Improved Routes to Unsaturated Ketones and Heterocycles

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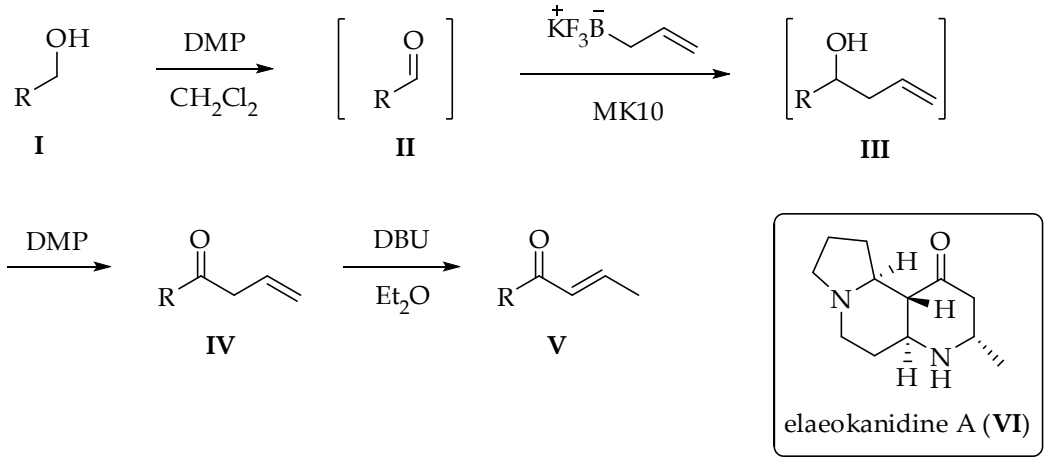
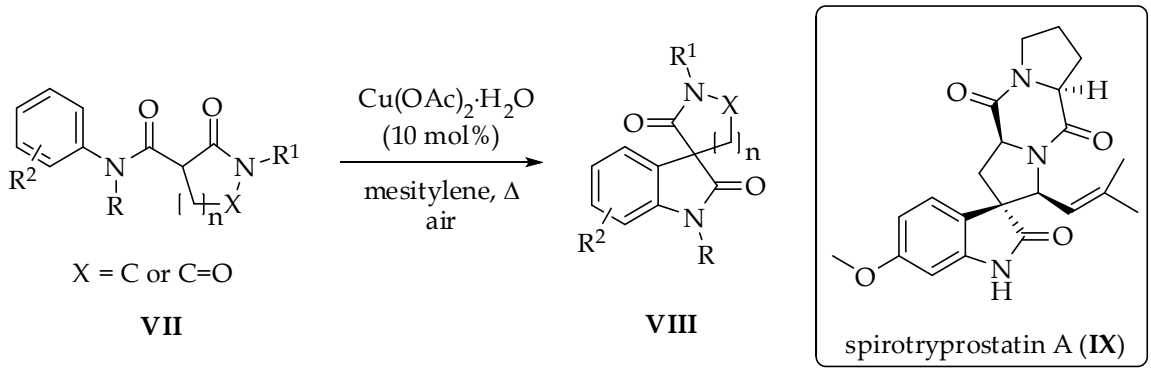
Abstract

The work herein comprises two distinct projects: the first involves the construction of allylic ketones **IV** and enones **V** directly from primary alcohols **I**, using a novel one-pot procedure (Scheme I). Following development of this methodology, its application to the synthesis of indolizidine alkaloid elaeokanidine A (**VII**) was investigated.



Scheme I: A one-pot procedure to construct unsaturated ketones IV and V from primary alcohols I

The second research area concerns the development of a copper(II)-catalysed radical cyclisation reaction to form spirocyclic oxindoles **VIII** directly from linear anilides **VII** (Scheme II), along with subsequent preliminary studies towards to the synthesis of spirotryprostatin A (**IX**).



Scheme II: Copper-catalysed cyclisation of anilides VII to form spirocyclic oxindoles VIII

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Acknowledgments

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Last but by no means least, thanks to Andy for keeping me (relatively) sane and for being generally wonderful, if a bit useless at times... Love you. x

Declaration

The research presented in this thesis was carried out at the University of York between October 2008 and September 2011. This work is, to the best of my knowledge, original, except where due reference has been made to other workers.

Catherine Laura Moody

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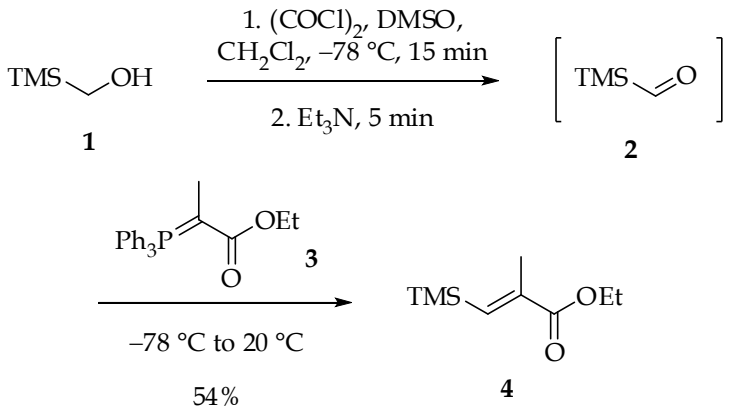
Chapter 1 – Overview

1.1 The importance of new methodologies for synthesis

In order to gain access to new useful organic molecules, whether for new technologies and commercial application, or to develop more effective and safer medicines for combating disease, we require the use of organic synthesis. Despite the utility of already established procedures, chemists are always striving to improve synthetic strategies on the basis of several criteria, including: cheaper and less toxic reagents; broader substrate scope and structural diversity; atom economy; and ease and efficiency of preparation.

1.2 One pot reactions

In recent years, "one-pot" or "telescoped" procedures, in which multiple transformations are performed without intermediate isolation, have become popular tools with the organic chemist due to their inherent potential benefits such as high efficiency, operational simplicity, reduced costs and lower waste products. In addition, they allow *in situ* preparation and elaboration of intermediates which may be problematic due to their reactivity, toxicity or stability when isolated. This area has been reviewed recently in a book by one of the pioneers of the area, and so only a brief introduction will be given here.[1]

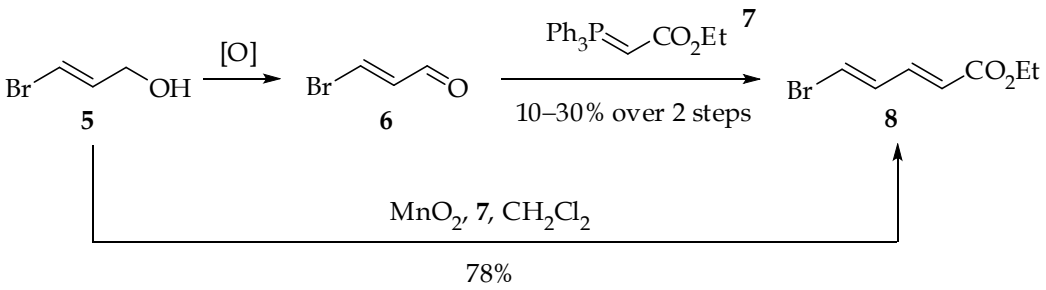


Scheme 1: Ireland's Swern/Wittig reaction

An early illustrative example is given by Ireland and Norbeck. From alcohol **1**, using the Swern procedure, they were able to synthesise acylsilane **2**, which they believed polymerises rapidly and thus had been previously undocumented. Maintaining the reaction mixture at −78 °C, ylide **3** was added and subsequently the novel alkene **4** was produced in 54% yield (Scheme 1).[2]

There are two distinct types of one-pot procedure: tandem and sequential. A tandem reaction is one in which two or more chemical processes occur under the same reaction conditions. In the context of this thesis, tandem refers to a reaction in which all reagents are added to the reaction mixture from the start, whereas in a sequential reaction, further reagents are added to the reaction mixture once the preceding transformation is complete, such as in the Ireland example (Scheme 1).

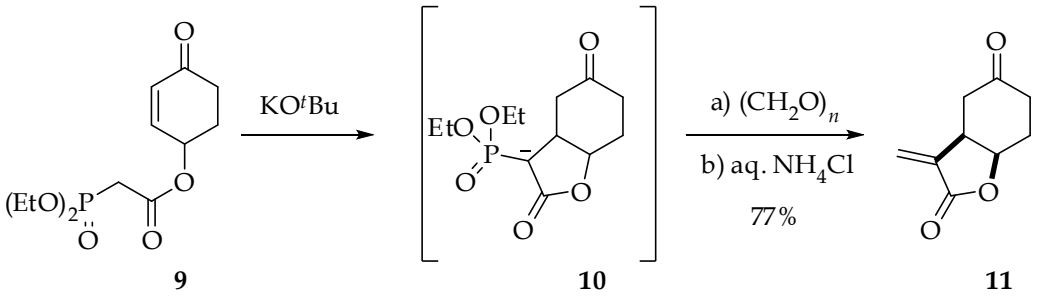
The advantages of a tandem one-pot synthesis are well illustrated in an example from the Taylor group (Scheme 2). In a two-step oxidation/Wittig reaction from (*E*)-3-bromoprop-2-en-1-ol (**5**), poor overall yields of diene **8** were obtained. However, in a one-pot procedure, whereby isolation of problematic aldehyde **6** was not necessary, the same set of transformations was achieved in a much improved 78% yield.[3] This is an example of a true tandem process.



Scheme 2: One-pot oxidation/Wittig reaction

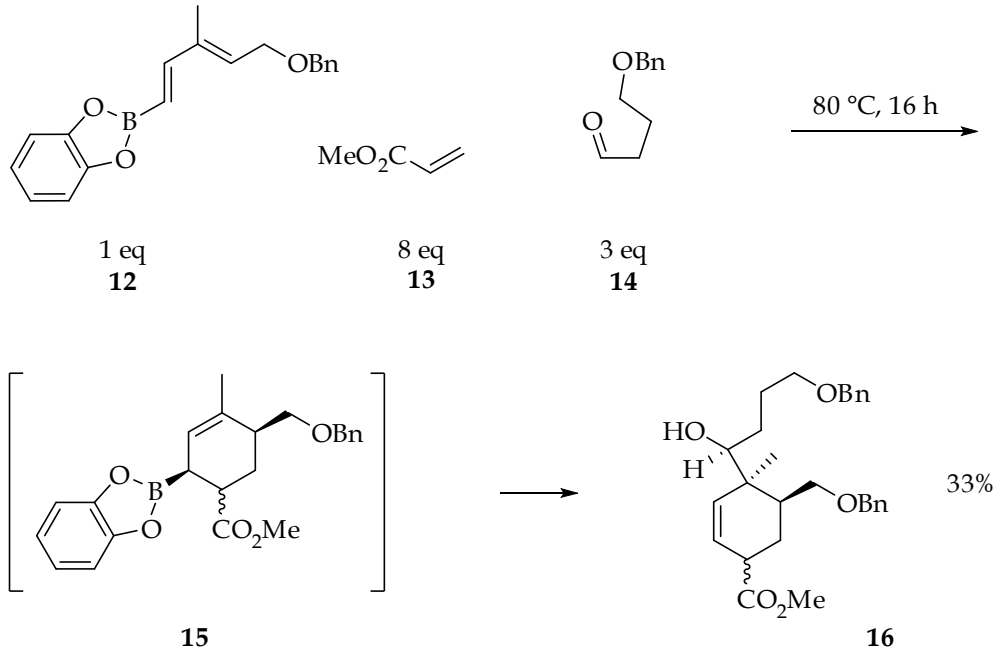
Perhaps one of the most commonly seen uses for one-pot synthesis in the York group involves the oxidation of primary alcohols to aldehydes,[3,4] yet it has also found utility in a number of other protocols,[5,6] such as the telescoped Intramolecular Michael/Olefination (TIMO) reaction developed by the Taylor group (Scheme 3).[7] The first step involves deprotonation of the phosphonate **9** which subsequently undergoes intramolecular Michael addition. The intermediate **10** is not isolated and instead paraformaldehyde is added to the reaction mixture in order to initiate the HWE

reaction. Performing these reactions stepwise with intermediate isolation gave an overall yield of only 42% whereas this TIMO approach affords the α-methylene-γ-butyrolactone product **11** in an improved 77% yield.



Scheme 3: TIMO approach to an α-methylene-γ-butyrolactone

As a representative example from another group, Lallemand *et al.* demonstrated the use of a tandem Diels–Alder/allylation process, a sequence originally developed by Vaultier,[8] in the preparation of **15** (Scheme 4).[9] The [4+2]-cycloaddition of catechol boronic ester **12** and methyl acrylate (**13**) creates the allylating agent **15** *in situ*, which then reacts with the already present aldehyde **14** to furnish the highly functionalised alcohol **16** with complete relative stereocontrol of three chiral centres.



Scheme 4: Lallemand's tandem Diels–Alder/allylation

1.3 Aims

There were two main aims in this research project. First, to develop a one-pot process for the construction of both α,β- and β,γ- unsaturated ketones **17** and **18**, and then to apply this methodology to the synthesis of elaeokanidine A (**19**) (Figure 1). This topic is described in Chapters 2 and 3.

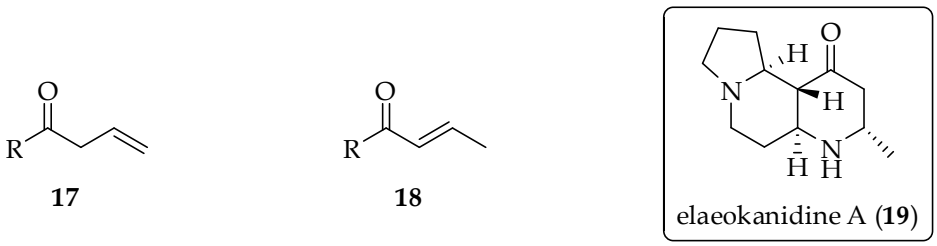


Figure 1: Unsaturated ketones 17 and 18, and elaeokanidine A (19)

The second aim was to extend a copper(II)-catalysed cyclisation methodology to the formation of spirocyclic oxindoles **21** directly from linear precursors **20**, and then showcase this reaction with the synthesis of a natural product, namely spirotryprostatin A (**22**) (Figure 2). This topic is described in Chapters 4 and 5.

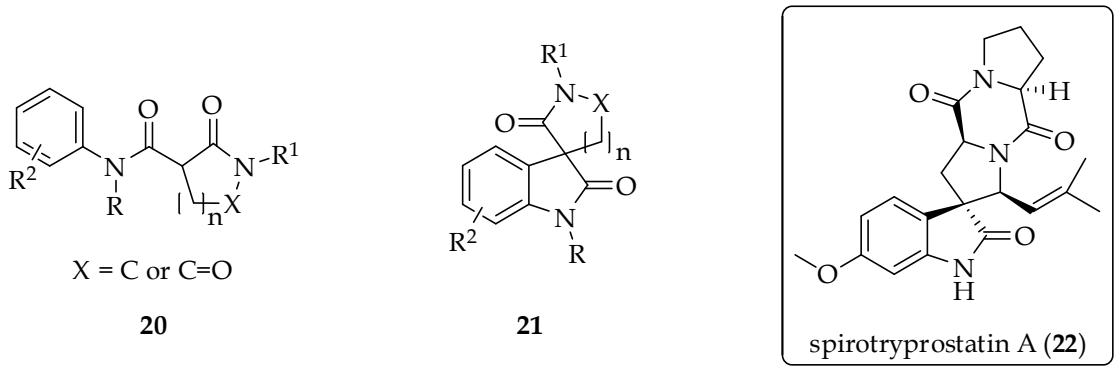


Figure 2: Linear anilides 20, spirocyclic oxindoles 21 and spirotryprostatin A (22)

Chapters 2–5 describe the results in each area, and each Chapter contains a more detailed overview and discussion.

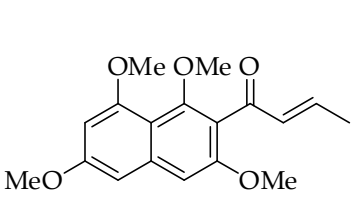
Chapter 2 – New telescoped routes to unsaturated ketones

2.1 Introduction to α,β- and β,γ-unsaturated ketones

2.1.1 Unsaturated ketones in natural products

The α,β-unsaturated ketone motif is widespread in both natural products and synthetic intermediates leading to them. α,β-Unsaturated ketones are frequently responsible for the biological activity of natural products due to their inherent ability to act as a Michael acceptor to nucleophilic amino acid residues.[10]

For example, guieranone A (**23**) is a naphthalene derivative with useful antifungal activity, originally isolated from the leaves of *Guiera senegalensis*.[11] It has recently succumbed to a total synthesis by McCullock *et al.* who utilised an *ortho*-directed metallation process for the installation of the α,β-unsaturated ketone unit in **23**.[12] 9-Oxo-*seco*-ratiferolide-5α-*O*-(2-methylbutyrate) (**24**) is one of several cytotoxic compounds isolated from the plant *Ratibida columnifera* and also exhibits an unsaturated ketone functionality (Figure 3).[13] At present, no synthesis of this compound has been reported.



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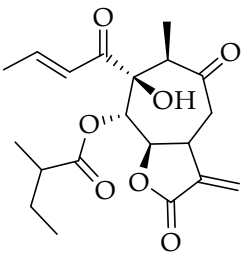

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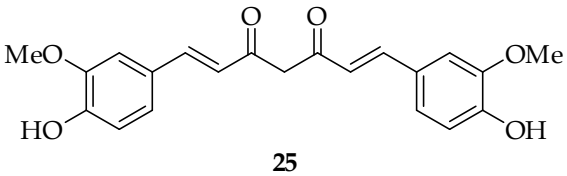

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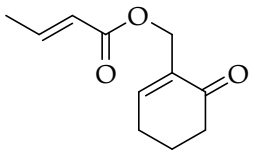
Figure 3: Natural products containing the α,β-unsaturated ketone motif

Curcumin (**25**), a constituent of the spice turmeric, has been shown to exhibit multiple biological responses including anti-oxidant activity, enhancement of wound healing

and anti-cancer effects,[14] presumably due to the presence of the α,β-unsaturated ketone functionality (Figure 3). A number of synthetic derivatives of curcumin containing the enone functionality have shown inhibition of angiogenesis in murine endothelial cells and this has important implications in cancer therapy.[15]

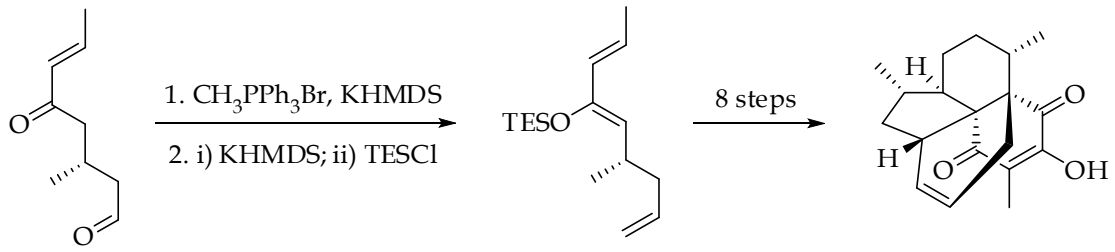
Due to the activity of α,β-unsaturated ketone-containing compounds, this feature can be exploited in synthetic drug molecules. A recent patent by Ganem *et al.* specifies that in their compounds, for example 2-crotonyloxymethylcyclohex-2-enone (**26**), an endocyclic enone was a requirement for anti-tumour activity.[16]



2-Crotonyloxymethylcyclohex-2-enone (**26**)

The structures shown above are just a few examples of the myriad of compounds that display the α,β-unsaturated ketone motif. Nevertheless, many other natural products have been prepared using key intermediates containing the important α,β-unsaturated ketone function and this demands efficient methods for its preparation.[17-20]

For example, Jacobsen *et al.* used enone **27** in their total synthesis of (−)-columbiasin (**29**) as a precursor to diene **28**, which then paved the way for a Diels–Alder reaction. Further chemical transformations gave the natural product **29** in 8 steps from the diene **28** (Scheme 5). [18]

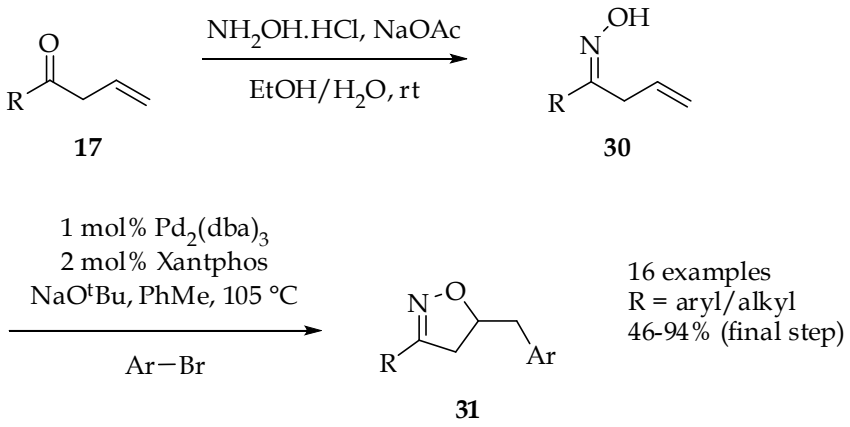


27 **28** (−)-columbiasin (**29**)

Scheme 5: Jacobsen's total synthesis of (−)-columniasin (29) via enone 27

On the other hand, β,γ-unsaturated ketones **17** are rarely seen in natural products,[21-24] due to the facile isomerisation that they can undergo to give the corresponding enones.

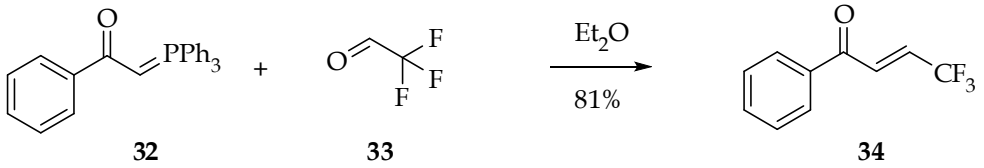
They are, however, interesting structures in their own right, as they can be useful building blocks for other structural motifs.[25,26] For example, Jiang and co-workers used β,γ-unsaturated ketones as a starting point to form isoxazolines **31** *via* oximes **30** by means of a palladium-catalysed cyclisation reaction (Scheme 6).[26]



Scheme 6: Construction of isoxazolines 31 from β,γ-unsaturated ketones 17

2.1.2 Previous methods for making α,β- and β,γ-unsaturated ketones

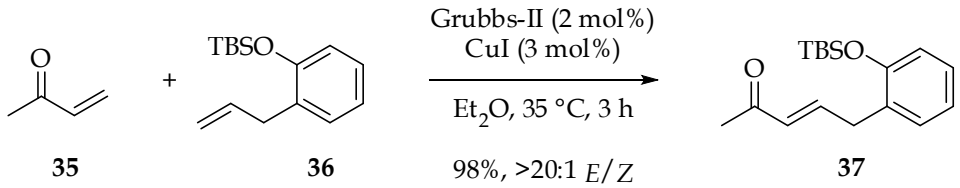
Many of the methods available for the construction of olefins can be applied to the synthesis of α,β-unsaturated ketones. Perhaps one of the most widely used of these is the Wittig reaction, and those related to it, such as the Peterson olefination and the Horner–Wadsworth–Emmons reaction. For examples, Aoyagi and co-workers reacted ylide **32** with trifluroacetaldehyde (**33**) to yield enone **34** in high yield (Scheme 7).[27]



Scheme 7: Formation of enone 34 *via* a Wittig reaction

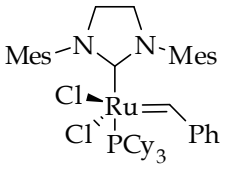
One popular method available for the construction of functionalised olefins is metathesis, a class of reactions for which Grubbs, Schrock and Chauvin shared the 2005 Nobel Prize in Chemistry.[28] There are a number of metal-based catalysts available which can be used for a variety of metathesis reactions including ring-closing metathesis (RCM),[29] enyne metathesis,[30] and ring-opening metathesis polymerisation

(ROMP).[31] For the compounds that we desire, a cross-metathesis is required, with one of the coupling partners already having the enone functionality in place.[32,33] For example, the reaction between methyl vinyl ketone (**35**) and alkene **36** in the presence of Grubbs' second generation catalyst (**38**) to provide functionalised enone **37** (Scheme 8).[34]



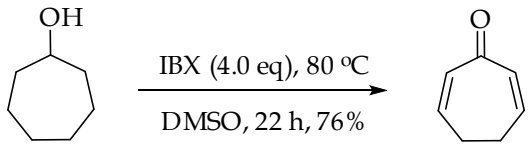
35 **36** **37**

Grubbs-II (**38**):



Scheme 8: **Cross metathesis reaction**

In 2002, Nicolaou *et al*. published a novel procedure utilising 2-iodoxybenzoic acid (IBX) for the one-pot oxidation of alcohols, *e.g.*, **39**, into their corresponding enones *e.g.*, **40** (Scheme 9).[35] Although efficient, the reaction is often not regioselective. Furthermore, the procedure uses DMSO as solvent at elevated temperatures with long reaction times and these are quite harsh conditions which we aimed to avoid.



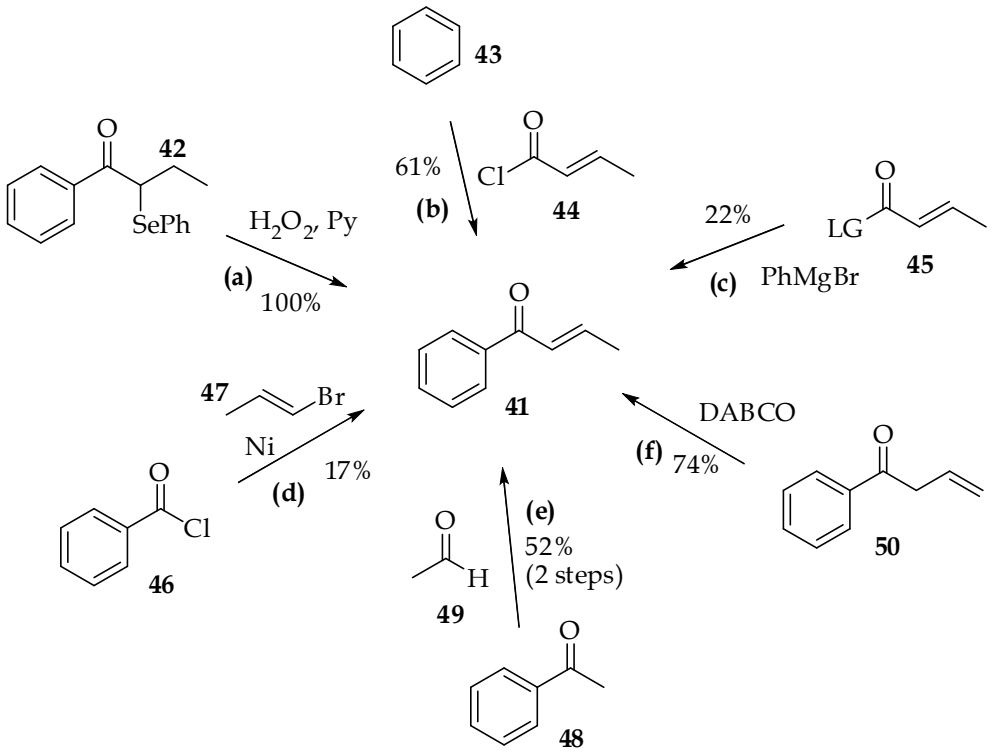
39 **40**

Scheme 9: IBX oxidation of an alcohol to a dienone

Using α,β-unsaturated ketone **41** as an example, Scheme 10 illustrates some of the other methods available for the construction of this system. It is worth noting, however, that each of these approaches poses its own potential difficulties.

As with other olefins, the double bond in α,β-unsaturated ketones can be constructed by elimination of sulfur or selenium-containing compounds such as **42** (**a**),[36] although synthesis of these species themselves may be cumbersome, involving several steps.

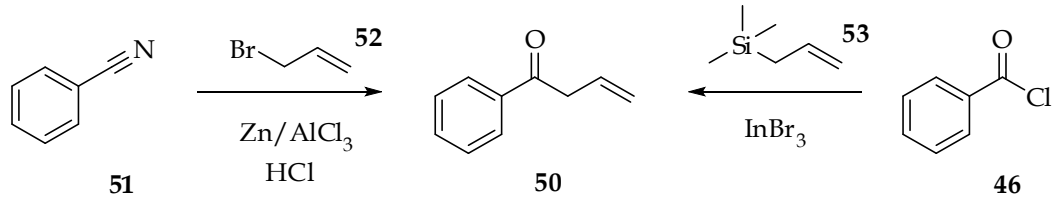
Friedel–Crafts acylation (**b**) with **44** is only suitable for aromatic compounds such as benzene (**43**),[37] and in cases where substituents on the ring are present, regioselectivity issues may occur. The Grignard reaction (**c**) illustrated below,[38] where LG is a leaving group such that the substrate **45** is an ester or acid halide, was shown to yield only 22% of the desired product **41**, whereas the nickel-mediated reaction of **46** with **47** (**d**) gave only 17% yield of enone **41**.[39] The aldol condensation (**e**),[40] which utilises simple starting materials **48** and **49**, is perhaps the most versatile and well established of these reaction processes, but yields are not always satisfactory.



Scheme 10: Current methods for the formation of (*E*)-1-phenylbut-2-en-1-one (41)

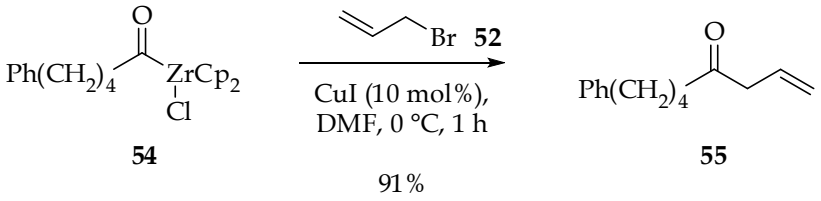
On the other hand, isomerisation of β,γ-unsaturated ketones such as **50** (**f**) can also provide useful entry into the desired class of compound,[41] and we hoped to exploit this method in the development of our own methodology.

Routes to β,γ-unsaturated ketones often involve the manipulation of carboxylic acid-derived compounds, for example the Barbier-type allylation of nitriles such as **51**,[42] or the Hosomi–Sakurai reaction of allyl silanes of type **53** with acid chlorides **46** (Scheme 11).[43]



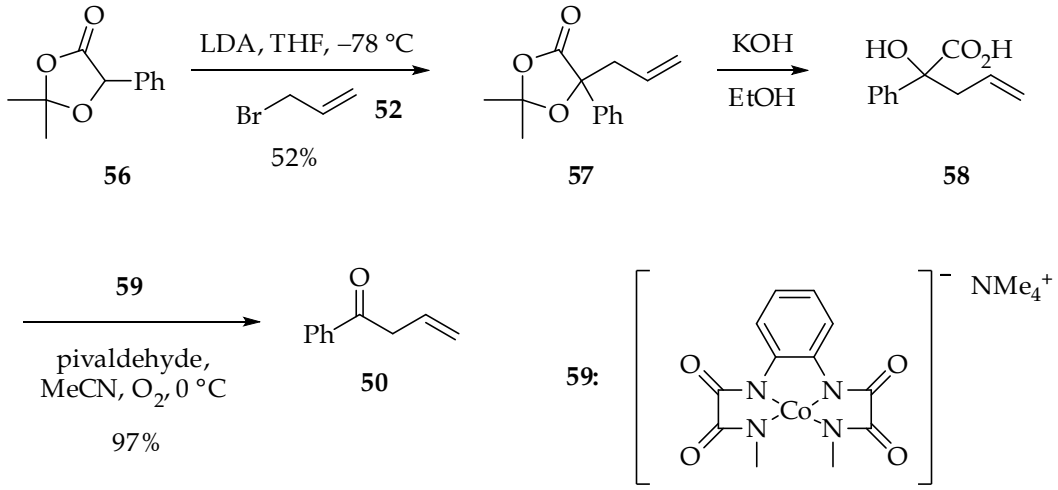
Scheme 11: Barbier allylation and Hosomi–Sakurai reaction

Taguchi and co-workers have used alkene-derived acylzirconocene chlorides, *e.g.*, **54**, as synthons for the acyl anion, for use in a copper(I)-catalysed cross-coupling reaction with allyl bromide (**52**) to form β,γ-unsaturated ketones such as **55** (Scheme 12).[44]



Scheme 12: Copper-catalysed cross-coupling of an acylzirconocene chloride with allyl bromide

In a procedure by Pedro and co-workers, acetal-protected mandelic acid (**56**) was subjected to alkylation with allyl bromide (**52**), followed by hydrolysis and oxidative decarboxylation with cobalt complex **59** to give allylic ketone **50** in good overall yield.[45]



Scheme 13: Alkylation/hydrolysis/decarboxylation route to allylic ketone 50

In contrast to these methods, we wished to use primary alcohols as starting materials. There are precedented routes to β,γ-unsaturated ketones from aldehydes,[46] and primary alcohols using ruthenium-catalysed transfer hydrogenation/diene coupling.[47]

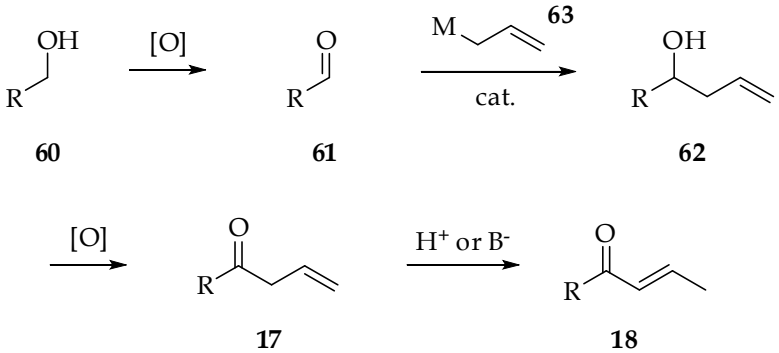
In addition, several groups have used allylations/oxidations in a stepwise fashion from aldehydes or primary alcohols to create β,γ-unsaturated ketones,[26,48,49] whereas we wished to use a one-pot approach.

As shown, several routes to α,β- and β,γ-unsaturated ketones already exist in the literature, but we believed there was still scope for improvement and increased versatility for making these compounds.

2.2 Aims of project I

Having given an overview of currently existing methods for α,β-unsaturated ketone preparation, we believed that the methodology proposed below would give an original starting point from which to construct these enone moieties under milder conditions and potentially improve on existing yields. Indeed, an excellent way to rapidly increase reaction efficiency and molecular complexity is to combine several discrete steps into a single one-pot process.

Therefore, the vision for this project was to develop a methodology for a novel one-pot oxidation/allylation/oxidation/isomerisation procedure, in order to provide a new scheme for the facile construction of β,γ- and α,β-unsaturated ketones **17** and **18** (Scheme 14).



Scheme 14: Proposed one-pot oxidation/allylation/oxidation/isomerisation process

Oxidation of a primary alcohol **60** to aldehyde **61** provides the substrate for allylation. The resulting allylic alcohol **62** could then be further oxidised *in situ* to β,γ-unsaturated

ketone **17** which under acidic or basic conditions should isomerise to the conjugated enone **18**.

Of the two types of one-pot procedures, tandem processes are practically easier to carry out than sequential reactions as the need for monitoring the reaction is reduced. We therefore hoped to be able to use a tandem process for this methodology.

In order to ensure success in developing such a process which is both practical and reliable, the reagents and reaction conditions for each step must be chosen with great care, and a selection of the most widely used of these processes, along with a brief optimisation of each individual step, is next described.

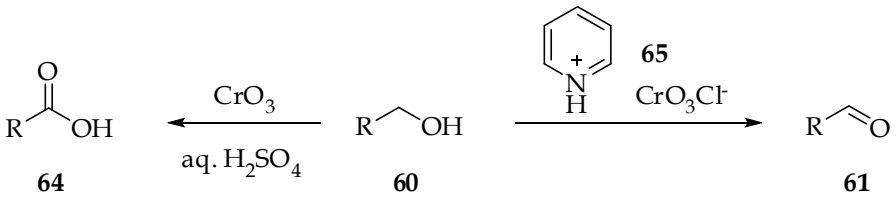
2.3 Optimisation of steps

2.3.1 Primary alcohol oxidation

2.3.1.1 Available methods

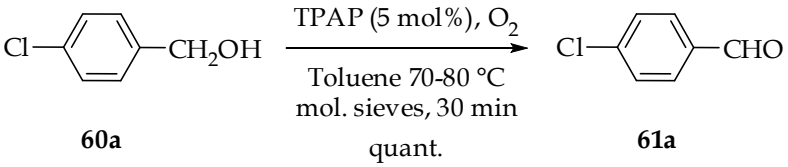
Of the four processes we aim to combine, two of these are oxidation. A wide variety of oxidising agents for a range of purposes are available to the synthetic chemist.[50] For the oxidation of alcohols to aldehydes or ketones, transition metal reagents in high oxidation states are frequently employed.

Manganese dioxide has seen extensive use previously in the Taylor group for the oxidation of alcohols **60** to aldehydes **61**, as illustrated earlier in Scheme 2.[3] Chromates, such as pyridinium dichromate (PDC) and pyridinium chlorochromate (**65**, PCC), are also widely used for alcohol oxidation, partially due to their ease of handling, however, they have the disadvantage of being carcinogenic. The Jones reagent can also be used but is significantly more reactive and will fully oxidise primary alcohols **60** directly to carboxylic acids **64** (Scheme 15).



Scheme 15: Chromate oxidations

Using catalytic TPAP under an oxygen atmosphere, *p*-chlorobenzyl alcohol (**60a**) can be oxidised to aldehyde **61a** in quantitative yield (Scheme 16).[51] Ley *et al*. have since reported room temperature variants whereby this type of reaction can be run using either NMO or oxygen as co-oxidant.[52,53]



Scheme 16: TPAP oxidation of *p*-chlorobenzyl alcohol

A number of oxidising agents which are not metal-based have also been developed. Of these, perhaps the most commonly used is Dess–Martin periodinane (DMP, **66**),[54] and its variant IBX (**67**),[55] both based on hypervalent iodine (Figure 4). These compounds both contain an iodine atom in a +5 oxidation state, which is reduced to I(III) during alcohol oxidation.

