.5 Hz, H-3), 7.53 (2H, dd, *J* = 7.5, 7.5 Hz, H-2), 7.48-7.39 (5H, m, ArH), 7.09 (2H, t, *J* = 8.5 Hz, H-5), 5.94 (1H, d, *J* = 10.5 Hz, CH), 5.87 (1H, d, *J* = 10.5 Hz, N-H), 1.25 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6 (C=O), 137.0 (C), 134.1 (CH), 130.0 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 125.1 (C), 81.4 (C), 74.0 (CH), 28.1 (CH_3) ppm; HRMS (ESI) 260.1257 (M + Na^+. $C_{13}H_{19}NNaO_3$ requires 260.1257 for the methanol adduct); IR (ATR): ν_{max} 3355, 3274, 2978, 1693 (C=O), 1508, 1306, 1141 cm^{-1}.



[Benzenesulfonyl-(4-fluoro-phenyl)-methyl]-carbamic acid *tert*-butyl ester (122e)

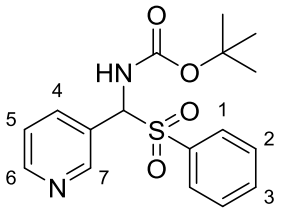
Following **general procedure A** with 4-fluorobenzaldehyde (9.61 mL, 90.0 mmol), *tert*-butyl carbamate (7.00 g, 59.8 mmol) and benzenesulfinic acid sodium salt (19.6 g, 120 mmol) gave the title compound (19.9 g, 54.4 mmol, 91% yield) as a white solid. Mp 167-170 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* = 7.5 Hz, H-1), 7.65 (1H, t, *J* = 7.5 Hz, H-3), 7.54 (2H, dd, *J* = 7.5, 7.5 Hz, H-2), 7.48-7.39 (2H, m, H-4), 7.13-7.04 (2H, m, H-5), 5.94 (1H, d, *J* = 10.5 Hz, CH),

5.85 (1H, d, J = 10.5 Hz, N-H), 1.24 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7 (d, J_F = 251 Hz, CF), 153.6 (C=O), 136.8 (C), 134.2 (CH), 131.0 (d, J_F = 8.5 Hz, CH), 129.6 (CH), 129.2 (CH), 125.9 (d, J_F = 3.5 Hz, C), 116.0 (d, J_F = 21.5 Hz, CH), 81.5 (C), 73.3 (CH), 28.1 (CH_3) ppm; HRMS (ESI) 278.1150 ($M + Na^+$. $C_{13}H_{18}FNNaO_3$ requires 278.1163 for the methanol adduct); IR (ATR): ν_{max} 3367, 2972, 1703 (C=O), 1506, 1309, 1140 cm^{-1}.



[Benzenesulfonyl-(4-methoxy-phenyl)-methyl]-carbamic acid *tert*-butyl ester (122f)

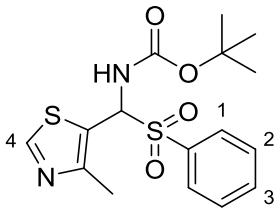
Following **general procedure A** with 4-anisaldehyde (3.85 mL, 31.7 mmol), *tert*-butyl carbamate (2.48 g, 21.1 mmol) and benzenesulfinic acid sodium salt (6.94 g, 42.3 mmol) gave the title compound (5.63 g, 14.9 mmol, 71% yield) as a white solid. Mp 156-158 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, J = 7.5 Hz, H-1), 7.63 (1H, t, J = 7.5 Hz, H-3), 7.53 (2H, dd, J = 7.5, 7.5 Hz, H-2), 7.37 (2H, d, J = 8.5 Hz, H-4), 6.93 (2H, d, J = 8.5 Hz, H-5), 5.88 (1H, d, J = 10.5 Hz, CH), 5.76 (1H, d, J = 10.5 Hz, N-H), 3.82 (3H, s, OCH_3), 1.24 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.4 (C), 153.2 (C=O), 137.1 (C), 134.0 (CH), 130.3 (CH), 129.6 (CH), 129.2 (CH), 121.8 (C), 114.4 (CH), 81.3 (C), 73.6 (CH), 55.5 (CH_3), 28.1 (CH_3) ppm; HRMS (ESI) 290.1350 ($M + Na^+$. $C_{14}H_{21}NNaO_4$ requires 290.1363 for the methanol adduct); IR (ATR): ν_{max} 3361, 2967, 1695 (C=O), 1503, 1310, 1162, 1149 cm^{-1}.



(Benzenesulfonyl-pyridin-3-yl-methyl)-carbamic acid *tert*-butyl ester (122g)

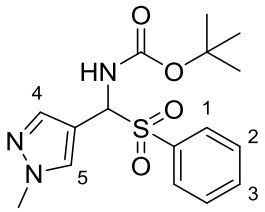
Following **general procedure A** with nicotinaldehyde (7.8 mL, 83.0 mmol), *tert*-butyl carbamate (6.50 g, 55.5 mmol) and benzenesulfinic acid sodium salt (18.2 g, 111 mmol) gave

the title compound (9.09 g, 26.1 mmol, 47% yield) as a white solid. Mp 168.5-171 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70-8.65 (2H, m, H-6 and H-7), 7.93 (2H, d, *J* = 7.5 Hz, H-1), 7.85 (1H, ddd, *J* = 8.0, 2.0, 2.0 Hz, H-4) 7.67 (1H, t, *J* = 7.5 Hz, H-3), 7.56 (2H, dd, *J* = 7.5, 7.5 Hz, H-2), 6.03 (1H, d, *J* = 10.5 Hz, N-H), 5.98 (1H, d, *J* = 10.5 Hz, CH), 1.25 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6 (C=O), 151.0 (CH), 150.1 (CH), 136.5 (CH), 136.4 (C), 134.5 (CH), 129.6 (CH), 129.4 (CH), 126.4 (C), 123.7 (CH), 81.8 (C), 72.0 (CH), 28.1 (CH_3) ppm; HRMS (ESI) 239.1392 (M + H^+. $C_{12}H_{19}N_2O_3$ requires 239.1390 for the methanol adduct); IR (ATR): ν_{max} 3200, 3064, 2979, 1716 (C=O), 1531, 1303, 1140 cm^{-1}.



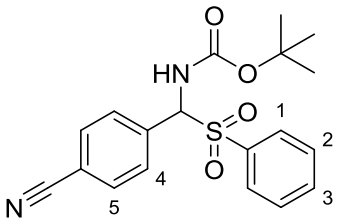
[Benzenesulfonyl-(4-methyl-thiazol-5-yl)-methyl]-carbamic acid *tert*-butyl ester (122h)

Following **general procedure A** with 4-methylthiazole-5-carbaldehyde (6.68 g, 52.5 mmol), *tert*-butyl carbamate (4.10 g, 35.0 mmol) and benzenesulfinic acid sodium salt (11.5 g, 70.0 mmol) gave the title compound (6.70 g, 18.2 mmol, 52% yield) as an off-white solid. Mp 167-169 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (1H, s, H-4), 7.90 (2H, d, *J* = 7.5 Hz, H-1), 7.67 (1H, t, *J* = 7.5 Hz, H-3), 7.56 (2H, dd, *J* = 7.5, 7.5 Hz, H-2), 6.26 (1H, d, *J* = 10.5 Hz, CH), 5.59 (1H, d, *J* = 10.5 Hz, NH), 3.42 (3H, s, CH_3), 1.27 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5 (C=O), 153.3 (CH), 136.2 (C), 134.5 (CH), 129.6 (CH), 129.4 (CH), 121.1 (C), 81.9 (C), 68.4 (CH), 28.1 (CH_3), 15.7 (CH_3) ppm; HRMS (ESI) 259.1114 (M + H^+. $C_{11}H_{19}N_2O_3$ requires 259.1111 for the methanol adduct); IR (ATR): ν_{max} 3153, 3071, 2976, 1707 (C=O), 1535, 1302, 1140 cm^{-1}.



[Benzenesulfonyl-(1-methyl-1H-pyrazol-4-yl)-methyl]-carbamic acid *tert*-butyl ester (122i)

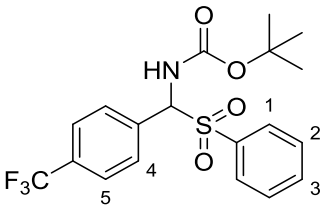
Following **general procedure A** with 1-methyl-1H-pyrazole-4-carbaldehyde (1.50 g, 13.6 mmol), *tert*-butyl carbamate (1.05 g, 8.96 mmol) and benzenesulfinic acid sodium salt (2.94 g, 17.9 mmol) gave the title compound (1.42 g, 4.04 mmol, 71% yield) as a white solid. Mp 153.7-156.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, *J* = 7.5 Hz, H-1), 7.66 (1H, s, H-4), 7.66-7.59 (2H, m, H-3 and H-5), 7.54 (2H, dd, *J* = 7.5, 7.5 Hz, H-2), 5.95 (1H, d, *J* = 10.5 Hz, CH), 5.73 (1H, d, *J* = 10.5 Hz, N-H), 3.92 (3H, s, CH_3), 1.21 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5 (C=O), 138.9 (CH), 136.6 (C), 134.2 (CH), 130.7 (CH), 129.7 (CH), 129.2 (CH), 125.0 (C), 81.3 (C), 67.4 (CH), 39.4 (CH_3), 28.1 (CH_3) ppm; HRMS (ESI) 264.1305 (M + Na^+. $C_{11}H_{19}N_3NaO_3$ requires 264.1319 for the methanol adduct); IR (ATR): ν_{max} 3359, 2971, 1709 (C=O), 1521, 1303, 1148, 1136 cm^{-1}.



[Benzenesulfonyl-(4-cyano-phenyl)-methyl]-carbamic acid *tert*-butyl ester (122j)

Following **general procedure A** with 4-cyanobenzaldehyde (8.40 g, 64.1 mmol), *tert*-butyl carbamate (5.00 g, 8.96 mmol) and benzenesulfinic acid sodium salt (14.0 g, 85.4 mmol) gave the title compound (14.9 g, 40.1 mmol, 94% yield) as a white solid. Mp 151-154 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, dd, *J* = 7.5, 7.5 Hz, H-1), 7.73-7.64 (3H, m, H-3 and H-5), 7.62-7.53 (4H, m, H-2 and H-4), 6.00 (1H, d, *J* = 10.5 Hz, CH), 5.93 (1H, d, *J* = 10.5 Hz, NH), 1.24 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5 (C=O), 136.4 (C), 135.1 (C), 134.6 (C), 133.0 (CH), 132.5 (CH), 130.0 (CH), 129.8 (CH), 129.6 (CH), 129.4 (CH), 118.2 (C), 113.8 (C), 81.9 (C), 77.4 (CH), 28.1 (CH_3) ppm; HRMS (ESI) 285.1213 (M + Na^+. $C_{14}H_{18}N_2NaO_3$ requires 285.1210

for the methanol adduct); IR (ATR): ν_{max} 3369, 2962, 2235 (CN), 1701 (C=O), 1506, 1308, 1143 cm^{-1}.



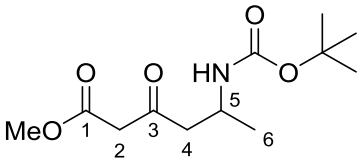
[Benzenesulfonyl-(4-trifluoromethyl-phenyl)-methyl]-carbamic acid *tert*-butyl ester (122k)

Following **general procedure A** with 4-(trifluoromethyl)benzaldehyde (6.00 g, 34.5 mmol), *tert*-butyl carbamate (2.69 g, 23.0 mmol) and benzenesulfinic acid sodium salt (7.54 g, 46.0 mmol). The white precipitate was triturated by stirring in diethyl ether (50 mL) for 1h at rt. Filtration gave the title compound (6.87 g, 16.6 mmol, 72% yield) as a white solid. Mp 174.5-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, *J* = 7.8 Hz, H-1), 7.70-7.65 (3H, m, H-3 and H-4), 7.63-7.53 (4H, m, H-2 and H-5), 6.02 (1H, d, *J* = 10.5 Hz, CH), 5.93 (1H, d, *J* = 10.5 Hz, NH), 1.23 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.6 (C=O), 136.6 (C), 134.4 (CH), 133.9 (C), 132.0 (q, J_F = 33.0 Hz, C), 129.6 (CH), 129.6 (CH), 129.4 (CH), 125.8 (q, J_F = 3.3 Hz, CH), 123.9 (q, J_F = 274 Hz, C), 81.7 (C), 73.4 (CH), 28.1 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8 ppm; HRMS (ESI) 438.0961 (M + Na^+. $C_{19}H_{20}F_3NNaO_4S$ requires 438.0957); IR (ATR): ν_{max} 3354, 2984, 1696 (C=O), 1508, 1325, 1313, 1166, 1142, 1130, 1068 cm^{-1}.

General Procedure B - Synthesis of *N*-Boc-δ-amino-β-ketoesters

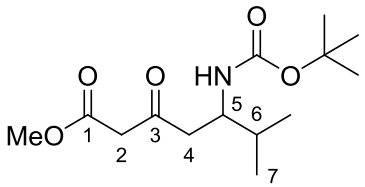
To a solution of diisopropylamine (21.0 mmol) in THF (60 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 21.0 mmol). The solution was stirred for 10 mins at -78 °C then a further 5 mins at room temperature. A solution of methyl acetoacetate (10.5 mmol) in THF (12 mL) was added over 10 mins at -78 °C, then stirred for a further 40 mins. The imine was prepared by the portionwise addition of sulfone (3.50 mmol) to a suspension of NaH (60% dispersion in mineral oil, 7.00 mmol) in THF (24 mL) at room temperature. The subsequent mixture was stirred for 20 mins, then immediately transferred to the dianion mixture at -50 °C. The reaction was stirred for 30 mins, then quenched with 10 M acetic acid in THF (2.5 mL). The

mixture was warmed to room temperature and concentrated *in vacuo.* The residue was partitioned between EtOAc (30 mL) and water (25 mL). The aqueous layer was extracted with EtOAc (2 x 25 mL). Organics were combined, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the *N*-Boc δ-amino-β-ketoester.



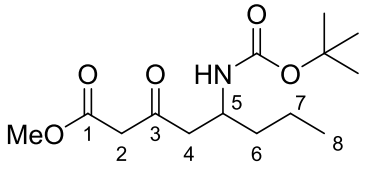
Methyl 5-*tert*-butoxycarbonylamino-3-oxo-hexanoate (126a)

Following **general procedure B** with sulfone **122a** (1 g, 3.50 mmol), NaH (60% dispersion in mineral oil, 280 mg, 7.00 mmol), methyl acetoacetate (1.16 mL, 10.5 mmol), diisopropylamine (2.94 mL, 21.0 mmol) and *n*-BuLi (1.91M in hexanes, 11.0 mL, 21.0 mmol). The crude residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (681 mg, 2.66 mmol, 76% yield) as a colourless oil that solidified to a white solid on standing. Mp 55-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.80 (1H, br s, NH), 4.07-3.95 (1H, m, H-5), 3.72 (3H, s, OCH_3), 3.48 (1H, d, *J* = 15.5 Hz, H-2), 3.43 (1H, d, *J* = 15.5 Hz, H-2), 2.79 (1H, dd, *J* = 16.5, 5.0 Hz, H-4), 2.69 (1H, dd, *J* = 16.5, 6.0 Hz, H-4), 1.41 (3H, s, $(CH_3)_3$), 1.20 (3H, d, *J* = 7.0 Hz, CH_3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 201.6 (C=O), 167.6 (C=O), 155.2 (C=O), 79.5 (C), 52.5 (CH_3), 49.4 (CH_2), 49.1 (CH_2), 43.3 (CH), 28.5 (CH_3), 20.6 (CH_3) ppm; HRMS (ESI) 282.1321 (M + Na^+. $C_{12}H_{21}NNaO_5$ requires 282.1312); IR (ATR): ν_{max} 3366, 3312, 3000, 2976, 1737 (C=O), 1702 (C=O), 1679 (C=O), 1535 cm^{-1}.



Methyl 5-*tert*-butoxycarbonylamino-6-methyl-3-oxo-heptanoate (126b)

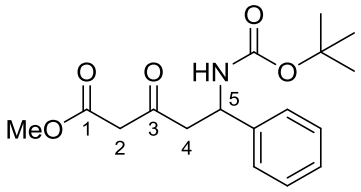
Following **general procedure B** with sulfone **122b** (2.00 g, 6.39 mmol), NaH (60% dispersion in mineral oil, 307 mg, 12.8 mmol), methyl acetoacetate (2.06 mL, 19.2 mmol), diisopropylamine (5.36 mL, 38.3 mmol) and *n*-BuLi (1.97M in hexanes, 19.5 mL, 38.3 mmol). The crude residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (917 mg, 3.20 mmol, 50% yield) as a colourless oil that solidified to a white solid on standing. Mp 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (1H, d, *J* = 9.2 Hz, NH), 3.81-3.71 (1H, m, H-5), 3.73 (3H, s, OCH_3), 3.56 (1H, d, *J* = 15.7 Hz, H-2), 3.47 (1H, d, *J* = 15.7 Hz, H-2), 2.77 (1H, dd, *J* = 16.2, 4.7 Hz, H-4), 2.69 (1H, dd, *J* = 16.2, 7.4 Hz, H-4), 1.91-1.79 (1H, m, H-6), 1.42 (9H, s, $(CH_3)_3$), 0.90 (6H, d, *J* = 9.2 Hz, H-7) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 202.0 (C=O), 167.7 (C=O), 155.7 (C=O), 79.4 (C), 52.7 (CH), 52.4 (CH_3), 49.0 (CH_2), 45.6 (CH_2), 31.8 (CH), 28.4 (CH_3), 19.5 (CH_3) ppm; HRMS (ESI) 310.1618 (M + Na^+. $C_{14}H_{25}NNaO_5$ requires 320.1625); IR (ATR): ν_{max} 3356, 2974, 2958, 1748 (C=O), 1713 (C=O), 1686 (C=O), 1525, 1307, 1128 cm^{-1}.



Methyl 5-*tert*-butoxycarbonylamino-3-oxo-octanoate (126c)

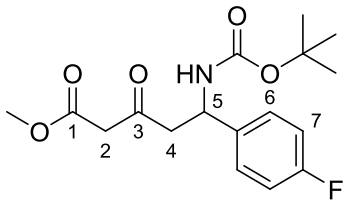
Following **general procedure B** with sulfone **122c** (400 mg, 1.28 mmol), NaH (60% dispersion in mineral oil, 61 mg, 2.56 mmol), methyl acetoacetate (413 µL, 3.84 mmol), diisopropylamine (1.07 mL, 7.68 mmol) and *n*-BuLi (1.91M in hexanes, 4.02 mL, 7.68 mmol). The crude residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (238 mg, 0.829 mmol, 65% yield) as a colourless oil that solidified to a white solid on standing. Mp 53-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (1H, d, *J* = 7.7 Hz, NH), 3.95-3.79 (1H, m, H-5), 3.72 (3H, s, OCH_3), 3.50 (1H, d, *J* = 15.7 Hz, H-2), 3.43 (1H, d, *J* = 15.7 Hz, H-2), 2.73 (2H, d, *J* = 5.7

Hz, H-4), 1.52-1.22 (4H, m, H-6 and H-7), 1.40 (9H, s, $(CH_3)_3$), 0.89 (3H, t, *J* = 7.2 Hz, H-8) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 201.9 (C=O), 167.6 (C=O), 155.6 (C=O), 79.4 (C), 52.5 (CH_3), 49.4 (CH_2), 47.7 (CH_2), 47.3 (CH), 36.8 (CH_2), 28.5 (CH_3), 19.5 (CH_2), 13.9 (CH_3) ppm; HRMS (ESI) 310.1636 (M + Na^+. $C_{14}H_{25}NNaO_5$ requires 310.1625); IR (ATR): ν_{max} 3288, 2964, 2933, 1742 (C=O), 1704 (C=O), 1679 (C=O), 1539, 1262, 1173 cm^{-1}.



Methyl 5-*tert*-butoxycarbonylamino-3-oxo-5-phenyl-pentanoate (126d)

Following **general procedure B** with sulfone **122d** (1.00 g, 2.89 mmol)**,** NaH (60% dispersion in mineral oil, 134 mg, 5.78 mmol), methyl acetoacetate (934 µL, 17.3 mmol), diisopropylamine (2.43 mL, 17.3 mmol) and *n*-BuLi (9.08 mL, 17.3 mmol). The residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (672 mg, 2.09 mmol, 73% yield) as a colourless oil that solidified on standing. Mp 83.7-85.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.22 (5H, m, ArH), 5.34 (1H, br. s, NH), 5.10 (1H, br. s, H-5), 3.68 (3H, s, OCH_3), 3.42 (1H, d, *J* = 15.5 Hz, H-2), 3.38 (1H, d, *J* = 15.5 Hz, H-2), 3.17 (1H, *J* = 16.5, 6.5 Hz, H-2), 3.04 (1H, dd, *J* = 16.5, 5.0 Hz, H-2) 1.41 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.9 (C=O), 172.8 (C), 167.4 (C=O), 155.2 (C=O), 128.8 (CH), 127.7 (CH), 126.3 (CH), 79.9 (C), 52.5 (CH_3), 50.9 (CH), 49.5 (CH_2), 48.8 (CH_2), 28.4 (CH_3) ppm; HRMS (ESI) 344.1463 (M + Na^+. $C_{17}H_{23}NNaO_5$ requires 344.1468); IR (ATR): ν_{max} 3393, 2978, 1752 (C=O), 1718 (C=O), 1681 (C=O), 1170, 1152 cm^{-1}.



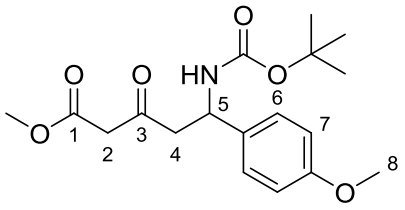
Methyl 5-*tert*-butoxycarbonylamino-5-(4-fluoro-phenyl)-3-oxo-pentanoate (126e)

Method A: Following **general procedure B** with sulfone **122e** (5.00 g, 13.7 mmol)**,** NaH (60% dispersion in mineral oil, 1.66 g, 41.1 mmol), methyl acetoacetate (4.42 mL, 41.1 mmol), diisopropylamine (11.6 mL, 82.2 mmol) and *n*-BuLi (2.5 M in hexanes, 32.9 mL, 82.2 mmol). The residue was purified by column chromatography (15-20% EtOAc/hexane) to give the title compound (3.59 g, 10.6 mmol, 77% yield) as a white solid.

Method B: To a solution of **189e** (120 mg, 0.538 mmol) in THF (5.4 mL) at -78 ^{o}C was added $ZnCl_2$ (1.9M in Me-THF, 283 µL, 0.538 mmol). The mixture was stirred for 30 mins before the dropwise addition of Chan's diene (350 mg, 1.35 mmol). The reaction was stirred for 1h then quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was warmed to rt and THF was removed *in vacuo.* CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous was extracted with CH_2Cl_2 (3 x 5 mL). The organics were combined, washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15-20% EtOAc/petroleum ether (40-60)) to give the title compound (111 mg, 0.334 mmol, 62% yield) as a white solid.

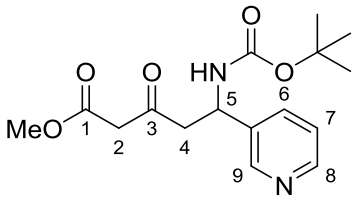
Method C: To a solution of **189e** (113 mg, 0.507 mmol) in CH_2Cl_2 (5 mL) at -78 ^{o}C was added $TiCl_4$ (56 µL, 0.507 mmol). Chan's diene (263 mg, 1.01 mmol) was added and the mixture was stirred for 25 mins, then quenched with 1.59M citric acid in MeOH (1 mL). Water (5 mL) was added and the mixture was warmed to rt. The layers were separated and the aqueous was extracted with CH_2Cl_2 (5 x 5 mL). The organics were combined, washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15-20% EtOAc/petroleum ether (40-60)) to give the title compound (106 mg, 0.309 mmol, 61% yield) as a white solid. Mp 87-88.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (2H, m, H-6), 7.04-6.97 (2H, m, H-7), 5.33 (1H, br. s, NH), 5.13-5.01 (1H, m, H-5), 3.69 (3H, s, OCH_3), 3.42 (1H, d, *J* = 15.5 Hz, H-2), 3.38 (1H, d, *J* = 15.5 Hz, H-2), 3.16 (1H, dd, *J* = 17.0, 6.0 Hz, H-4), 3.02 (1H, dd, *J* = 17.0 Hz, 6.0 Hz, H-4), 1.41 (9H, s, $(CH_3)_3$)

ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.7 (C=O), 167.4 (C=O), 162.1 (d, J_F = 247.0 Hz, CF), 155.2 (C=O), 137.2 (C), 128.1 (d, J_F = 8.0 Hz, CH), 115.6 (d, J_F = 21.5 Hz, CH), 80.1 (C), 52.6 (CH_3), 50.4 (CH), 49.5 (CH_2), 48.7 (CH_2), 28.4 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -116.7 ppm; HRMS (ESI) 340.1556 (M + H^+. $C_{17}H_{23}FNO_5$ requires 340.1555); IR (ATR): ν_{max} 3306, 2982, 1741 (C=O), 1713 (C=O), 1673 (C=O), 1535, 1511, 1365, 1328, 1286, 1221, 1161, 999 cm^{-1}.