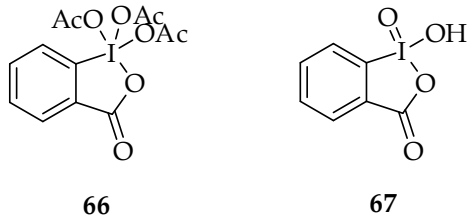


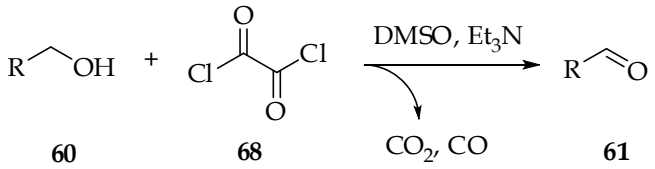
Figure 4: Dess–Martin periodinane and IBX

TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) can be used catalytically as a mild oxidant for transforming primary and secondary alcohols into their respective aldehydes and ketones, with a variety of secondary oxidants available.[56-58]

Another set of oxidising agents which avoid the use of metals are based on the reduction of DMSO to dimethyl sulfide with concomitant alcohol oxidation. A number

of variants on this method exist, dependant on the reagent used for activation of DMSO: The Pfitzner–Moffatt (DCC),[59] Parikh–Doering (SO_3·py),[60] Albright–Goldman (Ac_2O),[61] and Onodera (P_2O_5) oxidations to name a few.[62]

Of these DMSO-containing methods, one of the most commonly used is the Swern oxidation which utilises oxalyl chloride (**68**) for activation.[63] The driving force for the Swern oxidation is release of CO_2 and CO (Scheme 17).[64]



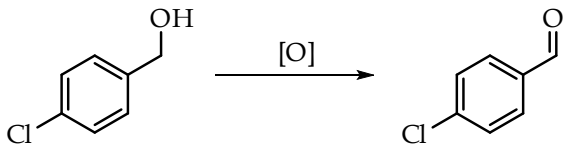
Scheme 17: Swern oxidation

Whilst well documented, the Swern and related oxidations are not always practical for one-pot synthesis due to their multistep and multicomponent procedures as well as use of DMSO, the removal of which can be problematic. Simple reagents such as DMP, MnO_2 or PCC would offer a better alternative for our methodology.

2.3.1.2 Results

As a test substrate for optimisation of the individual steps in the tandem sequence, the commercially available compound *p*-chlorobenzyl alcohol (**60a**) was chosen, and the oxidation was examined first. Of the various oxidising systems tested, including TPAP with O_2 (Table 1, entries 1 and 2),[53] or NMO as re-oxidant (entry 3),[52] and Markó's copper system (entry 4),[65] MnO_2 and DMP were found to be the most effective for this substrate (entries 5–7), with the reactions proceeding well in both acetonitrile and dichloromethane to give quantitative conversions.[66] Although no starting material was observed using PCC (entry 8), mass recovery was much lower than that seen with MnO_2 or DMP. Therefore, at this point, MnO_2 or DMP seemed the optimal choice for the tandem methodology.

Table 1: Conditions for oxidation to 4-chlorobenzaldehyde (61a)



60a **61a**

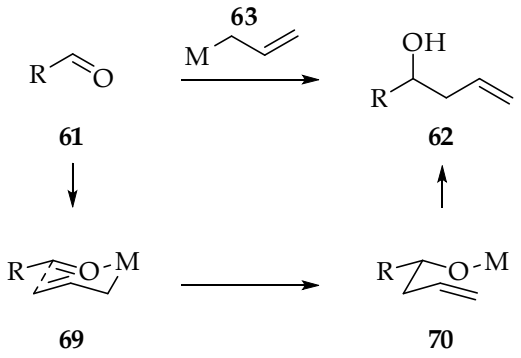
Entry	Oxidant	Solvent	Conversion to 61a (%)[c]
1	$TPAP/O_2$	CH_2Cl_2[b]	75
2	$TPAP/O_2$	10% MeCN in CH_2Cl_2[b]	96
3	TPAP/NMO	CH_2Cl_2	92
4	$CuCl/phen/O_2$[a]	Fluorobenzene	33
5	MnO_2	MeCN	100
6	DMP	MeCN	100
7	DMP	CH_2Cl_2	100
8	PCC	CH_2Cl_2	100

[a]Reaction also requires the addition of di-*t*-butyl azodicarboxylate (DBAD) and *N*-methylimidazole (NMI); [b]4Å mol. sieves added to the reaction mixture; [c]Quoted conversions are based on ^1H NMR spectra of the unpurified reaction mixture, relative to unreacted starting material

2.3.2 Allylation

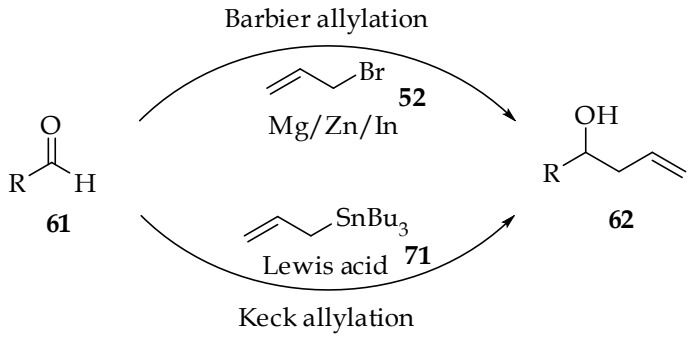
2.3.2.1 Available methods

The individual allylation reaction was studied next. Allylation reactions, as the name suggests, involve addition of an allyl group to an electrophilic centre. We were interested in the allylation of carbonyl compounds of type **61** to form a homoallylic alcohol **62**. The reaction is believed to proceed *via* a 6-membered chair transition state **69**, as depicted in Scheme 18,[67] and its modifications generally depend on the type of allylating agent **63** employed.



Scheme 18: Allylation reaction proceeding *via* a cyclic transition state

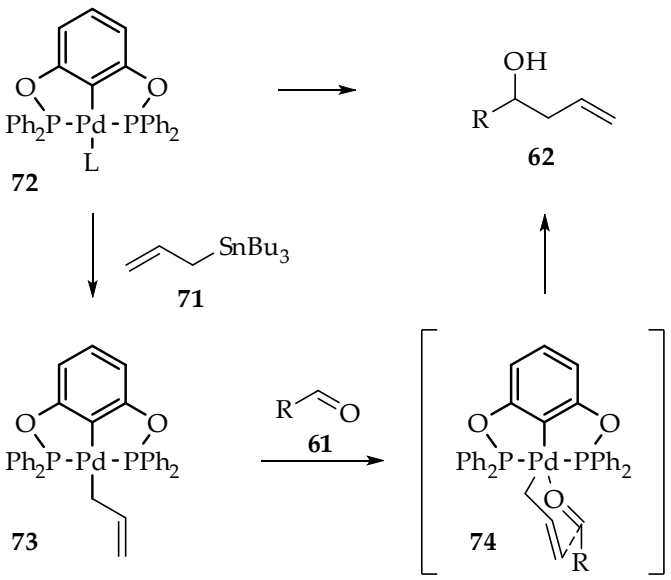
For example, the Barbier allylation utilises allyl bromide (**52**) and a metal such as magnesium, zinc or indium to form a Grignard-type reagent *in situ*.[68] By contrast, the Keck allylation uses allyltributyltin (**71**) as the source of allyl functionality and a Lewis acid for aldehyde activation (Scheme 19).[69]



Scheme 19: Barbier and Keck allylations

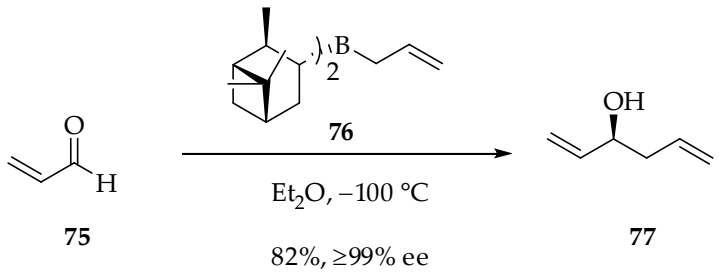
In 2004, Solin demonstrated the use of a palladium pincer-type catalyst **72** in conjunction with allyltributyltin (**71**) to perform allylation reactions *via* η^1−allyl-

palladium intermediate **73** (Scheme 14).[70] More specifically, intermediate **73** is first generated by means of transmetallation with stannane **71.** Coordination of aldehyde **61** then results in allylation *via* transition state **74** and, following ligand exchange, affords homoallylic alcohol **62**.



Scheme 14. Allylation using Solin's pincer catalyst

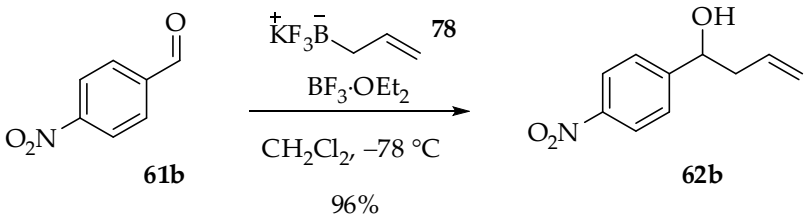
Owing to the cyclic nature of the transition state through which these allylic reactions are believed to proceed, an array of both diastereo- and enantioselective variants of this reaction process have been developed.[71] As an example, Brown allylation uses a chiral allylborane **76** which exploits the chirality of the allylating agent to control the stereochemistry of the resulting alcohol **77** (Scheme 16).[72]



Scheme 16. Asymmetric brown allylation of acrolein (75)

An alternative allyl source is potassium allyltrifluoroborate (**78**), synthesized by Batey *et al.* in 1999.[73] In combination with a Lewis acid, most aldehydes were shown to undergo allylation under very mild conditions.

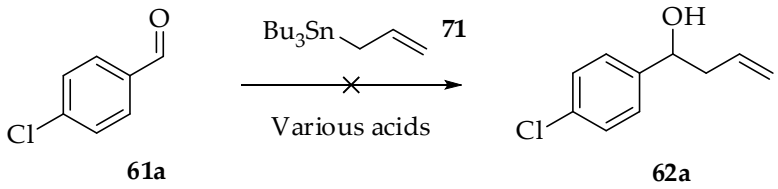
For example, 4-nitrobenzaldehyde (**61b**) underwent an efficient allylation in the presence of potassium allyltrifluoroborate, with boron trifluoride diethyl etherate as Lewis acid, affording homoallylic alcohol **62b** in 96% yield (Scheme 15).[73] Room temperature variants have also been described, along with the use of montmorillonite K10 clay as an alternative Lewis acid.[74]



Scheme 15. Allylation of 4-nitrobenzaldehyde (61b) using Batey's potassium allyltrifluoroborate salt 78

In our methodology we aim to use a procedure which is both mild and facile. Use of allyltributyl tin (**71**) or potassium allyltrifluoroborate (**78**) in combination with a Lewis acid would seem the sensible choice.

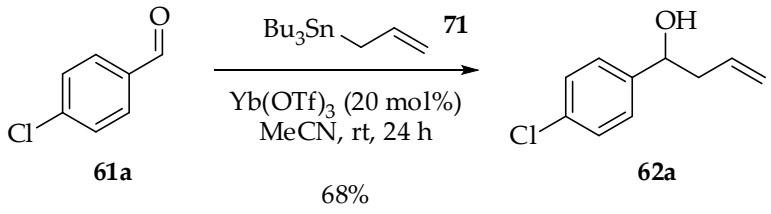
Initial studies in the group showed that in the allylation reaction of aldehyde **61a** with allyltributyltin (**71**), a number of Brønsted and Lewis acids were found to be inefficient, with scandium triflate, *p*-nitrobenzoic acid, maleic acid and magnesium bromide all failing to promote the desired reaction to allylic alcohol **62a** (Scheme 20).[66]



Scheme 20: Failed allylation reactions

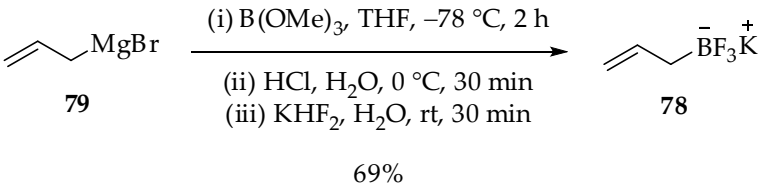
2.3.2.2 Results

Pleasingly, allylation of **61a** using catalytic amounts of ytterbium triflate with stannane **71** was successful,[75] giving a 68% yield of alcohol **62a** following overnight reaction. (Scheme 21).



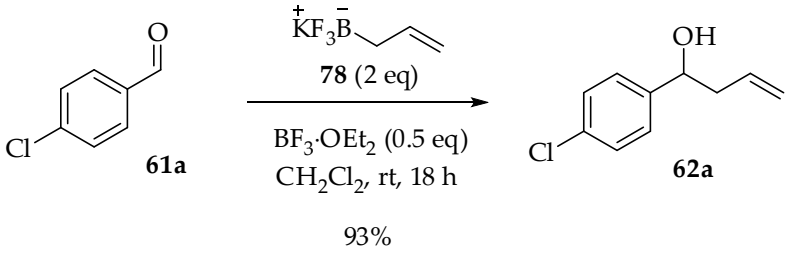
Scheme 21: Ytterbium triflate–catalysed allylation of *p*-chlorobenzaldehyde

We also wished to investigate the utility of potassium allyltrifluoroborate (**78**) for the methodology. Batey *et al*. have demonstrated the use of potassium allyl- and crotyltrifluoroborate salts in a number of allylation and crotylation reactions.[73] Potassium allyltrifluoroborate (**78**) was prepared according to Batey's procedure by reacting allylmagnesium bromide (**79**) with trimethyl borate followed by acidic hydrolysis.[76] The resultant boronic acid was converted into the corresponding trifluoroborate salt using potassium bifluoride to give an overall yield of 69% (lit.[73] yield 76%) (Scheme 22).



Scheme 22: Synthesis of potassium allyltrifluoroborate (78)

Potassium allyltrifluoroborate (**78**) was shown to perform well in the allylation reaction of **61a** with $BF_3{\cdot}OEt_2$ catalysis, giving an excellent yield of product **62a** following overnight reaction (Scheme 23).[76]

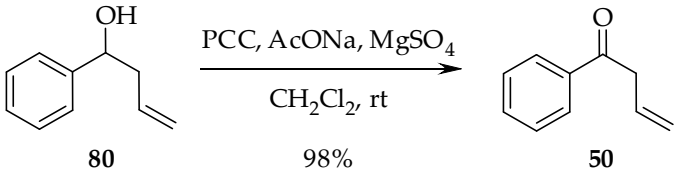


Scheme 23: Allylation with potassium allyltrifluoroborate

2.3.3 Secondary alcohol oxidation

2.3.3.1 Available methods

The next step in our model tandem sequence would be oxidation of alcohol **62a** to ketone **17a**. Generally, most of the oxidising agents used for primary alcohol oxidation (*vide supra*, Chapter 2.3.1) can also be applied to the oxidation of secondary alcohols to ketones, such as the DMSO-based procedures, hypervalent iodine compounds and chromate compounds. For example, using PCC in CH_2Cl_2 at room temperature, it was reported that allylic alcohol **80** was converted into the corresponding ketone **50** in 98% yield without alkene isomerisation (Scheme 24).[77]



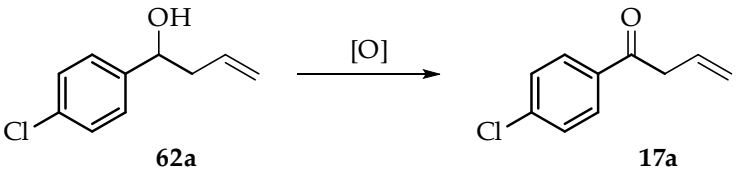
Scheme 24: PCC oxidation of an allylic alcohol

2.3.3.2 Results

With alcohol **62a** in hand, oxidation to ketone **17a** was next explored (Table 2). Ideally, for a one-pot procedure, we wished to be able to use the same reagent for oxidation of both the primary alcohol **60** and the secondary alcohol **62**. Surprisingly, manganese dioxide (entry 1) was unsuccessful in the oxidation of **62a**, as was TPAP (entry 2), with no trace of desired product **17a** observed. Only Dess–Martin periodinane (entries 3 and 4) and pyridinium chlorochromate (entry 5) were capable of oxidising allyl alcohol **62a** to the corresponding ketone, although the latter provided a poor mass recovery. Thus,

we concluded that Dess–Martin periodinane was the best oxidising agent for this methodology.

Table 2: Conditions for oxidation to 17a



62a **17a**

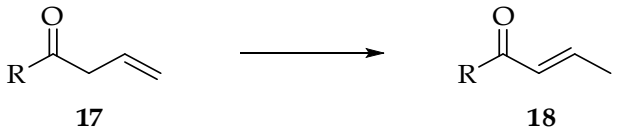
Entry	Oxidant	Solvent	Yield (%)[a]	Conversion (%)[b]
1	MnO_2	MeCN	0	0
2	TPAP/O_2	CH_2Cl_2[c]	0	0
3	DMP	MeCN	98	100
4	DMP	CH_2Cl_2	NI[d]	100
5	PCC	CH_2Cl_2	40	100

[a]Isolated yields; [b]Quoted conversions are based on ^{1}H NMR spectra of the unpurified reaction mixture; [c]4Å mol. sieves added to the reaction mixture; [d]NI = not isolated

2.3.4 Isomerisation

2.3.4.1 Available methods

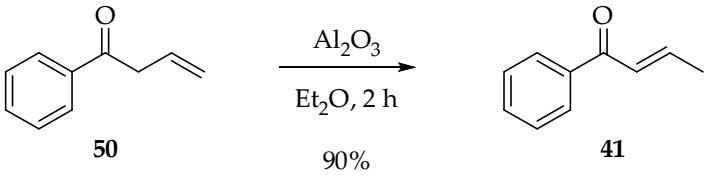
Following oxidation to β,γ-unsaturated ketone **17**, the final step in the proposed one-pot sequence is isomerisation of ketone **17** to conjugated ketone **18** (Scheme 25).



17 **18**

Scheme 25: Isomerisation to the conjugated ketone

This type of isomerisation is known to be effected with the use of acids such as TsOH,[78] and HCl,[79] or with bases such as DBU,[80] and DABCO.[41] There is even literature precedent for using neutral media such as alumina to effect the desired isomerisation (Scheme 26).[81,82]

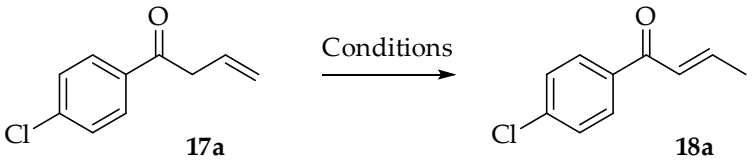


Scheme 26: Aluminium oxide isomerisation

2.3.4.2 Results

Initially, we investigated different reagents and conditions for the isomerisation of **17a** to **18a** (Table 3). Following migration of the double bond, a distinct change in the NMR signals of the compounds can be observed. The alkene peaks, previously a ddt at 6.06 ppm and a pair of dq at 5.21 and 5.25 ppm in **17a**, are shifted downfield and are now two doublets of quartets at 6.86 and 7.08 ppm, each integrating at 1H. The doublet of triplets at 3.73 ppm previously seen for the α-CH_2 in **17a** is no longer present, and instead a doublet of doublets at 2.00 ppm is seen for the terminal methyl group of **18a**, much further upfield.

Table 3: Attempted isomerisations of 17a to 18a



Entry	Reagent	Solvent	Estimated yield (%)[a]
1	Al_2O_3	Et_2O	73[b]
2	Al_2O_3	CH_2Cl_2	90
3	Oxalic acid, $BF_3.OEt_2$	CH_2Cl_2	Complex mixture
4	DBU	Et_2O	96
5	DABCO	IPA	81

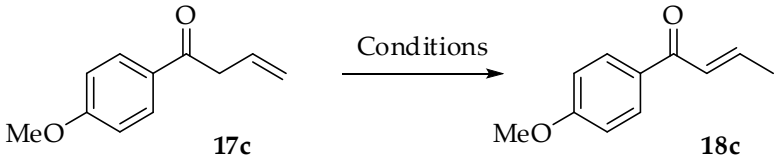
[a]Based on mass recovery and ^1H NMR analysis of the unpurified reaction mixture; [b]Purified yield

As anticipated from the literature precedent, stirring **17a** in diethyl ether in the presence of alumina resulted in a reasonable yield of enone **18a** (entry 1), whereas

reaction in CH_2Cl_2 resulted in high mass recovery with a small amount of an unidentified impurity (entry 2), which was encouraging for potential later incorporation into a one-pot process. On the other hand, oxalic acid,[80] whether used stoichiometrically or catalytically in the presence of $BF_3{\cdot}OEt_2$ gave a complex mixture of products and the desired enone could not be identified (entry 3). Catalytic DBU (entry 4),[80] and DABCO were both shown to perform the desired isomerisation (entry 5),[41] giving high mass recovery with only trace impurities.

We also investigated the use of other reagents in the isomerisation of **17c** to provide enone **18c** (Table 4). Under basic conditions with sodium hydroxide (entry 1), or acidic (HCl) conditions (entry 2), a complex mixture of products was observed by TLC and NMR spectroscopic analysis. Testing previously successful conditions, DABCO and DBU both resulted in full conversion to **18c,** with high mass recovery and only minor impurities (entries 3 and 4). Isomerisation with alumina was also successful, although in this case, the *E*-isomer of **18c** was not exclusively formed (entry 5).

Table 4: Attempted isomerisations of 17c to 18c



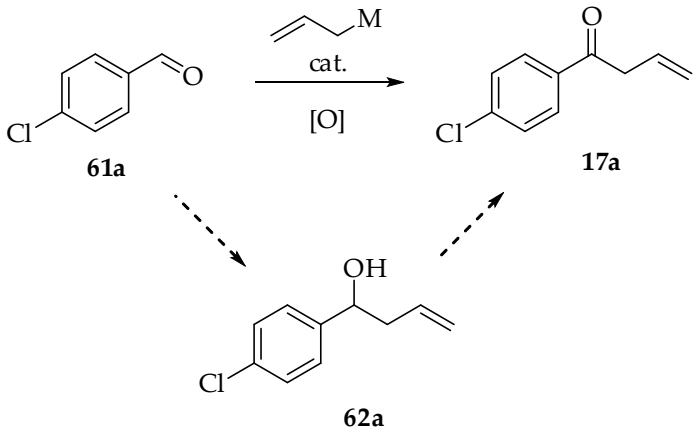
17c **18c**

Entry	Reagent	Solvent	Estimated yield (%)[a]
1	NaOH	THF	Complex mixture
2	HCl	THF	Complex mixture
3	DABCO	IPA	93
4	DBU	Et_2O	98
5	Al_2O_3	Et_2O	70 (95:5 *E*:*Z*)

[a]Based on mass recovery and ^{1}H NMR analysis of the unpurified reaction mixture

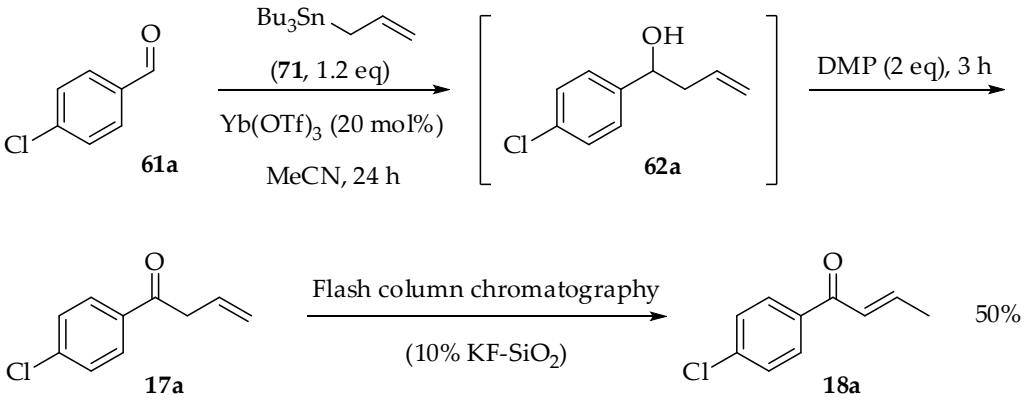
2.4 Tandem allylation/oxidation

Having investigated the individual steps of our proposed methodology, we now wished to combine these into a one-pot process. Initially, our aim was to effect a tandem allylation/oxidation reaction from *p*-chlorobenzaldehyde (**61a**) to generate the allyl ketone **17a** (Scheme 21). By choosing to not yet involve the primary alcohol oxidation, this would allow easier analysis of the reaction progress.



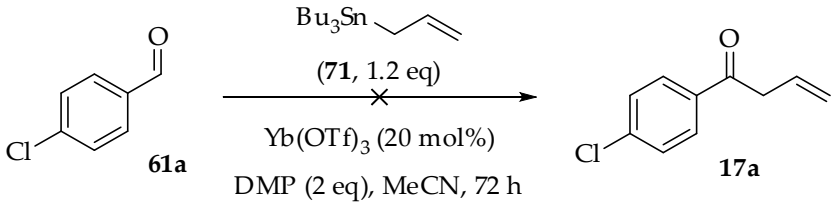
Scheme 21. Tandem allylation/oxidation

From previous investigations, it seemed that Dess–Martin periodinane (**66**) was the most preferable oxidant for this methodology. In an initial attempt at a sequential reaction using stannane **71** in the presence of ytterbium triflate for the allylation, followed by DMP oxidation, pleasingly ketone **17a** was successfully obtained with full conversion by TLC and NMR spectroscopy (Scheme 27). Interestingly, however, following column chromatography, using 10% KF-SiO_2 to aid removal of the tin residues,[83] the only observable product was enone **18a**, obtained in a 50% isolated yield over the complete process.



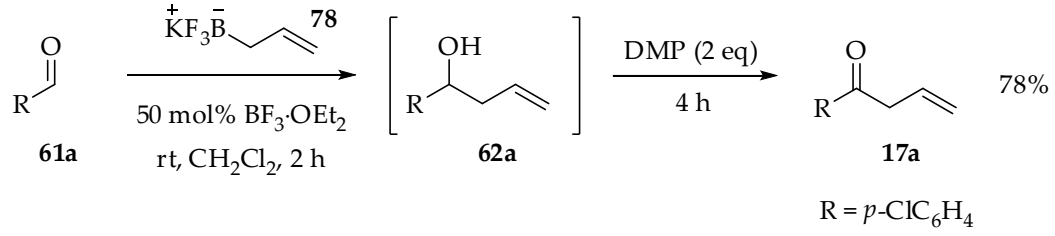
Scheme 27: Sequential allylation/oxidation reaction with stannane 71

Disappointingly, when these conditions were applied to a tandem process, whereby DMP was added to the reaction mixture at the start, predominantly starting material was seen after 72 h, possibly resulting from the stannane being oxidised before having a chance to react with the aldehyde in the slow allylation reaction (Scheme 23). Promotion of the allylation reaction with benzoic acid, as demonstrated by Aspinall,[84] also failed.



Scheme 23. Failed attempt at a tandem allylation/oxidation reaction with stannane 71

Attention then turned to the potassium allyltrifluoroborate (**78**) allylation. A sequential reaction using literature conditions for the allylation,[76] followed by 2 equivalents of DMP worked well to give ketone **17a** with full conversion, and a 78% yield following purification (Scheme 28).

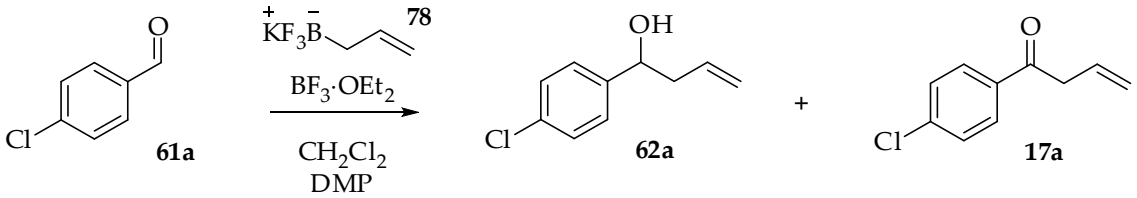


Scheme 28: Sequential allylation/oxidation with potassium allyltrifluoroborate (78)

In addition to the higher yield observed in the sequential reaction, the absence of tin by-products which can be difficult to remove, along with shorter reaction times, made **78** a superior allyl source to **71** for this methodology. Also, ketone **17a** was obtained without double bond isomerisation due to the simplified purification procedure.

These conditions were subsequently applied to the tandem process, and in this case, a 13:2 mixture of ketone:aldehyde was obtained (Table 5, entry 1). When the amount of allyl source **78** was increased, large quantities of alcohol were seen remaining (entries 2 and 3). Given these results, it was hypothesised that excess potassium allyltrifluoroborate (**78**) was being oxidised by DMP. This would reduce the amount of oxidant present and result in recovered alcohol (**62a**). To counter this, the ratios of potassium allyltrifluoroborate to $BF_3{\cdot}OEt_2$ were modified as an alternative method for increasing the rate of allylation (entries 4 and 5). Although almost full consumption of both aldehyde **61a** and alcohol **62a** were now seen, the super-stoichoimetric $BF_3{\cdot}OEt_2$ appeared to cause problematic side-products which could not be identified nor removed by chromatography. Attempts at instead altering the quantity of oxidant gave complex mixtures of intermediates and so this was not investigated any further.

Table 5: Conditions for tandem allylation/oxidation of aldehyde 61a to ketone 17a[a]



Entry	Eq. of 78	Eq. of $BF_3{\cdot}OEt_2$	61a : 62a : 17a[b]	Yield of 17a[b,c]
1	2	0.5	2 : 0 : 13	87
2	5	0.5	0 : 7 : 100	7
3	2.5	0.5	0 : 5 : 3	38
4	2	1	1 : 0 : 100	84[d]
5	1.5	1.5	3 : 0 : 100	81[d]

[a]Reagents were added to one pot with 2 eq of DMP in CH_2Cl_2 and stirred at rt for 18 h before work-up; [b]Based on ^1H NMR analysis of the unpurified reaction mixture; [c]Estimated percentage yield; [d]Impurities could not be removed by column chromatography

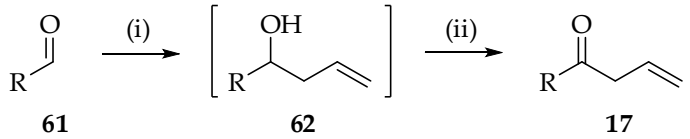
Due to the apparent sensitivity in the quantities of reagents added, and the problems this may cause with other substrates, it was decided to abandon work on the tandem reaction approach and concentrate on optimising the sequential reaction and incorporating the double bond migration.

2.5 Sequential allylation/oxidation

Focussing now on a sequential allylation/oxidation process, it was discovered that even with as little as 1.05 eq. of potassium allyltrifluoroborate (**78**) and 0.5 eq. of $BF_3{\cdot}OEt_2$, the allylation still went to completion within 5 minutes. The quantity of Dess–Martin periodinane used could also be reduced without significant effect on the conversion time. Adding 1.2 eq. of DMP in a sequential manner and stirring for a further hour followed by standard aqueous work-up gave the ketone **17a** in near quantitative yield, with purity as indicated by NMR spectroscopic analysis judged to be sufficient enough that column chromatography was not required. These conditions were then applied to a number of substrates, with results shown in Table 6.

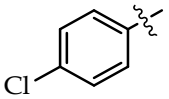
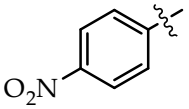
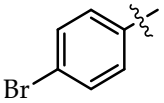
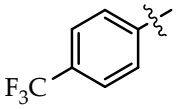
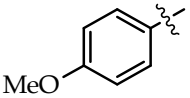
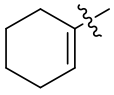
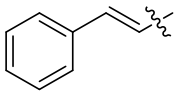
Good results were seen with the electron-withdrawing chloro-, bromo- and nitro-substrates (entries 1–3), and a moderate yield was observed with trifluoromethyl substrate **61e**. This lower yield could be attributed to the reported instability of ketone **17e**.[48] However, the same was not the case for substrates with electron-donating groups. These less electrophilic aldehydes seemed not to tolerate the addition of 0.5 eq. $BF_3{\cdot}OEt_2$ (Entries 4–8); immediate degradation of starting material was observed in these cases. Reduction to 20 mol% $BF_3{\cdot}OEt_2$ was shown to prevent degradation to an extent and some product was observed, but even with 1.5 eq. of potassium allyltrifluoroborate (**78**) the allylation did not go to completion. An alternative procedure for these substrates would therefore be required.

Table 6: Results of allylation/oxidation from aldehydes 61



61 **62** **17**

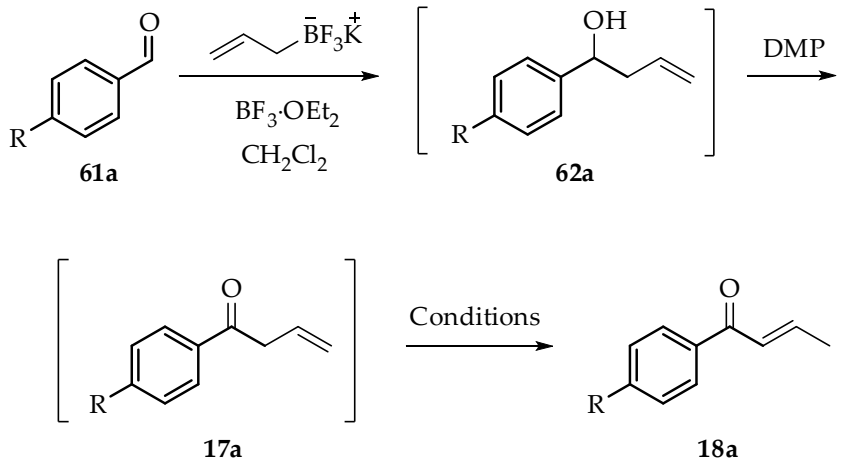
Reagents and conditions: i) Potassium allyltrifluoroborate (**78,** 1.05 eq), $BF_3{\cdot}OEt_2$ (0.5 eq), CH_2Cl_2, rt, 10 min; *ii)* DMP (2 eq), rt, 1 h

Entry	R		Yield of 17 (%)[a]
1		**17a**	97
2		**17b**	Quantitative
3		**17d**	Quantitative
4		**17e**	65[b]
5		**17c**	0
6		**17f**	0
7		**17g**	0
8		**17h**	0

[a]β,γ-unsaturated ketones required no further purification; [b]Purity approx. 85% by ^1H NMR analysis

2.6 Allylation/oxidation/isomerisation

We now wished to try to incorporate the isomerisation into the one-pot sequence to directly obtain the conjugated enone **18** (Scheme 29). Unfortunately, any attempts to incorporate previous isomerisation methods into the one-pot process by adding reagents to the reaction mixture following final oxidation, resulted in either no reaction or a complex mixture of products. Trying to perform isomerisation reactions on isolated but unpurified products, in a *pseudo*-sequential process, proved to be capricious; if the substrate had not been subjected to chromatography then yields were severely reduced. This suggests that the products of the $BF_3{\cdot}OEt_2$ allylation/oxidation reaction were not as pure as analysis had originally indicated, but that a residual impurity was the cause of the loss in efficiency of the isomerisation reaction.

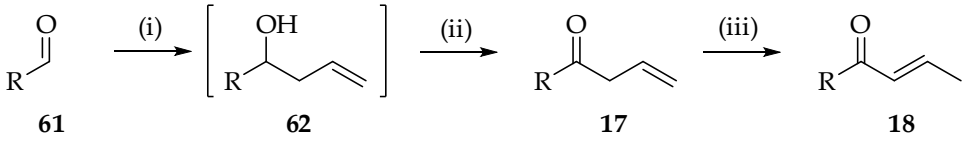


Scheme 29: Attempted incorporation of the isomerisation into a sequential reaction

This prompted us to consider other isomerisation methods which might be more amenable to a one-pot reaction. It was thought that addition of excess $BF_3{\cdot}OEt_2$ at the end of the sequential reaction might generate the isomerised product (**18a**) as desired. Although this was the case, a number of other unknown products were observed and the desired product was not easy to isolate. Addition of water at the end of the sequential reaction showed no isomerisation, and only served to hydrolyse the excess Dess–Martin periodinane present. In a publication by Curran it was suggested that similar isomerisation reactions can be performed with silica.[85] In our hands, however, column chromatography generally resulted in only a small amount of conversion and no significant amount of isomerised product was observed by stirring with SiO_2.

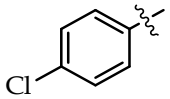
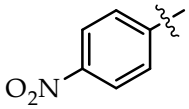
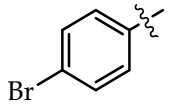
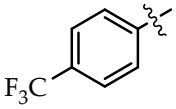
When allyltributyltin (**71**) had been used previously for the allylation, the subsequently formed ketone was purified by column chromatography using 10% w/w of finely ground KF and 90% w/w silica (KF-SiO_2) in order to aid removal of the tin residues.[83] Partial or total isomerisation of the ketone was often observed in this process and it was thought that this was due to the KF-SiO_2 itself. An attempt to incorporate this into the sequential reaction by adding KF-SiO_2 to the unpurified reaction mixture again showed no isomerisation. When the β,γ-unsaturated ketone **17a** was instead isolated after the allylation/oxidation sequence then re-dissolved in solvent, the attempted isomerisation was found to be capricious. Several attempts were made but varying degrees of isomerisation to the conjugated ketone **18a** were observed and a close-running impurity frequently appeared. If the KF-SiO_2 mixture was not freshly made, the resultant reaction mixture frequently appeared to contain more impurities.

Table 7: Results of allylation/oxidation and allylation/oxidation/isomerisation from aldehydes 61



61 **62** **17** **18**

Reagents and conditions: i) Potassium allyltrifluoroborate (**78**), $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 10 min; *ii)* DMP, rt, 1 h; *iii)* Column chromatography on KF-SiO_2

Entry	R		Yield of 17 (%)[a]		Yield of 18 (%)[c]
1		**17a**	97	**18a**	38
2		**17b**	Quantitative	**18b**	23
3		**17d**	Quantitative	**18d**	40
4		**17e**	65[b]	**18e**	0

[a]Isolated yields, β,γ-unsaturated ketones required no further purification; [b]Purity approx. 85% by ^1H NMR analysis; [c]Purified yields

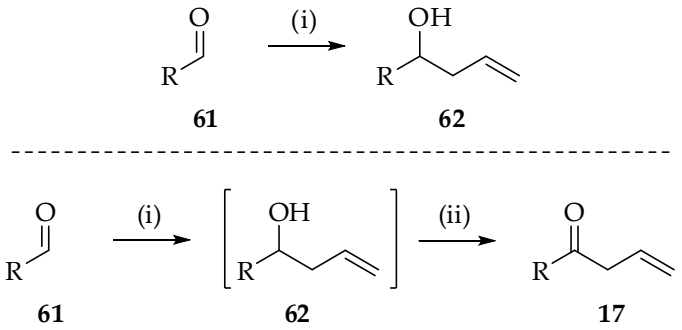
In order to obtain pure samples of the α,β-unsaturated ketones, the respective previously prepared β,γ-unsaturated ketones were subjected to column chromatography using freshly prepared KF-SiO_2. A number of examples are shown in Table 7 but unfortunately, yields are disappointing, and in the case of with trifluoromethyl substrate **17e**, no product or starting material were observed following chromatography, potentially due to the instability of these compounds.[48]

2.7 Alternative allylation

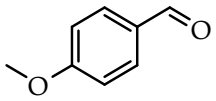
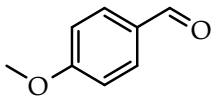
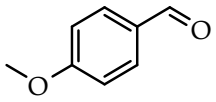
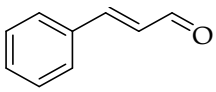
Given the incompatibility observed with several of the substrates under $BF_3{\cdot}OEt_2$ allylation conditions, we next sought to tackle this problem. At this time, Batey *et al*. had recently published a report on the use of montmorillonite K10 in allylation and crotylation reactions.[74] Montmorillonite K10 is an acidic clay catalyst, the use of which has precedent in a number of microwave reactions including the synthesis of bismaleimides and bisphthalimides.[86] The efficacy of this catalyst in place of $BF_3{\cdot}OEt_2$ for less activated aldehydes was subsequently investigated.

Individual allylation reactions were performed on a number of substrates, followed by a sequential allylation/oxidation, results of which are summarised in Table 8. The literature procedure uses 20:1 CH_2Cl_2:H_2O as the solvent,[74] however, in the allylation/oxidation process being investigated the use of water is detrimental as it causes hydrolysis of the Dess–Martin periodinane, such that even after stirring overnight with excess DMP (3 eq), full conversion was not seen (entry 1). The allylation reaction was run under anhydrous conditions but in the absence of water, the reaction failed to go to completion (entry 2).

Table 8: Results of allylations and allylation/oxidations using montmorillonite K10



Reagents and conditions: *i)* Potassium allyltrifluoroborate (**78**, 1.2 eq), montmorillonite K10, AcOH (11 eq), CH_2Cl_2, rt, 15 min; *ii)* DMP (1.8 eq), rt, 1 h

Entry	Substrate	Solvent system	Yield of 62 (%)[a]	Yield of 17 (%)[a]
1		CH_2Cl_2 H_2O	Not run	77[b] **(17c)** (+21% of **62c**) [b,c]
2		CH_2Cl_2	36[b] **(62c)**	Not run
3		CH_2Cl_2 AcOH	85	80
4		CH_2Cl_2 AcOH	92 **(62h)**	57 **(17h)**

[a]Isolated yield; [b]Based on ^{1}H NMR analysis of the unpurified reaction mixture; [c]3 eq. of DMP used

As an alternative proton source, acetic acid was tested in the allylation. Acetic acid is a by-product of the DMP oxidation and so it could be assumed that its presence would not cause problems in this step of the reaction. Satisfyingly, allylation of anisaldehyde in the presence of acetic acid (11 eq.) proceeded smoothly, and in combination with the DMP oxidation gave 80% of β,γ-unsaturated ketone after purification by flash column chromatography (entry 3). Cinnamaldehyde, a substrate which was not compatible with the previous allylation conditions, was also allylated successfully and further oxidised to give ketone **4h** in moderate yield (entry 4).

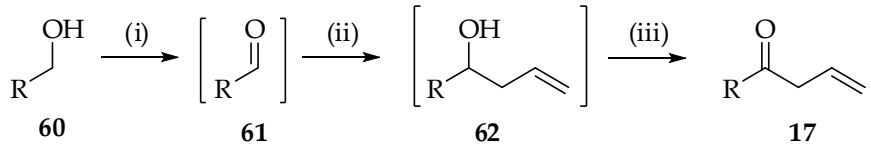
2.8 Oxidation/allylation/oxidation

With a general MK10-catalysed allylation/oxidation procedure for a range of aldehyde substrates now developed, we next wished to extend this to an oxidation/allylation/oxidation protocol. As acetic acid is a by-product of the DMP reaction, we envisioned that the acid formed in the first oxidation may be sufficient to aid catalysis in the allylation step. Pleasingly, this was indeed the case, and thus these conditions were applied to a number of primary alcohol substrates (Table 9).

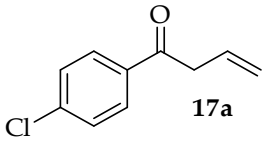
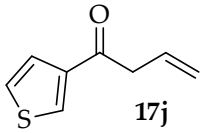
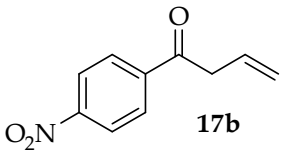
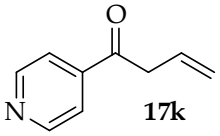
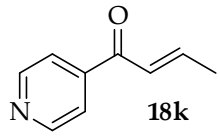
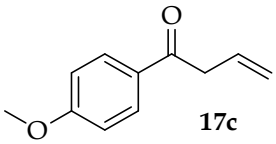
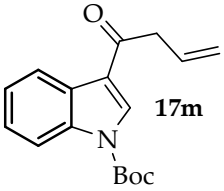
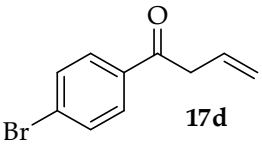
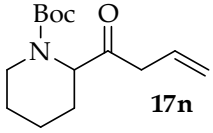
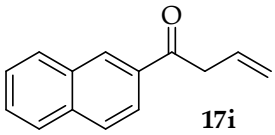
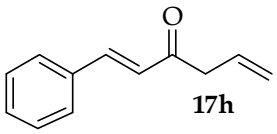
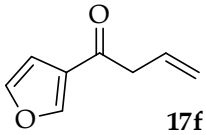
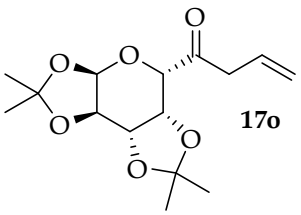
In order to ensure complete oxidation of the secondary alcohol, additional DMP was added in a sequential fashion. Different substrates exhibit differing reaction rates, making it not possible for a universal quantity of oxidant to be added from the start; too much resulted in oxidation of the allylating agent, whereas too little gave incomplete oxidation of the secondary alcohol.

The reaction proceeded well to give a range of aromatic products in good to excellent yields (entries 1-5). Conditions were also applied to a range of heterocyclic systems. Furan-derived ketone **17f** was observed by NMR analysis of the unpurified material, however, its apparent volatility prevented isolation of pure product (entry 6). On the other hand, thiophene-derived product **17j** was obtained in high yield (entry 7). With 4-pyridine methanol (**60k**) as substrate, a mixture of products was obtained. NMR analysis of the unpurified product following the reaction revealed the presence of β,γ-unsaturated ketone **17k** along with enone **18k** in a 4:5 ratio. This phenomenon is presumably due to the basic nature of pyridine bringing about self-isomerisation. In addition, the allylic ketone **17k** was shown to be unstable to silica, as attempted purification resulted in α,β-unsaturated ketone **18k** as the sole product (entry 8). Unfortunately, indole-derived product **17m** was only obtained in low yield (entry 9), whereas the aliphatic compound piperidine methanol (**60n**) provided ketone **17n** in moderate yield (entry 10). Pleasingly, cinnamyl alcohol (**60h**) and protected sugar **60o** were converted into the corresponding ketones **17h** and **17o** in moderate to high yield (entries 11 and 12).

Table 9: Oxidation/allylation/oxidation reactions



Reagents and conditions: *i)* DMP (1.5–2.0 eq), CH_2Cl_2, rt, 1 h; *ii)* montmorillonite K10, potassium allyltrifluoroborate (**78**, 1.5–2.0 eq), rt, 1 h; *iii)* DMP (2.0–2.5 eq), rt, 1 h

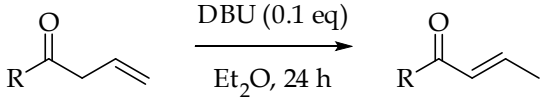
Entry	Product	Yield[a]	Entry	Product	Yield[a]
1	 **17a**	71	7	 **17j**	76
2	 **17b**	96	8	 **17k**  **18k**	41[b] 48
3	 **17c**	92	9	 **17m**	31
4	 **17d**	85	10	 **17n**	63
5	 **17i**	75	11	 **17h**	67
6	 **17f**	24[b]	12	 **17o**	75

[a]Percentage isolated yield; [b]Based on ^{1}H NMR analysis of the unpurified reaction mixture

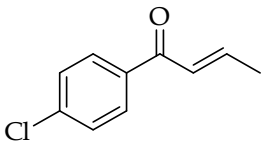
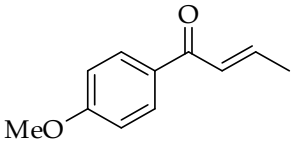
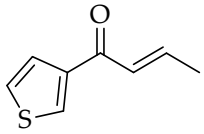
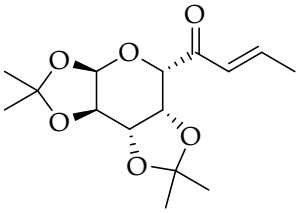
2.9 Oxidation/allylation/oxidation/isomerisation

Given the problems previously encountered with incorporating the isomerisation into a one-pot process, it was deemed necessary to subject β,γ-unsaturated ketones **17** to purification prior to isomerisation to the related enone **18**. A selection of β,γ-unsaturated ketones **17**, prepared using the oxidation/allylation/oxidation methodology outlined in Chapter 2.8, were stirred with a catalytic amount of DBU in diethyl ether. Results of the subsequent isomerisations were gratifying, and are summarised in Table 10.

Table 10: DBU-catalysed isomerisations to give α,β-unsaturated ketones



17 **18**

Entry	Product		Isolated yield (%)[a]
1		**18a**	95
2		**18c**	96
3		**18j**	87
4		**18o**	70 (>20:1 *E*:*Z*)

[a]*E*-only unless otherwise stated

2.10 Summary and future work

Our aim was to develop a one-pot oxidation/allylation/oxidation procedure to convert primary alcohols directly into β,γ- and α,β-unsaturated ketones. Following investigation of the individual steps, attempts were made at effecting a tandem allylation/oxidation reaction, but these were unsuccessful. A sequential allylation/oxidation protocol using $BF_3{\cdot}OEt_2$-catalysed allylation to give β,γ-unsaturated ketones was demonstrated, with incorporation of a KF-SiO_2 isomerisation in a *pseudo*-one-pot fashion. Unfortunately, this process was not compatible with the poorly electrophilic aldehydes tested, and so an alternative approach was investigated.

A one-pot oxidation/allylation/oxidation reaction from primary alcohols to β,γ-unsaturated ketones was subsequently developed. Using Dess–Martin periodinane as oxidant for both steps, potassium allyltrifluoroborate allylation proceeds with catalysis achieved by montmorillonite K10 along with acetic acid, which is present as a by-product of DMP oxidation. Attempts at involving isomerisation into a one-pot process were unsuccessful, however, DBU-catalysed isomerisation to give α,β-unsaturated ketones has been demonstrated on a selection of β,γ-unsaturated ketones following the novel one-pot reaction.

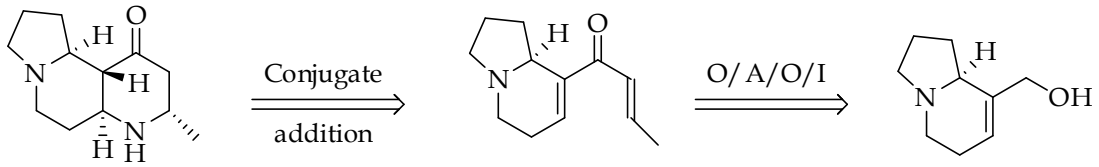
Future work will revisit the isomerisation and its incorporation into the one-pot procedure, as well as the application of this methodology to natural product synthesis. Studies towards the synthesis of elaeokanidine A will follow in the next Chapter.

Chapter 3 – Towards the synthesis of elaeokanidine A

3.1 Project aims and background

The indolizidine skeleton is ubiquitous in natural products, with well over 100 reported naturally occurring molecules containing this structural unit.[87] Eleaokanidine A (**19**) (Scheme 30) is an indolizidine alkaloid isolated from *Elaeocarpus kaniensis*.[88,89] Its structure and relative stereochemistry have been elucidated but its absolute stereochemistry has yet to be confirmed. To date, elaeokanidine A has never succumbed to total synthesis. It has not been tested for biological activity, although the activity of related alkaloids lead us to believe that it may have interesting pharmacological properties and obtaining larger quantities of this compound would allow this to be further investigated.

All of these factors make elaeokanidine A an attractive target for total synthesis, and thus our aim was to devise a synthetic route to this compound. Our proposed retrosynthetic strategy is based on addition of ammonia into an enone system (Scheme 30), which we believed could potentially be constructed using the oxidation/allylation/oxidation/isomerisation (O/A/O/I) methodology outlined in Chapter 2.

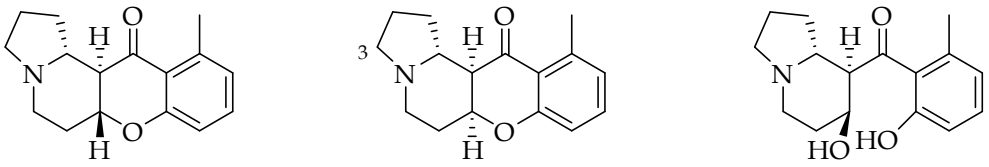


elaeokanidine A (**19**) **81** **82**

Scheme 30: Proposed retrosynthesis of elaeokanidine A (19)

3.1.1 *Elaeocarpus* indolizidine alkaloids

Alkaloids are a group of nitrogenous compounds that are derived from natural sources. Initial studies by Johns *et al.* in the late 1960s and early 1970s on extracts from the plant genus *Elaeocarpus* yielded numerous indolizidine alkaloids, *i.e.* those which contain a fused 5-6 ring system with a nitrogen atom shared between the two rings.[90-94] The first of these were (±)-elaeocarpine (**83**) and (±)-isoelaeocarpine (**84**), which differ only in the *cis*/*trans*-relationship at the ring junction, along with (+)-isoelaeocarpicine (**85**), all of which were extracted from *Elaeocarpus polydactylus* (Figure 5).[90,91] The complete relative stereochemistry of (±)-elaeocarpine (**83**) was obtained from an X-ray crystal structure of its hydrobromide salt.[95] Recently, all of these compounds have been shown to have affinity for the human δ-opioid receptor, which has implications in pain relief.[96]

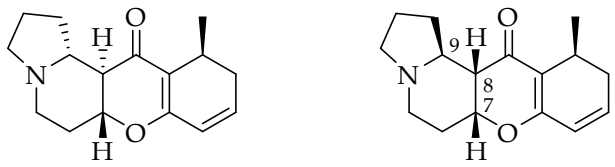


83 **84** **85**

Figure 5: (±)-Elaeocarpine (83), (±)-isoelaeocarpine (84) and (+)-isoeleaocarpicine (85), alkaloids from *Elaeocarpus polydactylus*

(Structures indicate relative stereochemistry only)

Extracts from *Elaeocarpus dolichostylis* yielded two new structurally related alkaloids, (+)-elaeocarpiline (**86**) and (−)-isoelaeocarpiline (**87**) (Figure 6).[92] The relationship between (+)-elaeocarpiline (**86**) and (±)-elaeocarpine (**83**) was proved by reducing the latter with H_2 over Pd/C in benzene to give (+)-elaeocarpiline (**86**).[97] Five further alkaloids were isolated from *Elaeocarpus sphaericus*; four of these differ from (+)-elaeocarpiline and (−)-isoelaeocarpiline only in the stereochemical configuration at C-7, C-8 and C-9, whereas the fifth is isomeric in its double bond placement.[98]

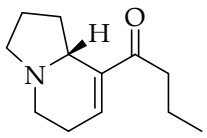


86 **87**

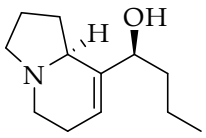
Figure 6: (+)-Elaeocarpiline (86) and (−)-isoelaeocarpiline (87), alkaloids from *Elaeocarpus dolichostylis*

In 2011, two more indolizidine alkaloids from *Elaeocarpus sphaericus*, closely related to elaeocarpine (**83**) and isoelaeocarpine (**84**), were discovered, namely (±)-3-oxoisoelaeocarpine, which possesses an addition carbonyl at the 3-position of isoelaeocarpine, and (±)-elaeocarpine *N*-oxide.[99]

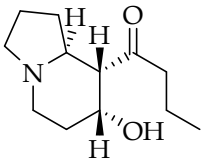
In 1971, extracts from *Elaeocarpus kaniensis* were investigated;[88,89] from these extracts, eight new alkaloids were isolated (Figure 7). Through a combination of spectroscopic studies, structures were assigned to elaeokanine A (**88**), elaeokanine B (**89**), elaeokanine C (**90**), elaeokanine D (**91**), elaeokanine E (**92**) and elaeokanidine A (**19**), but only the relative stereochemistry of these compounds was determined at this point. The remaining two natural products, elaeokanidine B and elaeokanidine C are stereoisomers of elaeokanidine A but there was insufficient data to unequivocally assign their structures.[89]



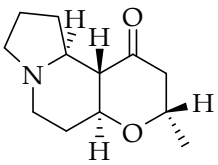
(+)-elaeokanine A (**88**)



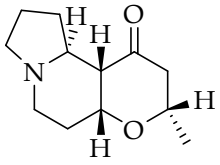
(−)-elaeokanine B (**89**)



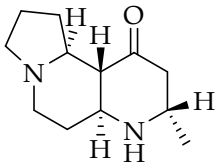
(−)-elaeokanine C (**90**)



elaeokanine D (**91**)



elaeokanine E (**92**)



elaeokanidine A (**19**)

Figure 7: Alkaloids isolated from *Elaeocarpus kaniensis*

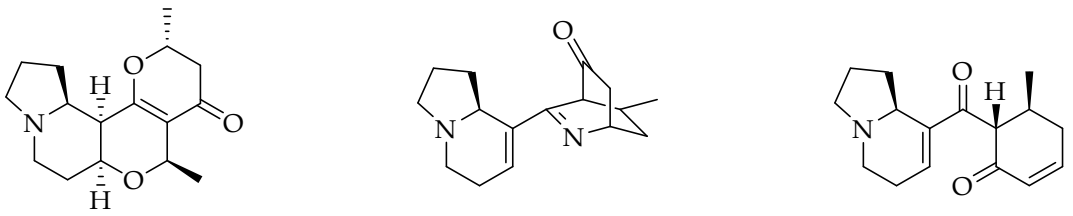
(In the cases of **91**, **92**, and **19**, the structures shown indicate relative stereochemistry only)

Over the years, elaeokanine A (**88**) has been the subject of a number of syntheses.[100-109] The majority of these have been racemic but more recently, asymmetric variants have also emerged.[101-104] Syntheses of elaeokanine B (**89**),[103,105,110] C (**90**),[104-107] and E (**92**) have also been reported,[111] however, to date, the synthesis of elaeokanidine A (**19**) has not been reported. The asymmetric syntheses of elaeokanines A, B and C were the ultimate proof of their respective structures, and enabled confirmation of their absolute stereochemistry.

3.1.2 Biological activity of related alkaloids

Studies in 2005 yielded two previously unknown alkaloids from the leaves of *Elaeocarpus grandis* (Figure 8), grandisine A (**93**) and grandisine B (**94**) which were shown to have affinity for the human δ-opioid receptor.[112] A further five alkaloids, grandisine C–G, were discovered from the same plant in 2006. Investigations into the bioactivity of these compounds revealed that, along with (−)-isoelaeocarpiline (**87**),

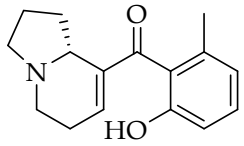
they all showed affinity for the human δ-opioid receptor, with IC_{50} values ranging from 1.55 to 75.4 μM.[113]



grandisine A (**93**) grandisine B (**94**) grandisine D (**95**)

Figure 8: Grandisines A (93), B (94) and D (95), alkaloids from *Elaeocarpus grandis*

Shortly afterwards, a novel indolizidine alkaloid, (±)-elaeocarpenine (**96**), along with three previously known compounds, was isolated from *Elaeocarpus fuscoides* (Figure 9).[96] This compound showed structural similarities to the *Elaeocarpus polydactylus* alkaloids (*vide supra*, Figure 5) and also exhibited human δ-opioid receptor binding affinity.



96

Figure 9: (±)-Elaeocarpenine (96), an alkaloid from *Elaeocarpus fuscoides*

In 2007, five novel pyrrolidine alkaloids were tested for biological activity. Habbemines A (**97**) and B (**98**) were isolated from *Elaeocarpus habbemensis*,[114] whilst peripentonines A–C (**99**, **100** and **101**, respectively) were isolated from *Peripentadenia mearsii* (Figure 10).[115] All of these natural products displayed a binding affinity for the human δ-opioid receptor.

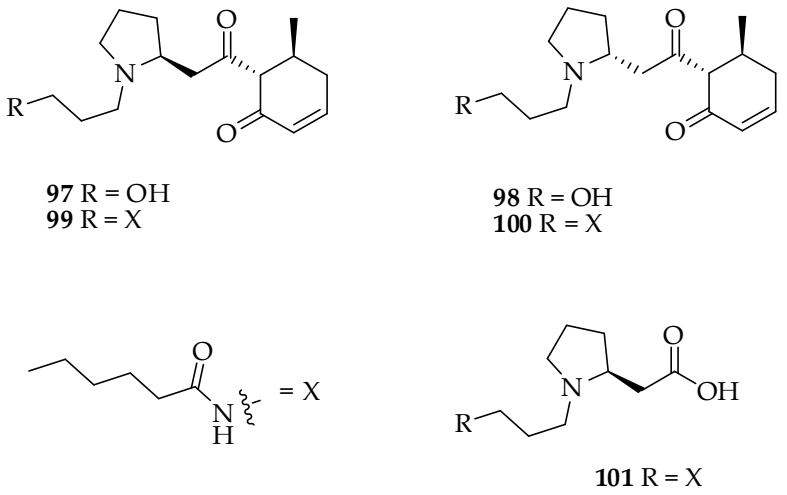
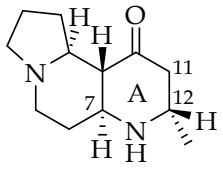


Figure 10: Habbemines A (97) and B (98) and peripentonines A–C (99–101)

The biological activity of these related indolizidine and pyrrolidine alkaloids, along with other indolizidine alkaloids such as castanospermine is encouraging regarding the potential bioactivity of elaeokanidine A.[116,117]

3.1.3 Structural elucidation of elaeokanidine A

The structure of elaeokanidine A (**19**) was solved primarily through NMR spectroscopic studies, aided by infrared and mass spectrometry data. Comparisons to the spectra of firmly established alkaloids also aided the assignment of the structure.[89]



elaeokanidine A (**19**)

The ^{1}H NMR spectrum indicated a close structural similarity to elaeokanine D (**91**). As was reported for elaeokanine D in the same publication, on evaluation of the coupling constants, the authors proposed that ring A sits in a twisted conformation. The $J_{11,12}$ coupling constants (J = 7.0 and 2.0 Hz) were found to be lower than those expected for *trans*-diaxial coupling (J = 9–13 Hz) if H-12 were to be in an axial position.[118] If, however, H-12 was in an equatorial position, typical equatorial-equatorial or equatorial-axial (J = 2–5 Hz) coupling constants of a cyclohexane ring in chair

conformation suggest that $J_{11,12}$ (7.0 Hz) is higher than should be expected.[118] Indeed, a twisted conformation which minimises the interaction between H-7 and the methyl group would explain this phenomenon (Figure 15).

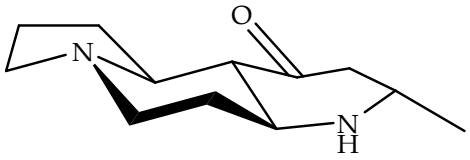
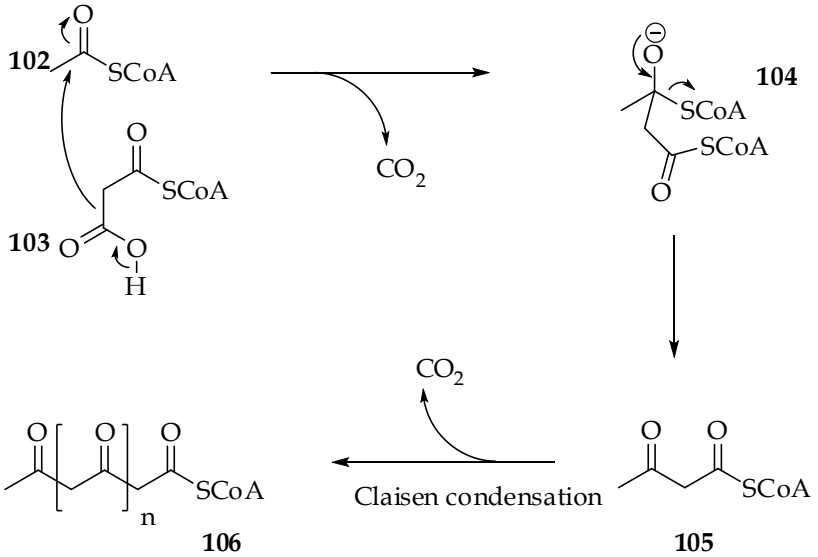


Figure 15. Three-dimensional representation of elaeokanidine A (19)

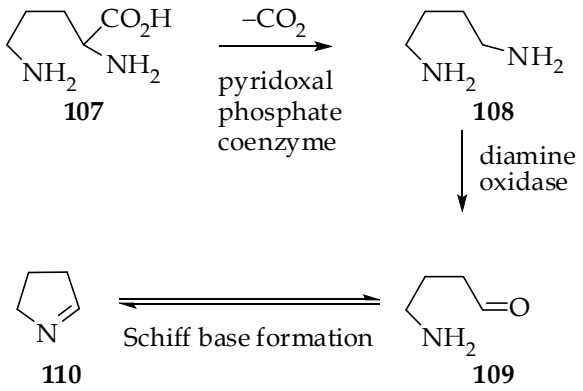
3.1.4 Biosynthesis

Alkaloids are formed from natural sources by the condensation of polyketides, the biosynthetic pathway of which is well established (Scheme 31). Polyketides of type **106** arise from the Claisen-type condensation of acetyl-CoA (**102**) with malonyl-CoA (**103**) to form a β-keto-thioester **105**, which subsequently undergoes further cycles of condensation with malonyl-CoA (**103**) leading to chain elongation.[119]



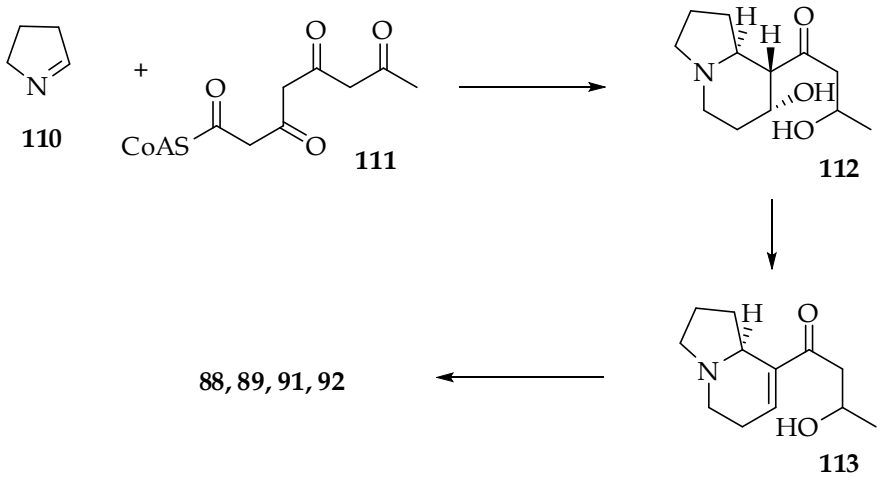
Scheme 31: The biosynthesis of poly-β-keto thioesters

Amino acids provide additional building blocks for biosynthesis. By undergoing several enzymatic processes, ornithine (**107**) can be converted into 3,4-dihydropyrrole (**110**),[120] and it is postulated that this moiety provides the nitrogen atom present in the indolizidine alkaloids (Scheme 32).[89]



Scheme 32: Formation of dihydropyrrole from ornithine

Hart proposed a biosynthesis of the *E. kaniensis* alkaloids whereby an 8-carbon polyketide, **111**, condenses with dihydropyrrole (**110**) to provide the indolizidine skeleton; further transformations led to the other alkaloids (Scheme 33).[89] The biogenesis of elaeokanidine A (**19**) with its extra nitrogen atom, however, was not explained.

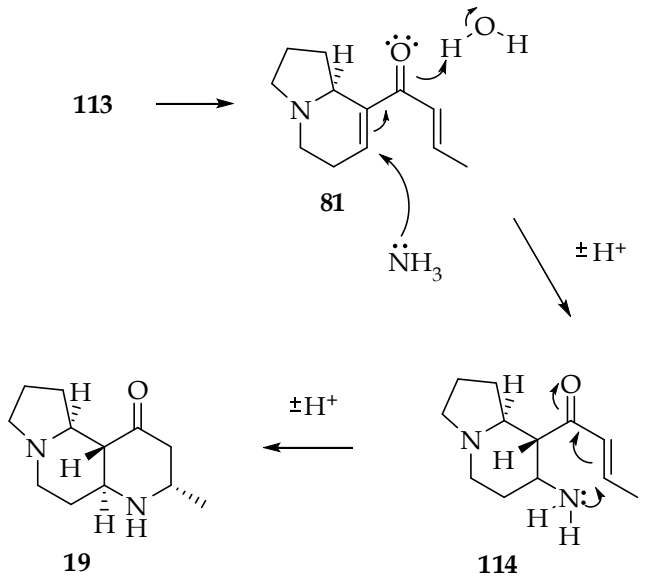


Scheme 33: Hart's proposed biosynthesis of *E. kaniensis* alkaloids

Following on from a report in which ammonia was shown to have an artefact-inducing effect,[121] it is suggested that elaeokanidine A (**19**), along with grandisine B (**94**), is in fact formed on treatment with aqueous ammonia during the extraction procedure as opposed to being a natural product in its own right.

Consequently, Katavic proposed a mechanism for the formation of elaeokanidine A, involving reaction of ammonia with the dehydrated product of **113** (Scheme 34).[122] Nucleophilic attack of ammonia on to the endocyclic enone in **81** first affords **114** and

an intramolecular Michael addition onto the remaining α,β-unsaturated ketone of **114** subsequently leads to elaeokanidine A (**19**).



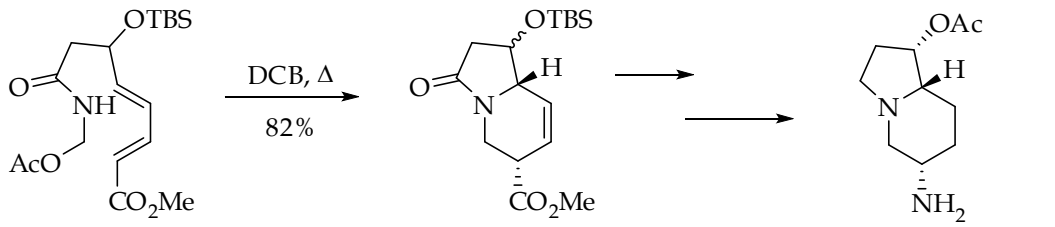
Scheme 34: Proposed ammonia-induced formation of elaeokanidine A (19)

Although elaeokanidine A may not be a natural product in itself, and merely an artefact, its synthesis is nevertheless interesting due to the aforementioned factors. We aim to exploit Katavic's proposed synthesis by preparing **81**, which may indeed be the true natural product derived from *Elaeocarpus kaniensis*, and using ammonia to install the nitrogen atom in the final compound. We plan to use precedented routes to construct the main indolizidine framework.

3.1.5 Previous syntheses of the indolizidine core

The literature contains a wealth of different synthetic strategies towards the indolizidine core.[87] Of these, some of the most common involve imino Diels–Alder reactions, 1,3-dipolar cycloadditions, or intramolecular cyclisation of acyliminium ions.

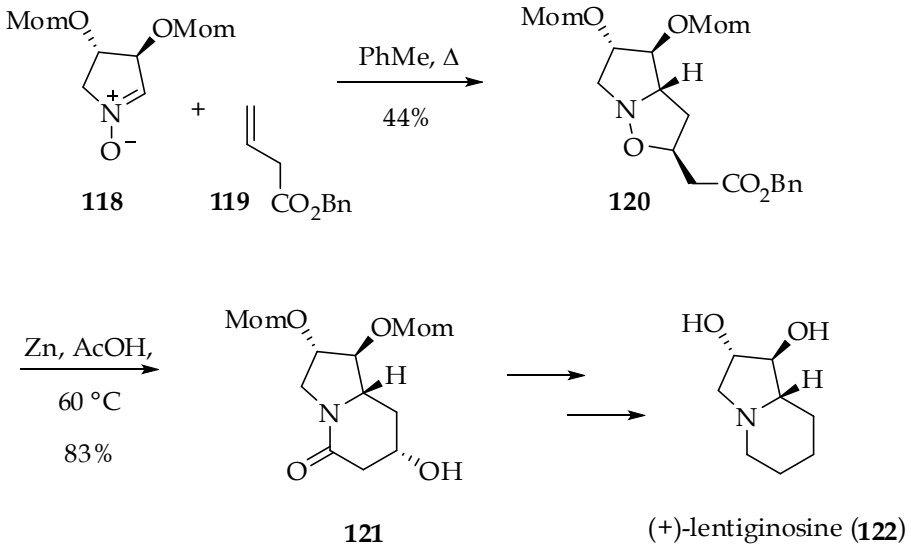
Weinreb and co-workers used compound **115** as a precursor for an imino Diels–Alder reaction, whereby thermally-assisted elimination of acetic acid provided an imine moiety as the dienophile for cyclisation. The bicyclic system **116** was obtained in 82% yield following reflux in *o*-dichlorobenzene, and this intermediate was then taken forwards for the racemic synthesis of the indolizidine alkaloid slaframine (**117**) (Scheme 35).[123]



115 **116** (±)-slaframine (**117**)

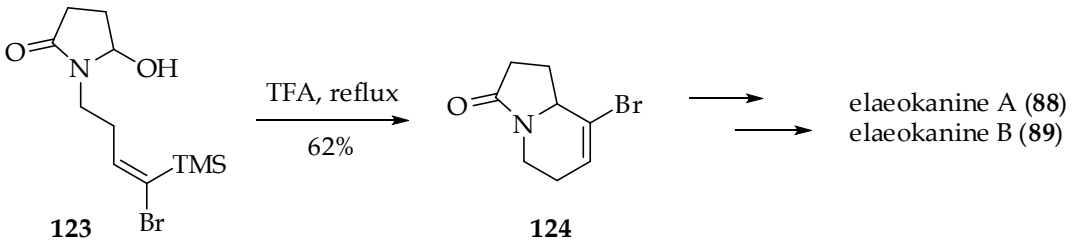
Scheme 35: Weinreb's imino Diels–Alder approach to the indolizidine core

Wightman *et al.* demonstrated a 1,3-dipolar cycloaddition of *N*-oxide **118** and alkene **119** to provide the bicyclic structure **120** in 44% after 4 days at reflux. Zinc-mediated N–O cleavage followed by lactamisation then furnished indolizidine **121** in 83% yield, which was further manipulated to provide the natural product (+)-lentiginosine (**122**) (Scheme 36).[124]



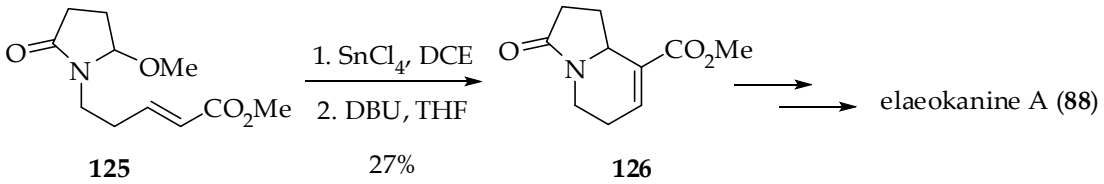
Scheme 36: Wightman's 1,3-dipolar cycloaddition approach to the indolizidine core

Overman established a route to the indolizidine structure **124**, by means of a TFA-induced acyliminium ion cyclisation of vinylsilane **123** as one of the key steps (Scheme 37).[125] The group went on to use this intermediate in the total synthesis of both elaeokanine A (**88**) and elaeokanine B (**89**).



Scheme 37: Overman's acyliminium ion cyclisation route to the indolizidine core.

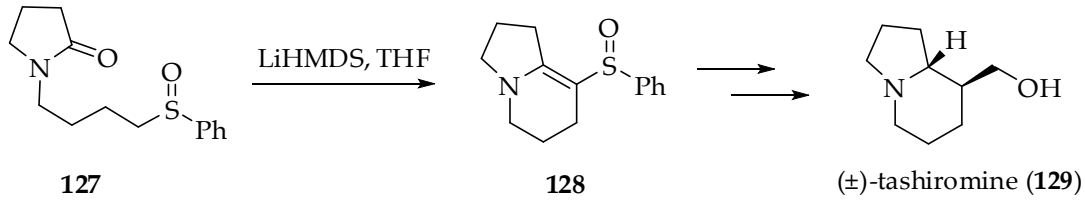
Similarly, Taber *et al.* used a Lewis acid–mediated acyliminium cyclisation to form lactam **126** from **125** as a key step in the group's route to elaeokanine A (Scheme 38).[100]



Scheme 38: Taber's acycliminium ion cyclisation approach to the indolizidine core

In contrast, Pohmakotr *et al.* used a base-induced cyclisation of sulfoxide **127** to afford indolizidine **128** as the key step in their route to racemic tashiromine (**129**) (Scheme

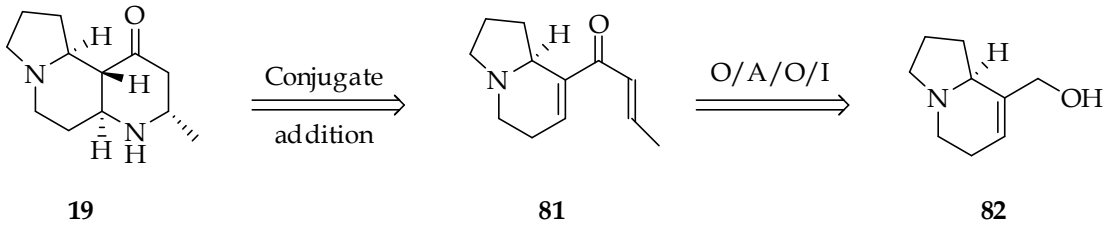
39).[126] Owing to the relevance of these latter two routes to our project, these will be discussed in more detail in a later section (*vide infra*, Chapters 3.2.1 and 3.2.2).



Scheme 39: Pohmakotr's base-induced cyclisation approach to the indolizidine core

3.1.6 Retrosynthetic analysis

To date, elaeokanidine A (**19**) has never succumbed to total synthesis. The unconfirmed absolute stereochemistry and the pharmacological activity of related structures make it an interesting target. Aside from the indolizidine core, the main structural feature of elaeokanidine A is the additional nitrogenous ring. As alluded to previously, this could in principle be formed by double Michael addition of ammonia to dienone **81** (*vide supra*, Scheme 34). Three of the stereocentres would be introduced in this final ammonia-trapping step. Attack of the nucleophile onto the two enones would install two stereocentres, with proton quenching installing the final. At this point we hoped to utilise our oxidation/allylation/oxidation/isomerisation (O/A/O/I) methodology for the synthesis of the α,β-unsaturated ketone functionality in **81** from alcohol **82** (Scheme 40).