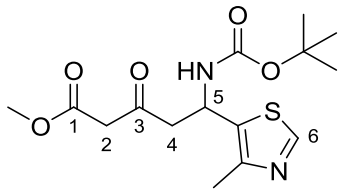
Methyl 5-((*tert*-butoxycarbonyl)amino)-5-(4-methoxyphenyl)-3-oxopentanoate (126f)

Following **general procedure B** with sulfone **122f** (3.00 g, 7.95 mmol)**,** NaH (60% dispersion in mineral oil, 0.954 g, 23.8 mmol), methyl acetoacetate (2.71 mL, 23.8 mmol), diisopropylamine (6.80 mL, 47.7 mmol) and *n*-BuLi (2.5 M in hexanes, 19.1 mL, 47.7 mmol). The residue was purified by column chromatography (15-20% EtOAc/hexane) to give the title compound (1.49 g, 4.25 mmol, 53% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.19 (2H, m, H-6), 6.89-6.84 (2H, m, H-7), 5.20 (1H, br. s, NH), 5.11-5.01 (1H, m, H-5), 3.80 (3H, s, H-8), 3.70 (3H, s, OCH_3),), 3.43 (1H, d, *J* = 16.0 Hz, H-2), 3.41 (1H, d, *J* = 16.0 Hz, H-2), 3.15 (1H, dd, *J* = 16.5, 6.5 Hz, H-4), 3.05 (1H, dd, *J* = 16.5, 6.5 Hz, H-4), 1.42 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.7 (C=O), 167.3 (C=O), 159.0 (C), 155.0 (C=O), 133.3 (C), 127.4 (CH), 114.1 (CH), 79.8 (C), 55.3 (CH_3), 52.4 (CH_3), 50.5 (CH), 49.4 (CH_2), 48.8 (CH_2), 28.3 (CH_3); HRMS (ESI) 352.1743 (M + H^+. $C_{18}H_{26}NO_6$ requires 352.1755); IR (ATR): ν_{max} 3356, 2974, 2839, 1748 (C=O), 1708 (C=O), 1679 (C=O), 1512, 1243, 1163, 1037 cm^{-1}.



Methyl 5-*tert*-butoxycarbonylamino-3-oxo-5-pyridin-3-yl-pentanoate (126g)

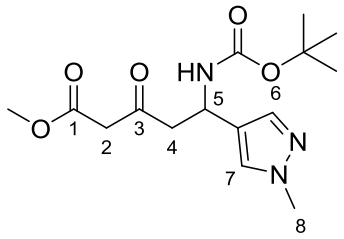
Following **general procedure B** with sulfone **122g** (5.00 g, 14.4 mmol)**,** NaH (60% dispersion in mineral oil, 1.73 g, 43.2 mmol), methyl acetoacetate (4.66 mL, 43.2 mmol), diisopropylamine (12.2 mL, 86.4 mmol) and *n*-BuLi (2.5 M in hexanes, 34.6 mL, 86.4 mmol). The residue was purified by column chromatography (50% EtOAc/hexane then 100% EtOAc) to give the title compound (2.58 g, 8.01 mmol, 56% yield) as an off-white solid. Mp 96.5-99.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (1H, d, *J* = 2.5 Hz, H-9), 8.50 (1H, dd, *J* = 4.5, 1.5 Hz, H-8), 7.64 (1H, dt, *J* = 8.0, 1.5 Hz, H-6), 7.26 (1H, dd, *J* = 8.0, 4.5 Hz, H-7), 5.51 (1H, br. s, NH), 5.13 (1H, br. s, H-5), 3.69 (3H, s, CH_3), 3.45 (1H, d, *J* = 15.5 Hz, H-2), 3.40 (1H, d, *J* = 15.5 Hz, H-2), 3.24 (1H, dd, *J* = 17.0, 4.0 Hz, H-4), 3.08 (1H, dd, *J* = 17.0, 4.0 Hz, H-4), 1.41 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.6 (C=O), 167.3 (C=O), 155.1 (C=O), 148.9 (CH), 148.2 (CH), 136.9 (C), 134.2 (CH), 123.5 (CH), 80.3 (C), 52.6 (CH_3), 49.3 (CH_2), 48.8 (CH), 48.1 (CH_2) ppm; HRMS (ESI) 323.1594 ($M + H^+$. $C_{16}H_{23}N_2O_5$ requires 323.1601); IR (ATR): ν_{max} 3208, 2982, 1756 (C=O), 1709 (C=O), 1542, 1365, 1282, 1178, 1082, 1005 cm^{-1}.



5-*tert*-Butoxycarbonylamino-5-(4-methyl-thiazol-5-yl)-3-oxo-pentanoic acid methyl ester (126h)

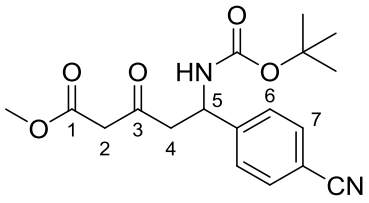
Following **general procedure B** with sulfone **122h** (5.00 g, 13.6 mmol), NaH (60% dispersion in mineral oil, 1.63 g, 40.8 mmol), methyl acetoacetate (4.40 mL, 40.8 mmol), diisopropylamine (11.5 mL, 81.6 mmol) and *n*-BuLi (2.5 M in hexanes, 32.6 mL, 81.6 mmol). The residue was purified by column chromatography (50% EtOAc/hexane then 100% EtOAc) to give the title compound (2.69 g, 7.87 mmol, 58% yield) as a red oil that solidified on

standing. Mp 91.5-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (1H, s, H-6), 5.40 (1H, dd, *J* = 14.0, 6.0 Hz, H-5), 5.27 (1H, br. s, NH), 3.71 (3H, s, OCH_3), 3.46 (1H, d, *J* = 15.5 Hz, H-2), 3.42 (1H, d, *J* = 15.5 Hz, H-2), 3.21 (1H, dd, *J* = 17.5, 6.0 Hz, H-4), 3.06 (1H, dd, *J* = 17.5, 6.0 Hz), 2.49 (3H, s, CH_3), 1.41 (3H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.2 (C=O), 167.2 (C=O), 154.8 (C=O), 150.5 (CH), 149.9 (C), 132.7 (C), 80.4 (C), 52.7 (CH_3), 49.4 (CH_2), 44.5 (CH_2), 28.4 (CH_3), 15.5 (CH_3) ppm; HRMS (ESI) 343.1314 (M + Na^+. $C_{15}H_{23}N_2O_5S$ requires 343.1322); IR (ATR): ν_{max} 3214, 2976, 1752 (C=O), 1719 (C=O), 1701 (C=O), 1532, 1277, 1172, 1127, 1003 cm^{-1}.



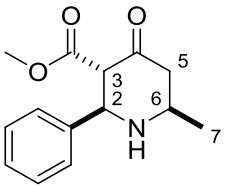
Methyl 5-((*tert*-butoxycarbonyl)amino)-5-(1-methyl-1H-pyrazol-4-yl)-3-oxopentanoate (126i)

Following **general procedure B** with sulfone **122i** (1.3 g, 3.51 mmol), NaH (60% dispersion in mineral oil, 0.422 g, 10.5 mmol), methyl acetoacetate (1.14 mL, 10.5 mmol), diisopropylamine (3.01 mL, 21.1 mmol) and *n*-BuLi (1.60M in hexanes, 13.2 mL, 21.1 mmol). The residue was purified by column chromatography (50% EtOAc/hexane then 100% EtOAc) to give the title compound (652 mg, 2.00 mmol, 57% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, s, H-6), 7.30 (1H, s, H-7), 5.22 (1H, br. s, NH), 5.12-5.03 (1H, m, H-5), 3.85 (3H, s, H-8), 3.73 (3H, s, OCH_3), 3.48 (1H, d, *J* = 15.5 Hz, H-2), 3.44 (1H, d, *J* = 15.5 Hz, H-2), 3.12 (1H, dd, *J* = 17.0, 5.5 Hz, H-4), 3.05 (1H, dd, *J* = 17.0, 6.5 Hz, H-4), 1.44 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.8 (C=O), 172.7 (C=O), 167.3 (C=O), 137.1 (CH), 128.3 (CH), 122.4 (C), 79.8 (C), 52.4 (CH_3), 49.3 (CH_2), 48.4 (CH_2), 43.0 (CH), 38.9 (CH_3), 28.4 (CH_3) ppm; HRMS (ESI) 326.1697 (M + H^+. $C_{15}H_{24}N_3O_5$ requires 326.1711); IR (ATR): ν_{max} 3355, 2976, 1744 (C=O), 1705 (C=O), 1512, 1365, 1245, 1162, 1015 cm^{-1}.



Methyl 5-*tert*-butoxycarbonylamino-5-(4-cyano-phenyl)-3-oxo-pentanoate (126j)

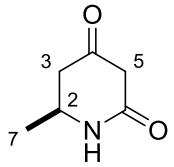
Following **general procedure B** with sulfone **122j** (2.00 g, 5.38 mmol)**,** NaH (60% dispersion in mineral oil, 0.644 g, 16.1 mmol), methyl acetoacetate (1.74 mL, 16.1 mmol), diisopropylamine (4.55 mL, 32.3 mmol) and *n*-BuLi (2.5 M in hexanes, 12.9 mL, 32.3 mmol). The residue was purified by column chromatography (15-25% EtOAc/hexane) to give the title compound (1.26 g, 3.64 mmol, 68% yield) as a white solid. Mp 93-95.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.59 (2H, m, H-7), 7.45-7.40 (2H, m, H-6), 5.53 (1H, br. s, NH), 5.13 (1H, br.s, H-5), 3.70 (3H, s, OCH_3), 3.43 (1H, d, *J* = 15.5 Hz, H-2), 3.38 (1H, d, *J* = 15.5 Hz, H-2), 3.22 (1H, dd, *J* = 17.5, 4.5 Hz, H-4), 3.05 (1H, dd, *J* = 17.5, 4.5 Hz, H-4), 1.41 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.3 (C=O), 167.3 (C=O), 155.1 (C=O), 147.0 (C), 132.6 (CH), 127.2 (CH), 118.8 (CN), 111.4 (C), 80.4 (C), 52.7 (CH_3), 50.5 (CH), 49.3 (CH_2), 47.9 (CH_2), 28.4 (CH_3) ppm; HRMS (ESI) 369.1421 (M + Na^+. $C_{18}H_{22}N_2NaO_5$ requires 369.1421); IR (ATR): ν_{max} 3343, 2995, 2955, 2228 (CN), 1751 (C=O), 1707 (C=O), 1676 (C=O), 1525, 1271, 1249, 1166, 1152 cm^{-1}.



Methyl 6-methyl-4-oxo-2-phenyl-piperidine-3-carboxylate (129)

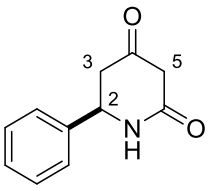
Following **general procedure C** with TFA salt **128a** (60 mg, 0.308 mmol), benzaldehyde (156 µL, 1.54 mmol) and $NaHCO_3$ (129 mg, 1.54 mmol) to give the title compound as a mixture of diastereomers (62.5 mg, 0.253 mmol, 82% yield) as a yellow oil after column chromatography (20% EtOAc/hexane then 100% EtOAc). Data presented is for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.40 (2H, m, ArH), 7.36-7.27 (3H, m, ArH), 4.28 (1H, d, *J* = 11.0 Hz, H-2), 3.57 (1H, dd, *J* = 11.0, 1.0 Hz, H-3), 3.57 (3H, s, OCH_3), 3.21 (1H, dqd, *J* = 11.5, 6.0, 3.0 Hz, H-6), 2.52 (1H, dd, *J* = 14.0, 3.0 Hz, H-5), 2.28 (1H, ddd, *J* = 14.0, 11.5, 1.0 Hz, H-5), 1.25 (3H,

d, *J* = 6.0 Hz, CH_3) ppm; HRMS (ESI) 248.1272 ($M + H^+$. $C_{14}H_{18}NO_3$ requires 248.1281), 270.1096 ($M + Na^+$. $C_{14}H_{17}NNaO_3$ requires 270.1101). ^1H data was in agreement with literature.[95]



2-Methylpiperidine-4,6-dione (130a)

To a stirred solution of TFA salt **128a** (70 mg 0.320 mmol) in CH_2Cl_2 (0.7 mL) was added sat. aq. $NaHCO_3$ (0.35 mL). The reaction was stirred at rt for 1h then acidified to pH 3 with 2M HCl. The layers were separated and the aqueous was extracted with EtOAc (2 x 5 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (4% MeOH/CH_2Cl_2) to give the title compound (12 mg, 0.096 mmol, 30% yield) as a sticky yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.89-3.76 (1H, m, H-2), 3.30 (1H, d, *J* = 20.1 Hz, H-5), 3.24 (1H, d, *J* = 20.1 Hz, H-5), 2.68 (1H, dd, *J* = 16.5, 4.1 Hz, H-3), 2.33 (1H, dd, *J* = 16.5, 9.6 Hz, H-3), 1.33 (3H, d, *J* = 6.5 Hz, H-7) ppm. ^1H NMR data was in agreement with literature.[206]



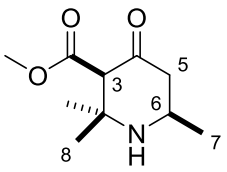
2-Phenylpiperidine-4,6-dione (130b)

To a stirred solution of TFA salt **128b** (190 mg 0.676 mmol) in CH_2Cl_2 (2.5 mL) was added sat. aq. $NaHCO_3$ (1.25 mL). The reaction was stirred at rt for 1h then acidified to pH 3 with 2M HCl. The layers were separated and the aqueous was extracted with EtOAc (2 x 5 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (4% MeOH/CH_2Cl_2) to give the title compound (83 mg, 0.439 mmol, 65% yield) as a sticky oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47-7.28 (5H, m, ArH), 4.81 (1H,

ddd, *J* = 9.0, 4.3, 1.0 Hz, H-2), 3.38 (2H, s, H-5), 2.89 (1H, dd, *J* = 16.0, 4.3 Hz, H-3), 2.76 (1H, dd, *J* = 16.0, 9.0 Hz, H-3) ppm. ^{1}H NMR data was in agreement with literature.[206]

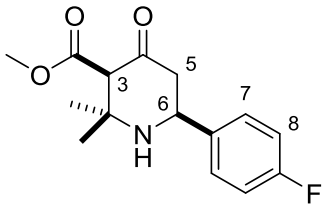
General Procedure C – Synthesis of 2-spiropiperidines from *N*-Boc-δ-amino-β-ketoesters

N-Boc protected δ-amino-β-ketoester (3.00 mmol) was stirred in 4M HCl in dioxane (11.5 mL) for 3h at room temperature. The mixture was concentrated *in vacuo* to afford the δ-amino-β-ketoester hydrochloride salt which was used without further purification. To a suspension of the δ-amino-β-ketoester hydrochloride salt (0.308 mmol) and ketone (1.54 mmol) in CH_2Cl_2 (1 mL), was added $NaHCO_3$ (129 mg, 1.54 mmol). The reaction was stirred for 16h at room temperature, then filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford 2-spiropiperidin-4-ones.



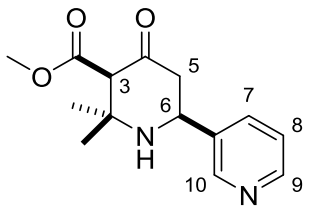
Methyl 2,2,6-trimethyl-4-oxo-piperidine-3-carboxylate (134a)

Following **general procedure C** with the hydrochloride salt of **126a** (60 mg, 0.308 mmol), acetone (113 µL, 1.54 mmol) and $NaHCO_3$ (129 mg, 1.54 mmol) to give the title compound as a mixture of diastereomers (52 mg, 0.246 mmol, 85% yield, 2.5:1 dr) as a yellow oil without further purification. Data presented is for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.69 (3H, s, OCH_3), 3.22 (1H, d, *J* = 1.0 Hz, H-3), 3.18 (1H, dqd, *J* = 10.5, 6.5, 3.5 Hz, H-6), 2.47 (1H, dd, *J* = 13.5, 10.5 Hz, H-5), 2.32 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 1.26 (3H, d, *J* = 6.3 Hz, H-7), 1.18 (3H, s, H-8), 1.09 (3H, s, H-8) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.7 (C=O), 169.7 (C=O), 66.8 (CH), 57.9 (C), 52.3 (CH_3), 48.4 (CH), 46.9 (CH_2), 28.2 (CH_3), 26.1 (CH_3), 22.8 (CH_3) ppm; HRMS (ESI) 200.1289 (M + H^+. $C_{10}H_{18}NO_3$ requires 200.1281); IR (ATR): ν_{max} 2967, 1705 (C=O), 1610, 1534, 1434, 1136 cm^{-1}.



Methyl 6-(4-fluorophenyl)-2,2-dimethyl-4-oxo-piperidine-3-carboxylate (134b)

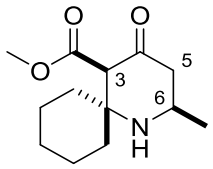
Following **general procedure C** with the hydrochloride salt of **126e** (110 mg, 0.399 mmol), acetone (146 µL, 1.99 mmol) and $NaHCO_3$ (167 mg, 1.99 mmol) to give the title compound as a mixture of diastereomers (108 mg, 0.387 mmol, 97% yield, 1.8:1) as a yellow oil without further purification. Data presented is for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (2H, m, H-7), 7.06 (2H, t, *J* = 8.5 Hz, H-8), 4.16 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 3.75 (3H, s, OCH_3), 3.33 (1H, d, *J* = 1.0 Hz, H-3), 3.00 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.50 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 1.24 (3H, s, CH_3), 1.21 (3H, s, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.7 (C=O), 169.7 (C=O), 162.4 (d, J_F = 247.0 Hz, CF), 137.9 (d, J_F = 3.5 Hz, C), 128.3 (d, J_F = 8.5 Hz, CH), 115.8 (d, J_F = 21.5 Hz, CH), 67.1 (CH), 58.0 (C), 56.2 (CH), 52.4 (CH_3), 46.0 (CH_2), 28.4 (CH_3), 26.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.42 ppm; HRMS (ESI) 280.1342 ($M + Na^+$. $C_{15}H_{19}FNO_3$ requires 280.1343); IR (ATR): ν_{max} 2969, 1748 (C=O), 1705 (C=O), 1603, 1509, 1222, 1195, 1152, 1125 cm^{-1}.



Methyl 6-(3-pyridyl)-2,2-dimethyl-4-oxo-piperidine-3-carboxylate (134c)

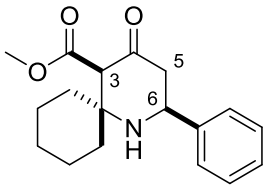
Following **general procedure C** with the hydrochloride salt of **126g** (80 mg, 0.310 mmol), acetone (114 µL, 1.55 mmol) and $NaHCO_3$ (130 mg, 1.55 mmol) to give the title compound as a mixture of diastereomers (69.8 mg, 0.266 mmol, 86% yield, 1.5:1) as a yellow oil without further purification. Data presented is for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (1H, d, *J* = 2.0 Hz, H-10), 8.55 (1H, dd, *J* = 4.5, 2.0 Hz, H-9), 7.80 (1H, dt, *J* = 8.0, 2.0 Hz, H-7), 7.31 (1H, dd, *J* = 8.0, 4.5 Hz, H-8), 4.21 (1H, dd, *J* = 11.5, 4.0 Hz, H-6), 3.73 (3H, s, OCH_3), 3.13 (1H, d, *J* = 1.0 Hz, H-3), 3.01 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.52 (1H, ddd, *J* = 13.5, 4.0,

1.0 Hz, H-5), 1.24 (3H, s, CH_3), 1.22 (3H, s, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.3(C=O), 169.7 (C=O), 149.5 (CH), 148.8 (CH), 137.4 (C), 134.1 (CH), 123.9 (CH), 66.9 (CH), 58.0 (C), 54.2 (CH), 52.2 (CH_3), 45.4 (CH_2), 28.3 (CH_3), 25.8 (CH_3) ppm; HRMS (ESI) 263.1393 (M + Na^+. $C_{14}H_{19}N_2O_3$ requires 263.1390); IR (ATR): ν_{max} 2969, 1707, 1429, 1197, 1153 cm^{-1}.



Methyl 6-methyl-4-oxo-1-aza-spiro[5.5]undecane-3-carboxylate (135a)

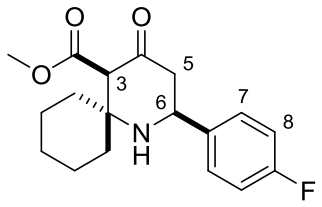
Following **general procedure C** with the hydrochloride salt of **126a** (60 mg, 0.308 mmol), cyclohexanone (159 µL, 1.54 mmol) and $NaHCO_3$ (129 mg, 1.54 mmol). The crude residue was dissolved in EtOAc (5 mL), washed with 2M NaOH (5 mL) and concentrated *in vacuo* to give the title compound as a mixture of diastereomers (63.4 mg, 0.265 mmol, 86% yield, 7:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^1H NMR (500 MHz, $CDCl_3$): δ 3.67 (3H, s, OCH_3), 3.34 (1H, br. s, H-3), 3.15 (1H, dqd, *J* = 10.5, 6.5, 3.5 Hz, H-6), 2.51 (1H, dd, *J* = 13.5, 10.5 Hz, H-5), 2.30 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 1.60-1.30 (10H, m, cyclohexyl), 1.25 (3H, d, *J* = 6.5 Hz, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.1 (C=O), 169.5 (C=O), 65.8 (CH), 60.3 (C), 52.1 (CH_3), 47.5 (CH_2), 47.2 (CH), 36.6 (CH_2), 33.7 (CH_2), 25.8 (CH_2), 22.9 (CH_3), 21.6 (CH_2), 21.1 (CH_2) ppm; HRMS (ESI) 240.1592 (M + H^+. $C_{13}H_{22}NO_3$ requires 240.1594); IR (ATR): ν_{max} 2930, 2856, 1703 (C=O), 1434, 1327, 1161 cm^{-1}.



Methyl 4-oxo-6-phenyl-1-aza-spiro[5.5]undecane-3-carboxylate (135b)

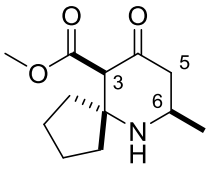
Following **general procedure C** with the hydrochloride salt of **126d** (116 mg, 0.451 mmol), cyclohexanone (234 µL, 2.26 mmol) and $NaHCO_3$ (190 mg, 2.26 mmol). The residue was dissolved in EtOAc (10 mL), washed with water (15 x 5 mL) and concentrated *in vacuo* to give

the title compound as a mixture of diastereomers (105 mg, 0.352 mmol, 78% yield, 7:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, CDCl3): δ 7.48-7.27 (5H, m, ArH), 4.11 (1H, dd, *J* = 11.0, 4.0 Hz, H-6), 3.72 (3H, s, OCH_3), 3.41 (1H, br s, H-3), 3.08 (1H, dd, *J* = 13.5, 11.0 Hz, H-5), 2.53 (1H, ddd, *J* = 13.5, 4.0, 1.0 Hz, H-5), 1.76-1.29 (10H, m, cyclohexyl) ppm; ^{13}C NMR (101 MHz, CDCl3): δ 205.4 (C=O), 169.5 (C=O), 142.5 (C), 128.9 (CH), 127.8 (CH), 126.7 (CH), 66.6 (CH), 60.4 (C), 55.5 (CH), 52.2 (CH_3), 46.3 (CH_2), 36.6 (CH_2), 33.3 (CH_2), 25.7 (CH_2), 21.5 (CH_2), 21.0 (CH_2) ppm; HRMS (ESI) 302.1754 (M + H^+. $C_{18}H_{24}NO_3$ requires 302.1751); IR (ATR): ν_{max} 2930, 2855, 1702, 1434, 1327, 1192, 1162 cm^{-1}.



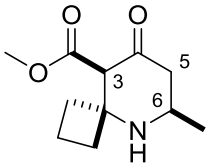
Methyl 6-(4-fluorophenyl)-4-oxo-1-aza-spiro[5.5]undecane-3-carboxylate (135c)

Following **general procedure C** with the hydrochloride salt of **126e** (68.5 mg, 0.248 mmol) cyclohexanone (128 µL, 1.24 mmol) and $NaHCO_3$ (104 mg, 1.24 mmol). The crude residue was dissolved in EtOAc (10 mL), washed with water (5 x 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a mixture of diastereomers (59.0 mg, 0.185 mmol, 75% yield, 5:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (2H, m, H-7), 7.10-7.03 (2H, m, H-8), 4.10 (1H, dd, *J* = 11.5, 4.0 Hz, H-6), 3.73 (3H, s, OCH_3), 3.41 (1H, br. s, H-3), 3.04 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.52 (1H, ddd, *J* = 13.5, 4.0, 1.0 Hz, H-5), 1.80-1.29 (10H, m, cyclohexyl) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.1 (C=O), 169.6 (C=O), 162.3 (d, *J* = 247 Hz, CF), 138.4 (C, d, *J* = 3.0 Hz), 128.4 (CH, d, *J* = 8.0 Hz), 115.8 (CH, d, *J* = 21 Hz), 66.5 (CH), 60.3 (C), 54.8 (CH_3), 52.3 (CH), 46.3 (CH_2), 36.6 (CH_2), 33.4 (CH_2), 25.7 (CH_2), 21.6 (CH_2), 21.1 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.7 ppm; HRMS (ESI) 320.1645 (M + H^+. $C_{18}H_{23}FNO_3$ requires 320.1656; IR (ATR): ν_{max} 2933, 2856, 1705 (C=O), 1600, 1510, 1439, 1329, 1224, 1159 cm^{-1}.



Methyl 6-methyl-4-oxo-1-aza-spiro[4.5]decane-3-carboxylate (136)

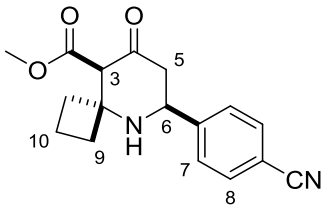
Following **general procedure C** with the hydrochloride salt of **126a** (65.8 mg, 0.337 mmol), cyclopentanone (149 µL, 1.69 mmol) and $NaHCO_3$ (142 mg, 1.69 mmol). The residue was purified by column chromatography (triethylamine deadened silica, 5% $MeOH/CH_2Cl_2$) to give the title compound as a mixture of diastereomers (32.4 mg, 0.144 mmol, 43% yield, 5:1 dr) as a pink oil. Data presented is for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (3H, s, OCH_3), 3.24 (1H, d, *J* = 1.0 Hz, H-3), 3.06 (1H, dqd, *J* = 10.5, 6.5, 3.5 Hz, H-6), 2.43 (1H, dd, *J* = 13.5, 10.5 Hz, H-5), 2.31 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 1.82-1.50 (7H, m, cyclopentyl), 1.36 (1H, m, cyclopentyl), 1.24 (3H, d, *J* = 6.5 Hz) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.3 (C=O), 169.9 (C=O), 69.2 (C), 66.1 (CH), 52.3 (CH_3), 49.6 (CH), 47.6 (CH_2), 39.2 (CH_2) 36.1 (CH_2), 24.3 (CH_2), 23.7 (CH_2), 22.3 (CH_3) ppm; HRMS (ESI) 226.1440 (M + H^+. $C_{12}H_{20}NO_3$ requires 226.1438); IR (ATR): ν_{max} 2957, 1704 (C=O), 1435, 1329, 1268, 1192, 1158 cm^{-1}.



Methyl 6-methyl-4-oxo-1-aza-spiro[3.5]nonane-3-carboxylate (137a)

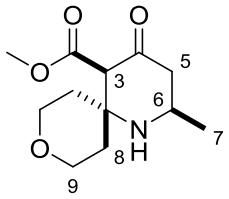
Following **general procedure C** with the hydrochloride salt of **126a** (72.4 mg, 0.371 mmol), cyclobutanone (139 µL, 1.86 mmol) and $NaHCO_3$ (156 mg, 1.86 mmol). The residue was purified by column chromatography (triethylamine deadened silica, 5% $MeOH/CH_2Cl_2$) to give the title compound as a mixture of diastereomers (52.6 mg, 0.249 mmol, 67% yield, 2.5:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (3H, s, OCH_3), 3.55 (1H, d, *J* = 1 Hz, H-3), 2.98 (1H, dqd, *J* = 10.5, 6.5, 4.0 Hz, H-6), 2.34 (1H, dd, *J* = 13.5, 10.5 Hz, H-5), 2.27 (1H, ddd, *J* = 13.5, 4.0, 1.0 Hz, H-5), 2.01-1.75 (6H, m, cyclobutyl), 1.23 (3H, d, *J* = 6.5 Hz, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.4 (C=O), 169.1 (C=O), 65.4 (CH), 63.0 (C), 52.3 (CH_3), 48.4 (CH), 48.1 (CH), 32.4 (CH_2), 31.6 (CH_2), 22.5 (CH_3),

14.4 (CH_2) ppm; HRMS (ESI) 212.1275 (M + H^+. $C_{11}H_{18}NO_3$ requires 212.1281); IR (ATR): ν_{max} 2956, 1705 (C=O), 1434, 1329, 1193, 1166 cm^{-1}.



Methyl 6-(4-cyano-phenyl)-4-oxo-1-aza-spiro[3.5]nonane-3-carboxylate (137b)

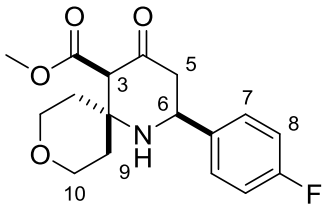
Following **general procedure C** with the hydrochloride salt of **126j** (102 mg, 0.362 mmol), cyclobutanone (133 µL, 1.81 mmol) and $NaHCO_3$ (152 mg, 1.81 mmol). The residue was purified by column chromatography (33% EtOAc/hexane) to give the title compound as a mixture of diastereomers (67.5 mg, 0.224 mmol, 63% yield, 1:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.64 (2H, m, H-8), 7.57-7.50 (2H, m, H-7), 4.04 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 3.76 (3H, s, OCH_3), 3.65 (1H, d, *J* = 1.0 Hz, H-3), 2.86 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.52 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 2.29-2.20 (1H, m, H-9), 2.15-2.05 (1H, m, H-9), 2.04-1.86 (4H, m, H-9 and H-10) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 202.9 (C=O), 169.0 (C=O), 147.1 (C), 132.8 (CH), 127.5 (CH), 118.7 (CN), 111.8 (C), 65.1 (CH), 63.0 (C), 56.0 (CH), 52.5 (CH_3), 46.8 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 14.2 (CH_2) ppm; HRMS (ESI) 299.1383 (M + H^+. $C_{17}H_{19}N_2O_3$ requires 299.1390); IR (ATR): ν_{max} 3313, 2952, 2227 (CN), 1707 (C=O), 1607, 1435, 1290, 1197, 1165 cm^{-1}.



Methyl 6-methyl-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (138a)

Following **general procedure C** with the hydrochloride salt of **126a** (280 mg, 1.44 mmol), tetrahydro-4*H*-pyran-4-one (664 µL, 7.20 mmol) and $NaHCO_3$ (605 mg, 7.20 mmol). The residue was purified by column chromatography (8-50% EtOAc/CH_2Cl_2) to give the title

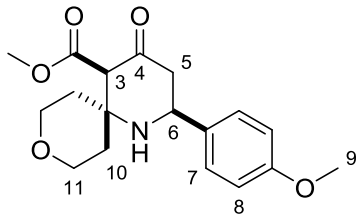
compound as a mixture of diastereomers (233 mg, 0.967 mmol, 67% yield, 4.5:1 dr) as a colourless oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (1H, ddd, *J* = 11.5, 10.0, 3.0 Hz, H-9), 3.72 (1H, ddd, *J* = 11.5, 10.0, 3.0 Hz, H-9), 3.67 (3H, s, OCH_3), 3.63 (1H, ddd, *J* = 11.5, 11.5, 4.0 Hz, H-9), 3.56 (1H, ddd, *J* = 11.5, 11.5, 4.0 Hz, H-9), 3.26 (1H, d, *J* = 1.0 Hz, H-3), 3.06 (1H, dqd, *J* = 10.5, 6.0 Hz, 3.7 Hz, H-6), 2.48 (1H, dd, *J* = 13.5, 10.5 Hz, H-5), 2.30 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 1.67-1.54 (2H, m, H-8), 1.48-1.36 (2H, m, H-8), 1.25 (3H, d, *J* = 6.0 Hz, H-7) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.0 (C=O), 168.9 (C=O), 66.8 (CH), 63.3 (CH_2), 62.8 (CH_2), 58.2 (C), 52.3 (CH_3), 47.5 (CH_2), 46.9 (CH), 36.5 (CH_2), 33.6 (CH_2), 22.8 (CH_3) ppm; HRMS (ESI) 242.1386 (M + H^+. $C_{12}H_{20}NO_4$ requires 242.1387); IR (ATR): ν_{max} 2956, 2867, 1703 (C=O), 1435, 1333, 1162 cm^{-1}.



Methyl 6-(4-fluorophenyl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (138b)

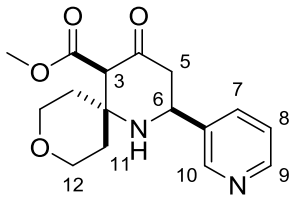
Following **general procedure C** with the hydrochloride salt of **126e** (129 mg, 0.468 mmol), tetrahydro-4*H*-pyran-4-one (216 μL, 2.34 mmol) and $NaHCO_3$ (196 mg, 2.34 mmol). The residue was purified by column chromatography (triethylamine deadened silica, 20% EtOAc/CH_2Cl_2) to give the title compound as a mixture of diastereomers (84.5 mg, 0.263 mmol, 56% yield, 2:1 dr) as a white solid. Data presented is for the major diastereomer. Mp 110.5-113 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.38 (2H, m, H-7), 7.13-7.04 (2H, m, H-8), 4.09 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 3.90 (1H, td, *J* = 11.5, 3.0 Hz, H-10), 3.81 (1H, td, *J* = 11.5, 3.0 Hz, H-10), 3.74 (3H, s, OCH_3), 3.72-3.64 (2H, m, H-10), 3.41 (1H, d, *J* = 1.0 Hz), 3.06 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.57 (1H, ddd, 13.5, 3.5, 1.0 Hz, H-5), 2.15 (1H, br. s, NH), 1.81-1.68 (2H, m, H-9), 1.63-1.54 (1H, m, H-9), 1.53-1.45 (1H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.2 (C=O), 169.0 (C=O), 162.1 (d, J_F = 245 Hz, CF), 138.8 (d, J_F = 3.0 Hz, C), 128.3 (d, J_F = 14.0 Hz, CH), 115.8 (d, J_F = 21.5 Hz, CH), 67.0 (CH), 63.4 (CH_2), 62.8 (CH_2), 58.3 (C), 54.9 (CH), 52.5 (CH_3), 46.1 (CH_2), 36.7 (CH_2), 33.4 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.0 ppm; HRMS

(ESI) 322.1445 (M + H^+. $C_{17}H_{21}FNO_4$ requires 322.1449), 344.1269 (M + Na^+. $C_{17}H_{21}FNO_4$ requires 344.1269); IR (ATR): ν_{max} 2963, 2868, 1706 (C=O), 1603, 1511, 1223, 1160 cm^{-1}.



Methyl 6-(4-methoxyphenyl)-4-oxo-9-oxa-1-azaspiro[5.5]undecane-3-carboxylate (138c)

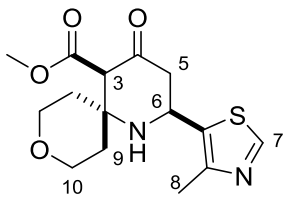
Following **general procedure C** with the hydrochloride salt of **126f** (757 mg, 2.63 mmol), tetrahydro-4H-pyran-4-one (1.22 mL, 13.2 mmol) and $NaHCO_3$ (1.11 g, 13.2 mmol). The residue was purified by column chromatography (0-80% EtOAc/cyclohexane) to afford the title compound as a mixture of diastereomers (290 mg, 0.870 mmol, 33% yield, 2:1 dr) as a red oil that solidified on standing. Data presented is for the major diastereomer. Mp 118-121 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43-7.36 (2H, m, H-7), 6.98-6.92 (2H, m, H-8), 4.08 (1H, dd, *J* = 11.0, 3.5 Hz, H-6), 4.03-3.64 (4H, m, H-11), 3.84 (3H, s, H-9), 3.76 (3H, s, OCH_3), 3.42 (1H, d, *J* = 1.0 Hz, H-3), 3.10 (1H, dd, *J* = 13.5, 11.0 Hz, H-5), 2.57 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 2.15 (1H, br. s, NH), 1.85-1.70 (2H, m, H-10), 1.65-1.44 (2H, m, H-10) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 204.4 (C=O), 168.9 (C=O), 159.2 (C), 134.1 (C), 127.7 (CH), 114.2 (CH), 67.0 (CH), 63.3 (CH_2), 62.7 (CH_2), 58.2 (C), 55.3 (CH_3), 54.9 (CH), 52.3 (CH_3), 46.2 (CH_2), 36.6 (CH_2), 33.3 (CH_2); HRMS (ESI) 334.1637 (M + H^+. $C_{18}H_{24}NO_5$ requires 334.1649); IR (ATR): ν_{max} 3318, 2965, 2947, 2865, 1732 (C=O), 1701 (C=O), 1515, 1297, 1243,1159, 1024 cm^{-1}.



Methyl 4-oxo-6-pyridin-3-yl-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (138d)

Following **general procedure C** with the hydrochloride salt of **126g** (1.50 g, 5.81 mmol), tetrahydro-4*H*-pyran-4-one (2.68 mL, 29.1 mmol) and $NaHCO_3$ (2.44 g, 29.1 mmol). The

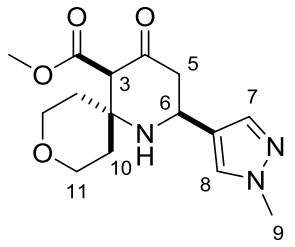
residue was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 100% EtOAc) to give the title compound as a mixture of diastereomers (1.40 g, 4.61 mmol, 79% yield, 1.5:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (1H, d, *J* = 2.0 Hz, H-10), 8.55 (1H, dd, *J* = 5.0, 2.0 Hz, H-9), 7.79 (1H, ddd, *J* = 8.0, 2.0, 2.0 Hz, H-7), 7.31 (1H, dd, *J* = 8.0, 5.0 Hz, H-8), 4.14 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 3.87 (1H, ddd, *J* = 11.5, 11.5, 2.5 Hz, H-12), 3.78 (1H, ddd, *J* = 11.5, 11.5, 2.5 Hz, H-12), 3.71 (3H, s, OCH_3), 3.70-3.60 (2H, m, H-12), 3.38 (1H, br. s, H-3), 3.06 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.58 (1H, dd, *J* = 13.5, 3.5 Hz, H-5) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.5 (C=O), 168.9 (C=O), 149.4 (CH), 148.7 (CH), 137.2 (C), 134.0 (CH), 123.8 (CH), 67.0 (CH), 63.3 (CH_2), 62.7 (CH_2), 58.3 (C), 53.1 (CH_3), 52.5 (CH), 45.3 (CH_2), 36.5 (CH_2), 33.2 (CH_2) ppm; HRMS (ESI) 305.1486 (M + H^+. $C_{16}H_{21}N_2O_4$ requires 305.1496); IR (ATR): ν_{max} 2952, 2872, 1706 (C=O), 1428, 1337, 1195, 1166 cm^{-1}.



Methyl 6-(4-methyl-thiazol-5-yl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (138e)

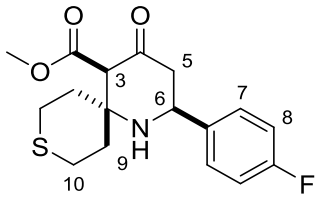
Following **general procedure C** with the hydrochloride salt of **126h** (99 mg, 0.356 mmol), tetrahydro-4*H*-pyran-4-one (164 µL, 1.78 mmol) and $NaHCO_3$ (150 mg, 1.78 mmol). The residue was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 100% EtOAc) to give the title compound as a mixture of diastereomers (86 mg, 0.265 mmol, 75% yield, 1:1 dr) as a white solid. Data presented is for the major diastereomer. Mp 98-101 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, s, H-7), 4.41 (1H, dd, *J* = 11.0, 3.5 Hz, H-6), 3.90-3.76 (2H, m, H-10), 3.73 (3H, s, OCH_3), 3.71-3.64 (2H, m, H-10), 3.38 (1H, br. s, H-3), 3.05 (1H, dd, *J* = 13.5, 11.0 Hz, H-5), 2.63 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 2.47 (3H, s, H-8), 1.80-1.54 (3H, m, H-9), 1.51-1.41 (1H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5 (C=O), 168.7 (C=O), 150.2 (CH), 149.9 (C), 133.0 (C), 66.8 (CH), 63.3 (CH_2), 62.7 (CH_2), 58.1 (C), 52.6 (CH_3), 48.8 (CH), 47.1 (CH_2), 36.5

(CH_2), 33.4 (CH_2), 16.6 (CH_3) ppm; HRMS (ESI) 325.1201 (M + H^+. $C_{15}H_{21}N_2O_4S$ requires 325.1217); IR (ATR): ν_{max} 2953, 2865, 1706 (C=O), 1435, 1338, 1255, 1196, 1165 cm^{-1}.



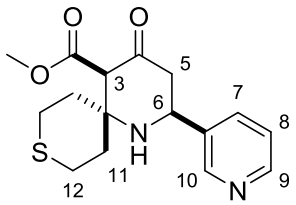
Methyl 6-(1-methyl-1H-pyrazol-4-yl)-4-oxo-9-oxa-1-azaspiro[5.5]undecane-3-carboxylate (138f)

Following **general procedure C** with the hydrochloride salt of **126i** (203 mg, 0.776 mmol), tetrahydro-4H-pyran-4-one (358 µL, 3.88 mmol) and $NaHCO_3$ (326 mg, 3.88 mmol). The residue was purified by column chromatography (0-50% EtOH/EtOAc) to give the title compound as a mixture of diastereomers (119 mg, 0.387 mmol, 50% yield, 2.5:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, s, H-7), 7.40 (1H, s, H-8), 4.13 (1H, dd, *J* = 11.0, 3.5 Hz, H-6), 4.00-3.63 (4H, m, H-11), 3.91 (3H, s, H-9), 3.72 (3H, s, OCH_3), 3.38 (1H, d, *J* = 1.0 Hz, H-3), 2.97 (1H, dd, *J* = 13.5, 11.0 Hz, H-5), 2.63 (1H, ddd, *J* = 13.5, 3.5, 1.0 Hz, H-5), 1.80-1.67 (2H, m, H-10), 1.61-1.44 (2H, m, H-10) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 203.7 (C=O), 168.7 (C=O), 137.1 (CH), 127.6 (CH), 123.8 (C), 67.1 (CH), 63.2 (CH_2), 62.7 (CH_2), 58.0 (C), 52.3 (CH_3), 47.4 (CH), 46.1 (CH_2), 39.0 (CH_3), 36.5 (CH_2), 33.3 (CH_2) ppm; HRMS (ESI) 308.1594 (M + H^+. $C_{15}H_{22}N_3O_4$ requires 308.1605); IR (ATR): ν_{max} 3282, 3248, 1704 (C=O), 1562, 1435, 1296, 1218, 1159 cm^{-1}.



Methyl 6-(4-fluoro-phenyl)-4-oxo-9-thia-1-aza-spiro[5.5]undecane-3-carboxylate (139a)

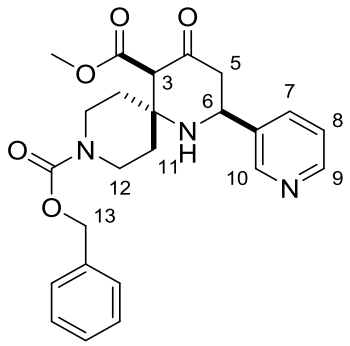
Following **general procedure C** with the hydrochloride salt of **126e** (189 mg, 0.686 mmol), tetrahydro-4H-thiopyran-4-one (398 mg, 3.43 mmol) and $NaHCO_3$ (288 mg, 3.43 mmol). The residue was purified by column chromatography (triethylamine deadened silica, 10-20% ethyl acetate/hexane) to give the title compound as a mixture of diastereomers (171 mg, 0.432 mmol, 63% yield, 1:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.39 (2H, m, H-7), 7.11-7.04 (2H, m, H-8), 4.04 (1H, dd, *J* = 11.0, 4.0 Hz, H-6), 3.73 (3H, s, OCH_3), 3.33 (1H, br s, H-3), 3.22-3.12 (1H, m, H-10), 3.04 (1H, dd, *J* = 13.5, 11.0 Hz, H-5), 3.06-2.93 (1H, m, H-10), 2.56 (1H, ddd, *J* = 13.5, 4.0, 0.5 Hz, H-5), 2.41-2.32 (2H, m, H-10), 2.12-1.93 (2H, m, H-9 and NH), 1.84-1.77 (2H, m, H-9), 1.70 (1H, ddd, *J* = 14.5, 11.5, 14.5 Hz, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.3 (C=O), 169.0 (C=O), 162.4 (d, J_F = 247.5 Hz, CF), 137.8 (d, J_F = 3.5 Hz, C), 128.3 (d, J_F = 8.0 Hz, CH), 115.8 (d, J_F = 21.5 Hz, CH), 67.4 (CH), 59.3 (C), 54.4 (CH), 52.5 (CH_3), 45.7 (CH_2), 37.3 (CH_2), 34.3 (CH_2), 23.4 (CH_2), 22.8 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.3 ppm; HRMS (ESI) 338.1205 (M + H^+. $C_{17}H_{21}FNO_3S$ requires 338.1221); IR (ATR): ν_{max} 2962, 2922, 1705 (C=O), 1510, 1226, 1196, 1161 cm^{-1}.



Methyl 4-oxo-6-pyridin-3-yl-9-thia-1-aza-spiro[5.5]undecane-3-carboxylate (139b)

Following **general procedure C** with the hydrochloride salt of **126g** (104 mg, 0.402 mmol), tetrahydro-4H-thiopyran-4-one (233 mg, 2.01 mmol) and $NaHCO_3$ (169 mg, 2.01 mmol). The residue was purified by column chromatography (50% ethyl acetate/hexane then 100% EtOAc) to give the title compound as a mixture of diastereomers (77.5 mg, 0.302 mmol, 75% yield, 0.95:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400

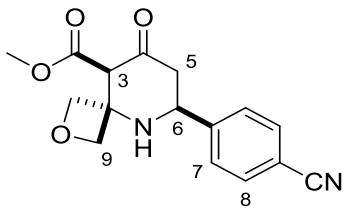
MHz, $CDCl_3$): δ 8.68-8.64 (1H, m, H-10), 8.56 (1H, dd, *J* = 5.0, 1.5 Hz, H-9), 7.79 (1H, ddd, 8.0, 2.0, 2.0 Hz, H-7), 7.35-7.28 (1H, m, H-8), 4.10 (1H, br s, H-6), 3.71 (3H, s, OCH_3), 3.33 (1H, d, 1.0 Hz, H-3), 3.20-3.09 (1H, m, H-12), 3.05 (1H, dd, 13.5, 11.5 Hz, H-5), 3.06-2.90 (1H, m, H-12), 2.58 (1H, ddd, 13.5, 4.0, 1.0 Hz, H-5), 2.40-2.28 (2H, m, H-12), 2.12-2.05 (1H, m, H-11), 1.82-1.77 (2H, m, H-11), 1.70 (1H, ddd, *J* = 14.5, 11.5, 3.0, H-11) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.6 (C=O), 168.9 (C=O), 149.5 (CH), 148.7 (CH), 137.1 (C), 134.0 (CH), 123.8 (CH), 67.4 (CH), 59.3 (C), 52.7 (CH), 52.5 (CH_3), 44.9 (CH_2), 37.2 (CH_2), 34.2 (CH_2), 23.3 (CH_2), 22.7 (CH_2) ppm; HRMS (ESI) 321.1260 (M + H^+. $C_{16}H_{21}N_2O_3S$ requires 321.1267); IR (ATR): ν_{max} 3310, 2952, 2920, 1703 (C=O), 1424, 1268, 1195, 1162 cm^{-1}.