Scheme 40: Proposed retrosynthesis of elaeokanidine A

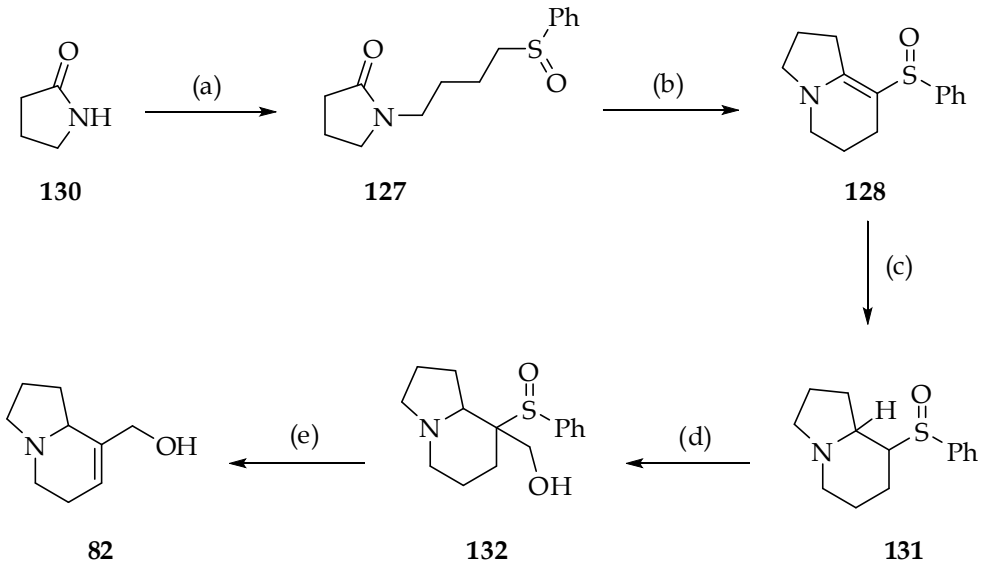
The following section will describe the results and current progress towards the synthesis of elaeokanidine A.

3.2 Results and discussion

Elaeokanidine A (**19**) is an indolizidine alkaloid isolated from the leaves of *Elaeocarpus kaniensis*, a rainforest species found in New Guinea. It contains four stereocentres, three of which are at ring junctions. The absolute configuration is unknown and only the relative stereochemistry has been reported.[88] Our proposed retrosynthesis involves the addition of ammonia into a dieneone system **81** (Scheme 40), to which we hope to gain access using the newly developed oxidation/allylation/oxidation/isomerisation methodology outlined in the Chapter 2, starting from alcohol **82**. In the first instance we wished to synthesise a racemic form of alcohol **82** in order to test the viability of our proposed route. In order to achieve this, we looked to the literature for inspiration.

3.2.1 Pohmakotr's route

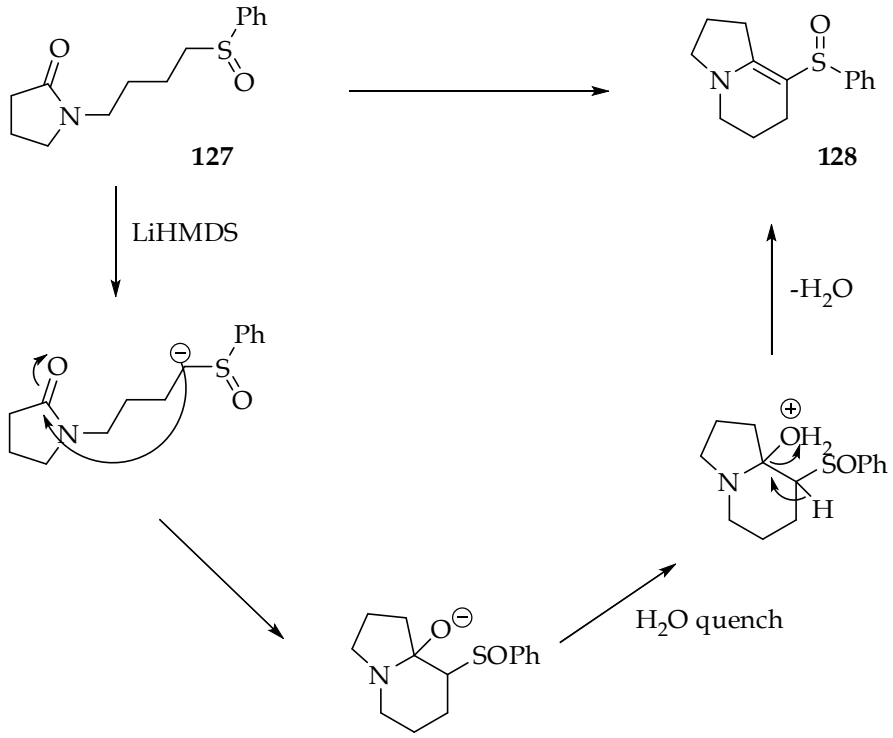
In 2008, Pohmakotr *et al.* described a route to the key intermediate **82** as part of their synthesis of (±)-tashiromine (Scheme 41).[126]



Reagents and conditions: (a) NaH, DMF, $PhS(CH_2)_4Br$, 0 °C to rt (75%); then $NaIO_4$, MeOH, H_2O, 0 °C to rt, 12 h (70%); (b) LiHMDS, THF, −78 °C to rt, 15 h; (c) $NaBH_4$, MeOH, 0 °C to rt (69% from **127**); (d) LDA, THF, $(CH_2O)_n$, −78 °C to rt, 15 h (55%); (e) toluene, reflux, 8 h (47%)

Scheme 41: Pohmakotr's route to 82

Beginning from pyrrolidinone (**130**), the first step of Pohmakotr's route was installation of a sulfide-containing side-chain by alkylation. Attack of the deprotonated pyrrolidinone displaces the bromine to install the alkyl chain, which was subsequently oxidised from the sulfide to give sulfoxide **127**. Deprotonation at the α-position of sulfoxide **127** with LiHMDS induced cyclisation by means of attack on to the carbonyl functionality, followed by elimination of water, gives indolizidine **128** (Scheme 42).

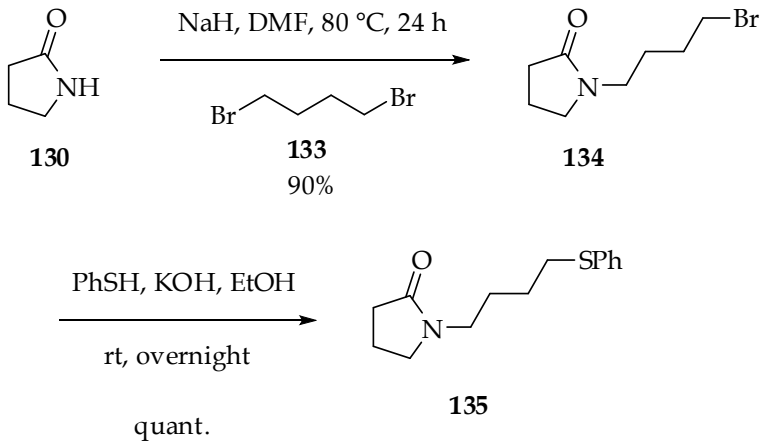


Scheme 42: Mechanism of LiHMDS-mediated cyclisation

Sodium borohydride reduction of intermediate **128** gave bicycle **131**, which with subsequent deprotonation and addition of paraformaldehyde, served to introduce the oxygen functionality in **132**. Finally, thermal elimination of the sulfoxide afforded the desired alcohol, **82**.[126] We therefore envisaged that we could use this route, or a modification thereof, for our synthesis of alcohol **82**.

3.2.1.1 Alkylation

Synthetic efforts began by initially following a modification of Pohmakotr's synthesis.[126] Rather than pre-making the side chain for a convergent synthesis, a linear approach was taken due to ease and the hope of improving on existing yields. Alkylation of pyrrolidinone (**130**) with dibromobutane (**133**) gave bromide **134**, which was subsequently substituted with thiophenol to afford sulfide **135**. Oxidation with *m*-CPBA provided the desired sulfoxide **127**, for Pohmakotr's cyclisation with LiHMDS (Scheme 43 and 46). The initial alkylation, as described by Comoy,[127] pleasingly surpassed the literature (65%) to afford the brominated compound **134** in 90% yield (Scheme 43). Reaction of bromide **134** with stoichiometric thiophenol in ethanolic potassium hydroxide gave the sulfide **135** in quantitative yield.[128]



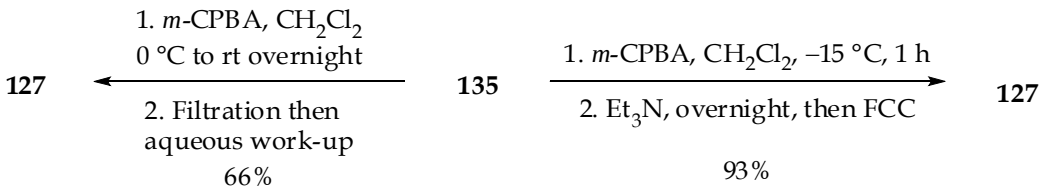
130 **133** 90% **134**

quant. **135**

Scheme 43: Alkylation and substitution steps

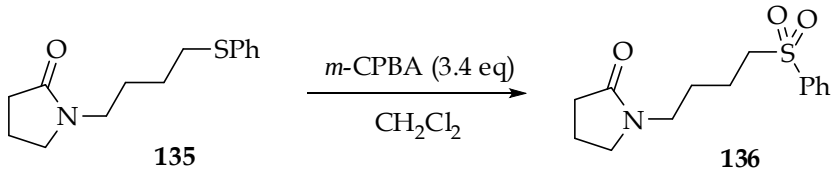
3.2.1.2 Oxidation

Oxidation of sulfide **135** with *m*-CPBA using conditions described by Barton, whereby isolation of the sulfoxide was achieved by filtering the reaction mixture followed by an aqueous work-up,[129] gave sulfoxide **127** in 66% yield. An alternative method, as used previously in the Taylor group was also attempted. This involved slow neutralisation with triethylamine followed by loading on to silica gel and subsequent column chromatography (Scheme 44).



Scheme 44: *m*-CPBA oxidation to sulfoxide 98

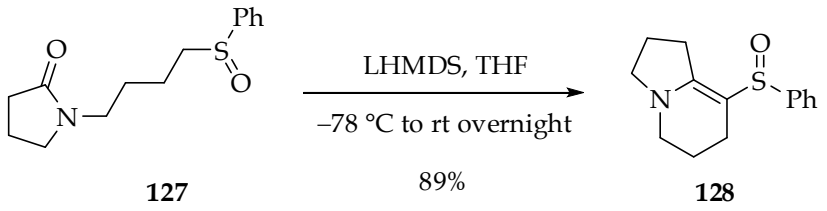
In this case, the conditions resulted in an improved 93% yield; but, in both cases partial over-oxidation to the sulfone was also observed (ca. 8%). This was confirmed by comparison of data with an authentic sample of sulfone **136** (Scheme 45). There are two distinct differences in the NMR spectra of the two compounds; firstly, the aromatic protons of the sulfone are shifted further downfield compared to those of the sulfoxide; secondly the spectrum of the sulfoxide is more complex than that of the sulfone due to the effect of the lone pair on the chiral sulfur centre. This makes it easy to identify the presence of over-oxidation although unfortunately the sulfone was not easily separable from the sulfoxide, therefore this small impurity was carried through the synthesis.



Scheme 45: Over-oxidation of sulfide to sulfone

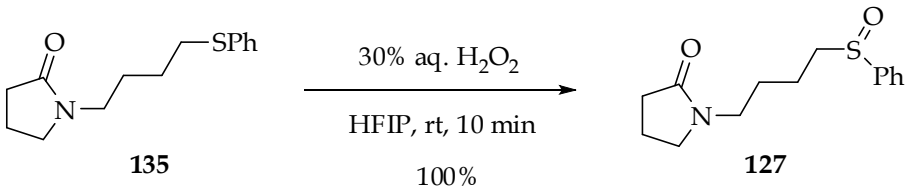
3.2.1.3 Cyclisation

The first attempt at the cyclisation using Pohmakotr's procedure went smoothly, giving compound **128** in 89% yield with 100% conversion by ^{1}H NMR spectroscopy (Scheme 46).



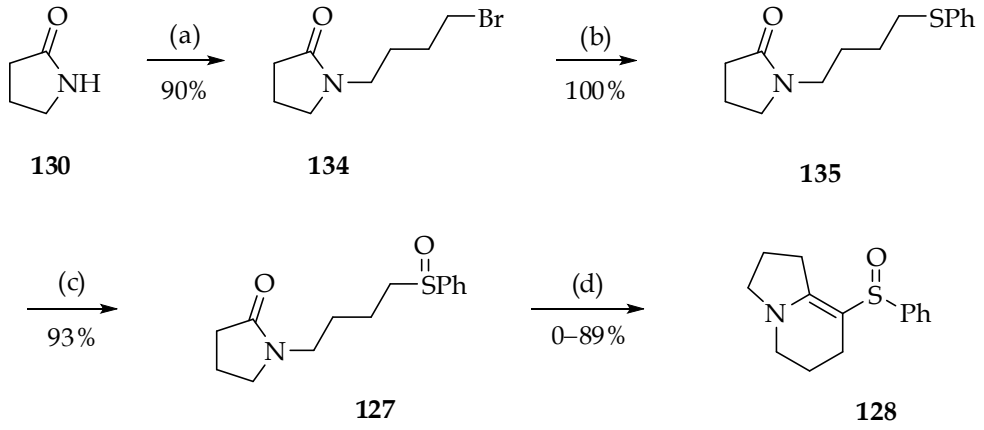
Scheme 46: Key cyclisation step

Problems arose when the cyclisation conditions were repeated; disappointingly, no product was observed. Subsequent attempts at this reaction had variable success, with differing degrees of conversion into product **128** observed. An alternative method was used for the synthesis of sulfoxide **127** as there were concerns that the sulfone present in the starting material could be having a detrimental effect. Ravikumar has shown that with hexafluoro*iso*propanol as solvent, only sulfoxide is observed from peroxide oxidation of the corresponding sulfide; no over-oxidation to the sulfone is seen. On our substrate this was indeed the case; oxidation was complete within 10 min and the pure sulfoxide **127** isolated in quantitative yield (Scheme 47). [130]



Scheme 47: Peroxide oxidation of sulfide 135 to sulfoxide 127

Unfortunately, when this material was subjected to the cyclisation conditions, no product was observed. The cyclisation was hence deemed not to be reproducible and the route was abandoned. Progress up until this point is summarised in Scheme 48.

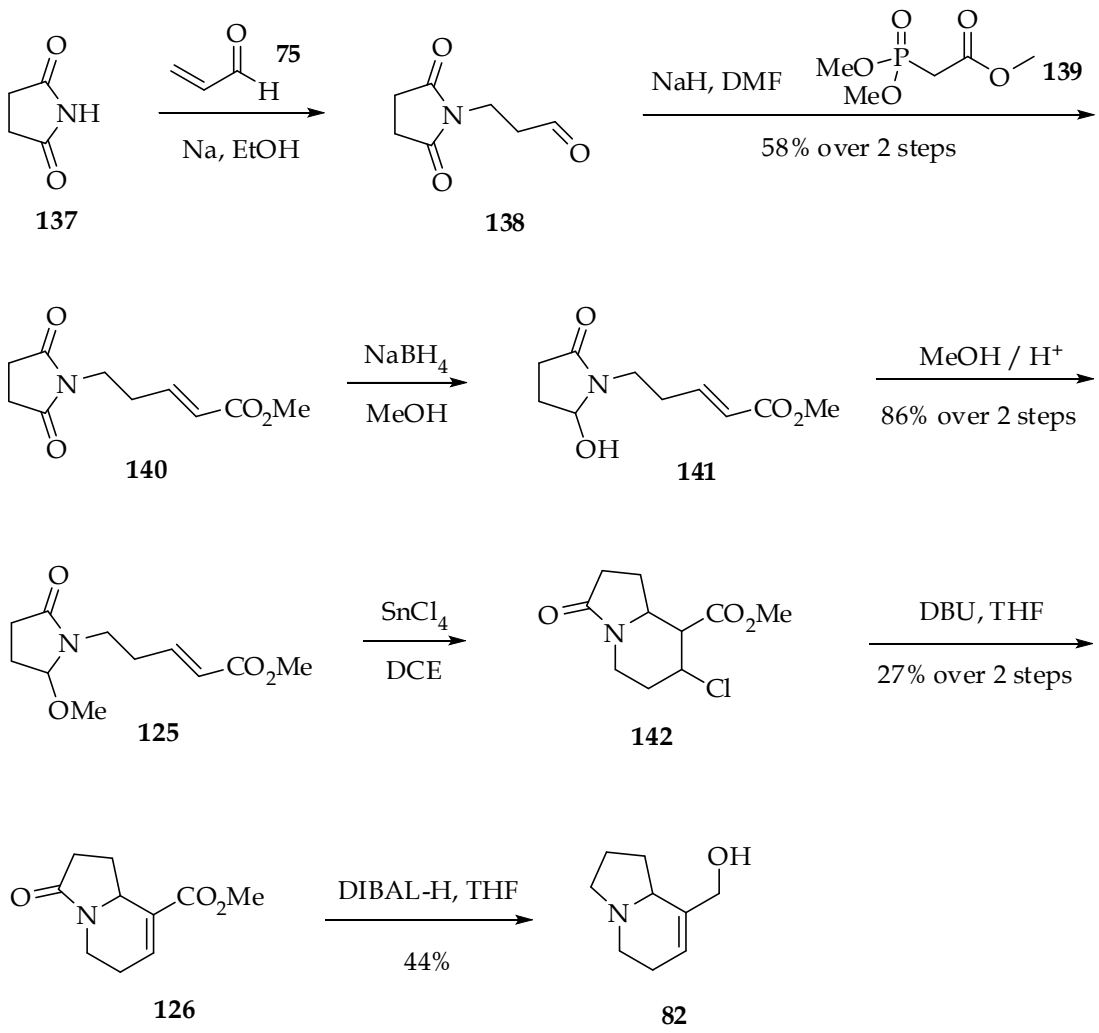


Reagents and conditions: (a) NaH, DMF, $Br(CH_2)_4Br$, 80 °C, 24 h; (b) PhSH, KOH, EtOH, r, 18 h; (c) *(i)* *m*-CPBA, CH_2Cl_2, −15 °C, 1 h *(ii)* Et_3N, rt, 16 h; (d) LHMDS, THF, −78 °C to rt, 16 h

Scheme 48: Progress made towards the synthesis of 62

3.2.2 Taber's route

An alternative route to compound **82** has been described by Taber's group (Scheme 53).[100]



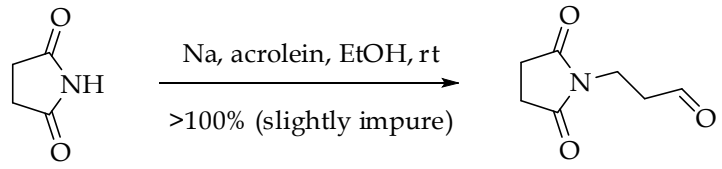
Scheme 49: Taber's synthesis of 82

They reported initial deprotonation of succinimide (**137**) using sodium in ethanol wherein conjugate addition of the generated nucleophile onto acrolein (**75**) gave the aldehyde **138**, which was subjected to Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate (**139**) to provide *E*-alkene **140**. Sodium borohydride reduction of the imide moiety resulted in a hydroxylactam **141**, which underwent methylation with acidic methanol to provide **125**. A tin-mediated cyclisation to give **142** and subsequent elimination afforded **126**. Reduction with di*iso*butylaluminium hydride of both the ester and amide functional groups then gave the desired product

82 in seven steps and 6% overall yield. We therefore chose to repeat this route to gain access to intermediate **82** for our synthesis of elaeokanidine A (**19**).

3.2.2.1 Horner–Wadsworth–Emmons reaction and reduction

In our hands, the conjugate addition proceeded smoothly with good mass recovery of the slightly impure aldehyde **138** following column chromatography (Scheme 50).

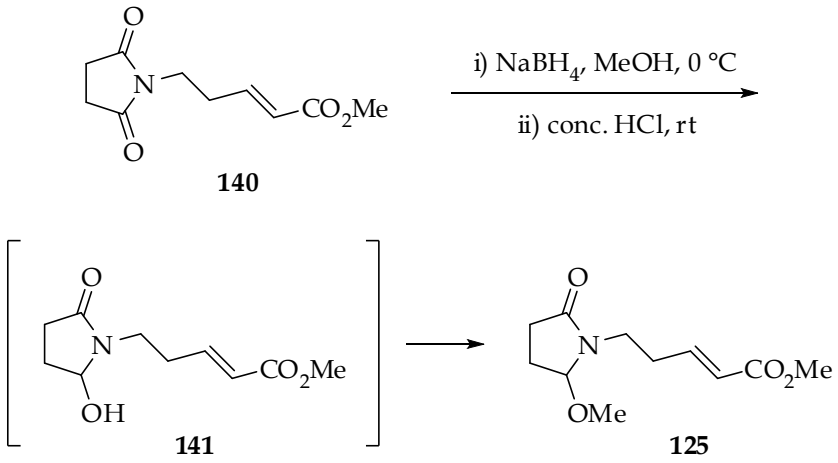


137 **138**

Scheme 50: Conjugate addition of succinimide (137) with acrolein (75)

The published HWE reaction on 100 mg scale followed by Kugelrohr distillation gave olefin **140** in 56% yield over 2 steps.[100] In our hands, on a 3 g scale, 65% of material was obtained following vacuum distillation.

The subsequent $NaBH_4$ reduction of **140** to **141** posed a number of problems. The ^1H NMR spectrum of alcohol **141** did not correspond to the data given in the literature, and indeed the carbon spectrum appeared to show an additional peak. On comparison with the data for **125**, it transpired in fact that methylation had occurred during the acidic work up, taking **140** straight through to methoxylactam **125** (Scheme 51).

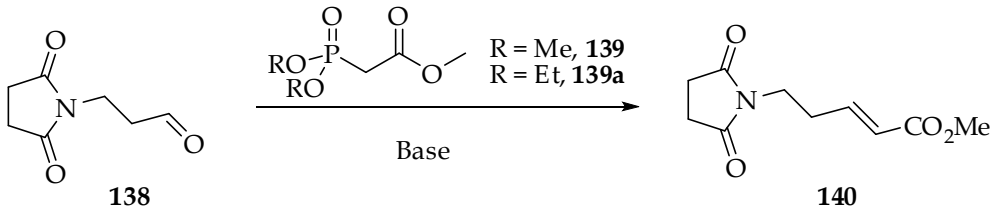


140 **141** **125**

Scheme 51: Direct reduction/methylation of 140

An additional difficulty encountered was that the reduction consistently failed to go to completion despite addition of up to 2 extra equivalents of sodium borohydride, thus resulting in a low yield of product. Due to this problem, a different approach was taken. It was hoped that by modifying the conditions used in the HWE reaction, cleaner starting material for the reduction would be obtained and this might result in a more reproducible reaction. Results of this optimisation are summarised in Table 11.

Table 11: Optimisation of the HWE reaction



138 **140**

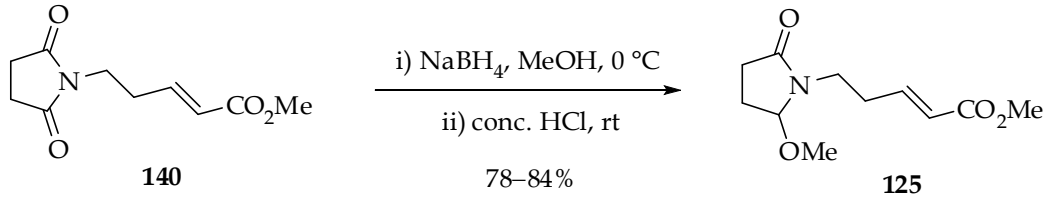
Entry	Base	Phosphonoacetate	Yield[a]	*E*:*Z*
1	NaH	**139**	65%[b]	100:8
2	NaHMDS	**139**	70%	100:12
3	NaHMDS	**139a**	52%	*E* only
4	K_2CO_3	**139**	97%	*E* only

[a]Unpurified yield, compounds did not require purification; [b]Yield following distillation

Using the original conditions with sodium hydride (entry 1), the product was purified by distillation which was time-consuming due to the very high boiling point of the

product; at 3 mbar pressure, temperatures of over 200 °C were required. Using sodium hexamethyldisilazide instead of sodium hydride as base, the unpurified product resulting from the reaction was much cleaner (entry 2), but a small amount of the *Z*-isomer was visible. Moving to methyl diethylphosphonoacetate **139a** (entry 3) it was reasoned that non-bonding interactions would give exclusively the *E*-isomer. Although this was the case, the yield of **140** obtained was only moderate (52%). Finally, using a procedure similar to that of Cordero,[131] potassium carbonate in aqueous THF was employed and satisfyingly gave very pure samples of **140** in near quantitative yield (entry 4).

Pleasingly, subsequent reductions on this material saw full conversion without trouble, resulting in a much improved yield; on a ~5 mmol scale, an 84% yield of **125** was achieved and when scaled up to ~50 mmol this was almost maintained, with a 78% yield observed.

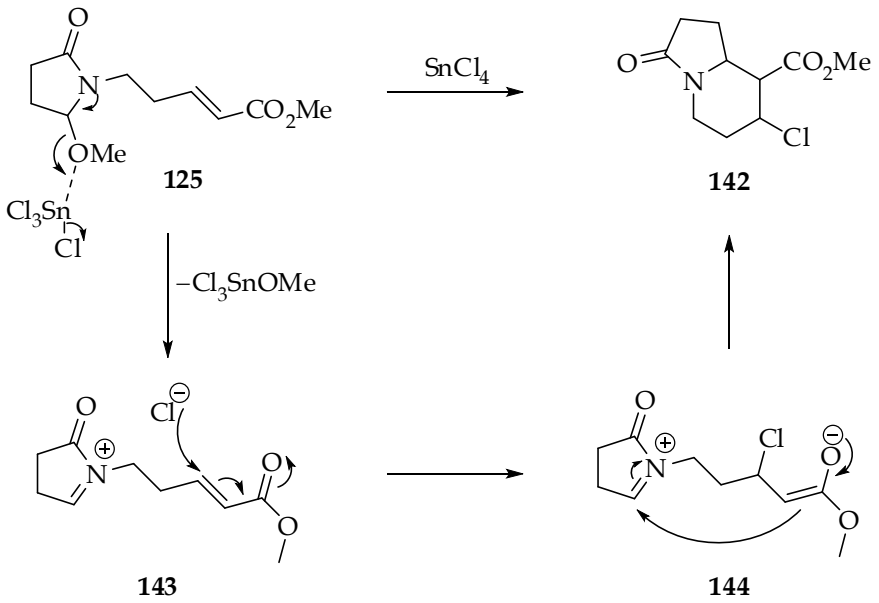


140 78–84% **125**

Scheme 52: Reduction/methylation of 140 to give methoxylactam 125

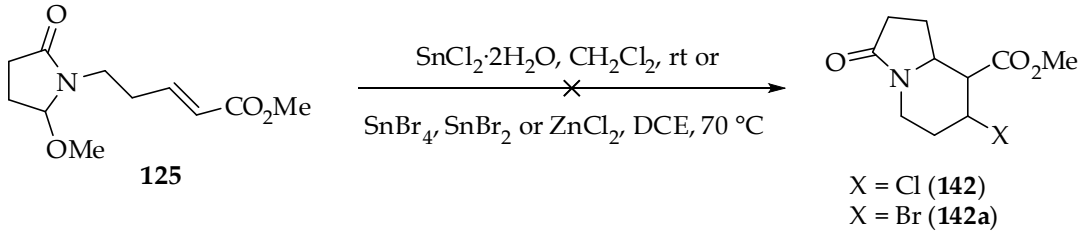
3.2.2.2 Cyclisation and elimination

Methoxy amides such as **125** have been shown to easily form *N*-acyliminium ions under acidic or Lewis acidic conditions and undergo subsequent inter- and intramolecular reactions.[132] As such, it is proposed that the mechanism for the tin-mediated cyclisation of **125** proceeds *via* an *N*-acyliminium intermediate (Scheme 53). Lewis acid catalysed removal of the methoxy group by tin(IV) chloride would furnish *N*-acyliminium ion **143**. Conjugate addition of a chloride ion onto the α,β-unsaturated ester would result in the enolate anion **144**, which as a nucleophile would then trap the iminium ion to afford the product, **142**.



Scheme 53: Proposed mechanism for the tin-mediated cyclisation

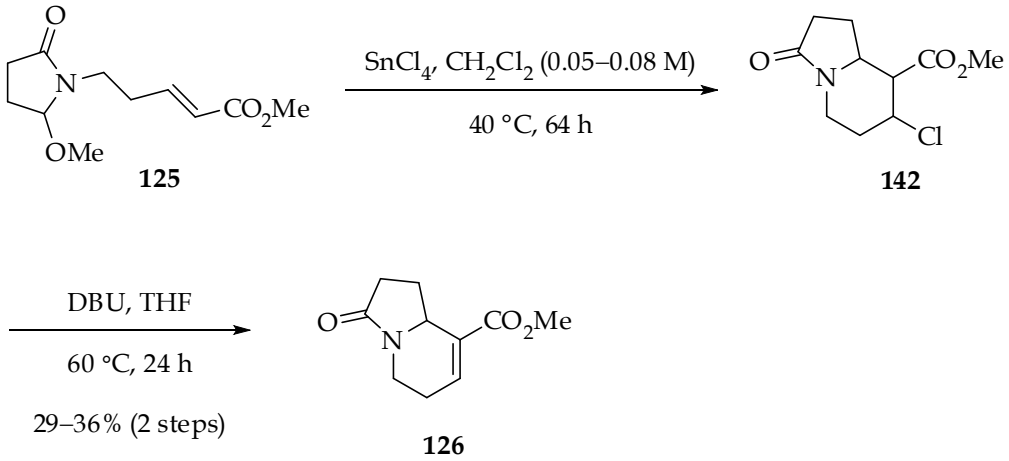
In our hands, the cyclisation/elimination sequence proceeded to give 26–28% yield of **126** over the two steps, comparable to the literature yield of 27%.[100] Thus far, the cyclisation and elimination were the least fruitful steps in this route and therefore required some optimisation. A number of alternative Lewis acids were tried in the hope of increasing yields, including tin(IV) bromide, tin(II) bromide, zinc(II) chloride and tin(II) chloride dihydrate (previously been used in the Taylor group for Lewis acid-mediated cyclisation reactions[133]), but none of these served to improve the reaction (Scheme 54). In most cases, the only compounds observed were starting material or what appeared by NMR spectroscopic analysis to be nucleophilic displacement of the methoxy group by the anion of the Lewis acid.



Scheme 54: Alternative Lewis acids for cyclisation

We wished to investigate the use of dichloromethane as a cheaper and less toxic alternative to dichloroethane for the reaction solvent. Pleasingly, performing the cyclisation reaction in CH_2Cl_2 at 40 °C resulted in a comparable yield to that seen in DCE, albeit requiring a longer reaction time (64 h compared to 40 h). The dilution of

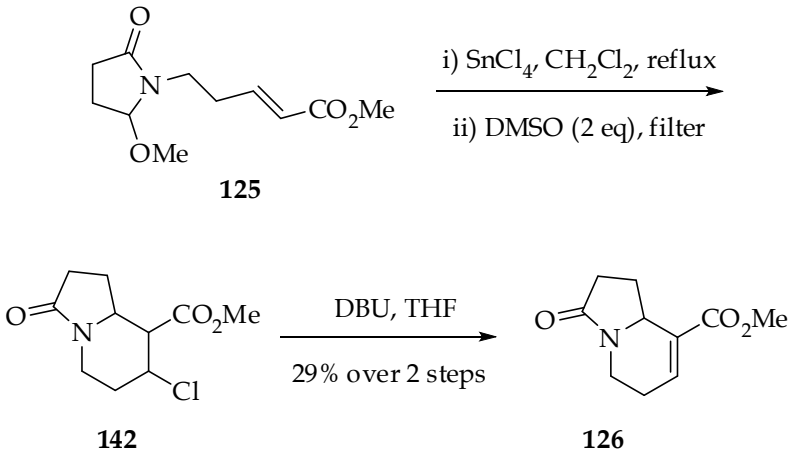
the reaction was also increased in order to reduce the possibilty of undesired polymerisation by means of intermolecular reaction of the reactive intermediate. Under these conditions, reactions on a 10–20 mmol scale consistently gave 29–36% yield of **126** over the two steps (Scheme 55).



Scheme 55: $SnCl_4$ cyclisation in CH_2Cl_2 followed by elimination

Although a marginal improvement in the yield for the cyclisation had been achieved, we still wished to investigate other methods. A patent by Eli Lilly and Co. describes a procedure using DMSO to remove tin(IV) chloride from waste streams by forming an $SnCl_4$·2DMSO complex which is insoluble in a range of alcoholic and hydrocarbon solvents.[134] It was hence envisioned that DMSO could be used to quench the tin salts in the cyclisation reaction as an alternative work-up procedure, which could improve the mass recovery and, consequently, the yield of the reaction. First, however, it was necessary to check that the complex was not soluble in dichloromethane, the reaction solvent. When two equivalents of DMSO were added to a solution of $SnCl_4$ in dichloromethane, a white solid immediately formed which could be filtered to leave a clear solution.

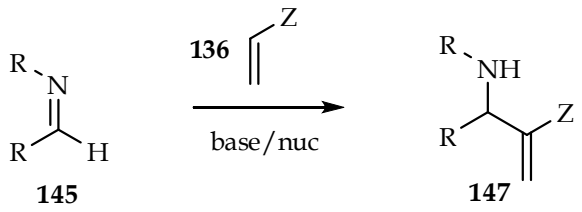
The DMSO quench was next tested in the cyclisation reaction itself, where satisfyingly, a large amount of white complex precipitated out of solution. Unfortunately, a slight solubility in the reaction solvent meant that complete removal of the complex could not be easily achieved, which led to problems in the following step and as such, no improvement in yield was seen (Scheme 56). Nevertheless, the DMSO technique avoids the possibility of ester hydrolysis during work-up and is more facile than the previous NaOH quench, making it a practical option for larger scale synthesis.



Scheme 56: Incorporation of the DMSO quench for the cyclisation reaction

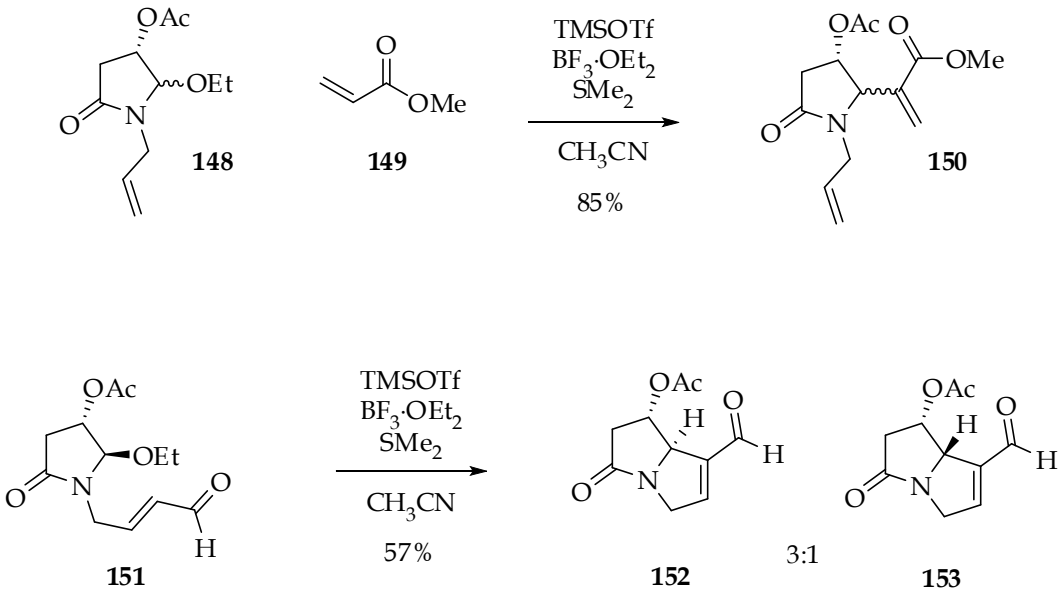
3.2.2.3 Aza-Baylis–Hillman reaction

Finally, we chose to investigate the aza-Baylis–Hillman reaction as an alternative way to improve the cyclisation/elimination sequence. The aza-Baylis-Hillman (ABH) reaction generally involves addition of a catalytic quanitity of a nucleophile onto a Michael acceptor, **136**, and subsequent coupling of the α-position with an imine of type **145** to give adducts of type **147** (Scheme 57).[135,136]



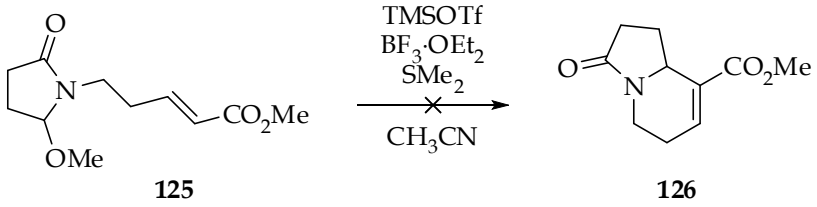
Scheme 57: General scheme for the Aza-Bayliss-Hilman reaction

It was reasoned that it should be possible to effect this transformation with an acyliminium ion as the electrophile, since it should be more reactive than an imine. Indeed, Aggarwal and co-workers demonstrated this using ethoxylactams **148** and **151** with TMSOTf/$BF_3{\cdot}OEt_2$ to form the acyliminium ions and dimethyl sulfide as the nucleophile for the aza-Baylis–Hillman reaction. Both inter- and intramolecular examples were reported (Scheme 58).[137]



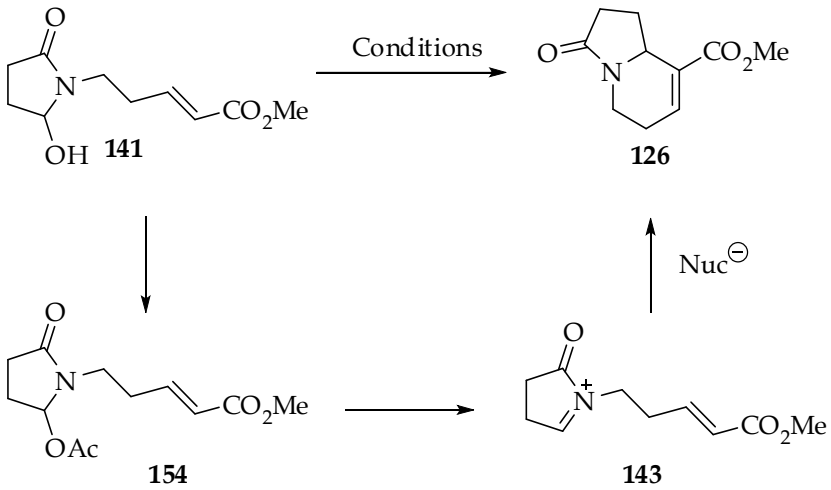
Scheme 58: Aggarwal's ABH reactions of an acyliminium ion

Unfortunately, when we tried this procedure with methoxylactam **125**, none of the desired product **126** was seen (Scheme 59).