4-Oxo-6-pyridin-3-yl-1,9-diaza-spiro[5.5]undecane-3,9-dicarboxylic acid 9-benzyl ester 3-methyl ester (140)

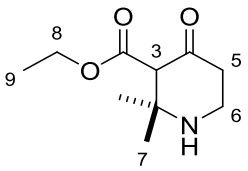
Following **general procedure C** with the hydrochloride salt of **126g** (145 mg, 0.562 mmol), 1-Z-4-piperidone (655 mg, 2.81 mmol) and $NaHCO_3$ (236 mg, 2.81 mmol). The residue was purified by column chromatography (50% EtOAc/CH_2Cl_2 then 100% EtOAc) to give the title compound as a mixture of diastereomers (145 mg, 0.376 mmol, 67% yield, 2:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (1H, br. s, H-10), 8.56 (1H, dd, *J* = 5.0, 1.5 Hz, H-9), 7.78 (1H, ddd, *J* = 8.0, 1.5, 1.5 Hz, H-7), 7.37-7.26 (6H, m, H-8 and ArH), 5.10 (2H, s, H-13), 4.20-4.06 (1H, m, H-6), 3.92-3.75 (2H, m, H-12), 3.71 (3H, s, OCH_3), 3.45-3.16 (2H, m, H-12), 3.30 (1H, d, *J* = 0.5 Hz, H-3), 3.07 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.60 (1H, dd, *J* = 13.5, 3.0 Hz, H-5), 1.91-1.34 (4H, m, H-11) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.1 (C=O), 168.8 (C=O), 155.2 (C=O), 149.5 (CH), 148.6 (CH), 137.0 (C), 136.7 (C), 133.9 (CH), 128.6 (CH), 128.1 (CH), 127.9 (CH), 123.8 (CH), 67.2 (CH_2), 66.8 (CH), 58.8 (C), 53.2 (CH), 52.5 (CH_3) 45.0 (CH_2), 39.5 (CH_2), 39.0 (CH_2), 35.5 (CH_2), 32.3 (CH_2) ppm; HRMS (ESI)

438.2032 (M + H^+. $C_{24}H_{28}N_3O_5$ requires 438.2023); IR (ATR): ν_{max} 2951, 1694 (C=O), 1427, 1246, 1164 cm^{-1}.



Methyl 6-(4-cyano-phenyl)-4-oxo-8-oxa-1-aza-spiro[3.5]nonane-3-carboxylate (141)

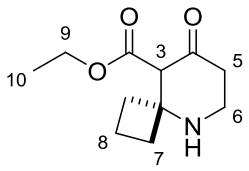
Following **general procedure C** with the hydrochloride salt of **126j** (93 mg, 0.330 mmol), 3-oxetanone (97 µL, 1.65 mmol) and $NaHCO_3$ (139 mg, 1.69 mmol). The residue was purified by column chromatography (60% EtOAc/hexane) to give the title compound as a mixture of diastereomers (42.8 mg, 0.142 mmol, 43% yield, 1.6:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.66 (2H, m, H-8), 7.57-7.51 (2H, m, H-7), 4.92 (1H, d, *J* = 7.5 Hz, H-9), 4.61 (1H, d, *J* = 7.5 Hz, H-9), 4.56 (1H, d, *J* = 6.5 Hz, H-9), 4.50 (1H, d, *J* = 6.5 Hz, H-9), 4.02 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 3.93 (1H, d, *J* = 1.5 Hz, H-3), 3.79 (3H, s, OCH_3), 2.72 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.56 (1H, ddd, *J* = 13.5, 3.5, 1.5 Hz, H-5) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 200.9 (C=O), 167.9 (C=O), 146.3 (C), 132.9 (CH), 127.5 (CH), 118.6 (CN), 112.3 (C), 80.9 (CH_2), 80.1 (CH_2), 62.9 (CH), 62.4 (C), 56.1 (CH), 53.0 (CH_3), 47.5 (CH_2) ppm; HRMS (ESI) 301.1179 (M + H^+. $C_{16}H_{17}N_2O_4$ requires 301.1183); IR (ATR): ν_{max} 3302, 2874, 2228 (CN), 1717 (C=O), 1608, 1441, 1345, 1297 1225 cm^{-1}.



Ethyl 2,2-dimethyl-4-oxo-piperidine-3-carboxylate (145)

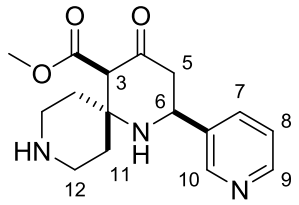
Following **general procedure C** with the hydrochloride salt of **144** (101 mg, 0.513 mmol), acetone (192 µL, 2.59 mmol) and $NaHCO_3$ (218 mg, 2.59 mmol) to give the title compound (85 mg, 0.425 mmol, 83% yield) as a colourless oil without further purification. ^{1}H NMR (400

MHz, $CDCl_3$): δ 4.21-4.10 (2H, m, H-8), 3.32 (1H, ddd, *J* = 14.0, 7.5, 2.8 Hz, H-6), 3.27 (1H, d, *J* = 1.0 Hz, H-3), 3.10 (1H, ddd, *J* = 14.0, 10.0, 4.5 Hz, H-6), 2.76 (1H, ddd, *J* = 14.0, 10.0, 7.5 Hz, H-5), 2.25 (1H, dddd, *J* = 14.0, 4.5, 2.8, 1.0 Hz, H-5), 1.26 (3H, t, *J* = 7.5 Hz, H-9), 1.20 (3H, s, H-7), 1.11 (3H, s, H-7) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.3 (C=O), 169.1 (C=O), 68.3 (CH), 61.3 (CH_2), 58.3 (C), 41.9 (CH_2), 39.8 (CH_2), 27.1 (CH_3), 26.1 (CH_3), 14.3 (CH_3) ppm; HRMS (ESI) 200.1288 (M + H^+. $C_{10}H_{18}NO_3$ requires 200.1281); IR (ATR): ν_{max} 3299, 2974, 2935, 1703 (C=O), 1652 (C=O), 1600, 1238, 1164, 1144, 1127 cm^{-1}.



Ethyl 4-oxo-1-aza-spiro[3.5]nonane-3-carboxylate (146)

Following **general procedure C** with the hydrochloride salt of **144** (100 mg, 0.513 mmol), cyclobutanone (192 µL, 2.57 mmol) and $NaHCO_3$ (215 mg, 2.57 mmol). The residue was purified by column chromatography (100% EtOAc) to give the title compound (53 mg, 0.251 mmol, 49% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21-4.07 (2H, m, H-9), 3.54 (1H, d, *J* = 1.5 Hz, H-3), 3.26 (1H, ddd, *J* = 13.5, 7.2, 2.0 Hz, H-6), 2.89 (1H, ddd, *J* = 13.5, 11.8, 3.5 Hz, H-6), 2.63 (1H, ddd, *J* = 13.5, 11.8, 7.2 Hz, H-5), 2.35 (1H, br. s, NH), 2.20 (1H, dddd, *J* = 13.5, 3.5, 2.0, 1.5 Hz, H-5), 2.13-1.74 (6H, m, H-7 and H-8) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.1 (C=O), 168.5 (C=O), 67.0 (CH), 63.8 (C), 61.4 (CH_2), 41.8 (CH_2), 40.7 (CH_2), 32.1 (CH_2), 30.9 (CH_2), 14.5 (CH_2), 14.3 (CH_3) ppm; HRMS (ESI) 212.1284 (M + H^+. $C_{11}H_{18}NO_3$ requires 212.1281); IR (ATR): ν_{max} 3326, 2978, 2937, 2874, 1701 (C=O), 1453, 1294, 1174, 1095 cm^{-1}.

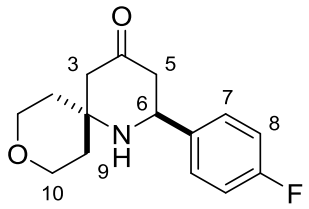


Methyl 4-oxo-6-pyridin-3-yl-1,9-diaza-spiro[5.5]undecane-3-carboxylate (142)

A mixture of 2-spiropiperidine **140** (71 mg, 0.162 mmol) and 10% Pd/C (7 mg, 6.86 µmol) in MeOH (3 mL) was evacuated and subjected to a balloon of H_2. The reaction was stirred for 5h before the addition of extra 10% Pd/C (4 mg, 3.92 µmol). The reaction was stirred overnight at rt, then filtered through Celite. The volatiles were removed *in vacuo* to give the title compound (44.2 mg, 0.146 mmol, 90% yield) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (1H, d, *J* = 1.8 Hz, H-10), 8.58 (1H, dd, *J* = 4.6, 1.8 Hz, H-9), 7.82 (1H, ddd, *J* = 7.8, 1.8, 1.8 Hz, H-7), 7.34 (1H, dd, *J* = 7.8, 4.6 Hz, H-8), 4.19 (1H dd, *J* = 11.0, 3.8 Hz, H-6), 3.74 (3H, s, OCH_3), 3.42 (1H, br. s, H-3), 3.14-3.05 (1H, m, H-12), 3.09 (1H, dd, *J* = 13.5, 11.0, H-5), 3.04-2.97 (1H, m, H-12), 2.88-2.77 (2H, m, H-12), 2.60 (1H, ddd, *J* = 13.5, 3.8, 1.0 Hz, H-5), 2.15 (1H, d, *J* = 11.9 Hz, NH), 1.84-1.75 (1H, m, H-9), 1.69-1.58 (1H, m, H-9), 1.56-1.46 (2H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.2 (C=O), 168.9 (C=O), 149.6 (CH), 148.6 (CH), 137.0 (C), 134.1 (CH), 123.9 (CH), 66.8 (CH), 58.5 (C), 53.1 (CH), 52.6 (CH_3), 45.2 (CH_2), 40.9 (CH_2), 40.4 (CH_2), 35.2 (CH_2), 31.8 (CH_2) ppm; HRMS (ESI) 304.1653 ($M + H^+$. $C_{16}H_{22}N_3O_3$ requires 304.1656).

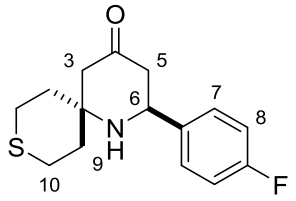
General Procedure D – Decarboxylation of the 2-spiropiperidines

Water (3.5 mL) was added to a suspension of 2-spiropiperidine (0.358 mmol) and LiOH (3.58 mmol) in THF (3.5 mL). The reaction was stirred for 16 hours at room temperature. The mixture was diluted with EtOAc (20 mL) and layers were separated. The aqueous was extracted with EtOAc (5 x 10 mL). Organics were combined, concentrated *in vacuo* and purified by column chromatography.



6-(4-Fluoro-phenyl)-9-oxa-1-aza-spiro[5.5]undecan-4-one (147b)

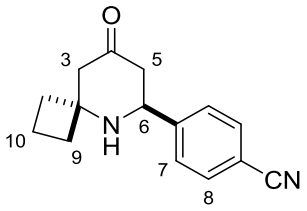
Following **general procedure D** with 2-spiropiperidine **138b** (115 mg, 0.358 mmol) and LiOH (86 mg, 3.58 mmol) gave the title compound (59.7 mg, 0.229 mmol, 64% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.37 (2H, m, H-7), 7.08-7.04 (2H, m, H-8), 4.18 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 3.86-3.72 (2H, m, H-10), 3.70-3.59 (2H, m, H-10), 2.58 (1H, dd, *J* = 13.5, 1.75 Hz, H-3), 2.53 (1H, ddd, *J* = 13.5, 3.5, 1.75 Hz, H-5), 2.44 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.35 (1H, *J* = 13.5 Hz, H-3), 1.83-1.71 (2H, m, H-9), 1.70-1.57 (3H, m, H-9 and N-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.6 (C=O), 169.0 (C=O), 162.1 (d, J_F = 247 Hz, CF), 138.4 (d, J_F = 3.0 Hz, C), 128.3 (d, J_F = 8.5 Hz, CH), 115.8 (d, J_F = 21.5 Hz, CH), 63.9 (CH_2), 63.6 (CH_2), 54.0 (CH), 53.7 (C), 51.8 (CH_2), 50.2 (CH_2), 40.4 (CH_2), 33.9 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.2 ppm; HRMS (ESI) 264.1394 (M + H^+. $C_{15}H_{19}FNO_2$ requires 264.1394); IR (ATR): ν_{max} 2935, 2857, 1707 (C=O), 1509, 1221, 1101 cm^{-1}.



6-(4-Fluorophenyl)-9-thia-1-aza-spiro[5.5]undecan-4-one (147c)

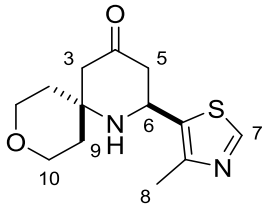
Following **general procedure D** with spirocycle **139a** (49 mg, 0.145 mmol) and LiOH (35 mg, 1.45 mmol) gave the title compound (28.2 mg, 0.101 mmol, 70% yield) as a colourless oil after column chromatography (20 % ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.36 (2H, m, H-7), 7.10-7.01 (2H, m, H-8), 4.13 (1H, dd, *J* = 11.5, 3.5 Hz, H-6), 2.90 (1H, ddd, *J* = 14.0, 9.5, 4.5 Hz, H-10), 2.76 (1H, ddd, *J* = 13.5, 10.5, 3.0 Hz, H-10), 2.57-2.44 (3H, m, H-5 and H-10), 2.41 (1H, dd, *J* = 13.5, 2.0 Hz, H-3), 2.41 (1H, dd, *J* = 13.5, 11.5 Hz, H-5), 2.27 (1H, d, *J* = 13.5 Hz, H-3), 2.05-1.86 (3H, m, H-9), 1.82 (1H, ddd, *J* = 13.5, 10.5, 3.0 Hz, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.6 (C=O), 162.4 (d, J_F = 248.0 Hz, CF), 138.3 (d, J_F = 3.0 Hz, C), 128.3 (d,

J_F = 8.0 Hz, CH), 115.7 (d, J_F = 21.5 Hz, CH), 54.6 (C), 53.8 (CH_2), 53.5 (CH_2), 50.0 (CH_2), 41.1 (CH_2), 33.8 (CH_2), 23.6 (CH_2), 23.6 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.2 ppm; HRMS (ESI) 280.1170 (M + H^+. $C_{15}H_{19}FNOS$ requires 280.1166); IR (ATR): ν_{max} 3302, 2924, 2847, 1707 (C=O), 1509, 1274, 1221 cm^{-1}.



4-(8-Oxo-5-aza-spiro[3.5]non-6-yl)-benzonitrile (147d)

Following **general procedure D** with spirocycle **137b** (56 mg, 0.188 mmol) and LiOH (45 mg, 1.88 mmol) gave the title compound (30.2 mg, 0.126 mmol, 67% yield) as a colourless oil after column chromatography (60% ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (2H, d, *J* = 8.0 Hz, H-7), 7.53 (2H, d, *J* = 8.0 Hz, H-8), 4.04 (1H, dd, *J* = 9.0, 6.0 Hz, H-6), 2.69 (1H, d, *J* = 13.5 Hz, H-3), 2.51 (1H, d, *J* = 13.5 Hz, H-3), 2.45-2.35 (2H, m, H-5), 2.18-2.02 (3H, m, H-9), 1.92-1.76 (4H, m, H-9 and H-10) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.6 (C=O), 147.9 (C), 132.8 (CH), 127.5 (CH), 118.7 (CN), 111.9 (C), 59.8 (C), 56.2 (CH), 51.3 (CH_2), 49.7 (CH_2), 35.8 (CH_2), 33.7 (CH_2), 13.0 (CH_2) ppm; HRMS (ESI) 241.1336 (M + H^+. $C_{15}H_{17}N_2O$ requires 241.1335); IR (ATR): ν_{max} 3310, 2960, 2929, 2227, 1710 (C=O), 1297 cm^{-1}.



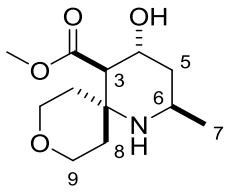
6-(4-Methyl-thiazol-5-yl)-9-oxa-1-aza-spiro[5.5]undecane-4-one (147e)

Following **general procedure D** with spirocycle **138e** (160 mg, 0.494 mmol) and LiOH (119 mg, 4.94 mmol) gave the title compound (52 mg, 0.198 mmol, 40% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (1H, s, H-7), 4.53 (1H, dd, *J* = 11.2, 3.5 Hz, H-6), 3.83-3.71 (2H, m, H-10), 3.68-3.57 (2H, m, H-10), 2.63-2.51 (2H, m, H-3 and H-5), 2.47-2.33 (2H, m, H-3 and

H-5), 2.41 (3H, s, H-8), 1.81-1.71 (2H, m, H-9), 1.69-1.58 (2H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.1 (C=O), 151.1 (CH), 148.7 (C), 134.2 (C), 63.9 (CH_2), 63.6 (CH_2), 53.7 (C), 51.2 (CH_2), 50.4 (CH_2), 47.9 (CH), 40.1 (CH_2), 34.1 (CH_2), 15.5 (CH_3) ppm; HRMS (ESI) 280.1170 (M + H^+. $C_{15}H_{19}FNOS$ requires 280.1166); IR (ATR): ν_{max} 2924, 2854, 1709 (C=O), 1414, 1357, 1238, 1101 cm^{-1}.

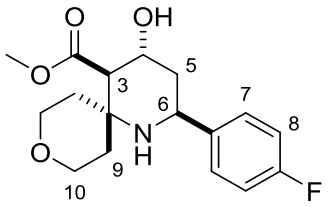
General Procedure E – Ketone reduction of the 2-spiropiperidines

Sodium borohydride (2.74 mmol) was added portionwise to a solution of 2-spiropiperidine (2.28 mmol) in methanol (11 mL) at 0 °C. The reaction was stirred at room temperature for 1h then quenched with acetone (11.4 mmol). Volatiles were removed *in vacuo*, and the residue was purified by column chromatography to give the 4-hydroxy-2-spiropiperidine.



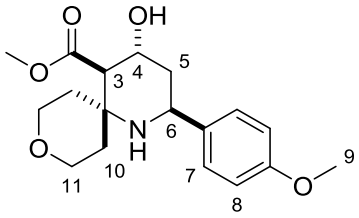
Methyl 4-hydroxy-6-methyl-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (148a)

Following **general procedure E** with spirocycle **138a** (48.2 mg, 0.200 mmol) and sodium borohydride (9.1 mg, 0.240 mmol). The residue was purified by column chromatography (50% EtOAc/CH_2Cl_2 followed by 50% EtOAc/MeOH) to give the title compound as a mixture of diastereomers (39.5 mg, 0.162 mmol, 81% yield) as a colourless oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (1H, dd, *J* = 6.5, 3.0 Hz, H-4), 3.94-3.79 (2H, m, H-9), 3.67 (3H, s, OCH_3), 3.65-3.55 (2H, m, H-9), 3.13 (1H, dqd, *J* = 13.0, 6.5, 3.5 Hz, H-6), 2.60 (1H, d, *J* = 2.0 Hz, H-3), 2.26 (1H, m, H-5), 1.85 (1H, ddd, *J* = 14.0, 10.0, 4.0 Hz, H-8), 1.76 (1H, ddd, *J* = 14.5, 11.5, 3.5 Hz, H-5), 1.65-1.55 (2H, m, H-8), 1.32-1.22 (1H, m, H-8), 1.12 (3H, d, H-7) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0 (C=O), 68.1 (CH), 63.6 (CH_2), 63.1 (CH_2), 53.2 (CH), 51.6 (CH_3), 51.4 (C), 40.0 (CH), 37.9 (CH_2), 37.8 (CH_2), 36.0 (CH_2), 22.9 (CH_3) ppm; HRMS (ESI) 244.1546 (M + H^+. $C_{12}H_{22}NO_4$ requires 244.1543); IR (ATR): ν_{max} 3407, 2952, 2866, 1722 (C=O), 1434, 1199, 1147, 1103 cm^{-1}.



Methyl 6-(4-fluorophenyl)-4-hydroxy-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (148b)

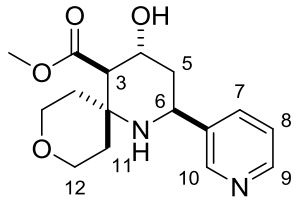
Following **general procedure E** with spirocycle **138b** (107 mg, 0.333 mmol) and sodium borohydride (15.2 mg, 0.400 mmol). The residue was purified by column chromatography (60-100% EtOAc/hexane) to give the title compound as a mixture of diastereomers (69 mg, 0.213 mmol, 64% yield) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): 7.43-7.36 (2H, m, H-7), 7.03 (2H, dd, *J* = 3.0, 8.5 Hz, H-8), 4.38 (1H, dd, *J* = 6.0, 3.0 Hz, H-4), 4.15 (1H, dd, *J* = 12.0, 3.0 Hz, H-6), 3.92-3.84 (2H, m, H-10), 3.69 (3H, s, OCH_3), 3.70-3.58 (2H, m, H-10), 2.66 (1H, d, *J* = 2.0 Hz, H-3), 2.45-2.36 (1H, m, H-5), 2.25 (1H, ddd, *J* = 15.5, 12.0, 3.5 Hz, H-5), 1.93-1.80 (2H, m, H-9), 1.69 (1H, ddd, *J* = 15.0, 10.5, 4.5 Hz, H-9), 1.29-1.21 (1H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9 (C=O), 162.0 (d, J_F = 246 Hz, CF), 140.0 (d, J_F = 3.0 Hz, C), 128.4 (d, J_F = 8.0 Hz, CH), 115.3 (d, J_F = 21.0 Hz, CH), 67.9 (CH), 63.5 (CH_2), 63.0 (CH_2), 53.6 (CH), 51.7 (CH_3), 47.5 (CH), 37.8 (CH_2), 35.9 (CH_2), 35.8 (CH_2) ppm; HRMS (ESI) 324.1614 ($M + H^+$. $C_{17}H_{23}FNO_4$ requires 324.1606); IR (ATR): ν_{max} 3395, 2951, 2867, 1720 (C=O), 1509, 1221, 1076 cm^{-1}.



Methyl 4-hydroxy-6-(4-methoxyphenyl)-9-oxa-1-azaspiro[5.5]undecane-3-carboxylate (148c)

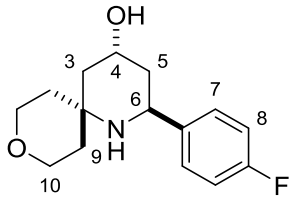
Following **general procedure E** with spirocycle **138c** (102 mg, 0.306 mmol) and sodium borohydride (17.4 mg, 0.459 mmol). The residue was purified by column chromatography (0-100% EtOAc/cyclohexane) to give the title compound as a mixture of diastereomers (58 mg,

0.173 mmol, 57% yield) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.33 (2H, m, H-7), 6.94-6.87 (2H, m, H-8), (1H, q, *J* = 3.0 Hz, H-4), (1H, dd, *J* = 12.0, 3.0 Hz, H-6), 3.91 (2H, td, *J* = 11.0, 2.5 Hz, H-11), 3.82 (3H, s, H-9), 3.70 (3H, s, OCH_3), 3.69-3.59 (2H, m, H-11), 2.67 (1H, d, *J* = 2.0 Hz, H-3), 2.46-2.37 (1H, m, H-10), 2.27 (1H, ddd, *J* = 14.0, 12.0, 3.5 Hz, H-5), 1.94-1.86 (1H, m, H-10), 1.83 (1H, dt, *J* = 14.0, 3.0 Hz, H-5), 1.31-1.23 (1H, m, H-10) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.8 (C=O), 158.6 (C), 136.4 (C), 127.7 (CH), 113.8 (CH), 67.8 (CH), 63.3 (CH_2), 62.9 (CH_2), 55.3 (CH_3), 53.5 (CH), 51.5 (CH_3), 51.4 (C), 47.4 (CH), 37.7 (CH_2), 35.8 (CH_2), 35.7 (CH_2) ppm. HRMS (ESI) 336.1789 (M + H^+. $C_{18}H_{25}NO_5$ requires 336.1806); IR (ATR): ν_{max} 3341, 2966, 2867, 1720 (C=O), 1427, 1306, 1193, 1161, 1139, 1101, 1079, 1026 cm^{-1}.