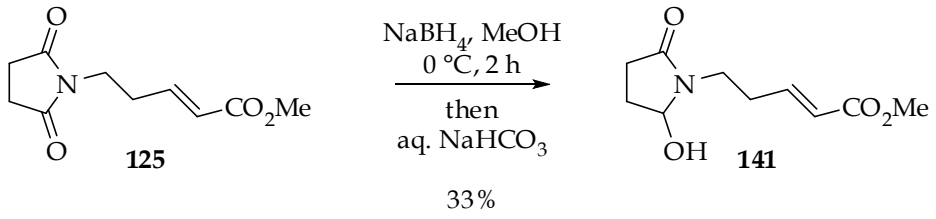
Scheme 59: Attempt at Aggarwal's ABH reaction with methoxylactam 125

According to a review by Speckamp and Hiemstra, where the alkoxylactam bears an acetate or mesylate as a leaving group, no catalyst is required to form the acyliminium ion.[132] It was therefore conceived that if an acetoxylactam **154** was formed *in situ*, it might be possible to achieve the synthesis of lactam **126,** without having to go through compound **142,** by effecting an aza-Baylis–Hillman-type reaction with acyliminium ion **143** (Scheme 60).



Scheme 60: Desired Aza-Baylis–Hillman reaction

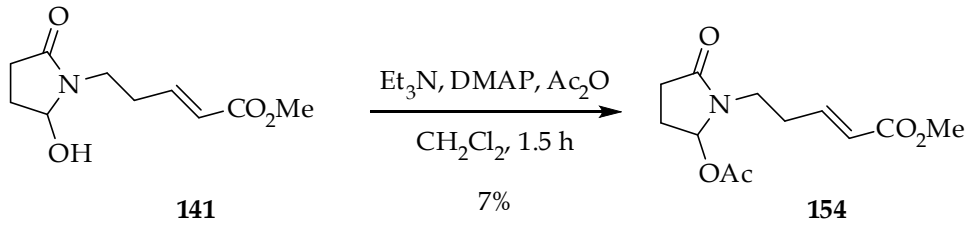
The hydroxylactam **141** could be made by acid hydrolysis of methoxylactam **125** or from reduction of imide **140**, using a non acidic work-up. Using the latter method gave **141** in 33% yield (Scheme 61). Although the data for this compound does not fit with those reported in the literature,[100] our evidence strongly suggests that the correct compound had been formed. In addition to mass spectrometry giving the correct mass for the sodium adduct, ^{1}H NMR spectroscopy showed a clear coupling (J = 8.5 Hz) between the alcohol proton and the proton alpha to the nitrogen. When we previously attempted to make **141** using the conditions reported in the literature,[100] instead only methoxylactam **125** was observed *(vide supra*, Scheme 51). This suggests that hydroxylactam **141** may not have been formed in the original paper.



Scheme 61: Preparation of the hydroxylactam 141

On attempting mesylation of this hydroxylactam, elimination of the resulting mesylate was seen and so no further attempts were made to prepare this compound. In contrast, the acetoxy compound **154** could be easily formed by treatment of hydroxylactam **141** with acetic anhydride in the presence of base and catalytic DMAP, leading to a near quantitative yield based on mass recovery and ^{1}H NMR analysis of the unpurified product. This compound was isolated for characterisation, although, it was inevitably

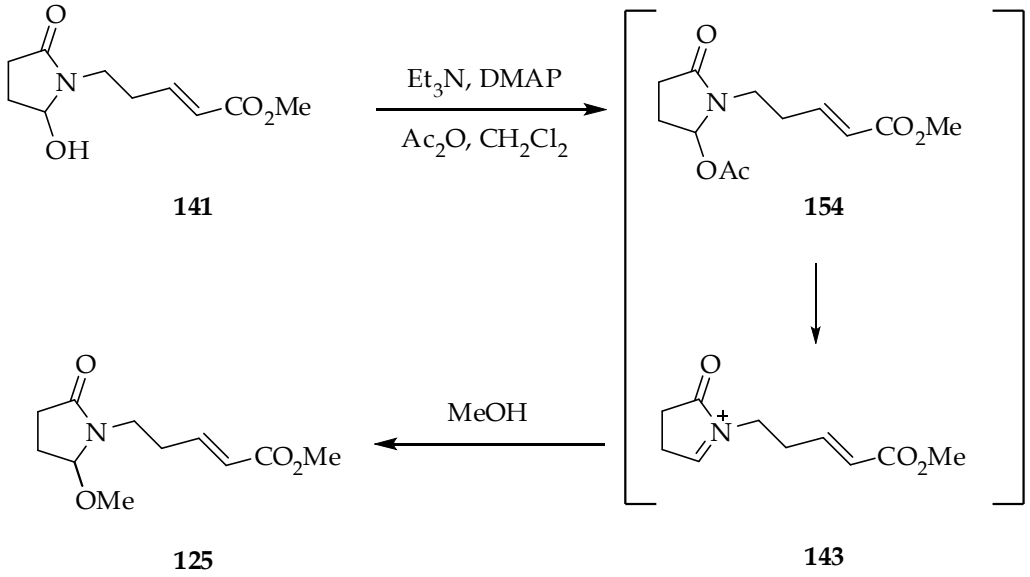
prone to hydrolysis back to the starting hydroxylactam **141**, thus giving a low isolated yield following purification (Scheme 62).



141 **154**

Scheme 62: Formation of acetoxylactam 154

Treatment of the reaction mixture containing acetoxylactam **154** with methanol led to formation of the methoxylactam **125**, suggesting that **154** does indeed form the acyliminium ion **143** under the reaction conditions (Scheme 63).

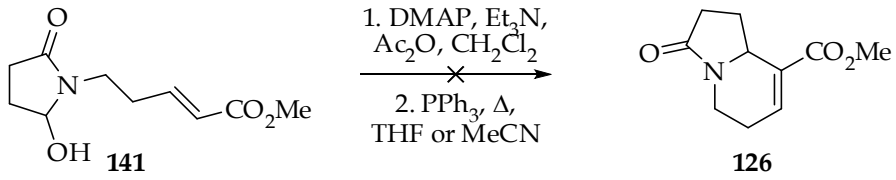


141 **154**

125 **143**

Scheme 63: Formation of acetoxylactam 154 and acyliminium ion 143

Although a number of attempts were made to effect the desired cyclisation using acetate **154**, none were successful. DMAP has been shown to be an effective base in Aza-Baylis-Hillman reactions,[136] and therefore it was conceived that heating the reaction vessel following acylation with DMAP still present should initiate the desired cyclisation. In some cases, additional Et_3N and PPh_3 were added as an alternative nucleophile, and the solvent was also replaced with THF or acetonitrile. However, unfortunately, no product **126** was ever observed.

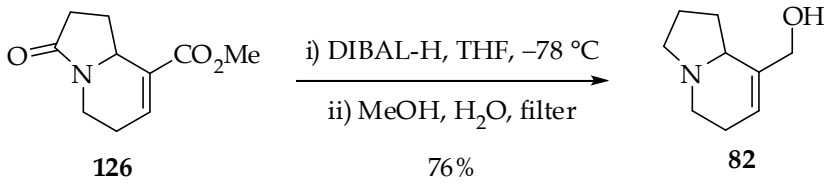


Scheme 64: Failed attempts at an ABH reaction

Given these difficulties we therefore continued using **126** prepared by the cyclisation/elimination method previously described (Scheme 55).

3.2.2.4 Reduction

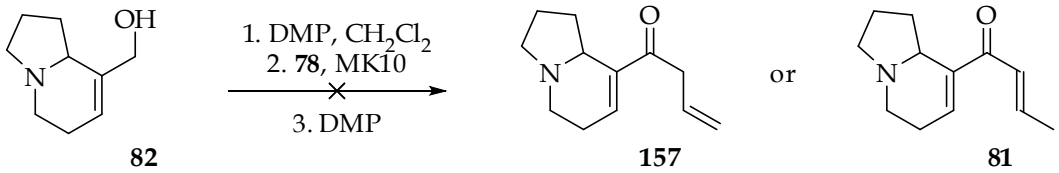
The next step of the synthesis is the reduction of ester **126** to give alcohol **82**. In Taber's route,[100] a modest yield of 44% is quoted for this reduction using DIBAL-H. In our hands, using this method, despite complete consumption of starting material only a 15% yield of product was achieved following chromatography. It was believed that these low yields were a result of the work-up procedure. Therefore, a simplified work-up was employed involving quenching with methanol and water followed by filtration of the resultant gel,[138] which served to improve the yield for this step to 76% (Scheme 65). The NMR spectroscopic data obtained for this compound were consistent with those given in the literature.[100]



Scheme 65: Reduction of 126 to alcohol 82

3.2.3 Oxidation of indolizidine alcohol 82

With alcohol **82** in hand, it was time to try to incorporate our oxidation/allylation/oxidation/isomerisation methodology. We first tested the Dess–Martin periodinane oxidation of **82**, where unfortunately, the desired aldehyde **156** appeared to have been formed, but only as one of a complex mixture of products (Table 12, entry 1). Initial attempts a one-pot oxidation/allylation/oxidation procedure from alcohol **82** to avoid isolation of the aldehyde resulted in a complex mixture and the desired unsaturated ketones **157** and **81** could not be identified (Scheme 66).

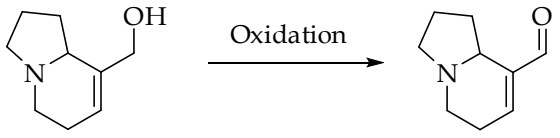


82 **157** **81**

Scheme 66: Failed attempt at an oxidation/allylation/oxidation procedure

For the oxidation of **82** to **156**, the literature describes the use of the Swern procedure, quoting a yield of 72% following column chromatography.[100] In our hands, unpurified yields were variable, ranging from 73–97% (Table 12, entry 2). Furthermore, the nature of the aldehyde and its potential limited stability, meant that it was preferable to take the unpurified material through without risking decomposition during purification. However, the unpurified residue obtained from work-up of the Swern reaction invariably contained some impurities. Thus, it was decided to investigate alternative oxidation procedures for this substrate. Buffering the Dess–Martin periodinane with sodium bicarbonate or pyridine gave little to no improvement on the previous attempt; whilst some aldehyde appeared to have formed, the residues obtained were of insufficient purity (entries 3 and 4). Manganese dioxide showed a partial reaction after 2 hours, but on trying to force complete conversion with higher temperatures or longer reaction times, the product was seen to decompose to polar material (entries 5–7). The same was true with CrO_2 (entry 8) and TPAP (entries 9 and 10). Parikh-Doering oxidation appeared to go cleanly by TLC analysis however no material was isolated as extraction from the aqueous layer proved fruitless (entry 11). It was hence deemed that Swern oxidation (entry 2) was indeed the optimum procedure.

Table 12: Oxidation of the indolizidine alcohol 82



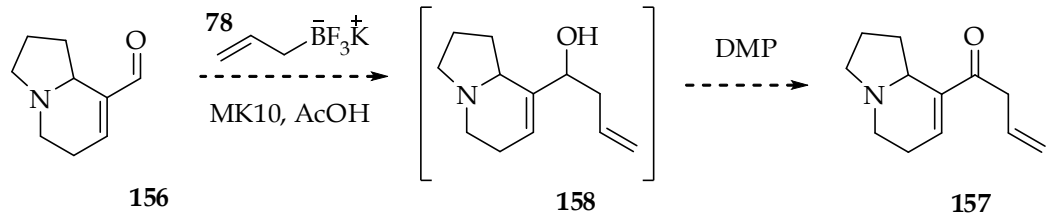
82 **156**

Entry	Oxidant	Solvent	Temperature	Observations/yield[a]
1	DMP	CH_2Cl_2	rt	Complex mixture
2	$(COCl)_2$/DMSO	CH_2Cl_2	−78 °C to rt	73–97%
3	DMP/$NaHCO_3$	CH_2Cl_2	rt	44%
4	DMP/Py	CH_2Cl_2	rt	Complex mixture
5	MnO_2	CH_2Cl_2	rt	Partial reaction, decomposed
6	MnO_2	CH_2Cl_2	reflux	Partial reaction, decomposed
7	MnO_2	PhMe	reflux	Partial reaction, decomposed
8	CrO_2	PhMe	rt	Partial reaction, decomposed
9	TPAP/O_2	CH_2Cl_2	rt	Partial reaction, decomposed
10	TPAP/NMO	CH_2Cl_2	rt	Partial reaction, decomposed
11	SO_3·Py/DMSO	CH_2Cl_2	rt	No material isolated

[a]Unpurified yield, based on mass recovery and ^1H NMR analysis of the unpurified reaction mixture; [b]CrO_2 is also known as magtrieve™

3.2.4 Allylation and oxidation of indolizidine aldehyde 156

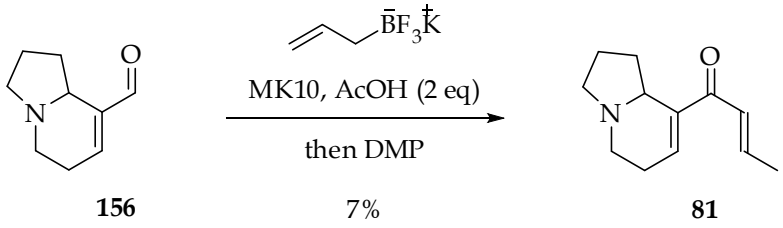
In order to allylate and oxidise the aldehyde, we wanted to use the conditions from our allylation/oxidation methodology (Scheme 67).



156 **158** **157**

Scheme 67: Desired allylation/oxidation procedure

Aldehyde **156** was subjected to the allylation conditions using potassium allyltrifluoroborate (**78**) and montmorillonite K10, although only 2 eq. of acetic acid were added due to the sensitivity of the substrate. On consumption of the starting material, Dess–Martin periodinane was added to the reaction mixture and stirred for one hour. Reasonable mass recovery was seen following work-up, but it appeared that the desired product **157** had not been formed, as the alkene peaks visible in the ^{1}H NMR spectrum were not as expected. Further analysis revealed that in fact the β,γ-unsaturated ketone **157** had isomerised to the α,β-unsaturated ketone **81** under the reaction conditions (Scheme 68). Disappointingly, a large loss of product was seen following purification by column chromatography, yielding only 7% of **81** from aldehyde **156**.

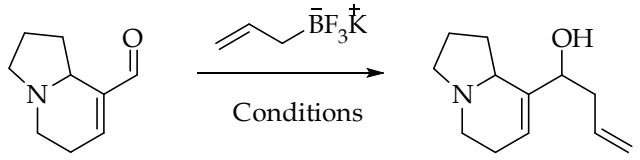


156 7% **81**

Scheme 68: Formation of dienone 81

It was decided to first look at optimising the individual steps for this substrate, starting with the allylation. Using water instead of acetic acid with the montmorillonite K10 clay, as per the original publication,[74] a 38% yield of **158** was achieved following purification (Table 13, entry 1). $BF_3{\cdot}OEt_2$ allylation gave a poor yield of 16% (entry 2). Montmorillonite K10 with two equivalents of acetic acid gave material that was sufficiently pure to take on without chromatography, with a 48% unpurified yield (entry 3). It was thought that the relatively low mass recovery observed in each case may be due to the water solubility of the product and so a non-aqueous work-up was tested on the MK10/H_2O system, whereby a simple filtration through silica was performed. This resulted in a slightly improved 45% yield following purification (entry 4).

Table 13: Allylation of the indolizidine aldehyde 156



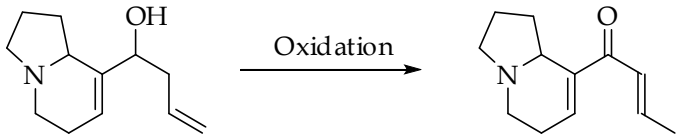
156 **158**

Entry	Catalyst system	Work-up used	Yield (%)[a]
1	MK10/H_2O	Aqueous	38
2	BF_3·OEt_2	Aqueous	16
3	MK10/AcOH	Aqueous	48[b]
4	MK10/H_2O	Non-aqueous filtration	45

[a] Isolated yield following column chromatography; [b] Unpurified yield

This demonstrated that the allylation could be performed in either acetic acid or water, both giving moderate yields. Given that the allylation step on its own proceeded well in acetic acid, it would appear that the DMP oxidation was the problematic step in the allylation/oxidation procedure detailed previously in Scheme 68. Our efforts now turned to investigating alternative oxidation procedures which are outlined in Table 14.

Table 14: Oxidation of the indolizidine allylic alcohol 158



158 **81**

Entry	Oxidation system	Observations/yield[a]
1	PCC	Complex mixture of products
2	MnO_2	No reaction
3	TPAP/O_2	No reaction
4	Buffered DMP	Non-aqueous work-up, no product seen
5	Swern	26%

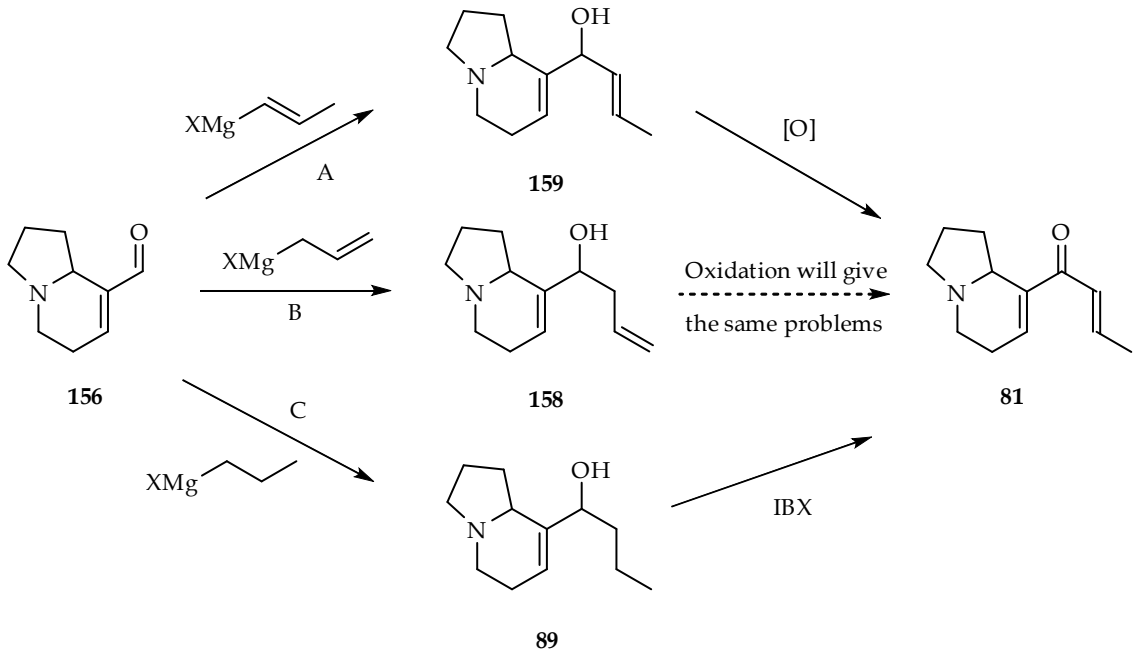
[a] Isolated yield following purification

Dess–Martin periodinane buffered with sodium bicarbonate offered no improvement to the previous procedure. In this case, a simple filtration was employed as work-up in case water solubility was an issue but no product was observed in the ^{1}H NMR spectrum of the unpurified material. Pyridinium chlorochromate, manganese dioxide and TPAP/O_2 showed no reaction. The standard Swern procedure offered the best result, with complete conversion of starting material seen by TLC and NMR spectroscopic analysis. However, only a 26% yield of dienone **81** was obtained; the low yield of the reaction may be partly attributed to difficulties in purification of the polar dienone.

In view of the disappointing yields observed with the oxidation/allylation/oxidation approach to dienone **81**, other routes were investigated.

3.2.5 Alternative routes to dienone 81

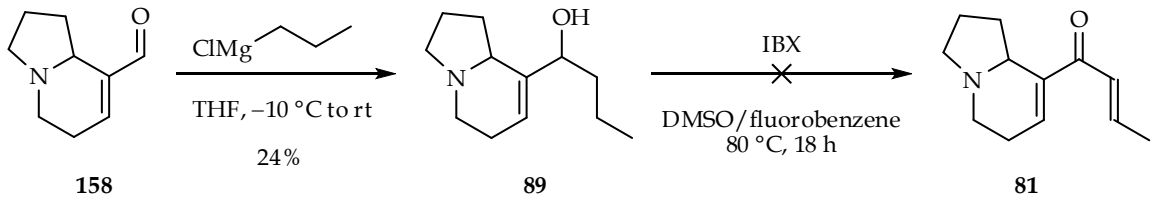
As an alternative to the allylation/oxidation approach, different routes from aldehyde **156** to enone **81** were probed (Scheme 69).



Scheme 69: Possible alternatives to the allylation/oxidation approach

Since Route B involves the same oxidation step that had caused problems with the previous approach, and Route A involves a very similar oxidation of **159** to **81**, the most promising of these possibilities was Route C, which utilises Nicolaou's IBX oxidation to transform elaeokanine B (**89**) into the desired dienone **81**.[35]

Grignard addition of propylmagnesium chloride to **156**, to give **89**, was achieved in a moderate 24% yield (Scheme 70). The subsequent IBX oxidation, however, proved highly problematic. Whilst the reaction appeared successful, with complete consumption of starting material and apparent appearance of dienone **81** observed by TLC analysis, extraction of the product from the DMSO was less successful.



158 **89** **81**

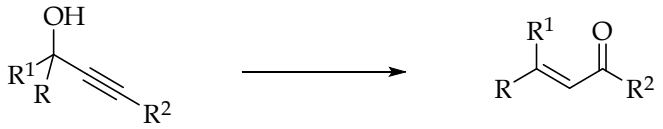
Scheme 70: Attempted IBX oxidation

Following the published work-up procedure,[35] no product was extracted into the organic layer. Treatment of the aqueous layer with 4 M NaOH did not aid this, and further extractions with dichloromethane, chloroform and ethyl acetate also failed to yield any product. Extraction with butan-2-ol served only to isolate the DMSO and unreacted IBX.

The reaction was repeated in deuterated DMSO in order to verify by NMR analysis whether the reaction had been successful. Once the fluorobenzene had been removed *in vacuo*, a ^{1}H NMR spectrum of the unpurified reaction mixture was obtained but disappointingly, none of the desired product **81** was visible. The starting material appeared to have been consumed and whilst IBX was clearly present, no other products could be identified.

3.2.5.1 The Meyer–Schuster reaction

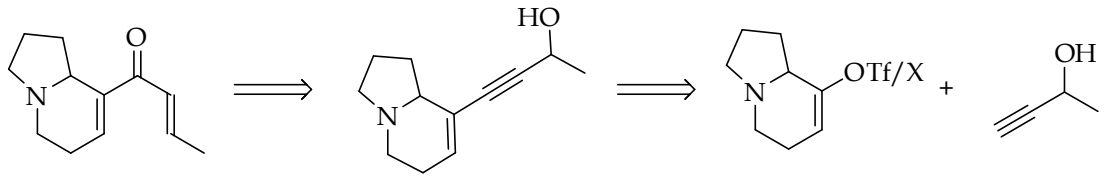
Due to the limited success with the oxidation/allylation/oxidation procedure, an initial investigation was made into the Meyer–Schuster reaction as an alternative method for installing the enone moiety. The Meyer–Schuster reaction is the re-arrangement of a propargylic alcohol into an enone whereby the placement of the unsaturation and oxygen functionality are reversed (Scheme 71).[139]



160 **161**

Scheme 71: General scheme for the Meyer–Schuster rearrangement

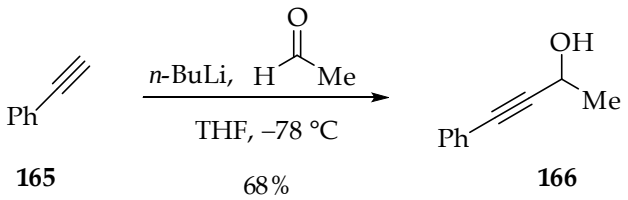
Retrosynthetically, for our desired compound **81** this would take us back to **162**, which could in turn be synthesised by Sonogashira coupling of **163** and **164**, using a vinyl halide or triflate **163** as an alternative handle for the indolizidine core (Scheme 72).



81 **162** **163** **164**

Scheme 72: Retrosynthetic analysis using the Meyer-Schuster reaction as a key step

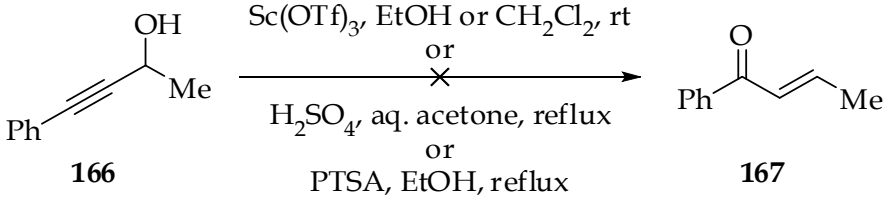
A test substrate for the Meyer–Schuster reaction was prepared by deprotonation of phenylacetylene (**165**) with *n*-BuLi and subsequent addition of acetaldehyde, which provided propargylic alcohol **166** in 68% yield (Scheme 73).



165 68% **166**

Scheme 73: Formation of propargylic alcohol 166

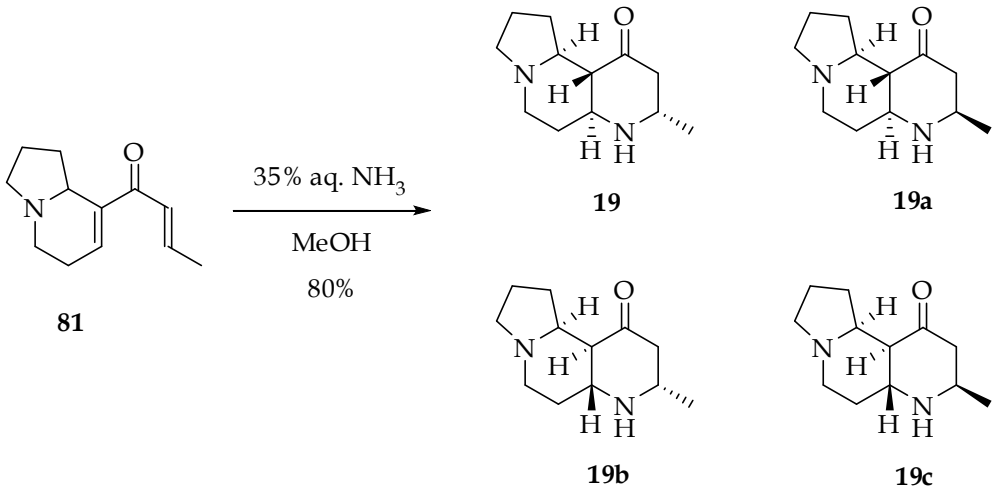
To our disappointment, none of the literature conditions attempted gave any rearrangement, including scandium triflate in either ethanol or dichloromethane,[139] sulfuric acid in aqueous acetone,[140] or *p*-TSA in ethanol at reflux (Scheme 74).[141]



Scheme 74: Failed Meyer–Schuster reactions

3.2.6 Ammonia Cyclisation

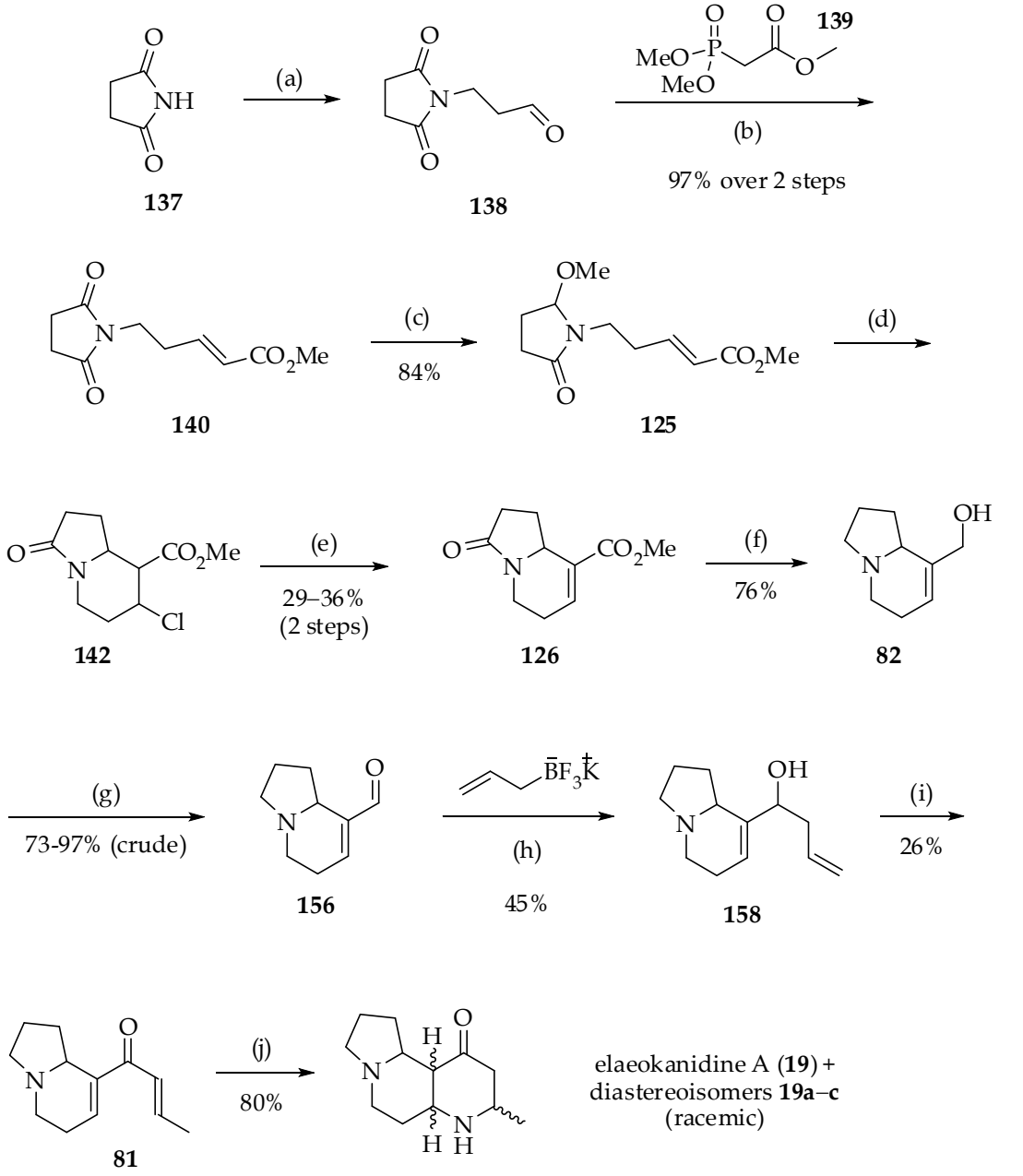
With a small quantity of dienone **81** in hand, obtained from the previous oxidation/allylation/oxidation chemistry, the final step in the synthesis was the ammonia cyclisation. The dienone was treated with 35% aqueous ammonia in methanol and allowed to stir for 16 h (Scheme 75). TLC analysis showed complete consumption of starting material **81** whilst ^{1}H NMR spectroscopic analysis of the unpurified product revealed that both the double bonds were no longer present and doublets corresponding to the methyl groups were clearly visible. This evidence suggested that a mixture of elaeokanidine A (**19**) and its diastereomers **19a–c** had been formed; this was confirmed by HRMS ([MH]$^+$ 209.1654) but unfortunately, no further information could be obtained by NMR spectroscopic analysis and attempts at separating the mixture by flash column chromatography were unsuccessful. Due to lack of material and time, this concluded the work on the racemic synthesis of elaeokanidine A (**19**).



Scheme 75: Ammonia cyclisation with possible products (relative stereochemistry shown)

3.2.7 Summary of racemic route

Following optimisation of the various steps, our racemic route to the indolizidine core of elaeokanidine A, and subsequent completion of the synthesis to give an inseparable mixture of diastereoisomers, is summarised in Scheme 76.



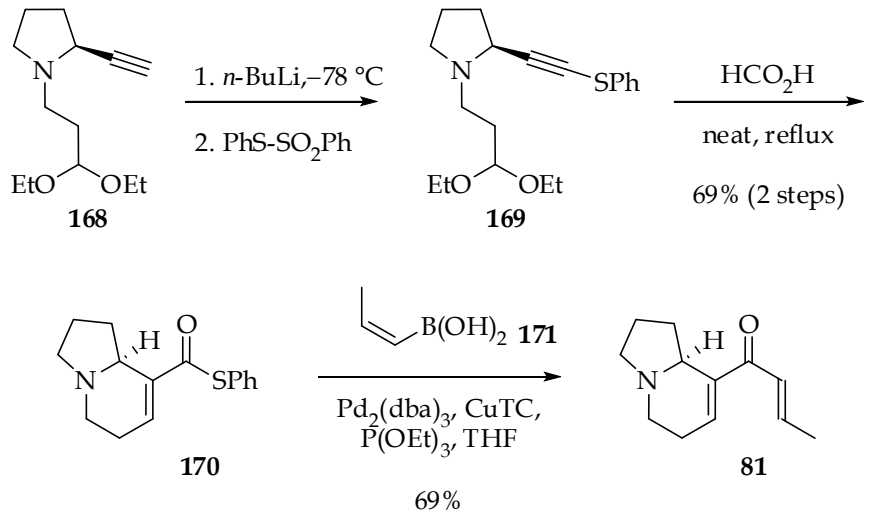
Reagents and conditions: (a) Na, acrolein (**75**), EtOH, rt, 3 h; (b) K_2CO_3, THF, H_2O, rt, 16 h; (c) *i)* NaBH4, MeOH, 0 °C to rt, 1 h; *ii)* conc. HCl; (d) $SnCl_4$, CH_2Cl_2, 40 °C, 64 h; (e) DBU, THF, 60 °C, 24 h; (f) DIBAL-H, THF, −78 °C, 1 h; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h; (h) MK10/H_2O, CH_2Cl_2, rt, 30 min; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 30 min; (j) 35% aq. NH_3, MeOH, 16 h.

Scheme 76: Progress towards the synthesis of elaeokanidine A

3.2.8 Further work

At a similar time to this work, James Cuthbertson was working on the synthesis of the alkaloids grandisine B (**94**) and grandisine D (**95**). As part of this project, an alkyne-acetal cyclisation methodology to gain access to α,β-unsaturated carbonyls was developed, the utility of which was demonstrated in the construction of an indolizidine framework for the synthesis of grandisines B and D.[142,143] This procedure was subsequently applied to the asymmetric synthesis of elaeokanidine A, using proline-derived alkyne **168** as a common intermediate.

Deprotonation of the alkyne followed by quenching with S-phenyl benzenethiosulfonate provided thiol **169**, which was then subjected to the cyclisation conditions. Stirring in formic acid at reflux afforded thioester **170** in 69% over the two steps, having formed the key indolizidine core. This was followed by a Liebeskind-Srogl coupling with boronic acid **171** to give enantiomerically pure dienone **81** in 43% yield (Scheme 77).



Scheme 77: Asymmetric route to dienone 81

On treatment with aqueous ammonia, as in the racemic series, an inseparable mixture of compounds was formed, thought to be elaeokanidine A and its diastereoisomers. These are likely to include elaeokanidines B and C, whose relative stereochemistry are unknown. Although complete separation of the diastereoisomers could not be achieved by chromatography, a sample enriched in elaeokanidine A (**19**) was obtained,

the identity of which was confirmed by comparison to the isolation data and NOE studies (Figure 11).[88]

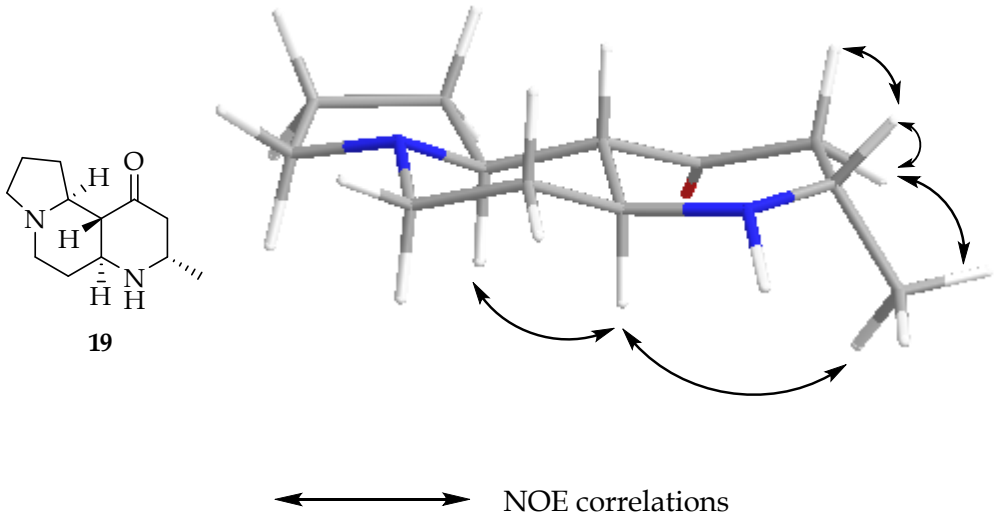
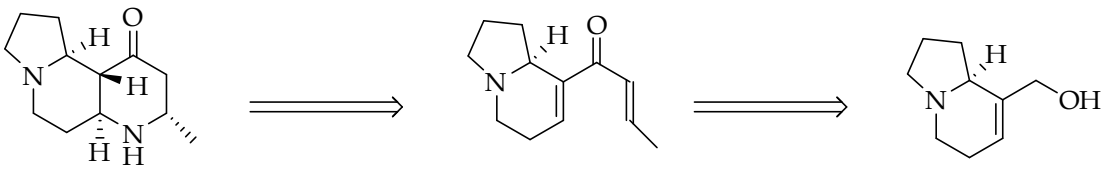


Figure 11: Structure and NOE correlations of elaeokanidine A (19)

Unfortunately the sample obtained was not of sufficient purity to obtain an optical rotation measurement in order to determine the absolute stereochemistry of the natural product. Further work to completely separate the diastereoisomers is thus required. The work detailed in this section was published in Cuthbertson's PhD thesis.[144]

3.3 Summary and future work



19 **81** **82**

Good progress was made following Pohmakotr's route towards **82** however this was halted by a lack of reproducibility with the cyclisation step. Following Taber's synthesis, the route to **82** has been repeated several times and each step has been optimised, providing an improved racemic synthesis of the indolizidine core. Application of the oxidation/allylation/oxidation/isomerisation methodology to this alcohol was not as successful as we had anticipated, however alternative conditions

have been investigated for the preparation of racemic **81** and the subsequent addition of ammonia was demonstrated.

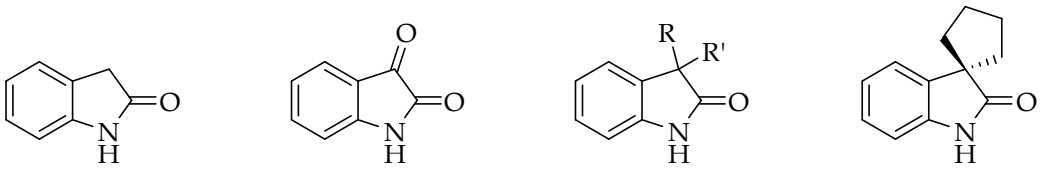
Further work by Cuthbertson successfully established a proline-derived asymmetric synthesis of dienone **81**, making use of an alkyne-acetal cyclisation reaction. Following addition of ammonia to provide a mixture of diastereoisomers, a sample enriched in elaeokanidine A was obtained, however, the purity of the sample was not sufficient to record an optical rotation, thus the absolute stereochemistry of the alkaloid cannot be confirmed at this stage.

Further studies will investigate alternative methods for separation of the isomeric alkaloids in order to obtain pure samples of elaeokanidine A along with its isomers for full characterisation.

Chapter 4 – Copper(II)-catalysed formation of spirooxindoles

4.1 Introduction to oxindoles and spirooxindoles

Oxindole (**171**) is a bicyclic aromatic heterocycle with a benzene ring fused to a pyrrolidinone (Figure 12), and is structurally related to the naturally occurring compound isatin (**172**). Structurally more complex 3,3-disubstituted oxindoles **173** are common in nature and as a consequence, are of great interest to synthetic chemists. For example, many stereoselective methods for the formation of 3,3-disubstituted oxindoles have been developed, such as the enantioselective hydroxyamination,[145,146] or fluorination of 3-oxindoles,[147] as well as the conjugate addition of oxindoles to Michael acceptors,[148-150] and asymmetric decarboxylative allylation.[151]



171 **172** **173** **174**

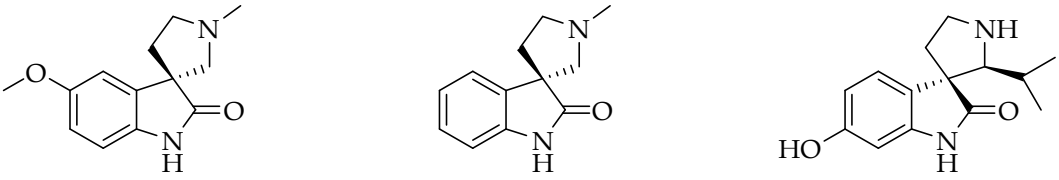
Figure 12: Oxindole compounds

Both oxindoles **171** and spirooxindoles **174** are important motifs in organic and medicinal chemistry, not only because they possess a structurally interesting framework, but also owing to the biological activity that many of these compounds exhibit. As a result, over recent years, much effort has been devoted to developing innovative ways to synthesise these structures rapidly and efficiently.[152-155]

Spirooxindoles **174** are a class of oxindole with a 3,3-spirocyclic junction. These compounds are extremely common in nature as part of natural products as well as many synthetic drugs.[152]

4.2 Important spirooxindole compounds

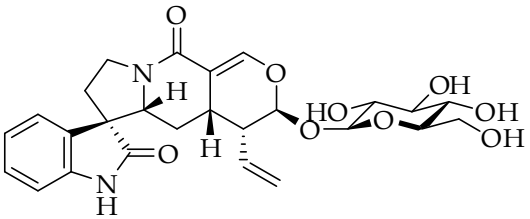
Compounds containing the spirooxindole motif frequently display a range of interesting biological activities, whether these be naturally occurring molecules or medicinally relevant analogues.[152] As well as several other classes of bioactive oxindole structures, a large number of pyrrolidine-containing spirocyclic oxindole natural products exist, and these have been the subject of much investigation in recent years.[152,154] An example of such a natural product is the analgesic horsfiline (**175**), which was isolated from the plant *Horsfieldia superba*,[156] and has already succumbed to a number of total syntheses.[157-164] Structural relatives of horsfiline (**175**) such as coerulescine (**176**),[165] and elacomine (**177**),[152,166] have also been studied in great detail (Figure 13).



(–)-horsfiline (**175**) (–)-coerulescine (**176**) (+)-elacomine (**177**)

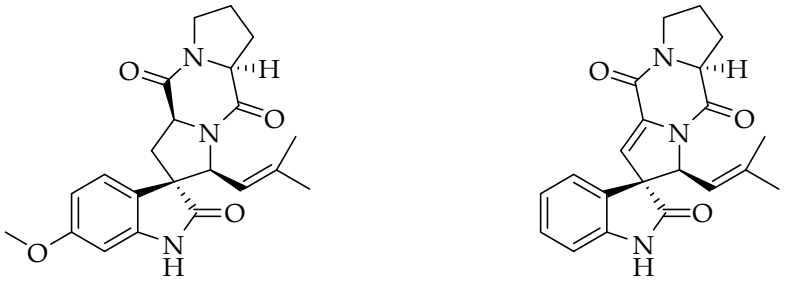
Figure 13: Horsfiline (175) and related natural products

Extracts from the leaves of *Alangium javanicum*, collected in Malaysian Borneo, were found to induce Cu^{2+}-dependent DNA strand scission,[167,168] and this property was attributed to the indole glycoside javaniside as the active component (**178**). DNA cleavage may be an important process in the treatment of cellular disorders and javaniside is therefore a potentially useful lead compound in the development of novel drugs for the therapy of cancer and certain other diseases.[167,168]



javaniside (**178**)

As a further example, spirotryprostatins A and B (**22** and **180**) were isolated in 1996 and have since been synthesised numerous times due to their interesting structure and biological profiles as mammalian cell cycle inhibitors (Figure 14).

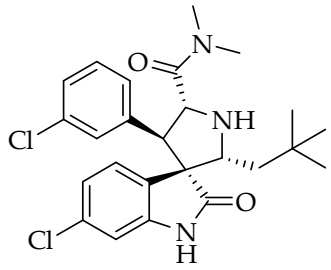


spirotryprostatin A (**22**) spirotryprostatin B (**180**)

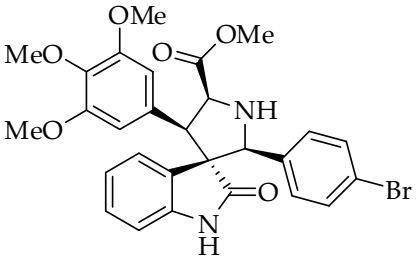
Figure 14: Spirotryprostatins A (22) and B (180)

In addition to natural products themselves, their analogues, as well as compounds inspired by natural product structures, are often developed as potential drug molecules. For instance, Wang and co-workers used a rational structure-based design in the discovery of a potent MDM2-binding compound **181** (Figure 15).[169] MDM2 is known to interact with the tumour suppressor protein p53, and thus the nature of this interaction was the basis for drug design. The oxindole core of **181** closely mimics the indole of tryptophan, the amino acid residue of p53 identified as being the most critical for protein binding. Two other important residues, phenylalanine and leucine, are mimicked by the phenyl ring and the *tert*-butyl group respectively, with the pyrrolidine ring providing a rigid backbone for the compound. The molecular architecture of this drug is indeed reminiscent of the spirotryprostatin structure.

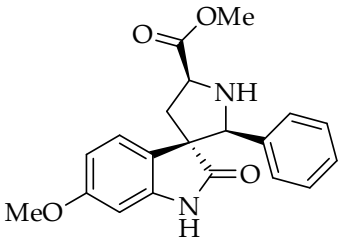
A range of structurally similar compounds were prepared by Waldmann's group, one of which, **182**, was submitted for biological evaluation and found to interfere with microtubule polymerisation, ultimately leading to incomplete cell division (Figure 15).[170] It therefore has potential use in cancer therapy. The Proctor group have also been developing a samarium-mediated route to spirotryprostatin-inspired molecules (*e.g.*, **183**) which are currently undergoing biological evaluation (Figure 15).[171]



181



182



183

Figure 15: Potential spirooxindole drug candidates

We were ourselves also interested in the spirotryprostatin natural product family and our work in the area will be discussed in Chapter 5.

Given the evident abundance and importance of spirocyclic oxindoles, the following section focuses on the synthetic methods towards these structural units.

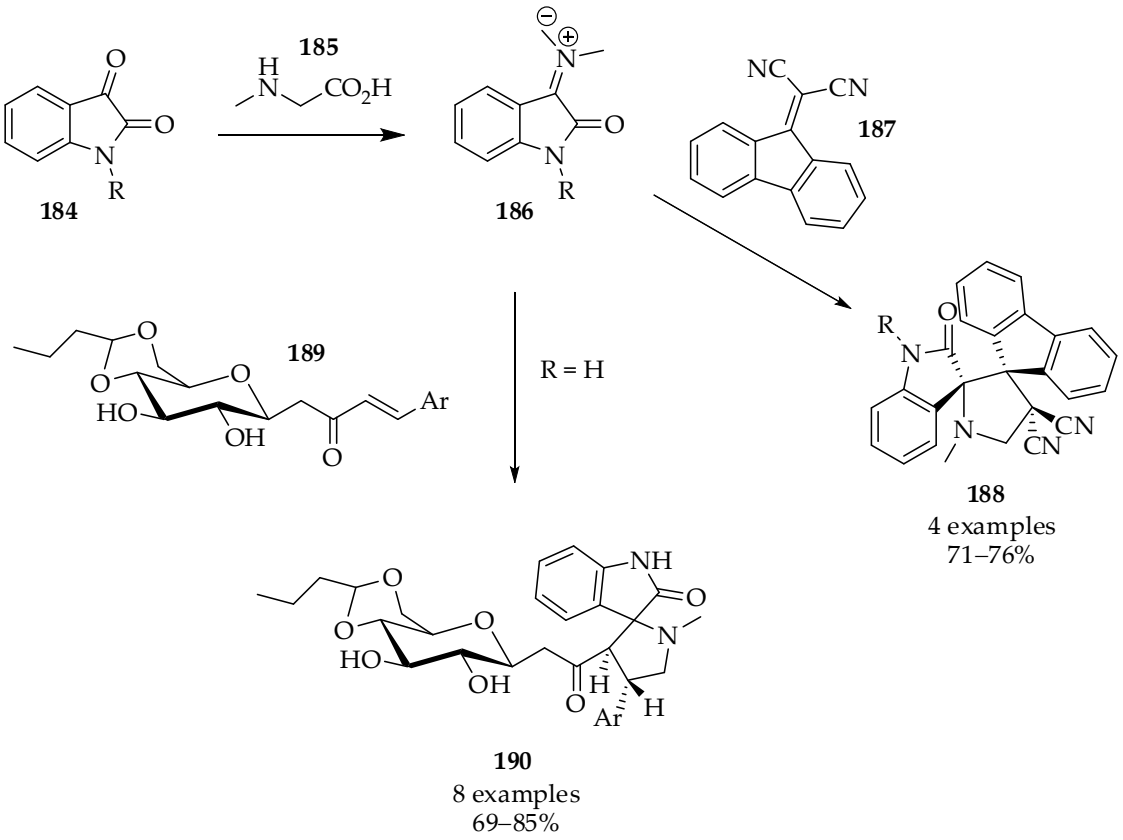
4.3 Current methods for spirooxindole formation

A large number of spirooxindole natural products have been isolated over the years, with more and more coming to light as time progresses.[172] As such, interest in this field has grown, resulting in vast arrays of publications in recent literature for the construction of spirooxindole structures.[154] Given recent reviews in this area, only publications post-2010 will be discussed.

4.3.1 Isatin-derived methods

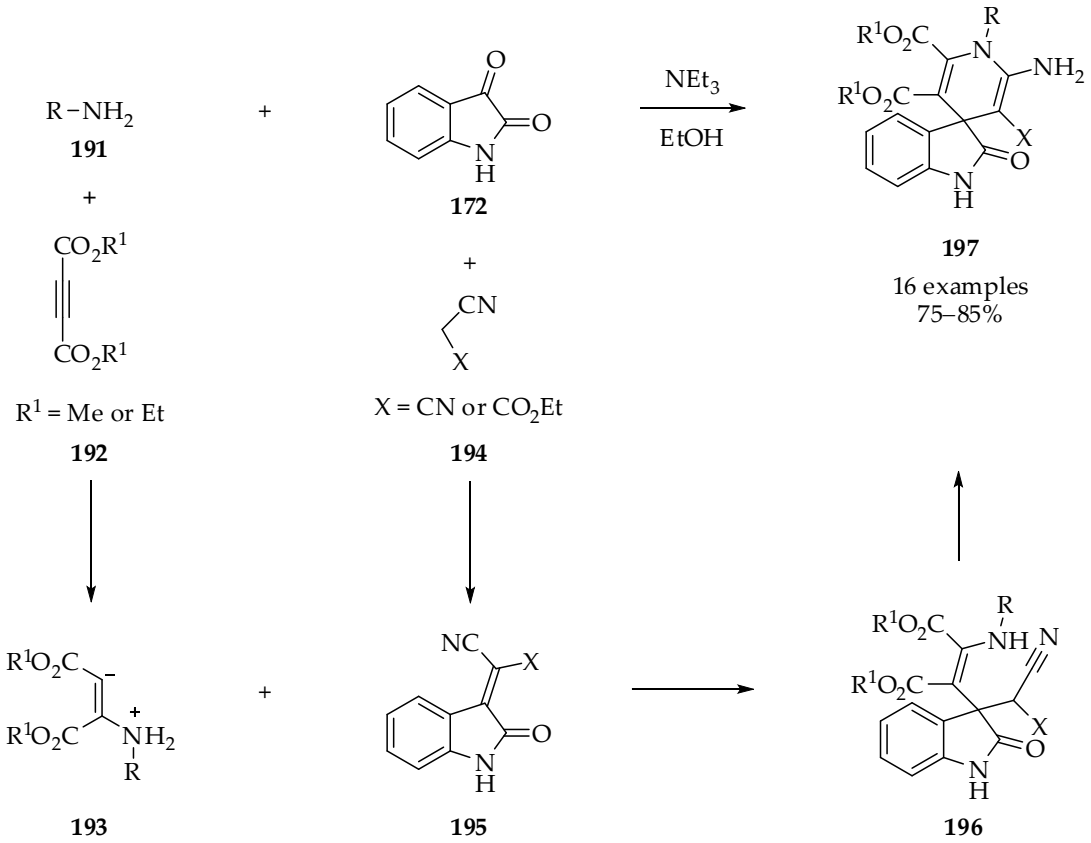
Many of the methods for spirooxindole formation focus on the derivatization of isatin (**172**), a naturally occurring molecule and in recent literature, multiple procedures were unveiled for using isatin-type molecules to create spirooxindole scaffolds.

Several of these protocols involve cycloaddition reactions, such as the Diels–Alder reaction,[173] and dipolar cycloadditions,[174,175] and frequently involve the use of azomethine ylides.[176,177] For instance, Bhati and co-workers used isatin-derived molecules **184** as a starting point for making azomethine ylides **186**, which then underwent a [3+2]-dipolar cycloaddition with alkene **187** to yield complex spirooxindoles **188** with very high regioselectivity (Scheme 78).[178] A very similar procedure was used by Das *et al.* in the synthesis of sugar-based pyrrolidine spirooxindoles **190** (Scheme 78).[179]



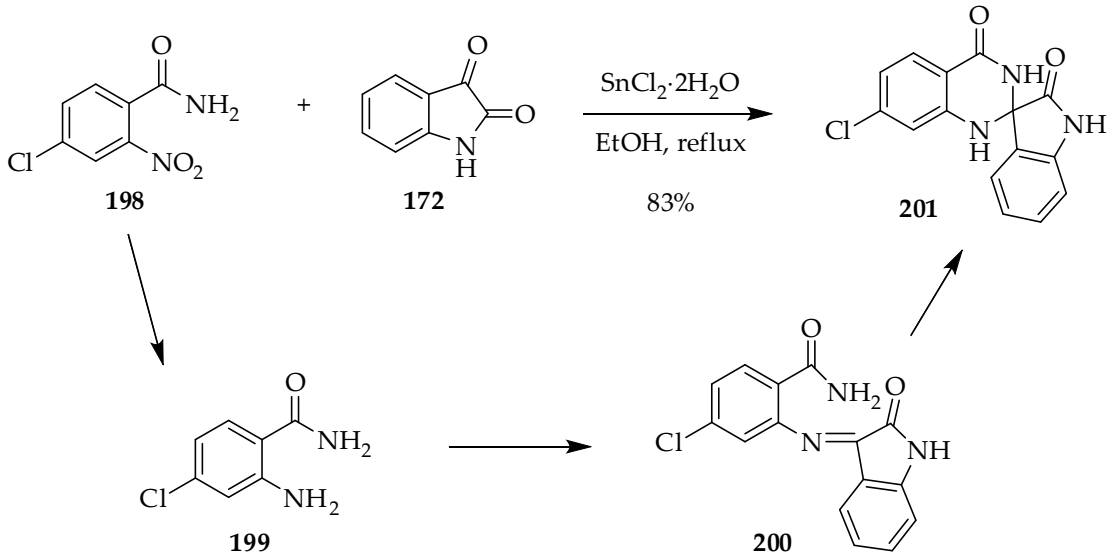
Scheme 78: Spirocyclic oxindole formation *via* azomethine ylides

Numerous multicomponent reactions for the synthesis of drug-like molecules have also been reported.[180-184] For example, Perumal and co-workers developed a 4-component synthesis of spiro-dihydropyridines **197** (Scheme 79).[180] The proposed mechanism is that an initial reaction of amine **191** and alkyne **192** forms zwitterion **193** and is followed by a 1,4-addition to Michael acceptor **195**, formed by Knoevenagel condensation of isatin (**172**) and **194**. Intramolecular cyclisation of **196** and tautomerization then forms the product **197**.



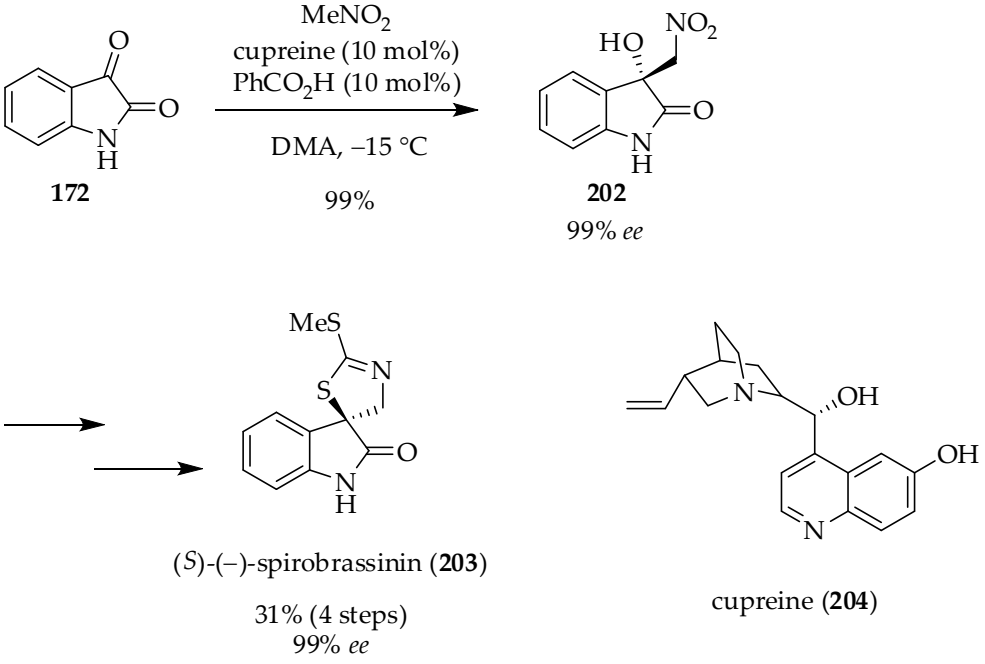
Scheme 79: Perumal's multicomponent approach to spirooxindoles

Shi and co-workers have demonstrated a process using tin dichloride, whereby a tandem reduction/cyclisation mechanism is proposed (Scheme 80). The tin(II) first reduces the nitro group of **198** to an amine **199**, then activates isatin (**172**) ready for attack. Cyclisation then occurs *via* an acetal-type mechanism to give the product **201**.[185]



Scheme 80: Shi's tin(II) dichloride reduction/cyclisation

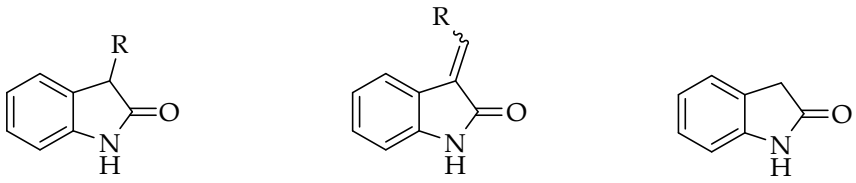
A number of asymmetric isatin-derived reactions towards spirooxindoles have also been reported. For example, Bencivenni and co-workers performed a Pictet-Spengler reaction of tryptamines with isatins, using a BINOL-derived chiral phosphoric acid catalyst to form a range of spirooxindoles in good yields and enantioselectivities.[186] Wang and co-workers performed an asymmetric Henry reaction of isatin (**172**) with nitromethane in the presence of a chiral organocatalyst cupreine (hydroxycinchonine) (**204**) to form 3,3-disubstituted oxindole **202** which, after further manipulation, was cyclised to give the natural product (*S*)-(−)-spirobrassinin (**203**) in high enantioselectivity following recrystallisation (Scheme 81).[187]



Scheme 81: Wang's synthesis of (*S*)-(−)-spirobrassinin

4.3.2 Other methods from oxindoles

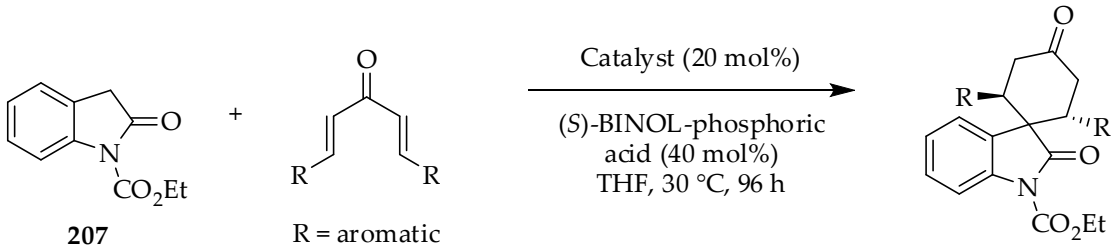
In addition to isatin-derived methods, many methods for the formation of spirooxindoles involve manipulation of precursors which already contain the core oxindole structure, such as 3-substituted-oxindoles **205**, 3-alkenyl-oxindoles **206**, or indeed unsubstituted oxindole itself (**171**) (Figure 16).[188]



205 **206** **171**

Figure 16: Oxindole compounds utilised for spirooxindole formation

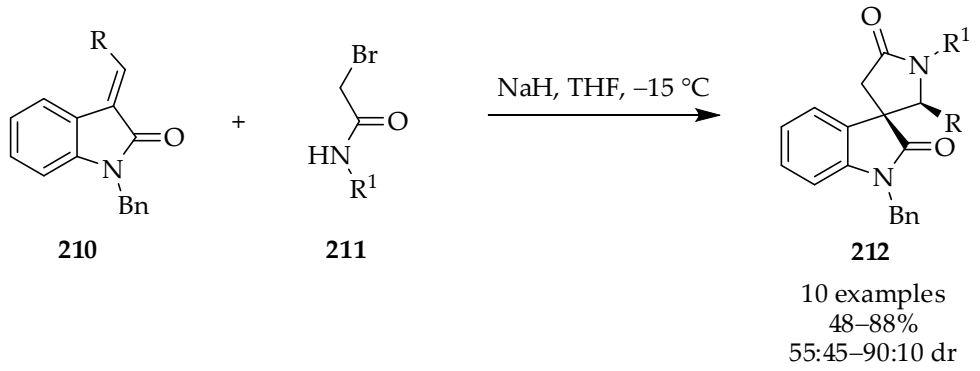
Wang and co-workers performed a double Michael addition of unfunctionalised oxindole **207** to a variety of symmetric dienones **208** using a cinchona-based catalyst to provide product **209** with good to excellent enantioselectivity (Scheme 82).[189]



207 **208** **209**
14 examples
22–96%
83–98% *ee*

Scheme 82: Wang's asymmetric double Michael addition

Daïch *et al.* synthesised spiro-γ-lactam oxindoles **212** from α-bromoacetamides **211** and methylene oxindoles **210** *via* an aza-Michael-initiated ring closure (Scheme 83).[190] As such, a variety of pyrrolidinone spirooxindole products **212** were obtained in moderate to good yields and a range of diastereoselectivities. Wang and co-workers have also used a similar Michael addition/cyclisation approach with isothiocyanato imides as the coupling partner, forming 3,3-thiopyrrolidinyl spirooxindole compounds.[191]

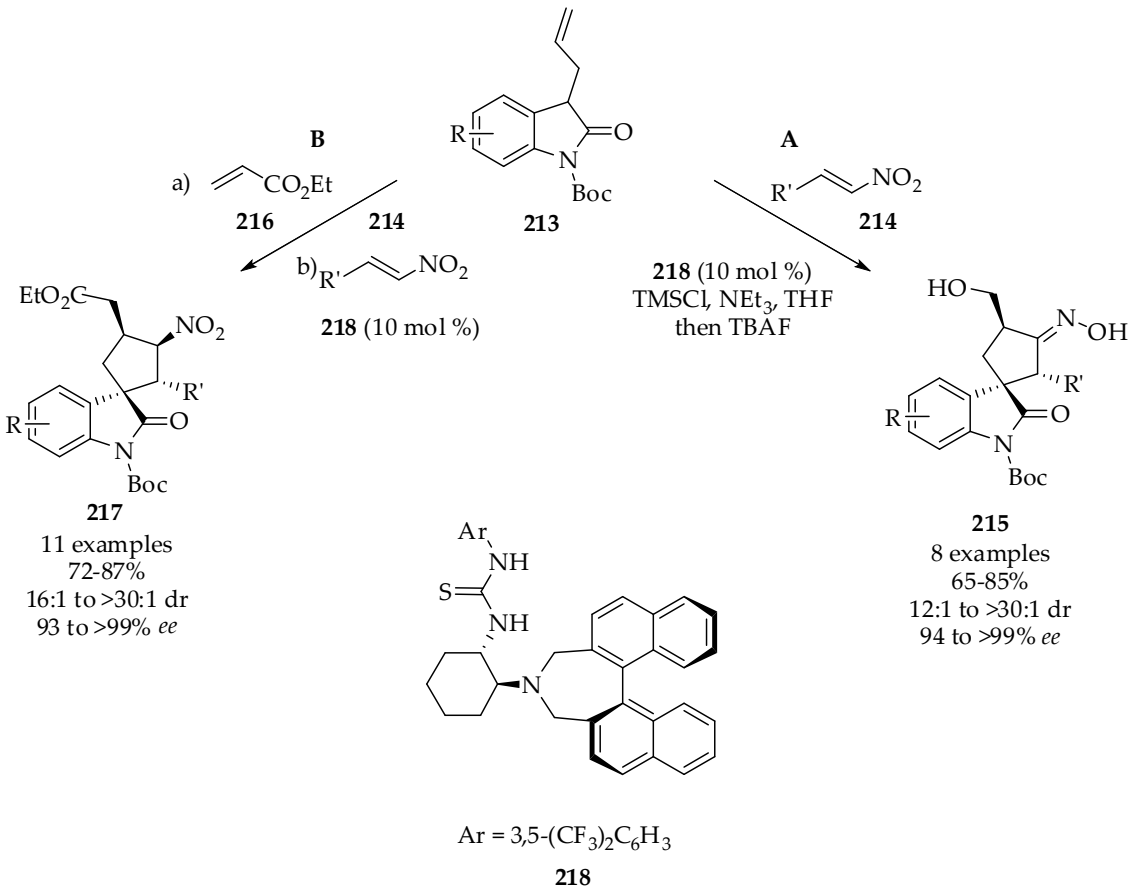


210 **211** **212**

10 examples
48–88%
55:45–90:10 dr

Scheme 83: Daïch's aza-Michael-initiated ring closure

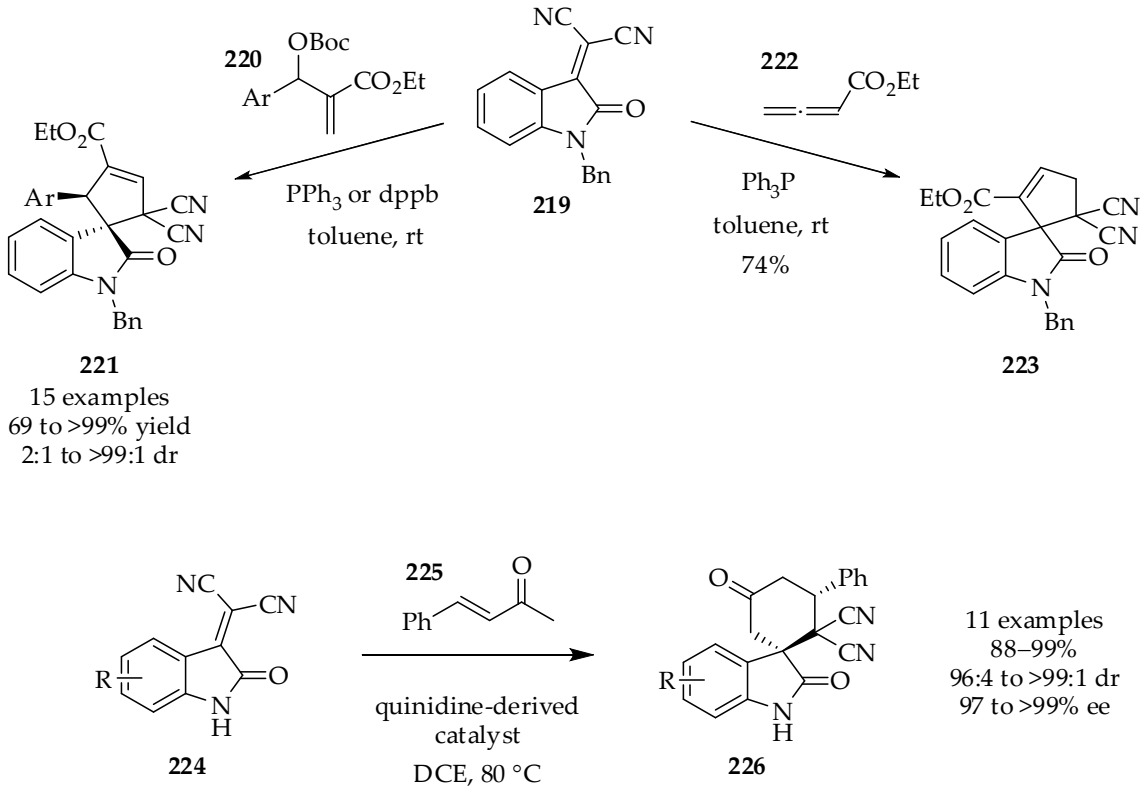
The Shao group have published two routes for constructing spirocyclopentaneoxindoles from 3-allyloxindoles **213**, both using the same bifunctional thiourea catalyst **218** (Scheme 84).[192,193]



Scheme 84: Shao's routes to spirocyclopentaneoxindoles

Route A involves an organocatalysed Michael addition of **214**, followed by an intramolecular silyl nitronate-olefin cycloaddition/fragmentation sequence.[192] Route B begins with a cross metathesis with **216**, followed by two consecutive Michael additions.[193] Both procedures form products **215** and **217** in very good yield with excellent diastereo- and enantioselectivity. Similar products have also been obtained by Barbas III *et al*. using an organocatalysed Michael/Henry cascade reaction.[194]

Electron-poor alkenes of type **219** are also useful substrates for spirocycle formation and could be utilised in a number of processes.[195] In this context, Shi and co-workers demonstrated this in the formation of spirocyclopenteneoxindoles **221** *via* a [3+2]-cycloaddition with Morita–Baylis–Hillman adducts of type **220** to give product in good yield and often excellent diastereoselectivity (Scheme 85).[196]

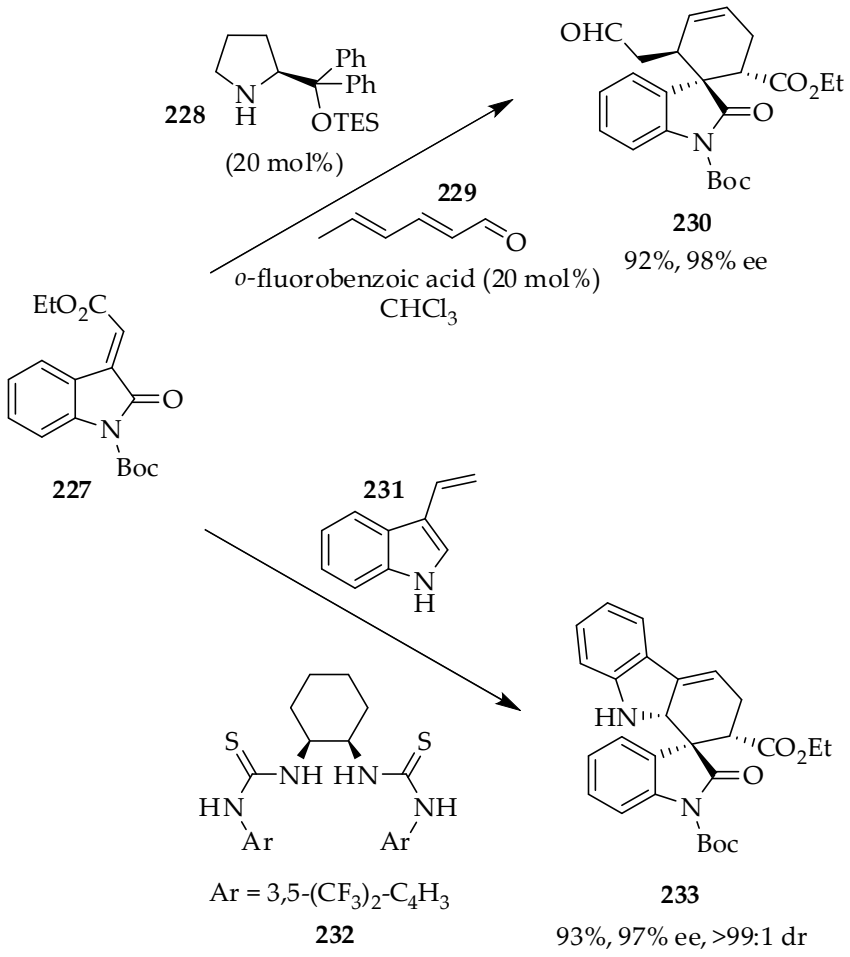


Scheme 85: Spirocycle formation from electron-poor alkenes

Almost concomitantly, an enantioselective version of this type of reaction was shown by Lu,[197] and Barbas III has also published a stereoselective variant using similar substrates.[198] An alternative cycloaddition strategy was also employed by Jia and co-workers,[199] which made use of allene substrate **222** to give spirocyclopenteneoxindoles

223 with contrasting regiochemistry to that in products **221** (Scheme 85). Finally, Wang and coworkers used alkenes of type **224** as substrates for an organocatalytic double Michael addition protocol, giving rise to cyclohexanone products **226** with excellent yields, diastereoselectivity and enantioselectivity (Scheme 85).[200]

Jørgensen and co-workers have developed an asymmetric organocatalytic Diels-Alder reaction of 3-alkenyl-oxindoles **227** to form cyclohexene-spirooxindoles **230** *via* a trienamine intermediate (Scheme 86).[201]

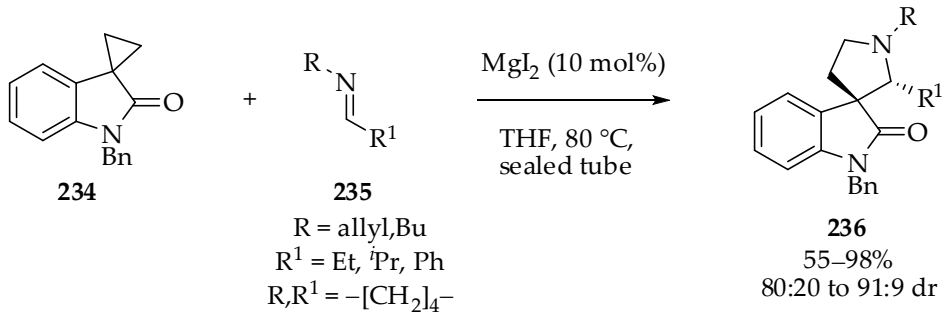


Scheme 86: Organocatalytic Diels-Alder approaches to spirooxindoles

A very similar protocol was utilised by Melchiorre and co-workers, employing the same proline-derived organocatalyst **228** but with 2-methylindole–based substrates.[202] A Diels–Alder approach using similar oxindole substrates (*e.g.*, **227**) has also been developed by Barbas III and co-workers, employing a dithiourea organocatalyst **232**, and using 3-vinylindole (**231**) as the diene couple partner (Scheme 86). Not only were

products of type **233** obtained in high yields and enantioselectivity, but diastereoselectivity was excellent in all cases.[203]

Another important and well-established method for the construction of spiropyrrolidine oxindoles is that of Carreira's cyclopropane ring expansion. Using magnesium iodide as a bifunctional catalyst, cyclopropane oxindoles of type **234** can be reacted with a range of imines **235**, forming products of type **236** in both high yield and diastereoselectivity (Scheme 87).[152] This procedure was effectively utilised in the synthesis of indole alkaloids horsfiline,[163] strychnofoline,[204] and spirotryprostatin B.[205,206]



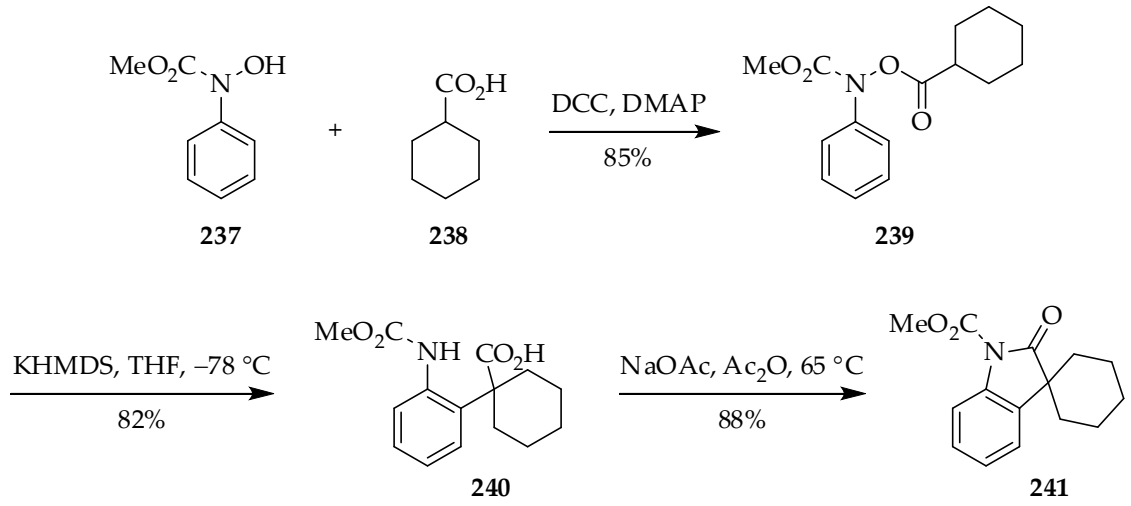
Scheme 87: Carreira's cyclopropane ring expansion

4.3.3 Methods from linear substrates

Although the above procedures are undoubtedly synthetically useful, they focus on the functionalisation of intermediates derived from cyclic oxindoles or isatin. Whilst isatin-derived methods make good use of a naturally occurring scaffold, one drawback is the lack of functionality on the aromatic ring, a feature which is desired or required for several natural products and drug molecules. In contrast, and of direct relevance to this project, is the synthesis of spirooxindoles by means of the cyclisation of linear precursors, and these methods are discussed in the following section.