Methyl 4-hydroxy-6-pyridin-3-yl-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (148d)

Following **general procedure E** with spirocycle **138d** (694 mg, 2.28 mmol) and sodium borohydride (104 mg, 2.74 mmol). The residue was purified by column chromatography (7.5-10% methanol/ethyl acetate) to give the title compound as a mixture of diastereomers (538 mg, 1.76 mmol, 77% yield) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): 8.65 (1H, d, *J* = 2.0 Hz, H-10), 8.49 (1H, dd, *J* = 4.5, 1.0 Hz, H-9), 7.83-7.78 (1H, m, H-7), 7.30 (1H, dd, *J* = 8.0, 4.5 Hz, H-8), 4.44-4.40 (1H, m, H-4), 4.27 (1H, dd, 12.0, 3.0 Hz, H-6), 3.94-3.83 (2H, m, H-12), 3.69-3.60 (2H, m, H-12), 3.68 (3H, s, OCH_3), 2.72 (1H, d, *J* = 2.0 Hz, H-3), 2.54-2.44 (1H, m, H-5), 2.30-2.17 (1H, m, H-5), 1.99-1.86 (2H, m, H-5 and H-11), 1.75-1.65 (1H, m, H-11), 1.31-1.22 (1H, m, H-11) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0 (C=O), 148.6 (CH), 148.1 (CH), 139.9 (C), 134.6 (CH), 123.7 (CH), 67.3 (CH), 63.4 (CH_2), 62.9 (CH_2), 53.4 (CH), 52.6 (C), 51.6 (CH_3), 46.1 (CH), 37.9 (CH_2), 35.6 (CH_2), 35.4 (CH_2) ppm; HRMS (ESI) 307.1644 (M + H^+. $C_{16}H_{23}N_2O_4$ requires 307.1652); IR (ATR): ν_{max} 3290, 2948, 2863, 1720 (C=O), 1426, 1192, 1139, 1101, 1078, 1025 cm^{-1}.



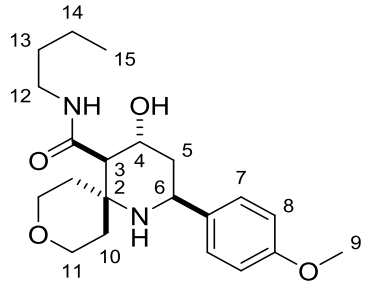
6-(4-Fluorophenyl)-9-oxa-1-aza-spiro[5.5]undecan-4-ol (149)

Method A: To a stirred solution of ketone **147b** (52.5 mg, 0.200 mmol) in MeOH (1 mL) at 0 ^{o}C was added $NaBH_4$ (9.1 mg, 0.240 mmol). The reaction was stirred for 1h at rt, then quenched with acetone (73 µL, 1.00 mmol). Volatiles were removed *in vacuo*, and the residue was purified by column chromatography (10% MeOH/EtOAc) to give the title compound as a mixture of diastereomers (35 mg, 0.132 mmol, 66% yield, 2:1 dr) as a yellow oil.

Method B: To a stirred solution of ketone **147b** (35.6 mg, 0.135 mmol) in THF (5 mL) at -78 ^{o}C was added L-Selectride (1M in THF, 169 µL, 0.169 mmol). The reaction was stirred for 20 mins then quenched with MeOH (0.35 mL). The mixture was warmed to rt, and water (2.5 mL) was added. The Organic layer was extracted with CH_2Cl_2 (5 x 10 mL). The organics were combined and passed through a phase separator and concentrated *in vacuo*. The residue was purified by column chromatography (5% MeOH/CH_2Cl_2) to give the title compound (16 mg, 0.0581 mmol, 43% yield, >20:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.36 (2H, m, H-7), 7.06-6.97 (2H, m, H-8), 4.37-4.32 (1H, m, H-4), 4.28 (1H, dd, *J* = 11.5, 1.8 Hz, H-6), 3.81-3.61 (4H, m, H-10), 2.29-2.16 (1H, m, H-9), 2.12-1.96 (2H, m, H-3 and H-9), 1.91-1.84 (1H, m, H-5), 1.83-1.59 (1H, m, H-5 and H-9), 1.48 (1H, dd, *J* = 14.5, 3.0 Hz, H-3), 1.44-1.35 (1H, m, H-9) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1 (d, J_F = 243 Hz, CF), 140.6 (C), 128.6 (d, J_F = 7.8 Hz, CH), 115.3 (d, J_F = 21.0 Hz, CH), 66.7 (CH), 64.4 (CH_2), 63.7 (CH_2), 49.9 (CH_2), 48.5 (CH), 41.8 (CH_2), 41.7 (CH_2), 35.6 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.4 ppm; HRMS (ESI) 266.1545 (M + H^+. $C_{15}H_{21}FNO_2$ requires 266.1551); IR (ATR): ν_{max} 3391, 2925, 2858, 1604, 1510, 1424, 1300, 1222, 1159, 1099 cm^{-1}.

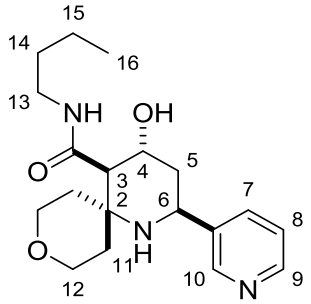
General Procedure F – Direct amidation of the 2-spiropiperidines

A mixture of amine (1.19 mmol) and DABAL.Me_3 (0.796 mmol) in THF (2.5 mL) was heated to 40 °C for 1h. A solution of 4-hydroxy-2-spiropiperidine (0.199 mmol) in THF (1 mL) was added and the reaction was heated under reflux for 16 hours. Upon cooling to room temperature, the reaction was quenched with water (1 mL) and diluted with CH_2Cl_2 (10 mL). The mixture was passed through a phase separator, washing with CH_2Cl_2 (2 x 5 mL), and concentrated *in vacuo*. The residue was purified by column chromatography.



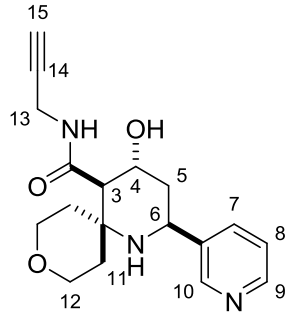
***N*-Butyl-4-hydroxy-6-(4-methoxyphenyl)-9-oxa-1-azaspiro[5.5]undecane-3-carboxamide (150a)**

Following **general procedure F** with spirocycle **148c** (40 mg, 0.119 mmol), butylamine (71 µL, 0.716 mmol) and DABAL.Me_3 (122 mg, 0.477 mmol). The residue was purified by column chromatography (0-30% EtOH/EtOAc) to give the title compound as a mixture of diastereomers (19.9 mg, 0.053 mmol, 44% yield) as a yellow oil. Data presented is for the major diastereomer. Mp 148-151 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47-8.36 (1H, m, NH), 7.32-7.27 (2H, m, H-7), 6.94-6.89 (2H, m, H-8), 4.39-4.35 (1H, m, H-4), 4.33 (1H, dd, *J* = 12.0, 3.0 Hz, H-6), 3.83 (3H, s, H-9), 3.79-3.67 (4H, m, H-11), 3.40-3.18 (2H, m, H-12), 2.83 (1H, br. s, H-3), 2.58-2.47 (1H, m, H-5), 2.20-2.06 (2H, m, H-5 and H-10), 1.92-1.83 (2H, m, H-10), 1.61-1.47 (3H, m, H-10 and H-13), 1.41 (2H, app. sext, *J* = 7.0 Hz, H-14), 0.96 (3H, t, *J* = 7.0 Hz, H-15) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.5 (C=O), 159.1 (C), 136.2 (C), 127.7 (CH), 114.1 (CH), 68.6 (CH), 64.0 (CH_2), 63.4 (CH_2), 55.3 (CH_3), 54.8 (CH), 51.5 (C), 48.7 (CH), 38.9 (CH_2), 38.1 (CH_2), 37.7 (CH_2), 35.8 (CH_2), 31.6 (CH_2), 20.4 (CH_2) 13.7 (CH_3) ppm; HRMS (ESI) 377.2429 (M + H^+. $C_{21}H_{33}N_2O_4$ requires 377.2435); IR (ATR): ν_{max} 3301, 2965, 2931, 2871, 1638 (C=O), 1514, 1247, 1102 cm^{-1}.



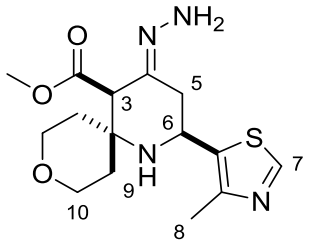
***N*-Butyl-4-hydroxy-6-pyridin-3-yl-9-oxa-1-aza-spiro[5.5]undecane-3-carboxamide (150b)**

Following **general procedure F** with spirocycle **148d** (61 mg, 0.199 mmol), butylamine (117 µL, 1.19 mmol) and DABAL.Me_3 (204 mg, 0.796 mmol). The residue was purified by column chromatography (7.5-10% MeOH/EtOAc) to give the title compound as a mixture of diastereomers (61 mg, 0.175 mmol, 88% yield) as an off-white solid. Data presented is for the major diastereomer. Mp 147-149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (1H, d, *J* = 2.0 Hz, H-10), 8.55 (1H, dd, *J* = 5.0, 1.5 Hz, H-9), 7.86 (1H, br s, NH), 7.69 (1H, ddd, *J* = 8.0, 2.0, 2.0 Hz, H-7), 7.31 (1H, dd, 8.0, 5.0 Hz, H-8), 4.42-4.36 (2H, m, H-4 and H-6), 3.83-3.62 (4H, m, H-12), 3.37-3.18 (2H, m, H-13), 2.76 (1H, br s, H-3) 2.50-2.38 (1H, m, H-11), 2.23-2.07 (2H, m, H-5 and H-11), 1.97-1.81 (2H, m, H-5 and H-11), 1.60-1.45 (H-11 and H-14), 1.38 (2H, dddd, *J* = 15.0, 7.5, 7.5, 7.5 Hz, H-15), 0.94 (3H, d, *J* = 7.5 Hz, H-16) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 172.2 (C=O), 149.2 (CH), 148.8 (CH), 139.5 (C), 134.4 (CH), 123.8 (CH), 68.5 (CH), 64.0 (CH_2), 63.5 (CH_2), 54.5 (CH), 51.7 (C), 47.3 (CH), 39.1 (CH_2), 38.1 (CH_2), 37.5 (CH_2), 35.9 (CH_2), 31.8 (CH_2), 20.5 (CH_2), 13.9 (CH_3) ppm; HRMS (ESI) 348.2265 (M + H^+. $C_{19}H_{30}N_3O_3$ requires 348.2282); IR (ATR): ν_{max} 3280, 2955, 2930, 2864, 1637 (C=O), 1547, 1425, 1225, 1101, 1079 cm^{-1}.



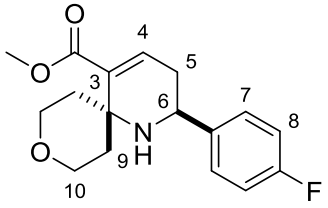
_N_-propargyl-4-hydroxy-6-pyridin-3-yl-9-oxa-1-aza-spiro[5.5]undecane-3-carboxamide (150c)

Following **general procedure F** with spirocycle **148d** (104 mg, 0.340 mmol), propargylamine (130 µL, 2.04 mmol) and DABAL.Me_3 (348 mg, 1.36 mmol). The residue was purified by column chromatography (10% MeOH/EtOAc) to give the title compound as a mixture of diastereomers (68.5 mg, 0.207 mmol, 61% yield) as a pale orange solid. Data presented is for the major diastereomer. Mp 186-188 ^{o}C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.66 (1H, d, *J* = 2.0 Hz, H-10), 8.54-8.49 (1H, m, H-9), 8.41 (1H, br s, NH), 7.80-7.75 (1H, m, H-7), 7.31 (1H, dd, *J* = 8.0, 5.0 Hz, H-8), 4.38 (1H, dd, *J* = 12.0, 3.0 Hz, H-6), 4.36-4.29 (1H, m, H-4), 4.14-4.05 (1H, m, H-13), 4.00 (1H, ddd, *J* = 18.0, 5.0, 2.5 Hz, H-13), 3.78-3.58 (4H, m, H-12), 2.75 (1H, br s, H-3) 2.48-2.31 (2H, m, H-11 and H-15), 2.25-2.09 (2H, m, H-5 and H-11), 1.92-1.79 (2H, m, H-5 and H-11), 1.56-1.45 (1H, m, H-11) ppm; ^{13}C-NMR (101 MHz, CD_2Cl_2): δ 172.2 (C=O), 149.3 (CH), 149.2 (CH), 139.8 (C), 134.8 (CH), 124.0 (CH), 80.1 (CH), 71.6 (C), 68.6 (CH), 64.0 (CH_2), 63.5 (CH_2), 54.8 (CH), 52.0 (C), 47.6 (CH), 38.1 (CH_2), 37.6 (CH_2), 35.9 (CH_2), 28.9 (CH_2) ppm; HRMS (ESI) 330.1808 (M + H^+. $C_{18}H_{24}N_3O_3$ requires 330.1808); IR (ATR): ν_{max} 3286, 2927, 2865, 1648 (C=O), 1537, 1425, 1101, 1027 cm^{-1}.



Methyl 4-hydrazono-6-(4-methyl-thiazol-5-yl)-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (151)

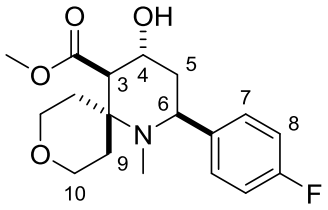
To a solution of 2-spiropiperidine **138e** (81.5 mg, 0.251 mmol) in THF (1 mL) in a sealed tube was added hydrazine (1M in acetonitrile, 377 µL, 0.377 mmol). The reaction was stirred at 70 ^{o}C for 1h. The mixture was cooled to rt and diluted with EtOAc (10 mL). The layers were separated and the organic layer was washed with water (2 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a mixture of diastereomers (49 mg, 0.143 mmol, 58% yield) as a yellow oil, used in the next reaction without further purification. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (1H, s, H-7), 4.24 (1H, dd, *J* = 12.0, 4.0 Hz, H-6), 3.93-3.76 (2H, m, H-10), 3.74-3.63 (2H, m, H-10), 3.71 (3H, s, OCH_3), 3.28 (1H, s, H-3), 2.93 (1H, dd, *J* = 14.0, 4.0 Hz, H-5), 2.48 (3H, s, H-7), 2.45 (1H, dd, *J* = 14.0, 12.0 Hz, H-5), 1.92-1.83 (1H, m, H-9), 1.77-1.59 (2H, m, H-9), 1.44-1.36 (1H, m, H-9) ppm; HRMS (ESI) 267.1163 (M + H^+. $C_{13}H_{19}N_2O_2S$ requires 267.1162); IR (ATR): ν_{max} 3377, 2951, 2863, 1721 (C=O), 1643 (C=N), 1433, 1252, 1195, 1096 cm^{-1}.



Methyl 6-(4-fluoro-phenyl)-9-oxa-1-aza-spiro[5.5]undec-3-ene-3-carboxylate (156)

To a solution of 2-spiropiperidine **148b** (19 mg, 0.0588 mmol) in toluene (0.2 mL) in a plastic vessel was sequentially added PyFluor (10.4 mg, 0.0647 mmol) and DBU (17.6 µL, 0.118 mmol) at rt and the reaction mixture was stirred overnight. Volatiles were removed *in vacuo* and the residue was purified by column chromatography (60% EtOAc/hexane) to give the title

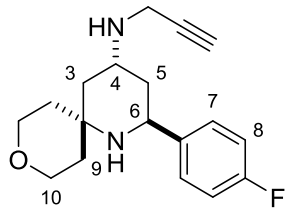
compound (5.3 mg, 0.0176 mmol, 30% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (2H, m, H-7), 7.11 (1H, dd, *J* = 6.5, 2.3 Hz, H-4), 7.09-7.02 (2H, m, H-8), 3.96-3.82 (3H, m, H-6 and H-10), 3.80-3.72 (2H, m, H-10), 3.76 (3H, s, OCH_3), 2.76 (1H, ddd, *J* = 13.1, 13.1, 5.5 Hz, H-9), 2.63-2.52 (2H, m, H-5 and H-9), 2.27 (1H, ddd, *J* = 18.5, 10.8, 2.3 Hz, H-5), 1.66-1.59 (1H, m, H-9), 1.20-1.12 (1H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 (C=O), 162.1 (d, *J* = 247.0 Hz, C), 139.6 (CH), 139.4 (d, *J* = 3.4 Hz, C), 138.0 (C), 128.2 (d, *J* = 7.8 Hz, CH), 115.4 (d, *J* = 21.2 Hz, CH), 63.4 (CH_2), 63.0 (CH_2), 53.6 (C), 51.7 (CH_3), 49.5 (CH), 36.3 (CH_2), 33.8 (CH_2), 32.0 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.4 ppm; HRMS (ESI) 306.1490 (M + H^+. $C_{17}H_{21}FNO_3$ requires 306.1500); IR (ATR): ν_{max} 2950, 2923, 2863, 1708 (C=O), 1509, 1434, 1237, 1220, 1101, 1058 cm^{-1}.



Methyl 6-(4-fluorophenyl)-4-hydroxy-1-methyl-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (159)

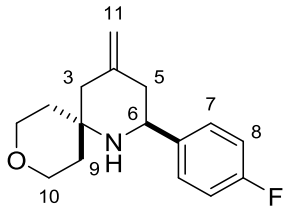
Silver (I) oxide (75.8 mg, 0.327 mmol) and iodomethane (20.4 µL, 0.327 mmol) were successively added to a solution of spirocycle **148b** (35.1 mg, 0.109 mmol) in 1,2-dichloroethane (0.5 mL) at rt. The mixture was heated to 85 °C in a sealed vial in the darkness for 54 hours. Extra iodomethane (20.4 µL, 0.327 mmol) was added at 24 and 48 hours. The mixture was cooled to rt, diluted with methanol and passed through a plug of Celite. The filtrate was concentrated *in vacuo* and purified by column chromatography (60% ethyl acetate/hexane) to afford the title compound (18.3 mg, 0.0545 mmol, 50% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.37 (2H, m, H-7), 7.03-6.95 (2H, m, H-8), 4.48 (1H, ddd, *J* = 7.2, 7.0, 4.5 Hz, H-4), 4.23 (1H, br t, *J* = 6.0 Hz, H-6), 3.91-3.83 (1H, m, H-10), 3.72 (3H, s, OCH_3), 3.73-3.66 (1H, m, H-10), 3.65-3.57 (1H, m, H-10), 3.45 (1H, dt, *J* = 11.0, 4.0 Hz, H-10), 2.78 (1H, d, *J* = 7.0 Hz, H-3), 2.59 (1H, ddd, *J* = 14.0, 7.2, 4.5 Hz, H-5), 2.31 (3H, s, NCH_3), 2.10-2.01 (1H, m, H-9), 1.91-1.80 (2H, m, H-5 and H-9), 1.57-1.49 (2H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8 (C=O), 161.7 (d, *J* = 246.0 Hz, C), 139.7 (d, *J* = 2.5 Hz, C), 129.0 (d, *J*

= 8.0 Hz, CH), 115.1 (d, *J* = 21.0 Hz, CH), 65.9 (CH), 64.4 (CH_2), 63.9 (CH_2), 58.0 (CH), 57.4 (C), 53.5 (CH), 51.8 (CH_3), 35.6 (CH_3), 34.8 (CH_2), 33.2 (CH_2), 30.8 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -116.0 ppm; HRMS (ESI) 338.1753 ($M + H^+$. $C_{18}H_{25}FNO_4$ requires 338.1762); IR (ATR): ν_{max} 3407, 2952, 2872, 1727 (C=O), 1603, 1508, 1435, 1222, 1158, 1143, 1017 cm^{-1}.



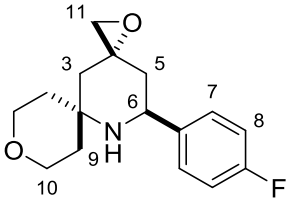
[6-(4-Fluorophenyl)-9-oxa-1-aza-spiro[5.5]undec-4-yl]-prop-2-ynyl-amine (161)

To a solution of spirocycle **147b** (28 mg, 0.106 mmol) and amine (7.5 µL, 0.117 mmol) in 1,2-dichloromethane (0.4 mL) was added sodium triacetoxyborohydride (35 mg, 0.164 mmol) and acetic acid (6 µL, 0.106 mmol). The mixture was stirred for 2 hours at room temperature, then quenched with 1M NaOH (0.2 mL). Product was extracted with diethyl ether (3 x 2 mL) and volatiles were removed *in vacuo*. The residue was purified by column chromatography (5% methanol/ethyl acetate) to afford the title compound as a single diastereomer (13.3 mg, 0.0445 mmol, 42% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.34 (2H, m, H-7), 7.04-6.97 (2H, m, H-8), 4.20 (1H, dd, *J* = 11.0, 3.0 Hz, H-6), 3.77-3.58 (4H, m, H-10), 3.45 (1H, dd, *J* = 2.25, 2.25 Hz, H-11), 3.41 (1H, dddd, *J* = 7.0, 7.0, 3.5, 3.5 Hz, H-4), 2.21 (1H, dd, *J* = 2.25, 2.25 Hz, H-11), 2.17-2.04 (2H, m, H-9), 1.82-1.55 (6H, m, H-3, H-5 and H-13), 1.49 (1H, dd, *J* = 14.5, 4.5 Hz, H-9), 1.40-1.32 (1H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.0 (d, J_F = 246.0 Hz, CF), 140.8 (C), 128.6 (d, J_F = 8.0 Hz, CH), 115.3 (d, J_F = 21.0 Hz, CH), 82.3 (C), 71.6 (C), 64.3 (CH_2), 63.8 (CH_2), 50.5 (CH), 49.0 (CH), 41.8 (CH_2), 38.7 (CH_2), 36.1 (CH_2), 36.0 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.5 ppm; HRMS (ESI) 303.1863 ($M + H^+$. $C_{18}H_{24}FN_2O$ requires 303.1867); IR (ATR): ν_{max} 3297, 2928, 2852, 1603, 1509, 1431, 1221, 1158, 1099 cm^{-1}.



6-(4-Fluorophenyl)-4-methylene-9-oxa-1-aza-spiro[5.5]undecane (162)

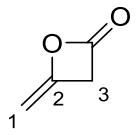
To a suspension of methyl triphenylphosphonium bromide (84.0 mg, 0.228 mmol) in THF (1.2 mL) was added *n*-BuLi (2.5 M in hexanes, 96 µL, 0.228 mmol) at 0 ^{o}C. The mixture was stirred at for 1h before the addition of spirocycle **147b** (50 mg, 0.190 mmol) in THF (0.2 mL). The reaction was stirred at 0 ^{o}C for 4h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (40% EtOAc/petroleum ether (40-60)) to afford the title compound (17.7 mg, 0.0684 mmol, 36% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.34 (2H, m, H-7), 7.06-6.97 (2H, m, H-8), 4.83 (1H, br d, *J* = 1.5 Hz, H-11), 4.74 (1H, br d, *J* = 1.5 Hz, H-11), 3.87 (1H, dd, *J* = 11.5, 3.0 Hz, H-6), 3.82-3.64 (3H, m, H-10), 3.60 (1H, ddd, *J* = 11.0, 7.5, 3.5 Hz, H-10), 2.45-2.37 (2H, m, H-3), 2.11 (1H, ddd, *J* = 12.5, 11.5, 1.5 Hz, H-5), 2.02 (1H, d, *J* = 12.5 Hz, H-5), 1.79 (1H, ddd, *J* = 13.5, 7.5, 3.5 Hz, H-9), 1.72-1.60 (2H, m, H-9), 1.56-1.48 (1H, m, H-9), 1.42 (1H, br s, NH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1 (d, J_F = 246.5 Hz, CF), 143.9 (C), 140.3 (d, J_F = 3.0 Hz, C), 128.4 (d, J_F = 8.0 Hz, CH), 115.3 (d, *J* = 21.0 Hz, CH), 110.6 (CH_2), 64.4 (CH_2), 63.9 (CH_2), 54.8 (CH), 51.3 (C), 44.6 (CH_2), 43.8 (CH_2), 40.9 (CH_2), 32.9 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.4 ppm; HRMS (ESI) 262.1592 (M + H^+. $C_{16}H_{21}FNO$ requires 262.1602); IR (ATR): ν_{max} 3070, 2936, 2852, 1651, 1603, 1508, 1221, 1156, 1102, 1014 cm^{-1}.