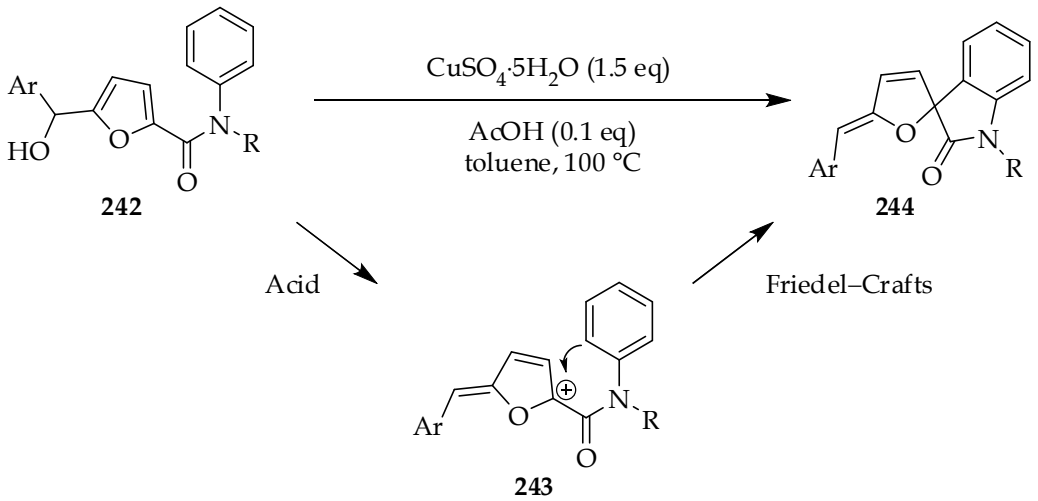
Several methods for the preparation of spirocyclic oxindoles from linear substrates have been developed. In 2004, Baldwin and Mao published an efficient route to spirooxindoles *via* a hetero-Claisen rearrangement, starting from a hydroxylamine **237** and a carboxylic acid **238**. In this particular case, DCC coupling enabled access to the acylated carbamate **239**, whereas subsequent formation of the enolate of **239** led to a

[3,3]-sigmatropic rearrangement as the key feature of this method. Finally, lactamisation yielded the spirooxindole **241** in excellent overall yield (Scheme 88).[207]



Scheme 88: Baldwin's hetero-Claisen approach to spirocyclic oxindoles

More recently, Jiang and co-workers have used copper(II) as a Lewis acid catalyst in a tandem dearomatisation/intramolecular Friedel–Crafts reaction of **242** for the formation of spirofurooxindoles **244** (Scheme 89).[208]

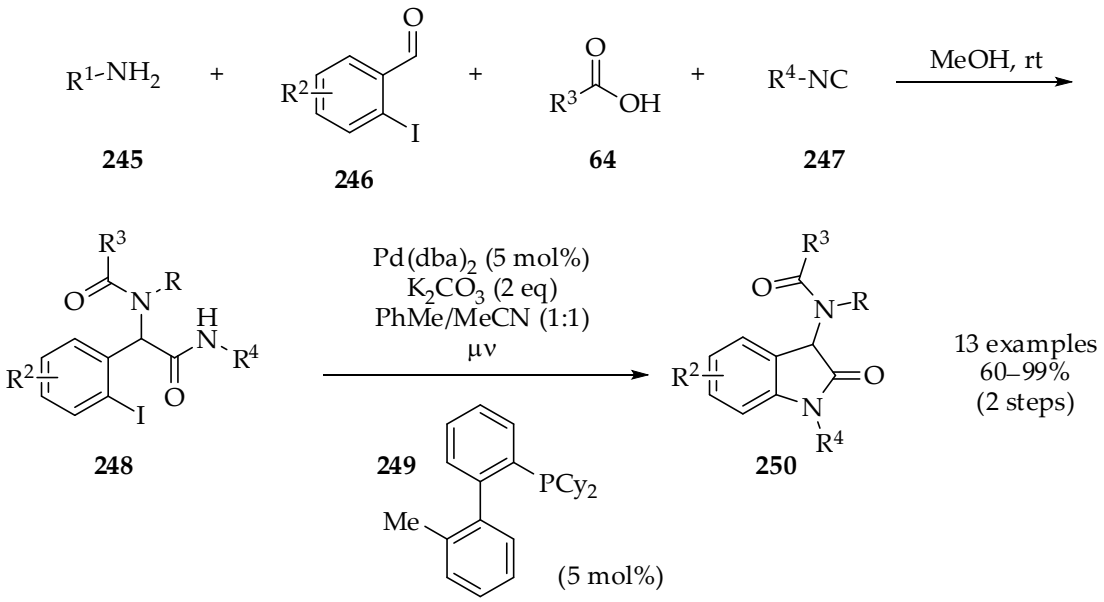


Scheme 89: Jiang's tandem dearomatisation/intramolecular Friedel–Crafts reaction

Several palladium-mediated processes towards spirocyclic oxindoles are also known,[209,210] including Schönhaber and Müller's Diels–Alder domino cascade,[211] and Takemoto's intramolecular carbosilylation.[212]

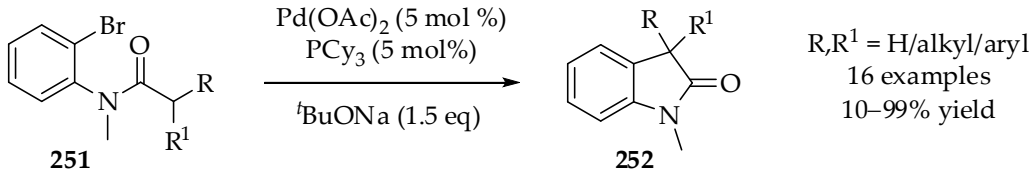
4.4 Metal-mediated cyclisation reactions

Of particular importance is the palladium-mediated cyclisation of linear precursors towards oxindoles. These methods are by far the most established means of entry to oxindoles.[155] For example, the palladium-catalysed amination and amidation reactions of aryl halides, as developed by Buchwald and Hartwig, have been known for many years.[213,214] An intramolecular variant of this reaction can be utilised for the construction of oxindoles, as shown in Scheme 90. Zhu and co-workers used a 4-component Ugi reaction followed by intramolecular Buchwald–Hartwig amidation of **248** under microwave irradiation to rapidly access a diverse range of 3-substituted oxindoles **250** in good to excellent yield.[215]



Scheme 90: Zhu's Ugi/intramolecular Buchwald–Hartwig amidation sequence to form oxindoles

In 1998, Hartwig's group demonstrated an alternative to this reaction, using the α-arylation of anilides **251** to form oxindoles of type **252**.[216] This procedure was later improved by the group with use of a different ligand (Scheme 91), including an asymmetric variant.[217] Since then, a large number of enantioselective variants with chiral ligands for palladium have been reported.[218]

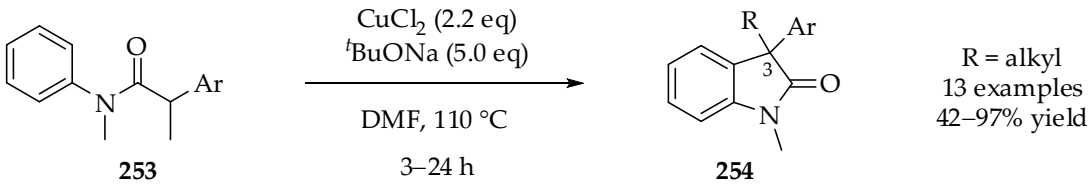


Scheme 91: Hartwig's α-arylation of anilides

Whilst useful, these reactions have the disadvantage of requiring pre-functionalised anilides (*e.g.*, aryl iodide or bromide) and often utilise expensive ligands for palladium.

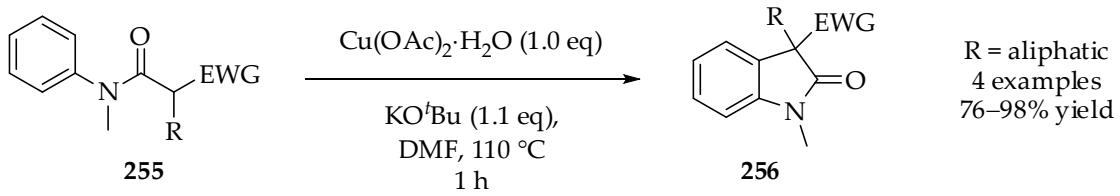
4.4.1 Copper(II)-mediated cyclisation reactions

In 2009, Kündig's group reported a new method using non-prefunctionalised aryl substrates **253** and enabled cyclisation mediated by copper(II) chloride instead of the more expensive palladium.[219] The main drawbacks of this method were that the use of a stoichiometric amount of oxidant, a large excess of a strong base, and anhydrous/inert conditions were required. In addition, substrate scope was limited to having an aromatic group in the 3-position (Scheme 92).



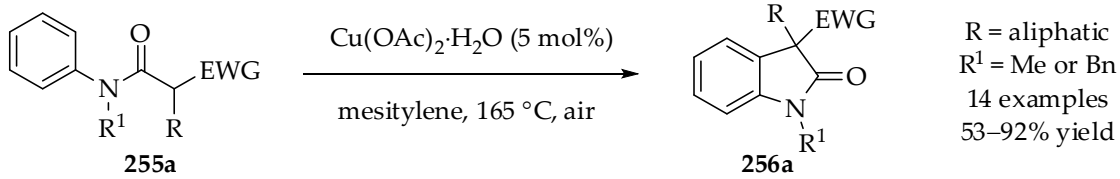
Scheme 92: Kündig's copper-mediated cyclisation

Almost concomitantly, the Taylor group reported a copper(II)-mediated cyclisation of unfunctionalised linear precursors **255** to form 3,3-disubstituted oxindoles,[220] but in contrast to Kündig's method, the reaction could now proceed without the use of excess base in wet solvent. An electron-withdrawing group, such as ester, nitrile or phosphonate was key to the success of this reaction and enabled rapid access to products **256** in good yield (Scheme 93).



Scheme 93: Taylor's stoichiometric copper(II) cyclisation

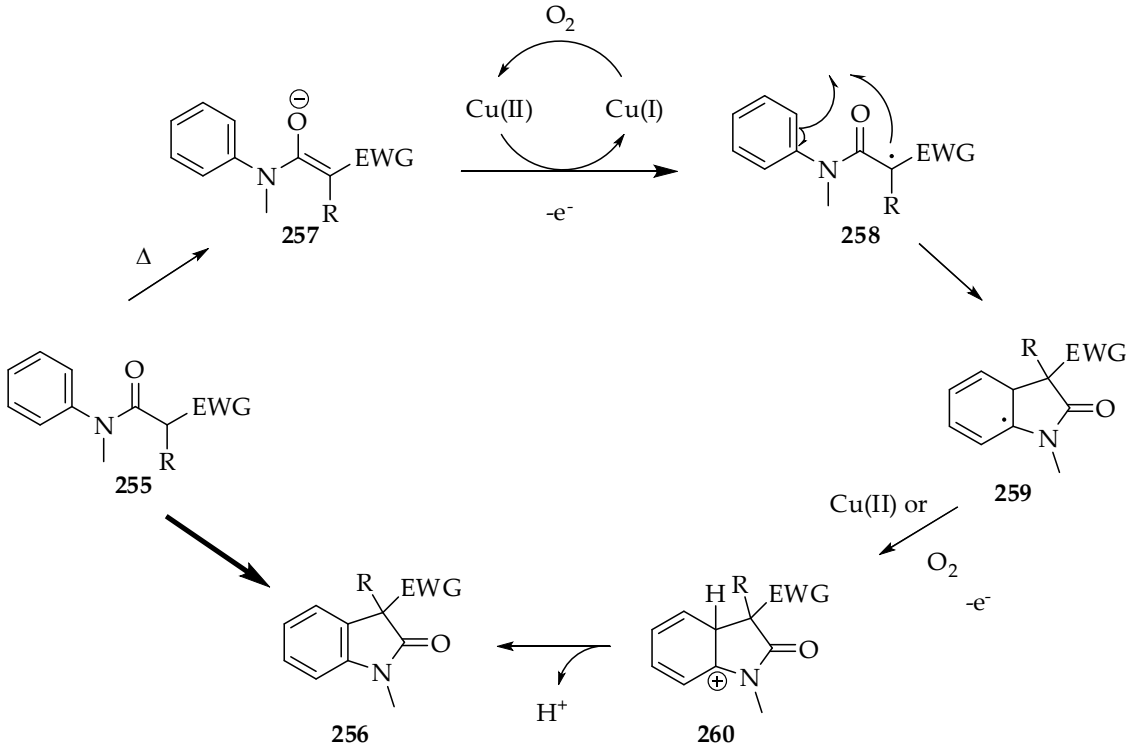
This reaction process was subsequently much improved, negating the need for a base, by using just catalytic amounts of inexpensive copper(II) acetate monohydrate at elevated temperatures under an air atmosphere (Scheme 94).[221]



Scheme 94: Taylor's catalytic Cu(II) cyclisation procedure

4.4.2 Proposed mechanism of Cu(II) cyclisation reactions

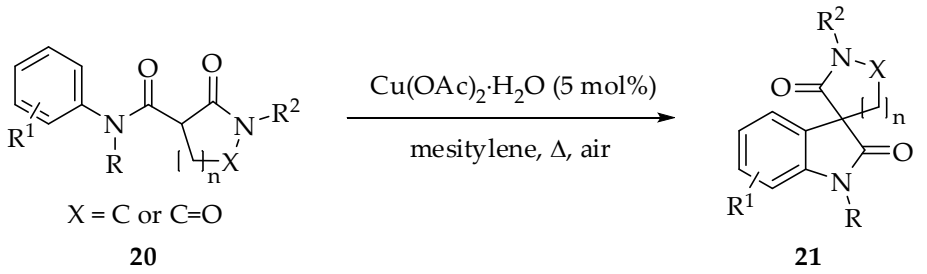
It is believed that the mechanism for the copper(II)-mediated cyclisation is radical-based,[219] which was further corroborated by the use of a cyclopropane radical probe.[68] In the case of the catalytic procedure, the enolate **257** is presumably formed by a weak base in the form of acetate from $Cu(OAc)_2 \cdot H_2O$, or the substrate itself (**255**), initiated by the high reaction temperature. Amide enolate oxidation takes place to form radical **258**. It is likely that this oxidation mediated by copper(II), which is then reoxidised by molecular oxygen from Cu(I) back to Cu(II), but could potentially also be brought about by oxygen itself. Radical **258** then undergoes homolytic aromatic substitution. Finally, oxidation of radical **259** and rapid loss of a proton gives rise to product **256**. This mechanism is therefore overall a formal double C–H activation (Scheme 95). Unpublished studies in the Taylor group, showed that both copper and oxygen are required for the reaction: the reaction does not proceed with oxygen alone, even under an oxygen atmosphere or with air bubbled through the reaction mixture.[222] However, the precise role of copper and oxygen in the mechanism is still unclear. It is unknown whether copper is required for the initial radical formation, or the oxidation to the carbocation **260**, or both.



Scheme 95: Proposed mechanism for the catalytic aerobic radical cyclisation

4.5 Aims of project II

It was envisaged that the catalytic copper(II) cyclisation methodology could be readily extended, simply by incorporating the electron withdrawing group in a ring in the form of a lactam or cyclic imide of type **20**, thus allowing access to spirocyclic oxindoles **21** (Scheme 96). Given the abundance of the spirocyclic oxindole unit in natural products and drugs, we recognised that the development of this reaction would constitute an appealing entry to this highly prevalent building block. Our aim was to investigate the substrate scope of the reaction and the results which have come out of this study are shown in the next section.

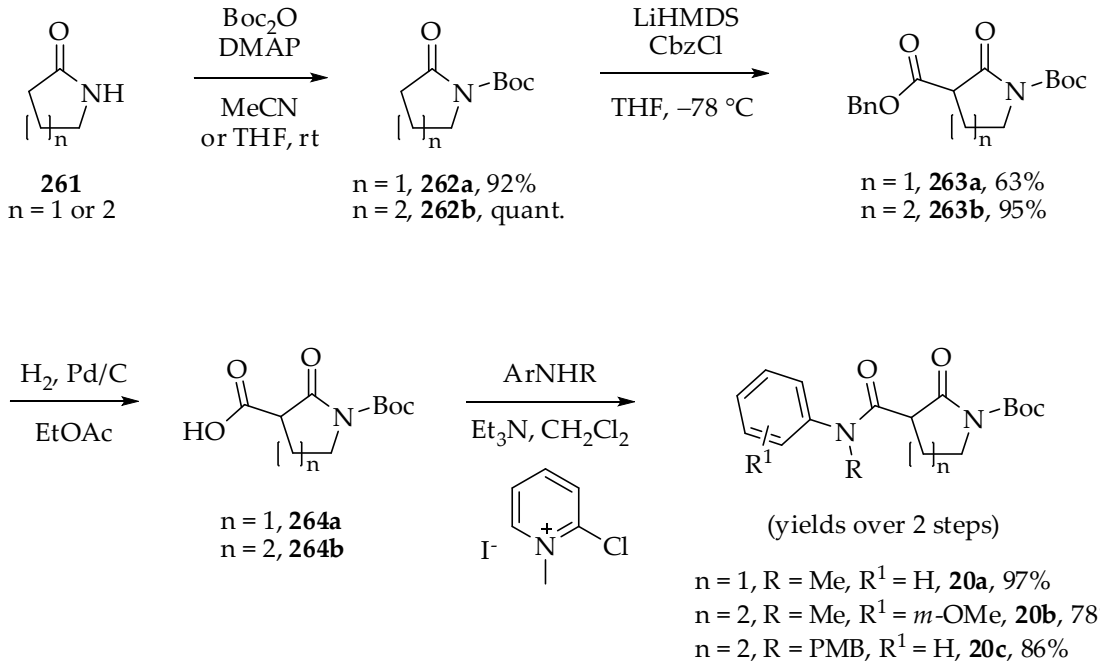


Scheme 96: Proposed route to spirocyclic oxindoles

4.6 Results and discussion

4.6.1 Synthesis of precursors

The linear substrates for the copper cyclisation can be synthesised in just a few simple steps from the parent lactam or imide (*e.g.*, **261**, Scheme 97). In the first step, *N*-protection with Boc anhydride affords *N*-substituted intermediate **262**. Deprotonation of **262** and subsequent treatment with benzyl chloroformate delivers the ester **263**. The benzyl group is cleaved by means of hydrogenolysis to give the carboxylic acid **264** which, in order to avoid decarboxylation, is immediately subjected to amide coupling with the desired aniline, furnishing the cyclisation precursor **20**.

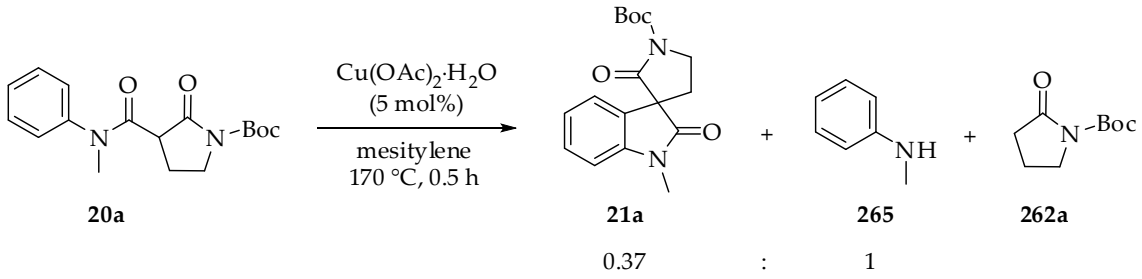


Scheme 97: Example of precursor synthesis

4.6.2 Optimisation of the copper cyclisation

Optimisation studies on the acyclic substrate system had identified 5 mol% copper(II) acetate in refluxing mesitylene under an air atmosphere as optimal conditions (*vide supra*, Scheme 94).[221]

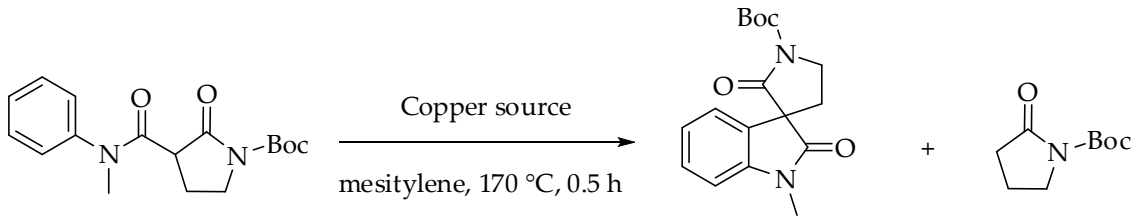
Applying the same conditions to substrate **20a**, the reaction failed to go to completion (Table 15, entry 1), even after a prolonged reaction time. In addition, a large amount of decomposition of the linear substrate **20a** was seen, resulting in the formation of aniline **265** and Boc-protected lactam **262a** (Scheme 98), which was difficult to separate from the desired product **21a**.



Scheme 98: Product and decomposition products of the cyclisation of 20a

Thus, a brief study into the optimal cyclisation conditions was carried out in the first instance. Pleasingly, by increasing the catalyst loading to 10 mol%, the reaction was complete within 30 min (Table 15, entry 2). However, some decomposition material was still observed. In an attempt to combat this, a number of different acetate-based copper sources and additives were investigated (Table 15).

Table 15: Optimisation of conditions for the cyclisation reaction of 20a to give 21a



20a **21a** **262a**

Entry	Copper source	Catalyst Loading	Additive	21a:262a[a]	Yield of 21a (%)[e]
1	$Cu(OAc)_2 \cdot H_2O$	5 mol%	-	0.38 : 1[b]	11
2	$Cu(OAc)_2 \cdot H_2O$	10 mol%	-	2.50 : 1	58
3	$Cu(OAc)_2$	10 mol%	-	2.56 : 1	59
4	$Cu(OAc)_2 \cdot H_2O$	10 mol%	4Å MS	0.24 : 1[c]	13
5	$Cu(OAc)_2$	10 mol%	4Å MS	0.62 : 1[d]	17
6	CuOAc	10 mol%	-	2.86 : 1	57
7	$Cu(OAc)_2 \cdot H_2O$	10 mol%	AcOH	2.63 : 1	61
8	$Cu(OAc)_2 \cdot H_2O$	10 mol%	Pyridine	3.13 : 1	48

[a]By ^{1}H NMR analysis of the unpurified reaction mixture; [b]Reaction terminated after 4.5 h (starting material remaining); [c]Reaction terminated after 1.5 h (starting material remaining); [d]Reaction terminated after 1 h (starting material remaining); [e]Yields based on mass recovery and ^{1}H NMR analysis of isolated material following column chromatography

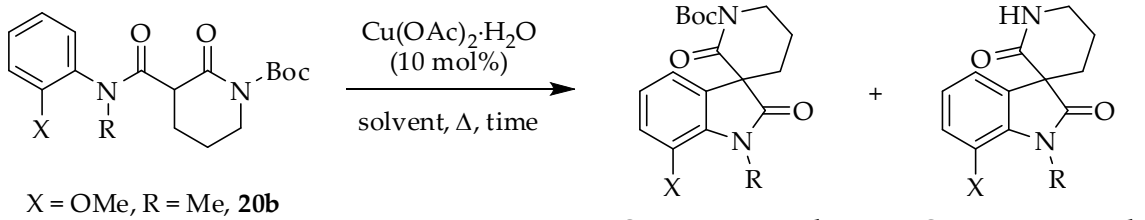
It was hypothesised that the decomposition may come about due to hydrolysis of the substrate with water, either produced in the reaction or derived from the catalyst itself. Anhydrous copper acetate as catalyst gave a comparable result (entry 3), but unexpectedly, the use of molecular sieves only served to slow down the cyclisation reaction, leading to an even larger proportion of decomposed material (entries 4 and 5). As the proposed cyclisation mechanism involves a re-oxidation of Cu(I), copper(I) acetate should also in principle be a suitable catalyst for the reaction. This was indeed the case (entry 6), with the yield of **21a** being comparable to that obtained with copper(II) acetate. Whilst this supports the theory of copper(I) re-oxidation, it did not enhance the efficiency of the reaction. To investigate whether a build up of either acid or base in the reaction mixture could be causing the unwanted side reaction, both acetic

acid (entry 7) and pyridine (entry 8) were employed as additives. Unfortunately, only a marginal improvement in yield was observed by the addition of acetic acid, and therefore the use of just 10 mol% copper(II) acetate (entry 2) was settled upon as optimal in this case.

4.6.2.1 Reaction times

We next explored the effect of reaction time on the yield of oxindole product on different substrates **20b** and **20c**. Extended reactions times were shown to result in a significant amount of Boc cleavage, giving **266b–c** (Table 16, entries 1 and 3), which is not unusual as the reaction is carried out at 170 °C. This cleavage could be minimised by keeping reaction times at 30 minutes (entries 2 and 4). Boc-cleavage could be eliminated altogether by performing the reaction at a lower temperature in toluene, resulting in a slightly improved yield, but much longer reaction times were required, typically overnight (entry 5).

Table 16: Different reaction times and temperatures for the cyclisation of 20b and 20c

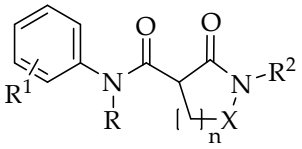


Entry	Substrate	Solvent	Temp /°C	Time /h	Yield of 21[a]	Yield of 266[a]
1	**20b**	mesitylene	170	1	37	16
2	**20b**	mesitylene	170	0.5	48	-
3	**20c**	mesitylene	170	1	42	15
4	**20c**	mesitylene	170	0.5	48	7
5	**20c**	toluene	120	16	56	-

[a]Isolated yields

4.6.3 Scope of the reaction

In order to investigate the scope of the cyclisation, a wide range of substrates were prepared, with variations in ring size, protecting groups and substitution pattern around the aromatic ring (Figure 17).



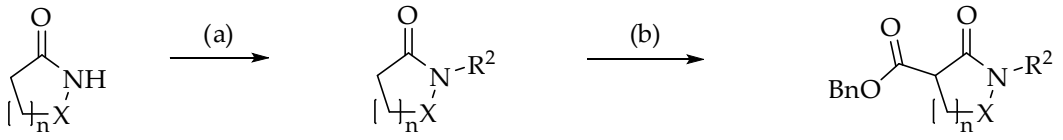
X = CH_2 or C=O
n = 0, 1, 2 or 3
R/R^2 = Boc, Me, Bn, PMB or Dmb
R^1 = H, OMe, Cl, Br, NO_2, CF_3 or CN

Figure 17: Range of substrates prepared to investigate the scope of the cyclisation reaction

4.6.3.1 Ring size and type

In the first instance, an investigation into the scope of the ring size of the spirocycle was launched and substrates ranging from 4-membered to 7-membered rings, including both lactams and imides were studied (Scheme 99).

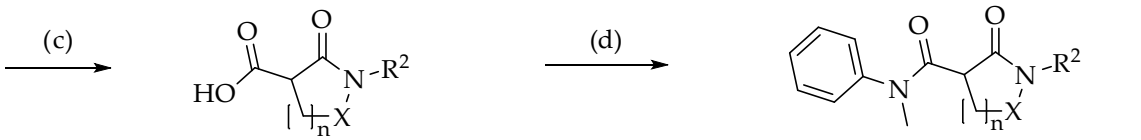
Boc-protection to form intermediates **262b,d,e,g,h** was trivial, giving near quantitative yields in all cases, whereas results from the benzylcarboxylation step were variable. In an attempt to prepare the Boc-protected succinimide substrate from **262e**, difficulties were encountered in the benzylcarboxylation step, thus a methyl succinimide substrate **263f** was prepared instead. Low yields were observed for this step with the imide substrates, and this was due to the presence of two acidic sites in the molecule, thus resulting in the double addition of the electrophile as the side reaction. Hydrogenolysis of intermediates **264b** to **264h** and subsequent amide coupling proceeded without incident, thus providing substrates **20d** to **20i** in good to excellent yield.



n = 0–4
261

n = 0, X = CH_2, R^2 = Boc, **262d**, 87%
n = 1, X = C=O, R^2 = Boc, **262e**, 91%
n = 1, X = C=O, R^2 = Me, **262f**
n = 2, X = CH_2, R^2 = Boc, **262b**, quant.
n = 2, X = C=O, R^2 = Boc, **262g**, 97%
n = 3, X = CH_2, R^2 = Boc, **262h**, 86%

n = 0, X = CH_2, R^2 = Boc, **263d** 54%
n = 1, X = C=O, R^2 = Boc, **263e**, 0%
n = 1, X = C=O, R^2 = Me, **263f**, 39%
n = 2, X = CH_2, R^2 = Boc, **263b**, 95%
n = 2, X = C=O, R^2 = Boc, **263g**, 39%
n = 3, X = CH_2, R^2 = Boc, **263h**, 41%



n = 0, X = CH_2, R^2 = Boc, **264d**
n = 1, X = C=O, R^2 = Me, **264f**
n = 2, X = CH_2, R^2 = Boc, **264b**
n = 2, X = C=O, R^2 = Boc, **264g**
n = 3, X = CH_2, R^2 = Boc, **264h**

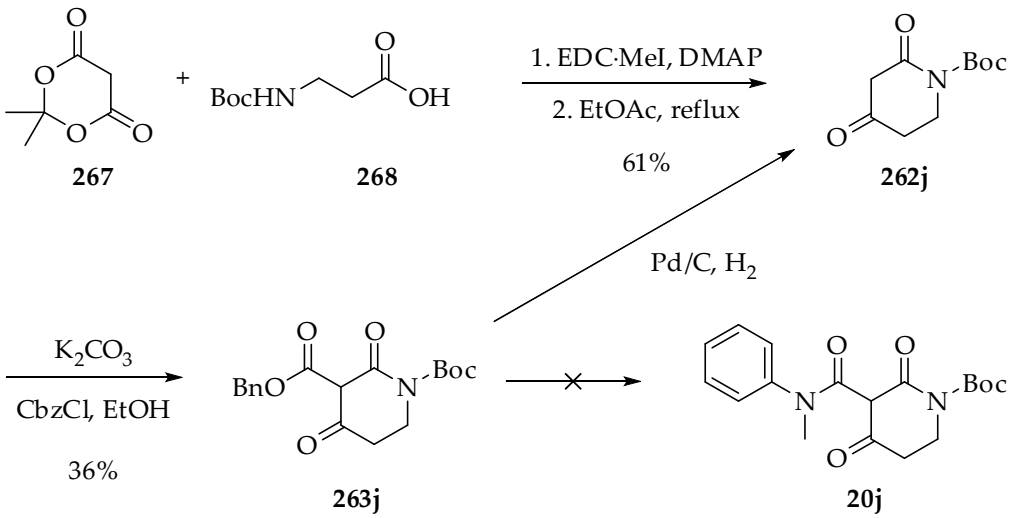
(yields over 2 steps)

n = 0, X = CH_2, R^2 = Boc, **20d**, 73%
n = 1, X = C=O, R^2 = Me, **20f**, 89%
n = 2, X = CH_2, R^2 = Boc, **20i**, 80%
n = 2, X = C=O, R^2 = Boc, **20g**, 78%
n = 3, X = CH_2, R^2 = Boc, **20h**, 60%

Reagents and conditions: a) Boc_2O, DMAP, THF or MeCN, rt, 16 h; b) LiHMDS, CbzCl, THF, −78 °C, 1 h; c) H_2, Pd/C, EtOAc, 0.5–2 h; d) 2-chloro-1-methylpyridinium iodide, Et_3N, PhNHMe, CH_2Cl_2, 0 °C to rt, 16 h

Scheme 99: Substrates prepared with differing ring sizes

We were also interested in the reactivity of substrate **20j**. Following the procedure by Vanotti *et al.*,[223] Meldrum's acid (**267**) was coupled with Boc-β-alanine (**268**) and the resulting intermediate was heated under reflux to give lactam **262j** in good yield (Scheme 100). Standard conditions for the benzylcarboxylation with LiHMDS as base led to decomposition. Nevertheless, the weaker base, K_2CO_3 was successful in providing ester **263j**. Unfortunately, on attempting to form **20j**, the acid resulting from the hydrogenolysis step was found to undergo immediate decarboxylation, reverting to compound **262j**. Thus, the synthesis of **20j** by this route was deemed fruitless.

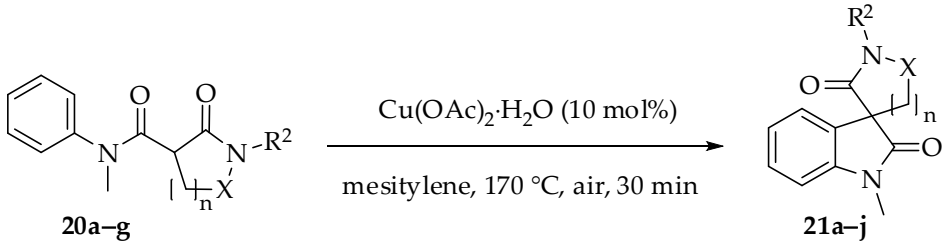


Scheme 100: Attempted formation of substrate 20j

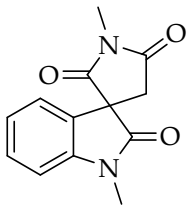
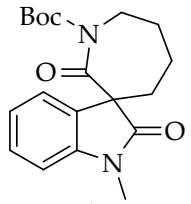
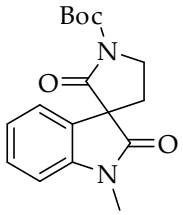
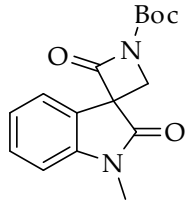
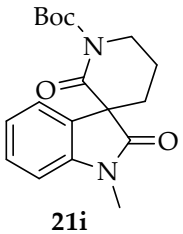
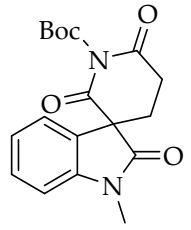
With a range of substrates in hand, attention was next turned to spirooxindole formation (Table 17). Pleasingly, all of the substrates were shown to successfully undergo cyclisation, with methyl succinimide **20f** showing the highest yield of product (entry 1). 5-, 6- and 7- membered lactams provided products **21a**, **21i** and **21h** in moderate to good yield, showing that a range of ring size is tolerated under the reaction conditions (entries 2–4). The 4-membered lactam **20d** was slow to react and ultimately gave rise to low yield of **21d** (entry 5), which is presumably due to the unfavourable ring strain of the planar enolate and radical intermediates, or due to the high reactivity of the product.

Cyclisation of the Boc-protected glutarimide substrate **20g** resulted in a large amount of Boc-cleavage (42% of free amine **266g** was isolated) (entry 6). This could be easily minimised and hence the yield of **21g** increased to 45% by performing the reaction in toluene for 16 h at 120 °C (Scheme 101).

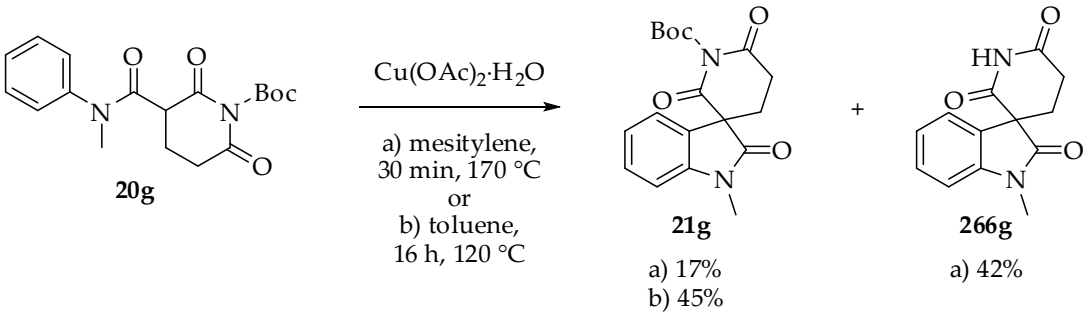
Table 17: Cyclisation of lactam and imide substrates of differing ring size



20a–g → **21a–j**

Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **21f**	70	4	 **21h**	64
2	 **21a**	58[c]	5	 **21d**	26[b,c]
3	 **21i**	56	6	 **21g**	17[d]

[a]Isolated yields; [b]Reaction terminated after 2 h; [c]Yield extrapolated; a small amount of Boc-protected lactam **262** co-eluted; [d]Reaction in PhMe gave 45%

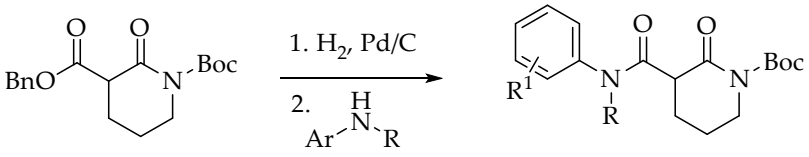


20g → **21g** a) 17% b) 45% + **266g** a) 42%

Scheme 101: Cyclisation of 20g at different temperatures

4.6.3.2 Substitution on the aromatic ring

We were next interested in looking at the effect of the substituents on the anilide aromatic ring on the cyclisation reaction. Towards this end, a range of *ortho*, *meta* and *para*-substituted compounds with electron-withdrawing and electron-donating groups **20k–r** were prepared (Scheme 102). This was achieved in generally good yields over 2 steps from **263b** and set the stage for the copper(II)-mediated cyclisation step (Tables 18 and 19).