6-(4-Fluorophenyl)-4,9-dioxa-1-aza-dispiro[2.1.5.3]tridecane (163)

To a suspension of NaH (60% dispersion in mineral oil, 12 mg, 0.304 mmol) in THF (0.5 mL) was added trimethylsulfoxonium iodide (67 mg, 0.304 mmol) at rt. After 10 mins, a solution of spirocycle **147b** (0.152 mmol) in THF (0.5 mL) was added dropwise and the reaction was

stirred for 3h at rt. The mixture was diluted with ethyl acetate (10 mL) and quenched with water (1 mL). Layers were separated and the aqueous was extracted with ethyl acetate (10 mL). Organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (60% EtOAc/petroleum ether (40-60)) to give the title compound as a single diastereomer (16.7 mg, 0.0603 mmol, 41% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.31 (2H, m, H-7), 7.06-6.98 (2H, m, H-8), 4.23 (1H, dd, *J* = 12.0, 2.5 Hz, H-6), 3.82-3.73 (2H, m, H-10), 3.62 (2H, dddd, *J* = 11.5, 9.5, 7.5, 3.5 Hz, H-10), 2.61 (1H, d, *J* = 4.5 Hz, H-11), 2.57 (1H, d, *J* = 4.5 Hz, H-11), 2.15 (1H, ddd, *J* = 13.0, 7.0, 3.0 Hz, H-9), 2.01 (1H, dd, *J* = 13.5, 12.0 Hz, H-5), 1.92-1.84 (1H, m, H-9), 1.87 (1H, d, *J* = 13.75, H-3), 1.66 (1H, dddd, *J* = 13.5, 7.0, 3.5, 1.5 Hz, H-9), 1.54 (1H, br s, NH), 1.52-1.44 (1H, m, H-9), 1.47 (1H, dd, *J* = 13.75, 2.5 Hz, H-3), 1.36 (1H, ddd, *J* = 13.5, 2.5, 2.5 Hz, H-5) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2 (d, J_F = 246.5 Hz, CF), 140.0 (d, J_F = 3.0 Hz, C), 128.4 (d, J_F = 8.0 Hz, CH), 115.4 (d, J_F = 21.5 Hz, CH), 64.6 (CH_2), 63.8 (CH_2), 56.5 (C), 51.6 (CH), 51.3 (CH_2), 51.2 (C), 41.6 (CH_2), 41.2 (CH_2), 41.2 (CH_2), 34.3 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.2 ppm; HRMS (ESI) 278.1553 ($M + H^+$. $C_{16}H_{21}FNO_2$ requires 278.1551); IR (ATR): ν_{max} 3293, 2951, 2855, 1604, 1509, 1221, 1156, 1102 cm^{-1}.

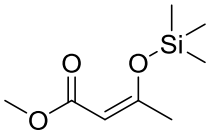


Diketene (168)

Method A: Triethylamine (344 µL, 2.47 mmol) was added to a solution of acetyl chloride (351 µL, 4.94 mmol) in diethyl ether (5 mL) at rt. The mixture was stirred for 60 mins, then the cream precipitate was filtered and washed with diethyl ether (2 x 3 mL). The filtrate was carefully blown down with nitrogen to give the title compound (68 mg, 0.809 mmol, 33% yield) as a brown oil.

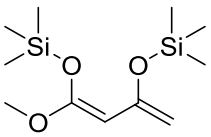
Method B: Triethylamine (600 µL, 4.31 mmol) was added to a solution of acetyl chloride (255 µL, 3.59 mmol) in toluene (3.6 mL) at rt. The mixture was stirred for 60 mins then filtered to give the title compound (150 mg, 1.80 mmol, 50% yield) as a 4.91 wt% solution in toluene. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 4.92-4.89 (1H, m, H-1), 4.52 (1H, dt, *J* = 4.0, 1.5 Hz, H-1), 3.92 (2H, t, *J* = 1.5 Hz, H-3) ppm. ^{1}H data was consistent with diketene purchased from Sigma Aldrich.[207]



3-Trimethylsilanyloxy-but-2-enoic acid methyl ester (169)

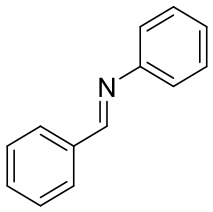
Trimethylsilyl chloride (15.0 mL, 118 mmol) was added over 20 mins via syringe pump to a solution of methyl acetoacetate (11.5 mL, 107 mmol) and triethylamine (17.8 mL, 128 mmol) in hexane (220 mL) at rt. The reaction mixture was stirred overnight at rt. The mixture was diluted with hexane (150 mL) and passed through Celite, washing with hexane (2 x 100 mL), and concentrated *in vacuo* to afford the title compound (18.7 g, 99.5 mmol, 93% yield) as a pale yellow oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (1H, s, CH), 3.65 (3H, s, OCH_3), 2.26 (3H, s, CH_3), 0.26 (9H, s, $Si(CH_3)_3$) ppm; IR (ATR): ν_{max} 2953, 1714 (C=O), 1621, 1435, 1385, 1337, 1286, 1254, 1189, 1132, 1035 cm^{-1}. ^{1}H NMR were in agreement with literature.[168]



1-Methoxy-1,3-bis-trimethylsilanyloxy-buta-1,3-diene (Chan's diene) (170)

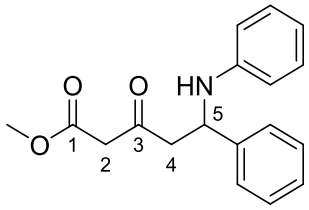
n-BuLi (2.24 M in hexanes, 42.9 mL, 96.1 mmol) was added to a solution of diisopropylamine (13.4 mL, 96.1 mmol) in THF (170 mL) at -78 ^{o}C. The mixture was stirred for 15 mins at -78 ^{o}C and 10 mins at rt, before being re-cooled to -78 ^{o}C. A solution of **169** (16.4 g, 87.4 mmol) in THF (40 mL) was added and the mixture was stirred for 30 mins at -78 ^{o}C. Trimethylsilyl chloride (15.0 mL, 118 mmol) was carefully added and the reaction was stirred for 1h at 0 ^{o}C. The mixture was warmed to rt, and volatiles were removed *in vacuo*. The residue was dissolved in hexane (200 mL) and passed through Celite, washing with hexane (2 x 100 mL). Organics were combined and concentrated *in vacuo* to afford the title compound (22.1 g, 85.0 mmol, 97% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48 (1H, s, CH), 4.14 (1H, d, *J* =

1.0 Hz, CH_2), 3.94 (1H, d, *J* = 1.0 Hz, CH_2), 3.56 (3H, s, OCH_3), 0.25 (9H, s, $(CH_3)_3$), 0.21 (9H, s, $(CH_3)_3$) ppm; IR (ATR): ν_{max} 2959, 1718, 1649, 1443, 1385, 1250, 1219, 1168, 1139, 1090, 1017 cm^{-1}. ^1H NMR were in agreement with literature.[168]



Benzylidene-phenylamine (174)

To a solution of benzaldehyde (2.00 mL, 20.0 mmol) and aniline (1.70 mL, 20.0 mmol) was added $MgSO_4$ (4.00 g, 33.3 mmol). The mixture was stirred at rt for 4h, filtered, and concentrated *in vacuo* to afford the title compound (2.04 g, 11.2 mmol, 56% yield) as an off-white solid. Mp 49.5-50.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (1H, s, NC*H*), 7.95-7.88 (2H, m, ArH), 7.52-7.46 (3H, m, ArH), 7.44-7.39 (2H, m, ArH), 7.28-7.19 (3H, m, ArH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.6 (CH), 152.2 (C), 136.3 (C), 131.5 (CH), 129.3 (CH), 128.9 (CH), 128.9 (CH), 126.1 (CH), 121.0 (CH) ppm; mp 49.5-50.5 °C; HRMS (ESI) 182.0963 (M + H^+. $C_{13}H_{12}N$ requires 182.0964); IR (ATR): ν_{max} 3060, 2886, 1626, 1590, 1578, 1484, 150, 1312, 1190, 1168 cm^{-1}.

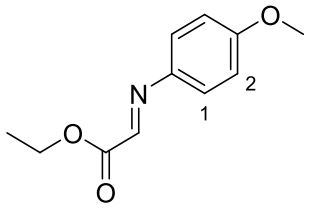


Methyl 3-oxo-5-phenyl-5-phenylamino-pentanoate (175)

Method A: To a solution of benzylidene-phenylamine **174** (105 mg, 0.580 mmol) in CH_2Cl_2 (5.5 mL) at -78 °C was added $ZnCl_2$ (79 mg, 0.580 mmol). The mixture was stirred for 30 mins before the addition of Chan's diene **170** (226 mg, 0.870 mmol). The reaction was stirred for 1h then quenched with sat. aq. $NaHCO_3$ (5.5 mL). The mixture was warmed to rt and the layers were separated. The aqueous was extracted with CH_2Cl_2 (5 mL). The organics were combined,

washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20 % EtOAc/petroleum ether (40-60)) to give the title compound (96 mg, 0.325 mmol, 56% yield) as a yellow oil.

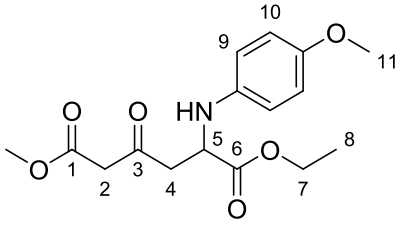
Method B: To a solution of benzylidene-phenyl-amine **174** (112 mg, 0.619 mmol) in CH_2Cl_2 (6 mL) at -78 ^oC was added $TiCl_4$ (68 µL, 0.619 mmol). Chan's diene **170** (241 mg, 0.929 mmol) was added and the reaction mixture was stirred for 45 mins at -78 ^oC. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and warmed to rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organics were combined, washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/hexane) to give the title compound (132 mg, 0.446 mmol, 72% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (4H, m, ArH), 7.27-7.22 (1H, m, ArH), 7.13-7.05 (2H, m ArH), 7.13-7.05 (2H, m, ArH), 6.71-6.64 (1H, m, ArH), 6.58-6.50 (2H, m, ArH), 4.90 (1H, dd, *J* = 7.8, 5.5 Hz, H-5), 3.70 (3H, s, OCH_3), 3.43 (1H, d, *J* = 15.5 Hz, H-2), 3.37 (1H, d, *J* = 15.5 Hz, H-2), 3.09 (1H, dd, *J* = 16.0, 7.8 Hz, H-4), 3.01 (1H, dd, *J* = 16.0, 5.5 Hz, H-4) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.1 (C=O), 167.6 (C=O), 146.8 (C), 142.3 (C), 129.3 (CH), 129.0 (CH), 127.6 (CH), 126.4 (CH), 118.0 (CH), 113.9 (CH), 54.3 (CH), 52.6 (CH_3), 50.6 (CH_2), 49.6 (CH_2) ppm; HRMS (ESI) 298.1432 ($M + H^+$. $C_{18}H_{20}NO_3$ requires 298.1438), 320.1252 ($M + Na^+$. $C_{18}H_{19}NNaO_3$ requires 320.1257); IR (ATR): ν_{max} 3401, 3026, 2952, 1743 (C=O), 1714 (C=O), 1601, 1504, 1451, 1436, 1317, 1266 cm^{-1}.



Ethyl (4-methoxy-phenylimino)-acetate (179)

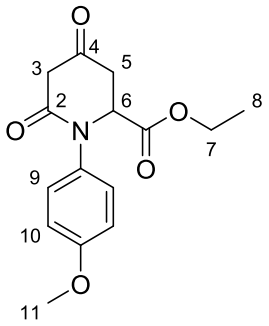
To a solution of ethyl glyoxylate (50% in toluene, 1.60 mL, 8.13 mmol) and *p*-anisidine (8.13 mmol) in toluene (16 mL) was added Na_2SO_4 (11.5 g, 81.3 mmol) at rt. The reaction was stirred for 2h then filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (700 mg, 3.90 mmol, 48% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, s, CH), 7.38-7.34 (2H, m, H-1),

6.95-6.91 (2H, m, H-2), 4.41 (2H, q, *J* = 7.0 Hz, CH_2), 3.83 (3H, s, OCH_3), 1.40 (3H, t, *J* = 7.0 Hz, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8 (C=O), 160.7 (C), 148.1 (CH), 141.5 (C), 123.8 (CH), 114.7 (CH), 62.1 (CH_2), 55.6 (CH_3), 14.4 (CH_3) ppm; HRMS (ESI) 208.0958 (M + H^+. $C_{11}H_{14}NO_3$ requires 208.0968); IR (ATR): ν_{max} 2981, 2936, 1740, 1713, 1590, 1504, 1465, 1370, 1282, 1248, 1214, 1192, 1160, 1028 cm^{-1}.



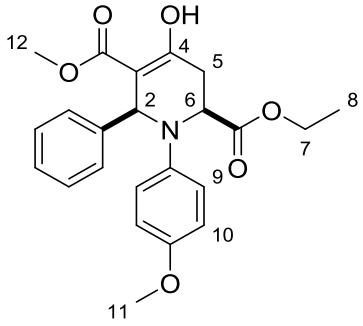
2-(4-methoxy-phenylamino)-4-oxo-hexanedioic acid 1-ethyl ester 6-methyl ester (180)

To a solution of (4-methoxy-phenylimino)-acetic acid ethyl ester **179** (100 mg, 0.483 mmol) in THF (5 mL) at -78 ^{o}C was added $ZnCl_2$ (66 mg, 0.483 mmol). The mixture was stirred for 30 mins before the addition of Chan's diene **170** (189 mg, 0.725 mmol). The reaction was stirred for 1h then quenched with sat. aq. $NaHCO_3$ (5 mL). The mixture was warmed to rt, diluted with EtOAc (15 mL), and the layers were separated. The aqueous was extracted with EtOAc (2 x 5 mL). The organics were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20 % EtOAc/petroleum ether (40-60)) to give the title compound (72 mg, 0.223 mmol, 46% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79-6.73 (2H, m, H-9), 6.66-6.60 (2H, m, H-10), 4.36 (1H, dd, *J* = 5.5, 5.5 Hz, H-5), 4.17 (2H, q, *J* = 7.0 Hz, H-7), 3.73 (3H, s, H-11), 3.70 (3H, s, OCH_3), 3.50 (1H, d, *J* = 16.0 Hz, H-2), 3.46 (1H, d, *J* = 16.0 Hz, H-2), 3.09 (1H, dd, *J* = 18.1, 5.5 Hz, H-4), 3.05 (1H, dd, *J* = 18.1, 5.5 Hz, H-4), 1.23 (3H, t, *J* = 7.0 Hz, H-8) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3 (C=O), 172.6 (C=O), 167.2 (C=O), 153.2 (C), 140.4 (C), 115.9 (CH), 114.9 (CH), 61.7 (CH_2), 55.8 (CH_3), 54.3 (CH), 52.5 (CH_3), 49.5 (CH_2), 45.2 (CH_2), 14.2 (CH_3) ppm; HRMS (ESI) 346.1262 (M + Na^+. $C_{15}H_{17}NNaO_5$ requires 346.1261); IR (ATR): ν_{max} 3377, 2954, 1717 (C=O), 1511, 1438, 1369, 1235, 1158, 1033 cm^{-1}.



Ethyl 1-(4-methoxy-phenyl)-2,4-dioxo-piperidine-6-carboxylate (181)

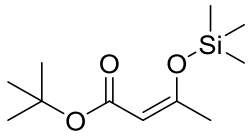
Isolated from column chromatography of **180** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.15 (2H, m, H-9), 6.96-6.90 (2H, m, H-10), 4.57 (1H, dd, *J* = 6.5, 2.5 Hz, H-6), 4.24 (2H, q, *J* = 7.0 Hz, H-7), 3.81 (3H, s, H-11), 3.65 (1H, d, *J* = 20.0 Hz, H-3), 3.45 (1H, d, *J* = 20.0 Hz, H-3), 3.09 (1H, dd, *J* = 17.5, 6.5 Hz, H-5), 3.02 (1H, dd, *J* = 17.5, 2.5 Hz, H-5), 1.27 (3H, t, *J* = 7.0 Hz, H-8) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5 (C=O), 170.5 (C=O), 167.0 (C=O), 159.0 (C), 134.2 (C), 128.0 (CH), 114.9 (CH), 62.8 (CH_2), 60.6 (CH), 55.6 (CH_3), 48.6 (CH_2), 42.1 (CH_2), 14.2 (CH_3) ppm; HRMS (ESI) 314.0982 (M + Na^+. $C_{15}H_{17}NNaO_5$ requires 314.0999); IR (ATR): ν_{max} 2980, 1735 (C=O), 1672 (C=O), 1510, 1430, 1298, 1243, 1200, 1030 cm^{-1}.



4-Hydroxy-1-(4-methoxy-phenyl)-2-phenyl-1,2,5,6-tetrahydro-pyridine-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester (182)

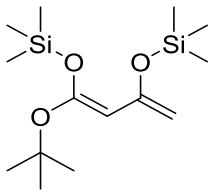
To a solution of (4-methoxy-phenylimino)-acetic acid ethyl ester **179** (115 mg, 0.556 mmol) in CH_2Cl_2 (5.5 mL) at -78 ^{o}C was added $ZnCl_2$ (76 mg, 0.556 mmol). The mixture was stirred for 30 mins before the addition of Chan's diene **170** (217 mg, 0.834). After 30 mins, benzaldehyde (282 µL, 2.78 mmol) was added and the reaction was stirred overnight at rt. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organics were combined, washed with water (10 mL)

and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10-20% EtOAc/petroleum ether (40-60)) to give the title compound as a mixture of diastereomers (107 mg, 0.261 mmol, 47% yield, 2.5:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.20 (1H, s, OH), 7.21-7.10 (5H, m, ArH), 6.83-6.77 (2H, m, H-9), 6.72-6.66 (2H, m, H-10), 5.52 (1H, s, H-2), 4.37 (1H, dd, *J* = 6.0, 5.5 Hz, H-6), 4.06 (2H, q, *J* = 7.3 Hz, H-7), 3.70 (3H, s, H-11), 3.64 (3H, s, H-12), 3.02 (1H, dd, *J* = 17.6, 5.5 Hz, H-5), 2.92 (1H, dd, *J* = 17.6, 6.0 Hz, H-5), 1.10 (3H, t, *J* = 7.3 Hz, H-8) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0 (C=O), 171.0 (C=O), 168.7 (C), 154.8 (C), 141.5 (C), 140.0 (C), 128.4 (CH), 128.3 (CH), 127.8 (CH), 122.5 (CH), 114.0 (CH), 101.4 (C), 61.1 (CH_2), 59.7 (CH), 57.3 (CH), 55.4 (CH_3), 51.6 (CH_3), 32.6 (CH_2), 14.1 (CH_3) ppm; HRMS (ESI) 412.1760 (M + H^+. $C_{23}H_{26}NO_6$ requires 412.1755), 434.1579 (M + Na^+. $C_{23}H_{26}NNaO_6$ requires 434.1574); IR (ATR): ν_{max} 2953, 1731 (C=O), 1662, 1623, 1510, 1443, 1242, 1225, 1181, 1036 cm^{-1}.



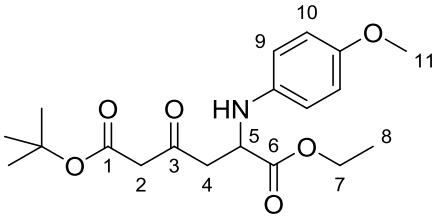
tert-Butyl 3-trimethylsilanyloxy-but-2-enoate (184)

Trimethylsilyl chloride (5.0 mL, 39.4 mmol) was added over 20 mins via syringe pump to a solution of *tert*-butyl acetoacetate (5.93 mL, 35.8 mmol) and triethylamine (5.98 mL, 43.0 mmol) in hexane (70 mL) at rt. The reaction mixture was stirred overnight at rt. The mixture was diluted with hexane (70 mL) and passed through Celite, washing with hexane (2 x 50 mL), and concentrated *in vacuo* to afford the title compound (8.06 g, 35.0 mmol, 98% yield) as a colourless oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (s) and 5.00 (1H total, s, CH), 2.21 (s) and 1.85 (3H total, s, CH_3), 1.46 (s) and 1.45 (9H total, s, $(CH_3)_3$), 0.26 (s) and 0.25 (9H total, s, TMS) ppm. ^{1}H NMR were in agreement with literature.[168]



1-*tert*-Butoxy-1,3-bis-trimethylsilanyloxy-buta-1,3-diene (*tert*-butyl Chan's diene) (185)

n-BuLi (2.37 M in hexanes, 11.0 mL, 26.2 mmol) was added to a solution of diisopropylamine (3.70 mL, 26.2 mmol) in THF (42 mL) at -78 ^{o}C. The mixture was stirred for 15 mins at -78 ^{o}C and 10 mins at rt, before being re-cooled to -78 ^{o}C. A solution of **184** (5.48 g, 23.8 mmol) in THF (24 mL) was added and the mixture was stirred for 30 mins at -78 ^{o}C. Trimethylsilyl chloride (4.08 mL, 32.1 mmol) was carefully added and the reaction was stirred for 1h at 0 ^{o}C. The mixture was warmed to rt, and volatiles were removed *in vacuo*. The residue was dissolved in hexane (100 mL) and passed through Celite, washing with hexane (2 x 50 mL). Organics were combined and concentrated *in vacuo*, and purified by kughelrohr distillation (0.7 mbar, 96 ^{o}C) to afford the title compound (6.72 g, 22.3 mmol, 94% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (1H, s, CH), 4.25 (1H, d, *J* = 1.5 Hz, CH_2), 4.20 (1H, d, *J* = 1.5 Hz, CH_2), 1.46 (s) and 1.36 (9H total, s, $(CH_3)_3$), 0.24 (s), 0.21 (s), 0.20 (s) and 0.17 (18H total, s, TMS) ppm. ^{1}H NMR were in agreement with literature.[168]



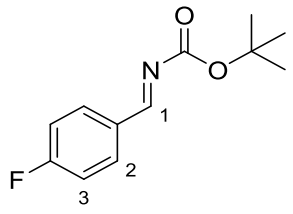
2-(4-Methoxy-phenylamino)-4-oxo-hexanedioic acid 6-*tert*-butyl ester 1-ethyl ester (186)

To a solution of diisopropylamine (2.04 mL, 14.5 mmol) in THF (30 mL) at -78 °C was added *n*-BuLi (2.35M in hexanes, 6.2 mL, 14.5 mmol). The solution was stirred for 10 mins at -78 °C then a further 5 mins at room temperature. A solution of *tert*-butyl acetoacetate (1.12 mL, 7.26 mmol) in THF (5 mL) was added at -78 °C, then stirred for a further 40 mins. A solution of imine (4-methoxy-phenylimino)-acetic acid ethyl ester **179** (500 mg, 2.42 mmol) was added at -50 °C and the reaction was stirred for 30 mins, then quenched with 10 M acetic acid in THF (3.63 mL, 36.3 mmol). The mixture was warmed to room temperature and concentrated *in*

vacuo. The residue was partitioned between EtOAc (40 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL). Organics were combined, washed with water (60 mL) and brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (15% ethyl acetate/hexane) to give the title compound (108 mg, 0.290 mmol, 12% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78-6.73 (2H, m, H-9), 6.66-6.61 (2H, m, H-10), 4.35 (1H, dd, *J* = 5.5, 5.5 Hz, H-5), 4.18 (1H, q, *J* = 7.0 Hz, H-7), 4.18 (1H, q, *J* = 7.0 Hz, H-7), 3.73 (3H, s, H-11), 3.40 (1H, d, *J* = 15.5 Hz, H-2), 3.36 (1H, d, *J* = 15.5 Hz, H-2), 3.10 (1H, dd, *J* = 17.5, 5.5 Hz, H-4), 3.05 (1H, dd, *J* = 17.5, 5.5 Hz, H-4), 1.44 (9H, s, $(CH_3)_3$), 1.22 (3H, t, *J* = 7.0 Hz, H-8) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.8 (C=O), 172.9 (C=O), 166.1 (C=O), 153.2 (C), 140.5 (C), 115.9 (CH), 115.0 (CH), 82.4 (C), 61.7 (CH_2), 55.8 (CH_3), 54.3 (CH), 51.1 (CH_2), 45.1 (CH_2), 28.0 (CH_2), 14.2 (CH_2) ppm; HRMS (ESI) 366.1914 (M + H^+. $C_{19}H_{28}NO_6$ requires 366.1911); IR (ATR): ν_{max} 3374, 2978, 2934, 1730 (C=O), 1716 (C=O), 1637, 1513, 1368, 1240, 1150 cm^{-1}.

General Procedure G - Synthesis of *N*-Boc-imines

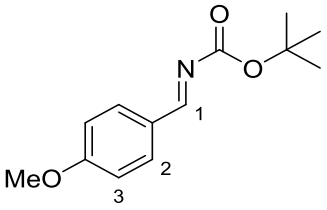
A suspension of benzenesulfonyl carbamic ester (8.15 mmol), K_2CO_3 (48.9 mmol) and Na_2SO_4 (57.1 mmol) in THF (82 mL) was stirred under reflux for 3h. The mixture was cooled to rt, filtered through a sintered funnel and concentrated *in vacuo*. The imine was used without further purification.



***tert*-Butyl (4-fluorobenzylidene)-carbamate (189e)**

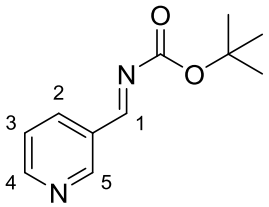
Following **general procedure G** with sulfone **122e** (1.12 g, 3.07 mmol), K_2CO_3 (2.54 g, 18.4 mmol) and Na_2SO_4 (3.05 g, 21.5 mmol) gave the title compound (635 mg, 2.86 mmol, 93% yield) as a white solid. Mp 66.0-68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (1H, s, H-1), 7.96-7.90 (2H, m, H-2), 7.18-7.11 (2H, m, H-3), 1.58 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$):

δ 168.5 (CH), 166.2 (d, J_F = 257 Hz, CF), 162.5 (C=O), 132.7 (d, J_F = 9.5 Hz, CH), 130.5 (d, J_F = 2.8 Hz, C), 116.4 (d, J_F = 22.2 Hz CH), 82.5 (C), 28.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -103.9 ppm; HRMS (ESI) 224.1086 (M + H^+. $C_{12}H_{15}FNO_2$ requires 224.1081), 278.1166 (M + Na^+. $C_{13}H_{18}FNNaO_3$ requires 278.1163 for the methanol adduct); IR (ATR): ν_{max} 3332, 2978, 1700 (C=O), 1606, 1507, 1367, 1225, 1155 cm^{-1}.



***tert*-Butyl (4-methoxy-benzylidene)-carbamate (189f)**

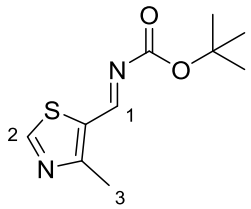
Following **general procedure G** with sulfone **122f** (1.07 g, 2.84 mmol), K_2CO_3 (2.35 g, 17.0 mmol) and Na_2SO_4 (2.83 g, 19.9 mmol) gave the title compound (601 mg, 2.56 mmol, 90% yield) as a white solid. Mp 85.5-88.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (1H, s, H-1), 7.91-7.85 (2H, m, H-2), 6.98-6.91 (2H, m, H-3), 3.86 (3H, s, H-4), 1.57 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0 (CH), 164.3 (C), 163.0 (C=O), 132.7 (CH), 127.0 (C), 114.4 (CH), 82.0 (C), 55.6 (CH_3), 28.0 (CH_3) ppm; HRMS (ESI) 236.1290 (M + H^+. $C_{13}H_{18}NO_3$ requires 236.1281), 290.1370 (M + Na^+. $C_{14}H_{21}NNaO_4$ requires 290.1363 for the methanol adduct); IR (ATR): ν_{max} 3374, 2977, 2935, 1705 (C=O), 1599, 1573, 1512, 1367, 1248, 1219, 1139 cm^{-1}.



***tert*-Butyl (pyridin-3-ylmethylene)-carbamate (189g)**

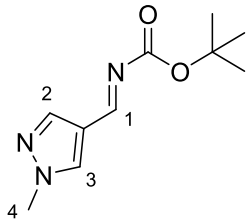
Following **general procedure G** with sulfone **122g** (1.01 g, 2.90 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and Na_2SO_4 (2.88 g, 20.3 mmol) gave the title compound (642 mg, 3.11 mmol, 107% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (1H, d, *J* = 1.5 Hz, H-5), 8.89 (1H, s, H-1), 8.77 (1H, dd, *J* = 4.8, 1.5 Hz, H-4), 8.28 (1H, ddd, *J* = 8.2, 1.5, 1.5 Hz, H-2), 7.42 (1H, dd, *J* =

8.2, 4.8 Hz, H-3), 1.59 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 (CH), 162.1 (C=O), 154.0 (CH), 136.0 (CH), 130.0 (CH), 83.0 (C), 28.0 (CH_3) ppm; HRMS (ESI) 207.1133 (M + H^+. $C_{11}H_{15}N_2O_2$ requires 207.1128); IR (ATR): ν_{max} 3199, 2977, 2932, 1708, 1511, 1367, 1269, 1247, 1155 cm^{-1}.



***tert*-Butyl (4-methyl-thiazol-5-ylmethylene)-carbamate (189h)**

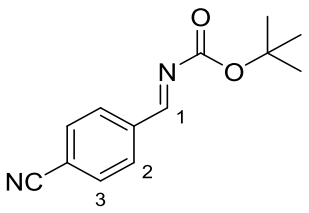
Following **general procedure G** with sulfone **122h** (3.00 g, 8.15 mmol), K_2CO_3 (6.75 g, 48.9 mmol) and Na_2SO_4 (8.11 g, 57.1 mmol) gave the title compound (1.81 g, 8.07 mmol, 99% yield) as an orange oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.17 (1H, d, *J* = 0.5 Hz, H-2), 8.88 (1H, s, H-1), 2.68 (3H, s, H-3), 1.55 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3 (C=O), 161.8 (C), 161.7 (CH), 158.2 (CH), 129.7 (C), 82.7 (C), 27.8 (CH_3), 16.3 (CH_3) ppm; HRMS (ESI) 281.0917 (M + Na^+. $C_{11}H_{18}N_2NaO_3S$ requires 281.0930 for the methanol adduct); IR (ATR): ν_{max} 2982, 2931, 1705 (C=O), 1600, 1512, 1366, 1243, 1150 cm^{-1}.



***tert*-Butyl (1-methyl-1H-pyrazol-4-ylmethylene)-carbamate (189i)**

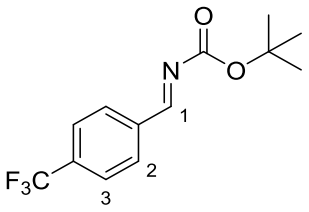
Following **general procedure G** with sulfone **122i** (1.06 g, 3.02 mmol), K_2CO_3 (2.50 g, 18.1 mmol) and Na_2SO_4 (3.00 g, 21.1 mmol) gave the title compound (602 mg, 2.87 mmol, 95% yield) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.92 (1H, s, H-1), 7.98 (1H, s, H-2), 7.94 (1H, s, H-3), 3.94 (3H, s, H-4), 1.55 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3 (CH), 162.8 (C=O), 141.8 (CH), 133.6 (CH), 119.9 (C), 81.9 (C), 39.6 (CH_3), 28.0 (CH_3) ppm; HRMS (ESI) 210.1239 (M + H^+. $C_{10}H_{16}N_3O_2$ requires 210.1237), 264.1318 (M + Na^+. $C_{11}H_{19}N_3NaO_3$

requires 264.1318 for the methanol adduct); IR (ATR): ν_{max} 2980, 1706 (C=O), 1613, 1392, 1367, 1246, 1149 cm^{-1}.



***tert*-Butyl (4-cyano-benzylidene)-carbamate (189j)**

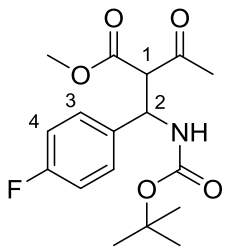
Following **general procedure G** with sulfone **122j** (1.15 g, 3.13 mmol), K_2CO_3 (2.59 g, 18.8 mmol) and Na_2SO_4 (3.11 g, 21.9 mmol) gave the title compound (723 mg, 3.13 mmol, 100% yield) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (1H, s, H-1), 8.03-7.97 (2H, m, H-3), 7.79-7.74 (2H, m, H-2), 1.58 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0 (CH), 162.0 (C=O), 137.9 (C), 132.7 (CH), 130.3 (CH), 118.1 (C), 116.5 (C), 83.3 (C), 28.0 (CH_3) ppm; HRMS (ESI) 231.1124 (M + H^+. $C_{13}H_{15}N_2O_2$ requires 231.1128); IR (ATR): ν_{max} 3357, 2979, 2230 (CN), 1709 (C=O), 1630, 1502, 1368, 1252, 1150 cm^{-1}.



***tert*-Butyl (4-trifluoromethyl-benzylidene)-carbamate (189k)**

Following **general procedure G** with sulfone **122k** (1.09 g, 2.63 mmol), K_2CO_3 (2.18 g, 15.8 mmol) and Na_2SO_4 (2.61 g, 18.4 mmol) gave the title compound (710 mg, 2.60 mmol, 99% yield) as a white amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (1H, s, H-1), 8.02 (2H, d, J = 8.2 Hz, H-2), 7.73 (2H, d, J = 8.2 Hz, H-3), 1.59 (9H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8 (CH), 162.2 (C=O), 137.2 (C), 134.7 (q, J_F = 32.8 Hz, C), 130.4 (CH), 126.0 (q, J_F = 3.7 Hz, CH), 123.7 (q, J_F = 274 Hz, CF_3), 83.1 (C), 28.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0 ppm; HRMS (ESI) 328.1131 (M + Na^+. $C_{14}H_{18}F_3NNaO_3$ requires 328.1131 for the

methanol adduct); IR (ATR): ν_{max} 3354, 2980, 1701 (C=O), 1496, 1366, 1322, 1164, 1126, 1064 cm^{-1}.

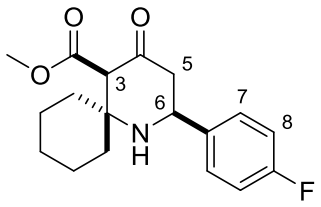


Methyl 2-[*tert*-butoxycarbonylamino-(4-fluorophenyl)-methyl]-3-oxo-butyrate (191)

To a solution of Chan's diene (87 mg, 0.336 mmol) in CH_2Cl_2 (1 mL) at -20 ^oC was added $Cu(OTf)_2$ (8.1 mg, 0.0224 mmol). A solution of imine **189e** (50 mg, 0.224 mmol) in CH_2Cl_2 (2 mL) was added and the reaction was stirred at -20 ^oC overnight. The reaction was quenched with the addition of sat. aq. $NaHCO_3$ (3 mL), and the mixture was warmed to rt with vigorous stirring. When the aqueous layer turned blue, the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The organics were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (47 mg, 0.139 mmol, 62% yield) as a colourless oil after column chromatography (10-15% EtOAc/petroleum ether (40-60)). A 1:1 ratio of rotamers was observed. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.21 (2H, m, H-3), 7.06-6.95 (2H, m, H-4), 6.15 (0.5H, br. s, NH), 5.80 (0.5H, br. s, NH), 5.50 (0.5H, br. s, H-2), 5.39 (0.5H, br. s, H-2), 4.7-3.88 (1H, m, H-1), 3.68 (1.5H, s, OCH_3), 3.63 (1.5H, s, OCH_3), 2.31 (1.5H, s, CH_3), 2.16 (1.5H, s, CH_3), 1.41 (4.5H, s, $(CH_3)_3$), 1.39 (4.5H, s, $(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.1 (C=O), 169.2 (C=O), 167.8 (C=O), 162.2 (d, J_F = 248 Hz, C), 155.3 (C), 155.1 (C), 135.7 (C), 135.5 (C), 128.3 (d, J_F = 8.0 Hz, CH), 128.0 (d, J_F = 8.2 Hz, CH), 115.8 (d, J_F = 5.1 Hz, CH), 115.6 (d, J_F = 4.9 Hz, CH), 80.3 (C), 80.2 (C), 64.4 (CH), 63.4 (CH), 52.9 (CH_3), 52.6 (CH_3), 30.6 (CH_3), 29.0 (CH_3), 28.4 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -114.6, -114.7 ppm; HRMS (ESI) 362.1374 (M + Na^+. $C_{17}H_{22}FNNaO_5$ requires 362.1374); IR (ATR): ν_{max} 3358, 2979, 1712 (C=O), 1510, 1366, 1287, 1250, 1226, 1159 cm^{-1}.

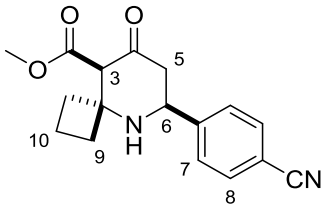
General Procedure H - One-Pot cyclisation

To a solution of imine (1.14 mmol) in CH_2Cl_2 (11.4 mL) at -78 ^oC was added $TiCl_4$ (4.56 mmol). Chan's diene (2.28 mmol) was added and the mixture was stirred for 30 mins at -78 ^oC. To the mixture was added MeOH (18.2 mmol), and the mixture was stirred for 4h at rt. Ketone (5.70 mmol) and $NaHCO_3$ (45.6 mmol) were sequentially added, and the reaction was stirred overnight at rt. The reaction was quenched with 1.59M citric acid in MeOH (11.4 mmol), and the mixture was cooled to 0 ^oC. Water (8 mL) was carefully added, followed by dilution with CH_2Cl_2 (10 mL). The mixture was stirred vigorously for 30 mins at rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). Organics were combined, washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography.



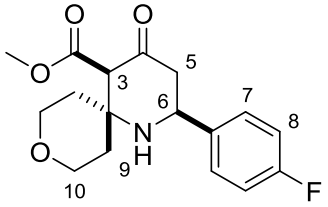
Methyl 6-(4-fluoro-phenyl)-4-oxo-1-aza-spiro[5.5]undecane-3-carboxylate (135c)

Following **general procedure H** with imine **189e** (175 mg, 0.785 mmol), $TiCl_4$ (344 µL, 3.14 mmol), Chan's diene (408 mg, 1.57 mmol), MeOH (509 µL, 12.6 mmol), cyclohexanone (406 µL, 3.93 mmol) and $NaHCO_3$ (2.63 g, 31.4 mmol). Purification by column chromatography (50% EtOAc/hexane then 100% EtOAc) gave the title compound as a mixture of diastereomers (153 mg, 0.479 mmol, 61% yield, 5:1 dr) as a yellow oil. Data was consistent with the reported data for **135c** on page 142.



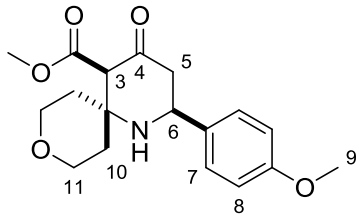
Methyl 6-(4-cyano-phenyl)-4-oxo-1-aza-spiro[3.5]nonane-3-carboxylate (137b)

Following **general procedure H** with imine **189j** (87 mg, 0.377 mmol), $TiCl_4$ (238 µL, 2.17 mmol), Chan's diene (283 mg, 1.09 mmol), MeOH (351 µL, 8.69 mmol), cyclobutanone (199 µL, 2.72 mmol) and $NaHCO_3$ (1.82 g, 21.7 mmol). Purification by column chromatography (25% EtOAc/hexane) gave the title compound as a mixture of diastereomers (41 mg, 0.139 mmol, 37% yield, 2.5:1 dr) as a yellow oil. Data was consistent with the reported data for **137b** on page 144.



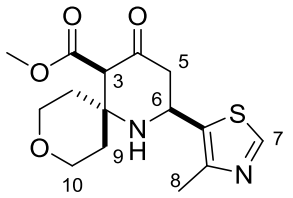
Methyl 6-(4-fluorophenyl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (138b)

Following **general procedure H** with imine **189e** (86 mg, 0.386 mmol), $TiCl_4$ (169 µL, 1.54 mmol), Chan's diene (200 mg, 0.772 mmol), MeOH (250 µL, 6.18 mmol), tetrahydro-4H-pyran-4-one (193 mg, 1.93 mmol) and $NaHCO_3$ (1.29 g, 15.4 mmol). Purification by column chromatography (20% EtOAc/hexane) gave the title compound as a mixture of diastereomers (86 mg, 0.266 mmol, 69% yield, 2:1 dr) as a yellow oil. Data was consistent with the reported data for **138b** on page 145.



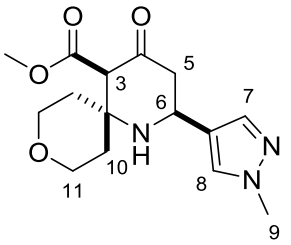
Methyl 6-(4-methoxyphenyl)-4-oxo-9-oxa-1-azaspiro[5.5]undecane-3-carboxylate (138c)

Following **general procedure H** with imine **189f** (138 mg, 0.587 mmol), $TiCl_4$ (258 µL, 2.35 mmol), Chan's diene (304 mg, 1.17 mmol), MeOH (379 µL, 9.39 mmol), tetrahydro-4H-pyran-4-one (294 mg, 2.94 mmol) and $NaHCO_3$ (1.97 g, 23.5 mmol). Purification by column chromatography (30% EtOAc/hexane) gave the title compound as a mixture of diastereomers (121 mg, 0.363 mmol, 62% yield, 1.5:1 dr) as a red oil. Data was consistent with the reported data for **138c** on page 146.



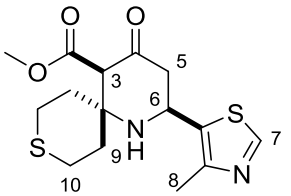
Methyl 6-(4-methyl-thiazol-5-yl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-3-carboxylate (138e)

Following **general procedure H** with imine **189h** (145 mg, 0.642 mmol), $TiCl_4$ (282 µL, 2.57 mmol), Chan's diene (333 mg, 1.28 mmol), MeOH (416 µL, 10.3 mmol), tetrahydro-4H-pyran-4-one (321 mg, 3.21 mmol) and $NaHCO_3$ (2.16 g, 25.7 mmol). Purification by column chromatography (50% EtOAc/hexane then 100% EtOAc) gave the title compound as a mixture of diastereomers (102 mg, 0.315 mmol, 49% yield, 2.5:1 dr) as an orange solid. Data was consistent with the reported data for **138e** on page 147.



Methyl 6-(1-methyl-1H-pyrazol-4-yl)-4-oxo-9-oxa-1-azaspiro[5.5]undecane-3-carboxylate (138f)

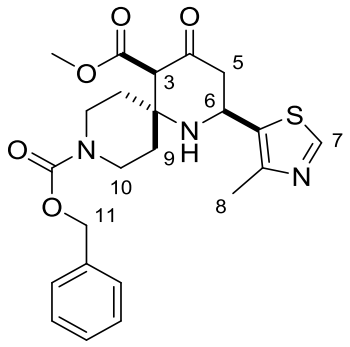
Following **general procedure H** with imine **189i** (138 mg, 0.660 mmol), $TiCl_4$ (289 µL, 2.64 mmol), Chan's diene (343 mg, 1.32 mmol), MeOH (428 µL, 10.6 mmol), tetrahydro-4H-pyran-4-one (330 mg, 3.30 mmol) and $NaHCO_3$ (2.22 g, 26.4 mmol). Purification by column chromatography (100% EtOAc) gave the title compound as a mixture of diastereomers (14 mg, 0.0462 mmol, 7% yield) as a red oil. Data was consistent with the reported data for **138f** on page 148.



Methyl 6-(4-methyl-thiazol-5-yl)-4-oxo-9-thia-1-aza-spiro[5.5]undecane-3-carboxylate (195)

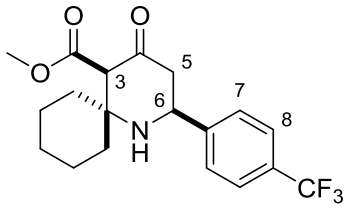
Following **general procedure H** with imine **189h** (149 mg, 0.659 mmol), $TiCl_4$ (289 µL, 2.64 mmol), Chan's diene (343 mg, 1.32 mmol), MeOH (424 µL, 10.5 mmol), tetrahydro-4H-thiopyran-4-one (383 mg, 3.30 mmol) and $NaHCO_3$ (2.22 g, 26.4 mmol). Purification by column chromatography (40% EtOAc/hexane) gave the title compound as a mixture of diastereomers (123 mg, 0.362 mmol, 55% yield, 3:1 dr) as a red oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, s, H-7), 4.43-4.32 (1H, m, H-6), 3.72 (3H, s, OCH_3), 3.31 (1H, br. s, H-3), 3.16-3.06 (1H, m, H-10), 3.02 (1H, dd, *J* = 13.7, 11.5 Hz, H-5), 3.05-2.94 (1H, m, H-10), 2.62 (1H, ddd, *J* = 13.7, 3.5, 1.0 Hz, H-5), 2.48 (3H, s, H-8), 2.42-2.33 (2H, m, H-10), 2.12-1.75 (4H, m, H-9 and NH), 1.71 (1H, ddd, *J* = 14.5, 11.7, 3.2 Hz, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6 (C=O), 168.7 (C=O), 150.3 (C), 149.8 (C), 133.1 (C), 67.2

(CH), 59.1 (C), 52.6 (CH_3), 48.4 (CH), 46.9 (CH_2), 37.2 (CH_2), 34.3 (CH_2), 23.3 (CH_2), 22.7 (CH_2), 15.7 (CH_3) ppm; HRMS (ESI) 341.0990 ($M + H^+$. $C_{15}H_{21}N_2O_3S_2$ requires 341.0988); IR (ATR): ν_{max} 3314, 2952, 2922, 1705 (C=O), 1434, 1415, 1315, 1266, 1196, 1163 cm^{-1}.



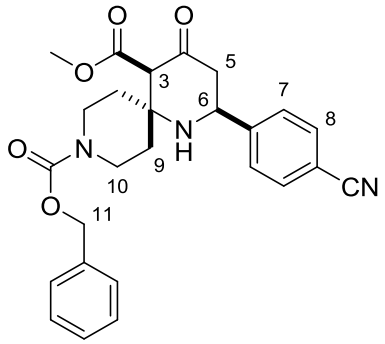
6-(4-Methyl-thiazol-5-yl)-4-oxo-1,9-diaza-spiro[5.5]undecane-3,9-dicarboxylic acid 9-benzyl ester 3-methyl ester (196)

Following **general procedure H** with imine **189h** (119 mg, 0.527 mmol), $TiCl_4$ (231 µL, 2.11 mmol), Chan's diene (260 mg, 1.05 mmol), MeOH (341 µL, 8.43 mmol), 1-Z-4-piperidone (615 mg, 2.64 mmol) and $NaHCO_3$ (1.77 g, 21.1 mmol). Purification by column chromatography (40% EtOAc/hexane then 80% EtOAc/hexane) gave the title compound as a mixture of diastereomers (107 mg, 0.473 mmol, 45% yield, 2.5:1 dr) as an orange oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, s, H-7), 7.39-7.27 (5H, m, ArH), 5.11 (2H, s, H-11), 4.46-4.33 (1H, m, H-6), 3.95-3.76 (2H, m, H-10), 3.73 (3H, s, OCH_3), 3.43-3.24 (2H, m, H-10), 3.29 (1H, br. s, H-3), 3.05 (1H, dd, *J* = 13.5, 11.2 Hz, H-5), 2.70-2.60 (1H, m, H-5), 2.46 (3H, s, H-8), 2.04 (1H, br. s, NH), 1.93-1.37 (4H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3 (C=O), 168.7 (C=O), 155.2 (C=O), 150.3 (CH), 149.9 (C), 136.7 (C), 132.9 (C), 128.6 (CH), 128.2 (CH), 128.1 (CH), 67.3 (CH_2), 66.7 (CH), 58.5 (C), 52.7 (CH_3), 48.9 (CH), 47.0 (CH_2), 39.5 (CH_2), 39.1(CH_2), 35.6 (CH_2), 32.4 (CH_2), 15.7 (CH_3) ppm; HRMS (ESI) 458.1747 ($M + H^+$. $C_{23}H_{28}N_3O_5S$ requires 458.1744); IR (ATR): ν_{max} 2951, 1698 (C=O), 1432, 1247, 1165 cm^{-1}.



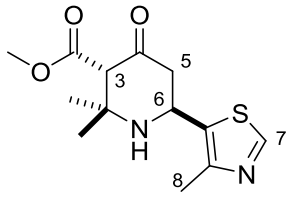
Methyl 4-oxo-6-(4-trifluoromethyl-phenyl)-1-aza-spiro[5.5]undecane-3-carboxylate (197)

Following **general procedure H** with imine **189k** (314 mg, 1.15 mmol), $TiCl_4$ (504 µL, 4.60 mmol), Chan's diene (598 mg, 2.30 mmol), MeOH (743 µL, 18.4 mmol), cyclohexanone (595 µL, 5.75 mmol) and $NaHCO_3$ (3.86 g, 46.0 mmol). Purification by column chromatography (10% EtOAc/hexane) gave an inseparable mixture of product and cyclohexanone. The mixture was dissolved in EtOAc (20 mL) and washed with water (10 x 10 mL), dried ($MgSO_4$), filtered and concentrated to give the title compound as a mixture of diastereomers (117 mg, 0.322 mmol, 28% yield, 1.5:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.55 (4H, m, H-7 and H-8), 4.18 (1H, dd, *J* = 11.2, 3.8 Hz, H-6), 3.73 (3H, s, OCH_3), 3.42 (1H, br. s, H-3), 3.06 (1H, dd, *J* = 13.5, 11.2 Hz, H-5), 2.57 (1H, ddd, *J* = 13.5, 3.8, 1.0 Hz, H-5), 1.78-1.29 (10H, m, cyclohexyl) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.6 (C=O), 169.5 (C=O), 146.4 (C), 130.0 (q, J_F = 32.4 Hz, C), 127.1 (CH), 125.9 (q, J_F = 3.5 Hz, CH), 124.1 (q, J_F = 273 Hz, C), 66.6 (CH), 60.3 (C), 54.9 (CH), 52.3 (CH_3), 45.8 (CH_2), 36.6 (CH_2), 33.3 (CH_2), 25.6 (CH_2), 21.5 (CH_2), 21.0 (CH_2) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4 ppm; HRMS (ESI) 370.1606 ($M + H^+$. $C_{19}H_{23}F_3NO_3$ requires 370.1625); IR (ATR): ν_{max} 2933, 2857, 1706 (C=O), 1324, 1164, 1123, 1068 cm^{-1}.



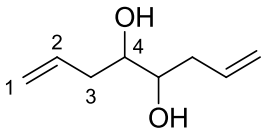
6-(4-Cyano-phenyl)-4-oxo-1,9-diaza-spiro[5.5]undecane-3,9-dicarboxylic acid 9-benzyl ester 3-methyl ester (198)

Following **general procedure H** with imine **189j** (131 mg, 0.570 mmol), $TiCl_4$ (250 µL, 2.28 mmol), Chan's diene (296 mg, 1.14 mmol), MeOH (368 µL, 9.12 mmol), 1-Z-4-piperidone (664 mg, 2.85 mmol) and $NaHCO_3$ (1.92 g, 22.8 mmol). Purification by column chromatography (30% EtOAc/hexane) gave the title compound as a mixture of diastereomers (62 mg, 0.137 mmol, 24% yield, 4:1 dr) as a yellow oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.64 (2H, m, H-8), 7.59-7.52 (2H, m, H-7), 7.39-7.28 (5H, m, ArH), 5.10 (2H, s, H-11), 4.19-4.08 (1H, m, H-6), 3.92-3.75 (2H, m, H-10), 3.73 (3H, s, OCH_3), 3.46-3.34 (1H, m, H-10), 3.32 (1H, d, *J* = 1.0 Hz, H-3), 3.32-3.18 (1H, m, H-10), 3.03 (1H, dd, *J* = 13.7, 11.5 Hz, H-5), 2.61 (1H, dd, *J* = 13.7, 3.5 Hz, H-5), 1.89-1.37 (4H, m, H-9) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.0 (C=O), 169.0 (C=O), 155.2 (C=O), 146.8 (C), 136.7 (C), 132.8 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.5 (CH), 118.6 (CN), 112.0 (C), 67.3 (CH_2), 66.7 (CH), 58.9 (C), 55.0 (CH), 52.6 (CH_3), 45.2 (CH_2), 39.5 (CH_2), 39.0 (CH_2), 35.6 (CH_2), 32.3 (CH_2) ppm; HRMS (ESI) 462.2025 (M + H^+. $C_{26}H_{28}N_3O_5$ requires 462.2023), 484.1841 (M + Na^+. $C_{26}H_{27}N_3NaO_5$ requires 484.1843); IR (ATR): ν_{max} 2952, 2227 (CN), 1694 (C=O), 1431, 1231, 1164, 1120 cm^{-1}.



Methyl 2,2-dimethyl-6-(4-methyl-thiazol-5-yl)-4-oxo-piperidine-3-carboxylate (199)

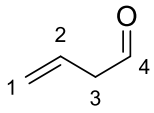
Following **general procedure H** with imine **189h** (321 mg, 1.42 mmol), $TiCl_4$ (623 µL, 5.68 mmol), Chan's diene (738 mg, 2.84 mmol), MeOH (917 µL, 22.7 mmol), acetone (630 µL, 8.52 mmol) and $NaHCO_3$ (4.77 g, 56.8 mmol). Purification by column chromatography (75% EtOAc/hexane) gave the title compound as a mixture of diastereomers (96 mg, 0.341 mmol, 24% yield, 1:1.5 dr) as a red solid. Data presented is for the major diastereomer. Mp 101.5-106 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (1H, s, H-7), 4.62 (1H, dd, *J* = 11.0, 3.5 Hz, H-6), 3.74 (3H, s, OCH_3), 3.61 (1H, s, H-3), 2.59 (1H, dd, *J* = 13.5, 3.5 Hz, H-5), 2.43-2.40 (1H, m, H-5), 2.41 (3H, s, H-8), 1.44 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3 (C=O), 168.4 (C=O), 151.2 (CH), 148.7 (C), 134.1 (C), 66.9 (CH), 56.8 (C), 52.0 (CH_3), 49.5 (CH_2), 48.9 (CH), 30.0 (CH_3), 22.7 (CH_3), 15.5 (CH_3) ppm; HRMS (ESI) 283.1112 (M + H^+. $C_{13}H_{19}N_2O_3S$ requires 283.1111); IR (ATR): ν_{max} 2953, 1747 (C=O), 1713 (C=O), 1435, 1341, 1276, 1192, 1121 cm^{-1}.



Octa-1,7-diene-4,5-diol (212)

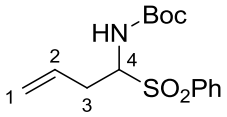
A suspension of glyoxal (40 wt. % in water) (3 mL, 26.2 mmol), allyl bromide (5.66 mL, 65.4 mmol), and tin powder (7.76 g, 65.4 mmol) in water (13 mL) and THF (13 mL) was sonicated in a rt water bath for 4.5h. The mixture was quenched with 25% aqueous KOH (30 mL) at rt. The mixture was diluted with diethyl ether (50 mL) and filtered through Celite, washing with diethyl ether (2 x 50 mL). The layers were separated and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (0-70% EtOAc/cyclohexane) to give the title compound (2.63 g, 18.6 mmol, 71% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92-5.80 (2H, m, H-2), 5.21-5.11

(4H, m, H-1), 3.71-3.51 (2H, m, H-4), 2.42-2.32 (2H, m, O-H), 2.32-2.13 (4H, m, H-3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 134.7 (CH), 134.4 (CH), 118.3 (CH_2), 118.1 (CH_2), 72.8 (CH), 72.7 (CH), 38.2 (CH_2), 36.4 (CH_2) ppm; HRMS (ESI) 165.0876 (M + Na^+. $C_8H_{14}NaO_2$ requires 165.0886); IR (ATR): ν_{max} 3310, 3077, 2978, 2941, 2901, 1642, 1497, 1434, 1214, 1050, 988, 913, 867 cm^{-1}.



But-3-enal (210b)

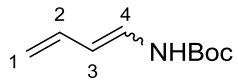
Sodium periodate (2.56 g, 12.0 mmol) was added to a biphase of octa-1,7-diene-4,5-diol **212** (1.70 g, 12.0 mmol) in CH_2Cl_2 (6 mL) and water (6 mL) at 0 °C. The mixture was stirred for 3h at 0 °C. Layers were separated and the aqueous was extracted with CH_2Cl_2 (2 x 1 mL). Organics were combined and passed through a phase separator to afford the title compound (1.38 g, 19.7 mmol, 82% yield) as a colourless 12.1 wt. % solution in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (1H, t, *J* = 2.0 Hz, H-4), 5.94 (1H, ddt, *J* = 17.0, 10.5, 7.0 Hz, H-2), 5.34-5.21 (2H, m, H-1), 3.23-3.18 (2H, m, H-3) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 199.6 (C=O), 128.1 (CH), 120.2 (CH_2), 48.2 (CH_2) ppm; HRMS (ESI) 93.0314 (M + Na^+. C_4H_6NaO requires 93.0311). Data was consistent with literature.[208]



***tert*-Butyl (1-phenylsulfonyl)but-3-en-1-yl)carbamate (214)**

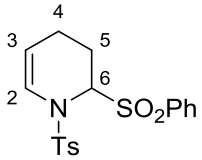
Water (19.5 mL), sodium benzenesulfinate (3.20 g, 19.5 mmol) and formic acid (3.74 mL, 98.0 mmol) were sequentially added to a solution of but-3-enal **210b** (12.1 wt. % in CH_2Cl_2) (11.3 g, 19.5 mmol) and *tert*-butyl carbamate (2.29 g, 19.5 mmol) in CH_2Cl_2 (12 mL) (19.5 mL total CH_2Cl_2). The biphasic mixture was stirred for 2 days at rt. Layers were separated and the aqueous was extracted with CH_2Cl_2 (2 x 20 mL). Organics were combined, passed through a phase separator and concentrated *in vacuo*. The white solid was stirred in 10% Et_2O/cyclohexane for 20 mins then filtered to give the title compound (3.90 g, 12.5 mmol,

64% yield) as a white solid. Mp 95.5-98 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.91 (2H, m, ArH), 7.68-7.52 (3H, m, ArH), 5.92-5.76 (1H, m, H-2), 5.28-5.20 (2H, m, H-1), 5.06 (1H, br. d, *J* = 10.0 Hz, NH), 4.96 (1H, td, *J* = 10.0, 4.0 Hz, H-4), 3.02-2.92 (1H, m, H-3), 2.70-2.58 (1H, m, H-3), 1.23 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 153.7 (C=O), 136.9 (C), 133.9 (CH), 131.1 (CH), 129.3 (CH), 129.1 (CH), 119.8 (CH_2), 80.8 (C), 69.9 (CH), 31.2 (CH_2), 28.0 (CH_3) ppm; HRMS (ESI) 334.1082 (M + Na^+. $C_{15}H_{21}NNaO_4S$ requires 334.1083); IR (ATR): ν_{max} 3326, 2985, 1686 (C=O), 1523, 1324, 1305, 1161, 1140, 1084 cm^{-1}.



tert-Butyl(buta-1,3-dien-1-yl)carbamate (219)

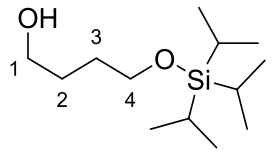
Isolated as a consequence of the reaction between *tert*-butyl (1-phenylsulfonyl)but-3-en-1-yl)carbamate **214** (1 eq) and NaH (3 eq) as an inseparable 4:1 *E*:*Z* mixture. (*E*)-*tert*-Butyl (buta-1,3-dien-1-yl)carbamate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (1H, dd, *J* = 11.0, 10.5 Hz, H-4), 6.26 (1H, ddd, *J* = 17.0, 11.0, 10.5 Hz, H-2), 5.64 (1H, dd, *J* = 11.0, 10.5 Hz, H-3), 5.00 (1H, d, *J* = 17.0 Hz, H-1), 4.87 (1H, d, *J* = 10.5 Hz, H-1), 1.47 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 152.5 (C=O), 134.7 (CH), 127.4 (CH), 112.7 (CH_2), 111.0 (CH), 80.9 (C), 28.2 (CH_3) ppm; (*Z*)-*tert*-Butyl (buta-1,3-dien-1-yl)carbamate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51-6.33 (2H, m, H-4 and H-2), 5.43-5.23 (1H, m, H-3), 5.21-5.14 (1H, m, H-3), 5.05-5.02 (1H, m, H-1), 1.49 (9H, s, $(CH_3)_3$) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 152.4 (C=O), 129.0 (CH), 123.1 (CH), 115.5 (CH_2), 107.1 (CH), 28.2 (CH_3) ppm; IR (ATR): ν_{max} 2971, 1694 (C=O), 1505, 1367, 1251, 1160, 950 cm^{-1}. ^{1}H NMR was consistent with literature.[209]



6-(Phenylsulfonyl)-1-tosyl-1,4,5,6-tetrahydropyridine (224)

Glutaraldehyde (50% in water) (1.13 mL, 6.00 mmol) was added to a stirred solution of 4-methylbenzenesulfonamide (1.03 g, 6.00 mmol) and sodium benzenesulfinate (0.985 g, 6.00

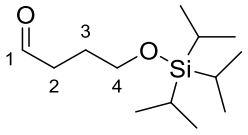
mmol) in water (10 mL) and formic acid (10 mL) at 40 °C. The mixture was stirred overnight at 40 °C. The white precipitate was filtered warm and washed with water (20 mL) and cyclohexane (20 mL). The white solid was stirred vigorously in a biphase of CH_2Cl_2 (20 mL) and sat. Aq. $NaHCO_3$ (20 mL) for 1h at rt. Layers were separated and the aqueous was extracted with water (2 x 20 mL). Organics were combined, passed through a phase separator and concentrated *in vacuo* to give the title compound (1.45 g, 3.84 mmol, 64% yield) as a white solid. Mp 133-133.5 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03-7.98 (2H, m, ArH), 7.76-7.71 (1H, m, ArH), 7.67-7.61 (2H, m, ArH), 7.54 (2H, d, *J* = 8.5 Hz, ArH), 7.30 (2H, d, *J* = 8.5 Hz, ArH), 6.60-6.54 (1H, m, H-2), 5.34-5.28 (1H, m, H-3), 5.04 (1H, br. d, *J* = 5.0 Hz, H-6), 2.70-2.62 (1H, m, H-5), 2.62-2.50 (1H, m, H-4), 1.96-1.86 (1H, m, H-4), 1.25-1.13 (1H, m, H-5) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 144.4 (C), 136.6 (C), 134.4 (C), 134.3 (CH), 129.9 (CH), 129.8 (CH), 129.0 (CH), 127.1 (CH), 112.5 (CH), 71.5 (CH), 21.6 (CH_3), 18.4 (CH_2), 17.9 (CH_2) ppm; HRMS (ESI) 400.0649 ($M + Na^+$. $C_{18}H_{19}NNaO_4S_2$) requires 400.0648); IR (ATR): ν_{max} 3059, 2922, 1659, 1595, 1450, 1364, 1322, 1308, 1172, 1144, 1084 cm^{-1}.



4-((Triisopropylsilyloxy)butan-1-ol (236)

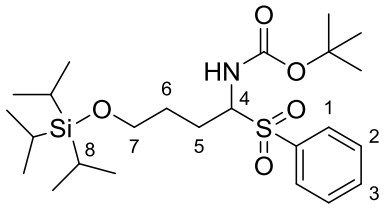
1,4-Butanediol (3.53 mL, 40.0 mmol) was added over 20 mins via syringe pump to a slurry of NaH (60% dispersion in mineral oil, 1.76 g, 44.0 mmol) in THF (57 mL) at 0 ^oC and the mixture stirred for 30 mins. Triisopropylsilyl chloride (8.56 mL, 40.0 mmol) was added over 20 mins via syringe pump at 0 ^oC, and the reaction was stirred overnight at rt. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and diluted with diethyl ether (100 mL). The layers were separated and the aqueous was extracted with diethyl ether (2 x 50 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (9.08 g, 36.8 mmol, 92% yield) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (2H, t, *J* = 5.5 Hz, H-4), 3.68-3.61 (2H, m, H-1), 1.73-1.60 (4H, m, H-2 and H-3), 1.09-1.01 (21H, m, OTIPS) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 63.7 (CH_2), 62.9 (CH_2), 30.5 (CH_2), 30.2 (CH_2), 18.1 (CH_3), 12.0 (CH)

ppm; HRMS (ESI) 269.1871 (M + Na^+. $C_{13}H_{30}O_2Si$ requires 269.1907); IR (ATR): ν_{max} 3334, 2941, 2891, 2865, 1463, 1247, 1103, 1061 cm^{-1}.



4-((Triisopropylsilyl)oxy)butanal (237)

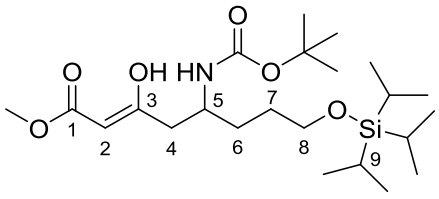
To a solution of oxalyl chloride (2.06 mL, 24.3 mmol) in CH_2Cl_2 (225 mL) at -78 °C was added DMSO (1.8 mL, 25.4 mmol). The mixture was stirred for 1h before the addition of alcohol **236** (5.00 g, 20.3 mmol) at -78 °C, and the reaction mixture was stirred for a further 1h. Triethylamine (14.2 mL, 102 mmol) was added and the mixture was stirred for 30 mins at rt. 2M HCl (15 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organics were combined, washed with 2M HCl (50 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% EtOAc/hexane) to give the title compound (4.22 g, 16.2 mmol, 85% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (1H, t, *J* = 1.5 Hz, H-1), 3.72 (2H, t, *J* = 6.0 Hz, H-4), 2.53 (2H, td, *J* = 7.0, 1.5 Hz, H-2), 1.87 (2H, tt, *J* = 7.0, 6.0 Hz, H-3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.9 (C=O), 62.5 (CH_2), 40.9 (CH_2), 25.8 (CH_2), 18.1 (CH_3), 12.0 (CH) ppm; HRMS (ESI) 267.1652 (M + Na^+. $C_{13}H_{28}NaO_2Si$ requires 267.1751); IR (ATR): ν_{max} 2942, 2892, 2865, 1727 (C=O), 1463, 1247, 1102, 1069, 1013 cm^{-1}.



(1-Benzenesulfonyl-4-triisopropylsilanyloxy-butyl)-carbamic acid *tert*-butyl ester (238)

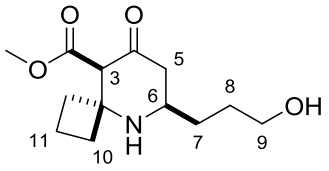
Following **general procedure A** with aldehyde **237** (3.09 g, 12.7 mmol), *tert*-butyl carbamate (991 mg, 8.47 mmol) and benzenesulfinic acid sodium salt (2.77 g, 16.9 mmol) to give the title compound (2.62 g, 5.59 mmol, 66% yield) as a white solid. Mp 80-82.5 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.91 (2H, d, *J* = 7.8 Hz, H-1), 7.65-7.58 (1H, m, H-3), 7.56-7.49 (2H, m, H-2), 5.10 (1H, d, *J* = 10.5 Hz, NH), 4.86 (1H, dt, *J* = 10.5, 3.2 Hz, H-4), 3.72 (2H, t, *J* = 6.0 Hz, H-7), 2.43-2.29 (1H, m, H-5), 1.93-1.80 (1H, m, H-5), 1.79-1.62 (2H, m, H-6), 1.21 (9H, s, $(CH_3)_3$), 1.07-1.01 (21H, m, OTIPS) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.0 (C=O), 137.1 (C), 133.9 (CH), 129.4 (CH), 129.1 (CH), 80.8 (C), 70.9 (CH), 62.3 (CH_2), 28.7 (CH_2), 28.1 (CH_3), 23.2 (CH_2), 18.1 (CH_3), 12.0 (CH) ppm; HRMS (ESI) 508.2538 (M + Na^+. $C_{24}H_{43}NNaO_5SSi$ requires 508.2523); IR (ATR): ν_{max} 3337, 2942, 2891, 2865, 1720 (C=O), 1516, 1447, 1367, 1308, 1245, 1166, 1141, 1083 cm^{-1}.



Methyl 5-*tert*-butoxycarbonylamino-3-hydroxy-8-triisopropylsilanyloxy-oct-2-enoate (239)

Following **general procedure B** with sulfone **238** (2.00 g, 4.12 mmol), NaH (60% dispersion in mineral oil, 0.496 g, 12.4 mmol), methyl acetoacetate (1.34 mL, 12.4 mmol), diisopropylamine (3.48 mL, 24.7 mmol) and *n*-BuLi (2.24 M in hexanes, 11.0 mL, 24.7 mmol). The residue was purified by column chromatography (20% EtOAc/hexane) to give the title compound (1.07 g, 2.35 mmol, 57% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.01 (1H, s, OH), 5.02 (1H, s, H-2), 4.78 (1H, br. d, *J* = 8.7 Hz, NH), 3.93-3.78 (1H, m, H-5), 3.73-3.63 (2H, m, H-8), 3.71 (3H, s, OCH_3), 2.39 (2H, br. d, *J* = 5.5 Hz, H-4), 1.69-1.50 (4H, m, H-6 and H-7), 1.42 (9H, s, $(CH_3)_3$), 1.09-0.99 (21H, m, OTIPS) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6 (C), 172.9 (C=O), 155.5 (C=O), 91.1 (CH), 79.3 (C), 63.0 (CH_2), 51.3 (CH_3), 48.8 (CH), 40.4 (CH_2), 30.8 (CH_2), 29.5 (CH_2), 28.5 (CH_3), 18.1 (CH_3), 18.1 (CH) ppm; HRMS (ESI) 482.2910 (M + Na^+. $C_{23}H_{45}NNaO_6Si$ requires 482.2908); IR (ATR): ν_{max} 3374, 2942, 2865, 1747 (C=O), 1711 (C=O), 1505, 1450, 1365, 1243, 1168, 1102 cm^{-1}.



Methyl 6-(3-hydroxy-propyl)-4-oxo-1-aza-spiro[3.5]nonane-3-carboxylate (241)

Following **general procedure C** with the hydrochloride salt of **239** (238 mg, 0.603 mmol), cyclobutanone (225 µL, 3.02 mmol) and $NaHCO_3$ (254 mg, 3.02 mmol). The residue was purified by column chromatography (100% ethyl acetate) to give the title compound as a mixture of diastereomers (21 mg, 0.0797 mmol, 8% yield, 6:1 dr) as a colourless oil. Data presented is for the major diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73-3.66 (1H, m, H-9), 3.71 (3H, s, OCH_3), 3.62-3.53 (1H, m, H-9), 3.58 (1H, d, *J* = 1.2 Hz, H-3), 2.87-2.77 (1H, m, H-6), 2.40 (1H, dd, *J* = 13.7, 11.5 Hz, H-5), 2.31 (1H, ddd, *J* = 13.7, 3.7, 1.2 Hz, H-5), 2.18-2.06 (1H, m, H-10), 2.04-1.59 (8H, m, H-7, H-8, H-10 and H-11), 1.56-1.44 (1H, m, H-7) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.2 (C=O), 169.1 (C=O), 65.6 (CH), 62.9 (CH_2), 62.6 (C), 53.2 (CH_3), 52.6 (CH), 46.9 (CH_2), 36.1 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 30.9, (CH_2), 14.6 (CH_2) ppm; HRMS (ESI) 256.1547 (M + H^+. $C_{13}H_{22}NO_4$ requires 256.1543); IR (ATR): ν_{max} 3299, 2937, 1705 (C=O), 1434, 1334, 1289, 1267, 1196, 1169, 1059 cm^{-1}.

9. Abbreviations

µW	microwaves
Ac	acetyl
AIBN	azobisisobutyronitrile
Ala	alanine
aq	aqueous
ax	axial
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
Bu	butyl
Cbz	carboxybenzyl
CCR5	C-C chemokine receptor type 5
CDI	carbonyldiimidazole
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DABAL.Me_3	bis(trimethylaluminium)-1,4-diazabicyclo[2.2.2]octane adduct
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMPU	N,N'-dimethylpropyleneurea
DMSO	dimethylsulfoxide
dr	diastereomeric ratio

DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ee	enantiomeric excess
eq	equatorial
Eq	equivalents
ESI	Electrospray ionisation
Et	ethyl
FBDD	Fragment-based drug discovery
Fmoc	fluorenylmethyloxycarbonyl
Fsp^3	Fraction of sp^3
HIV	Human immunodeficiency virus
HRMS	High-resolution mass spectometry
HSQC	Heteronuclear single quantum coherence
HPLC	High-performance liquid chromatography
HTS	High-throughput screening
J	coupling constant (Hz)
LCMS	Liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LiDBB	lithium 4,4'-di-*tert*-butylbiphenylide
LLAMA	Lead-likeness and molecular analysis
m	multiplet
*m*CPBA	*m*-chloroperoxybenzoic acid
MDAP	Mass-directed autopurification
Me	methyl
Mp	melting point
Ms	mesyl
n-Bu	*n*-butyl
NAD+	nicotinamide adenine dinucleotide
NFSI	N-fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance

PBF	Plane of best fit
pg	page
Ph	phenyl
PMB	paramethoxybenzyl
PMI	Principal moments of inertia
PMP	paramethoxyphenyl
pr	propyl
p-TSA	*p*-toluenesulfonic acid
q	quartet
rt	room temperature
s	singlet
sat	saturated
SnAP	tin-amine protocol
t	triplet
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBS	*tert*-butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	Thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl

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