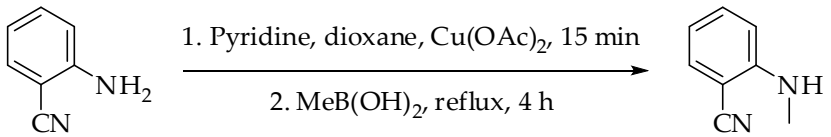
263b

(Yields over 2 steps)

R = Me, R^1 = *o*-NO_2, **20k**, 37%
R = Me, R^1 = *o*-CN, **20l**, 77%
R = Dmb, R^1 = *p*-OMe, **20m**, 74%
R = Me, R^1 = *p*-Cl, **20n**, 78%
R = Me, R^1 = *p*-CF_3, **20o**, 80%
R = Me, R^1 = *m*-OMe, **20p**, 76%
R = Me, R^1 = *m*-Br, **20q**, 42%

Scheme 102: Preparation of substrates to investigate substitution effects

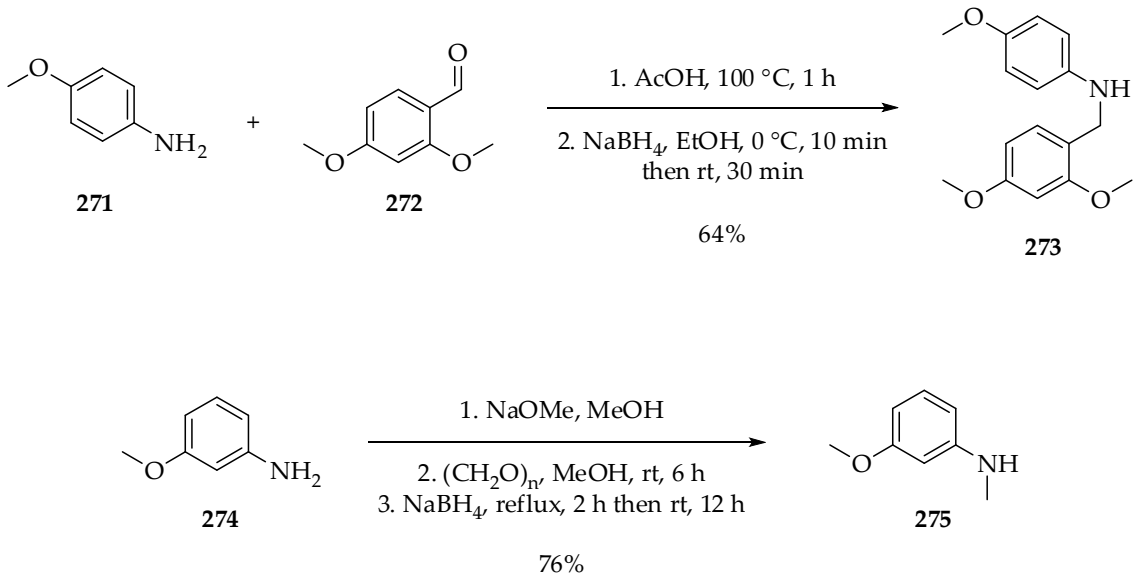
The aniline **270** required for the synthesis of substrate **20l** was prepared by a copper-mediated mono-methylation of 2-aminobenzonitrile (**269**) following the procedure of González (Scheme 103).[224]



269 41% **270**

Scheme 103: Preparation of 2-(methylamino)benzonitrile (270)

Anilines **273** and **275** were prepared by means of a reductive amination reaction, following procedures by Trost,[158] and Teichert,[225] respectively (Scheme 104). These were subsequently used in the synthesis of substrates **20m** and **20p**.



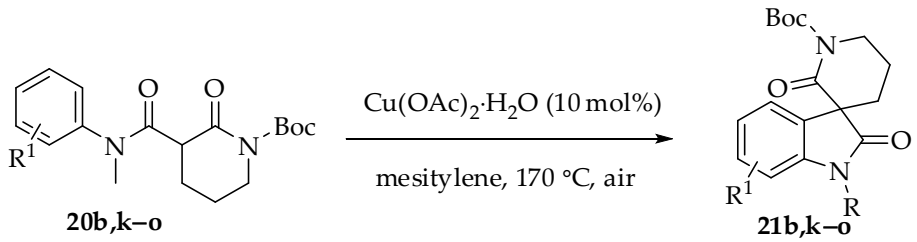
271 272 273 274 275

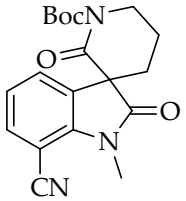
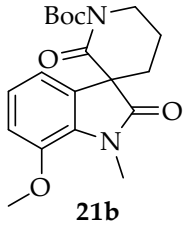
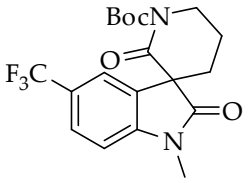
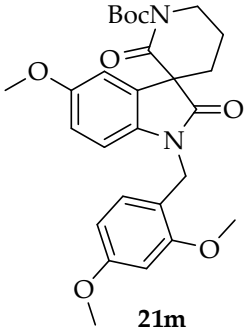
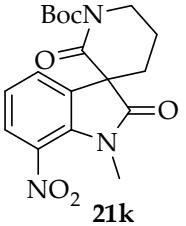
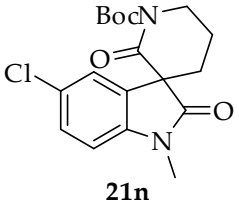
Scheme 104: Preparation of anilines 273 and 275

Electron-withdrawing groups were not well tolerated in the cyclisation reaction (Table 18). Nitrile-containing **20l** (entry 1), and trifluoromethyl-substituted **20o** (entry 2), did cyclise but afforded rather low yields of products **21l** and **21o**. In the case of the nitro-substituted **20k** (entry 3), cyclisation was halted altogether and the only observable products were those arising from the decomposition of precursor **20k**, namely the aniline and Boc-protected lactam **262b**.

In contrast, compounds with the electron-donating methoxy- group provided better yields of products **21b** and **21m** (Table 18, entries 4 and 5). Pleasingly, chloride-substituted **20n** (entry 6) was shown to be a compatible substrate in the reaction, and constitutes a useful handle for further cross coupling reactions to create drug-like molecules.

Table 18: Cyclisation of substrates with *ortho/para*- substituents

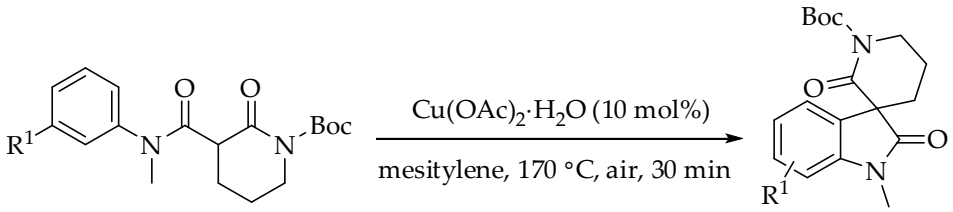


Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **21l**	19[b]	4	 **21b**	48[b]
2	 **21o**	32[b]	5	 **21m**	63
3	 **21k**	0[c]	6	 **21n**	62

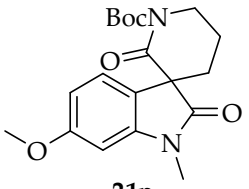
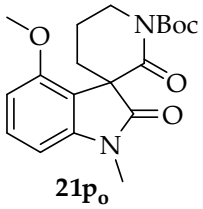
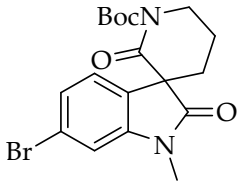
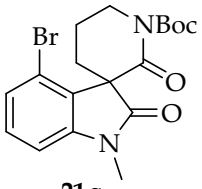
[a]Isolated yields; [b]Yield extrapolated; a small amount of Boc-protected lactam **262b** co-eluted; [c]Reaction in PhMe at 120 °C also failed

As could be predicted, the cyclisation of *meta*-substituted substrates **20p** and **20q** resulted in the formation of two isomeric products **$20p_p$/$20q_p$** and **$20p_o$/$20q_o$**, which were obtained in high overall yield (Table 19). More intriguing, was the ratio in which these isomeric products were formed.

Table 19: Cyclisation of substrates with *meta*-substituents

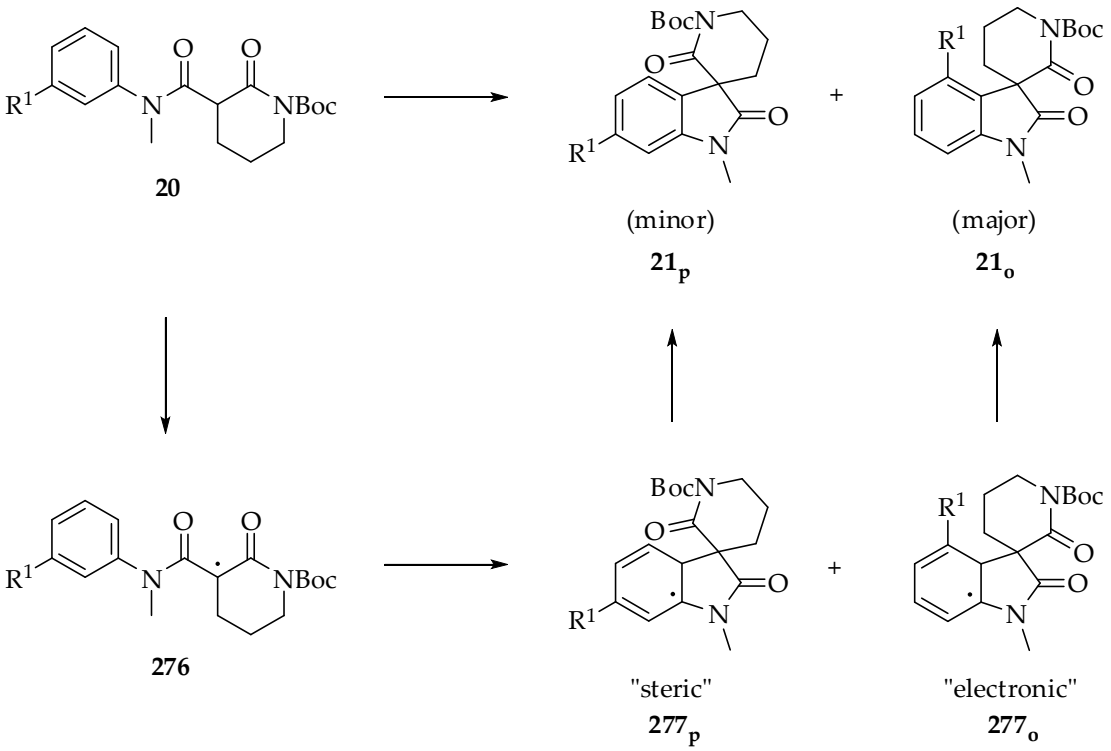


20p–q **21p–q**

Entry	Products		Yield of 21_p[a]	Yield of 21_o[a]
1	 **$21p_p$**	 **$21p_o$**	18	58[b]
2	 **$21q_p$**	 **$21q_o$**	25[b]	44

[a] Percentage isolated yields; [b]Yield extrapolated; a small amount of Boc-protected lactam **262b** co-eluted

More specifically, the major products **$21p_o$** and **$21q_o$** were found to be derived from radical addition to the position of the benzene ring with two adjacent substituents. Although this observation is counter-intuitive in light of steric arguments, formation of major isomers **21_o** could be explained by electronic factors, whereby adjacent substitution leads to a more stable cyclohexadienyl radical **277_o** intermediate following addition to the benzene ring (Scheme 105). In order for **277_p** to benefit from stabilisation by the *meta*-substituent (R^1), the radical is only required to be in conjugation with one of the two double bonds in the intermediate, therefore the second double bond is less likely to contribute significantly to stabilisation. In contrast, radical **277_o** has both double bonds arranged in a linear fashion between the nitrogen atom and the *meta*-substituent, allowing additional resonance stabilisation and thus a more stable intermediate. Similar regioselectivity in aromatic radical cyclisations has also been observed by others.[226]

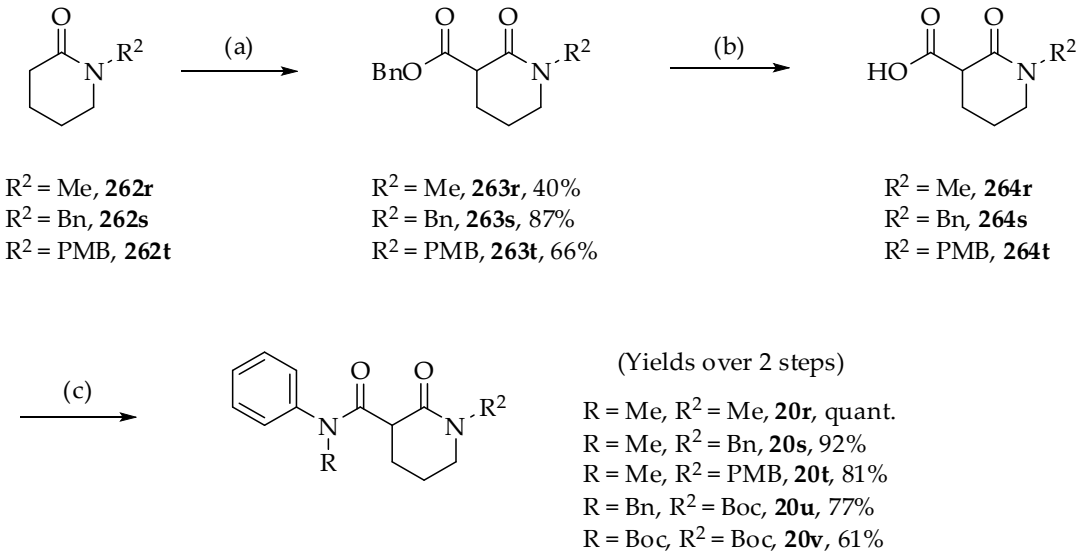


Scheme 105: Regioisomeric intermediates and products from the cyclisation of *meta*-substituted compounds

4.6.3.3 Protecting group variation

It was also important to us to establish that a range of protecting groups could be tolerated in the cyclisation reaction and thus broaden the synthetic utility of this process. Previous studies had shown that copper(II) cyclisation was ineffective in the case where the anilide bears a free NH, thus nitrogen protection is crucial.[219] First, the protection of both the lactam and the anilide nitrogen atoms was explored.

Boc carbamate as well as methyl, benzyl and PMB groups were chosen and precursors **20r–v** were obtained in good to quantitative yields (Scheme 106).



R^2 = Me, **262r**
R^2 = Bn, **262s**
R^2 = PMB, **262t**

R^2 = Me, **263r**, 40%
R^2 = Bn, **263s**, 87%
R^2 = PMB, **263t**, 66%

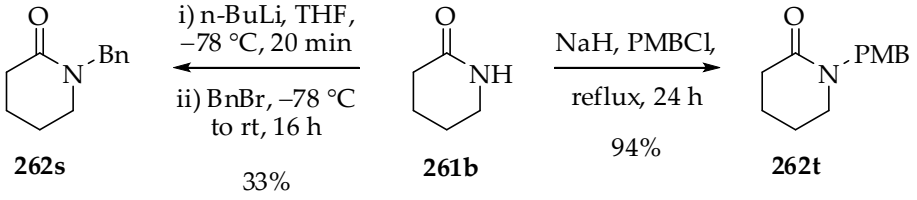
R^2 = Me, **264r**
R^2 = Bn, **264s**
R^2 = PMB, **264t**

(Yields over 2 steps)

Reagents and conditions: (a) LiHMDS, CbzCl, THF, −78 °C, 1 h; (b) H_2, Pd/C, EtOAc, 0.5–2 h; (c) 2-chloro-1-methylpyridinium iodide, Et_3N, PhNHR, CH_2Cl_2, 0 °C to rt, 16 h

Scheme 106: Preparation of differently protected substrates

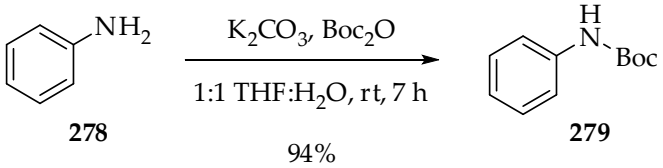
Benzyl-protected lactam **262s** and PMB-protected lactam **262t** were both prepared by *N*-alkylation of δ-valerolactam (**261b**), using procedures by Cossy,[227] and Winter,[228] respectively (Scheme 107).



262s **261b** **262t**

Scheme 107: Preparation of benzyl- and PMB-protected lactams 262s and 262t

The aniline **279** required for substrate **20v** was prepared by K_2CO_3-mediated Boc-protection of aniline (**278**), based on the procedure by Peterson (Scheme 108).[229]

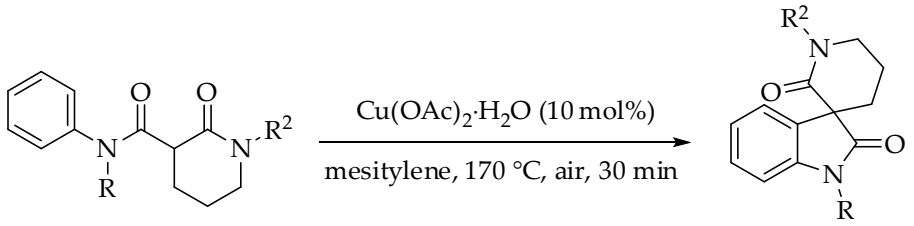


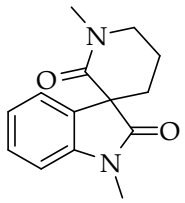
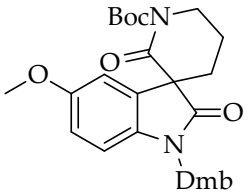
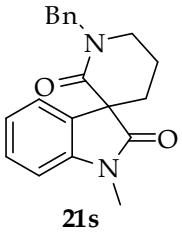
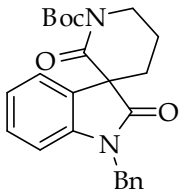
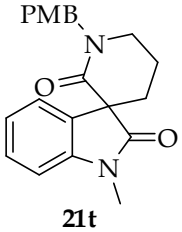
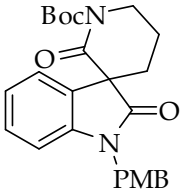
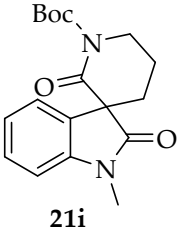
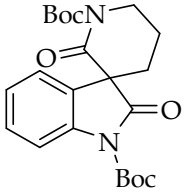
278 **279**

Scheme 108: Boc-protection of aniline (278)

Each of these substrates **20r–v** was then submitted to the cyclisation reaction conditions and the methyl group was shown to be the best protecting group for the lactam, closely followed by benzyl and PMB (Table 20, entries 1–3). The lower yield of the Boc-protected **21i** could be easily attributed to the thermal Boc cleavage under the reaction conditions (entry 4).

Table 20: Investigation into nitrogen protecting groups

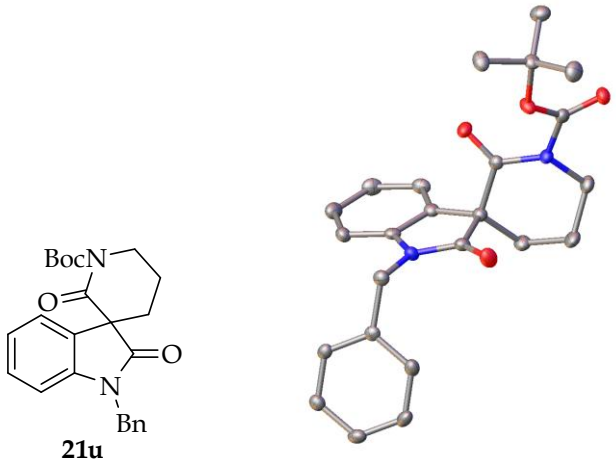


Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **21r**	65	5	 **21m**	63
2	 **21s**	64	6	 **21u**	51
3	 **21t**	64	7	 **21c**	48
4	 **21i**	56	8	 **21v**	0[b]

[a] Isolated yields, [b]Reaction in PhMe at 120 °C also failed

In terms of anilide protection, in addition to the Dmb group shown previously (Table 20, entry 5), both the benzyl and PMB groups were shown to be compatible (entries 6 and 7), albeit yields of products **21u** and **21c** were somewhat lower than in the case of the methyl protected substrates. Unfortunately, Boc protection of the anilide was not compatible under the reaction conditions (entry 8); the only observable products were those arising from decomposition of the linear precursor **20v**. Thus, the anilide nitrogen atom protecting group is limited to those with electron donating character only. We speculate that the electron-withdrawing nature of the Boc group significantly reduces the ability of the anilide nitrogen atom to stabilise the intermediate radical in the addition step, thus shutting down the desired reaction.

Pleasingly, we were able to obtain a suitable crystal of **21u**, thus allowing us to conclusively prove the structure of this spirocyclic oxindole (Figure 18).

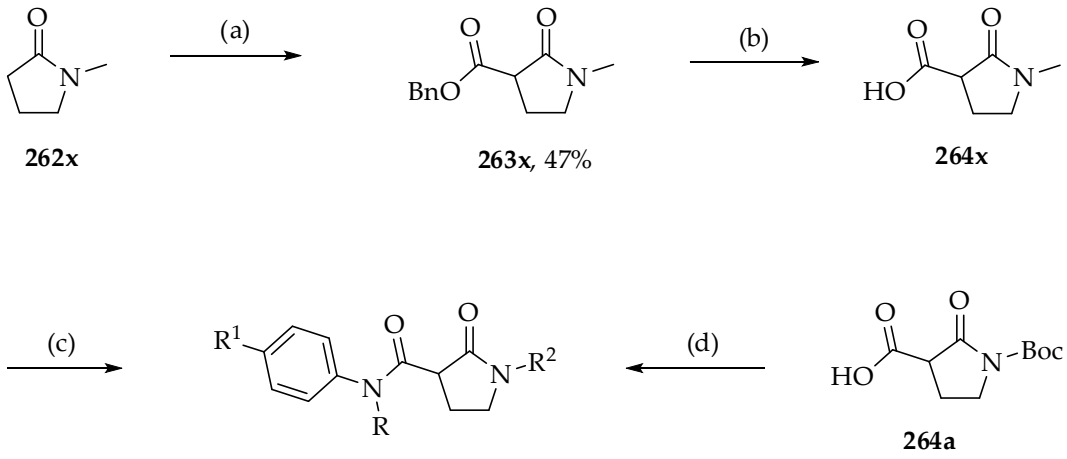


21u

Figure 18: Crystal structure of 21u

4.6.3.4 Five-membered compounds

A selection of 5-membered substrates with various protecting groups and aromatic ring substitution were synthesised and subjected to the cyclisation conditions (Table 21).



262x **263x**, 47% **264x**

264a

(yields over 2 steps)

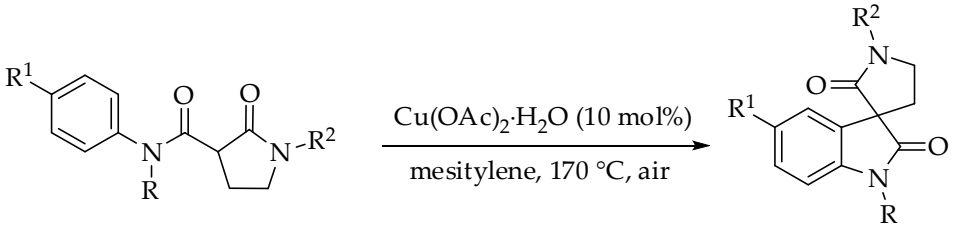
R = Bn, R^1 = H, R^2 = Boc, **20w**, 64%
R = Bn, R^1 = H, R^2 = Me, **20x**, 94%
R = PMB, R^1 = H, R^2 = Me, **20y**, 87%
R = Me, R^1 = H, R^2 = Me, **20z**, 74%
R = Me, R^1 = Cl, R^2 = Me, **20za**, 67%

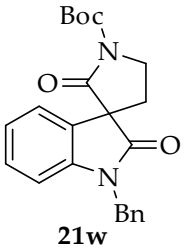
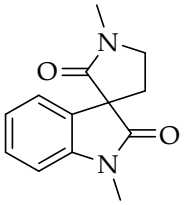
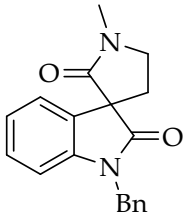
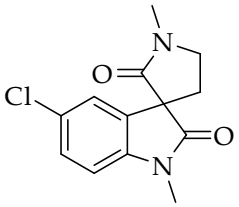
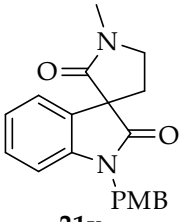
Reagents and conditions: (a) LiHMDS, CbzCl, THF, −78 °C, 1 h; (b) H_2, Pd/C, EtOAc, 2 h; (c) 2-chloro-1-methylpyridinium iodide, Et_3N, ArNHR, CH_2Cl_2, 0 °C to rt, 16 h; (d) 2-chloro-1-methylpyridinium iodide, Et_3N, PhNHBn, CH_2Cl_2, 0 °C to rt, 16 h

Scheme 109: Synthesis of 5-membered substrates

The results of these cyclisation reactions showed similar trends to those seen in the 6-membered series of substrates, whereby *N*-methyl protection showed superior yields to Boc/PMB groups (entry 2 *vs* entry 1, entry 4 *vs* entry 3), and that chlorine substitution on the aryl group gave one of the highest yielding reactions (entry 5).

Table 21: Cyclisation of selected 5-membered compounds



Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **21w**	55	4	 **21z**	58
2	 **21x**	58	5	 **21za**	66
3	 **21y**	55			

[a]Isolated yields

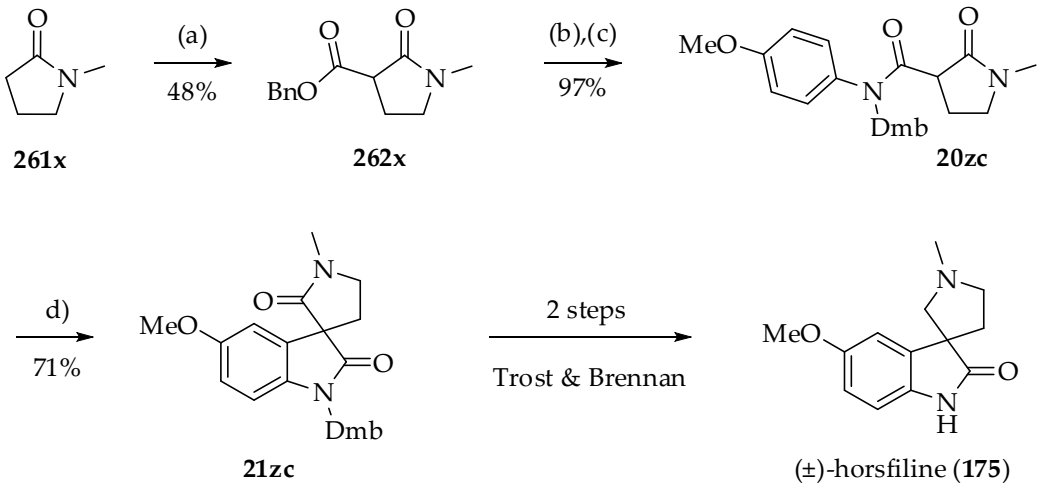
4.6.4 Additional work

Further work in the group, performed by Vilius Franckevičius and Pauline Drouhin, has addressed the problem of the unwanted side-reaction during the cyclisation procedure, namely the decomposition of the linear precursors. It has been shown that by vigorously bubbling air through the reaction mixture, rather than simply exposing the vessel to an air atmosphere, the rate of the cyclisation reaction relative to the decomposition can be increased, thus resulting in a higher yield of the desired oxindole product.

Using these conditions, the cyclisation of a number of previously synthesised substrates was repeated and a direct comparison of these results has been made (Table 22). Gratifyingly, in all cases the yield of product was improved over that obtained with the previous protocol (Tables 17 to 21). In addition, a PMB protected oxindole **21zb** analogous to the Boc-protected glutarimide product **21g** was prepared.[230] The use of this less labile protecting group allowed a much improved yield of 91% of **21zb** to be achieved (entry 10).

To demonstrate synthetic utility, this improved cyclisation procedure was applied to a formal synthesis of horsfiline (**175**),[230] intercepting intermediate **21zc** from the synthesis of Trost and Brennan (Scheme 110).[158]

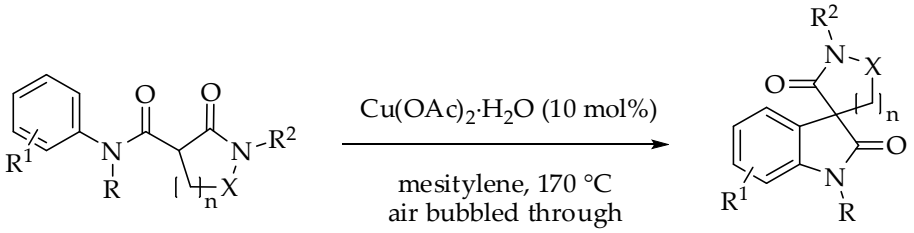
Future work will look at the possibility of an enantioselective variant of the copper-catalysed cyclisation reaction.

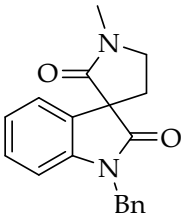
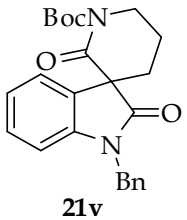
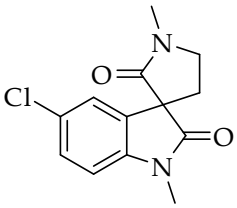
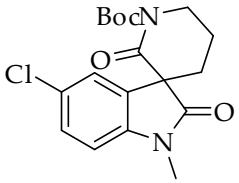
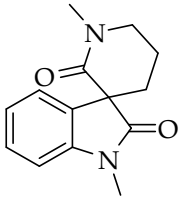
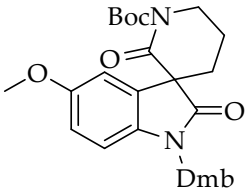
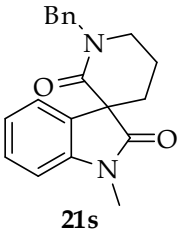
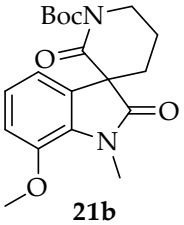
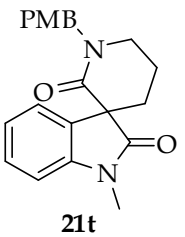
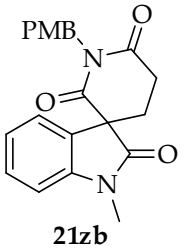


Reagents and conditions: (a) LDA, CbzCl, THF, −78 °C, 1 h; (b) H_2, Pd/C, EtOAc, 2 h; (c) 2-chloro-1-methylpyridinium iodide, Et_3N, **273**, CH_2Cl_2, 0 °C to rt, 1 h; (d) $Cu(OAc)_2 \cdot H_2O$ (10 mol%), mesitylene, air bubbled through, 1.5 h

Scheme 110: Taylor's formal synthesis of horsfiline *via* copper-catalysed spirooxindole formation

Table 22: A comparison of cyclisation reactions using both improved and previous procedures



Entry	Product	Yield (%)[a,b]	Entry	Product	Yield (%)[a,b]
1	 **21x**	80 (*58*)	6	 **21v**	69 (*51*)
2	 **21za**	76 (*66*)	7	 **21n**	70 (*62*)
3	 **21r**	76 (*65*)	8	 **21m**	73 (*63*)
4	 **21s**	83 (*64*)	9	 **21b**	60 (*48*)
5	 **21t**	73 (*64*)	10	 **21zb**	91

[a]Isolated yields. Reaction carried out with air vigorously bubbled through the reaction mixture, performed by Franckevičius or Drouhin; [b]Numbers in parenthesis denote previous yields. Reaction carried out under an air atmosphere

4.7 Summary of the methodological studies

Following on from previous work in the Taylor group, a simple and efficient route for the formation of lactam and imide-based spirocyclic oxindoles has been developed. This procedure has shown to be compatible with a wide range of ring sizes, substitution patterns and protecting groups.

Cyclisation of 5-, 6- and 7- membered lactam and imide substrates have been shown to proceed well, providing good yield of products. The 4-membered β-lactam substrate on the other hand gave a low yield of product.

A variety of protecting groups are compatible for the nitrogen of the lactam, with the less labile methyl, benzyl and PMB groups offering the highest yields. In terms of anilide protection, Me, Bn, PMB and Dmb were all shown to be compatible, although the more electron-withdrawing Boc group was not.

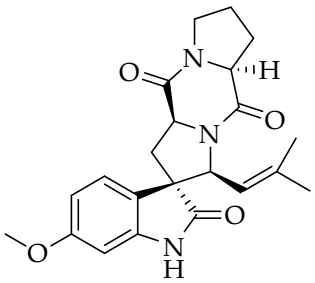
A range of substrates with aromatic substituents were cyclised, with electron-donating groups exhibiting high yields of product. Strongly electron-withdrawing groups, however, resulted in only small quantities of product or indeed none at all. In the case of *meta*-substituted substrates, an interesting regioselectivity was observed, with major products being those arising from cyclisation on the carbon between the two aromatic substituents.

With the simplicity of both the substrate synthesis and the cyclisation itself, it is possible to build up a large degree of molecular complexity in just a few synthetic steps in a straightforward fashion. Indeed, the ease with which oxindole products can be obtained with this methodology encouraged us to establish its utility in natural product synthesis, specifically the synthesis of spirotryprostatin A, and our work towards this goal is detailed in the following Chapter.

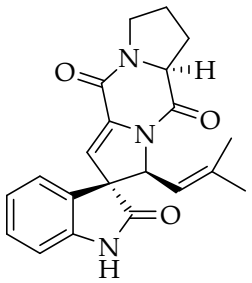
Chapter 5 – Towards the synthesis of spirotryprostatin A

5.1 Introduction to the spirotryprostatins

The spirotryprostatins have attracted much interest since their discovery in 1996 by Cui *et al.* (Figure 19).[231,232] Spirotryprostatin A (**22**) and spirotryprostatin B (**180**) were isolated from the fungus *Aspergillus fumigatus*, and have both been shown to exhibit cell cycle inhibition activity, making them potential lead compounds for cancer treatment.



spirotryprostatin A (**22**)



spirotryprostatin B (**180**)

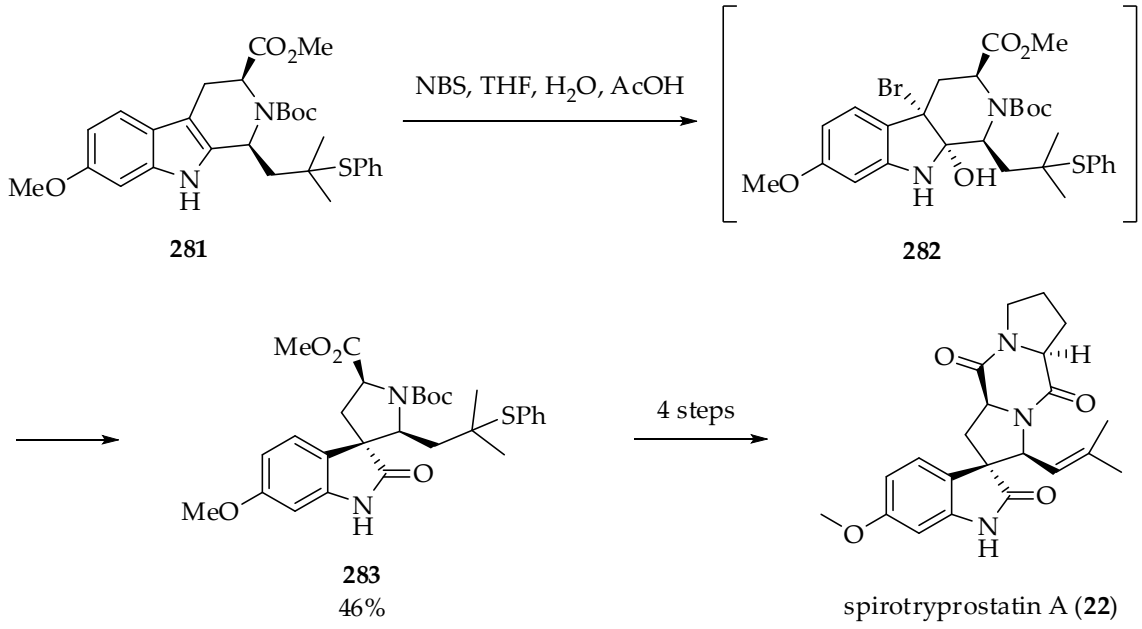
Figure 19: Spirotryprostatins A and B

Spirotryprostatin B is structurally the simpler variant in that it lacks a methoxy substituent on the aromatic ring and one of the stereogenic centres is absent due to additional unsaturation. Overall, both compounds bear a pentacyclic carbon skeleton and, most importantly, contain a spirocyclic oxindole motif.

5.1.1 Previous syntheses of spirotryprostatin A

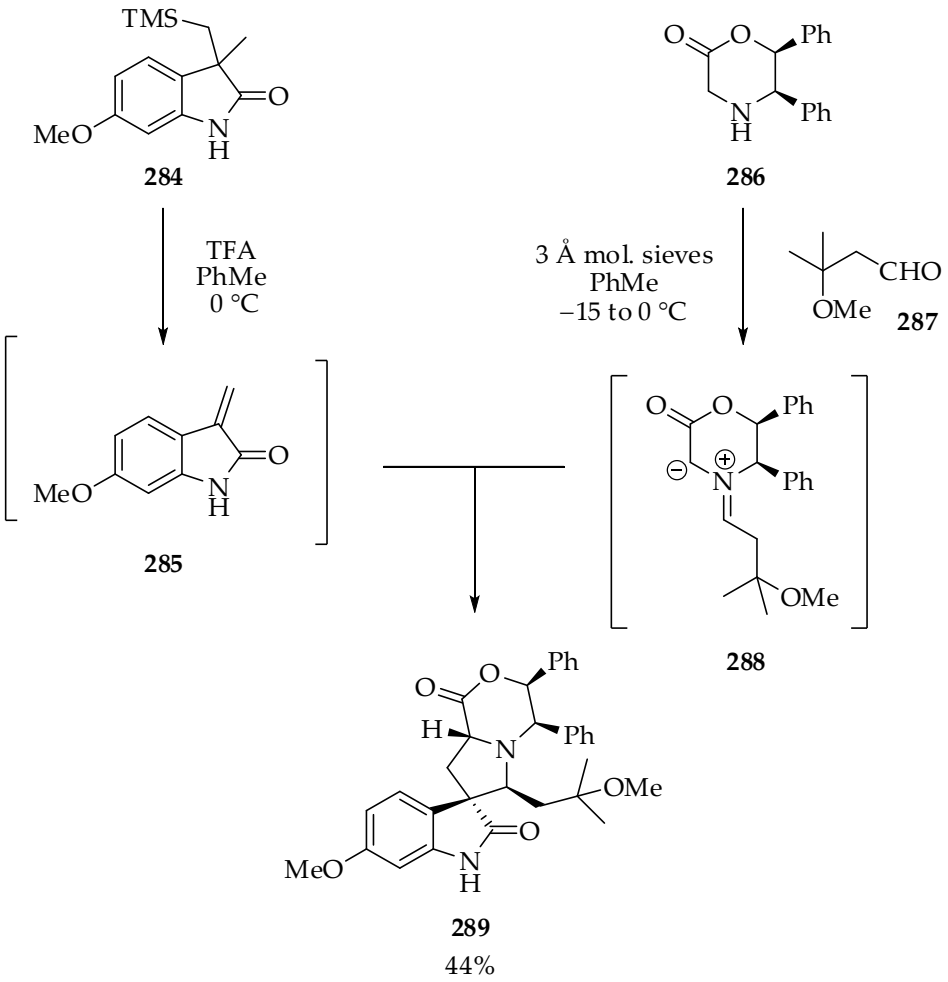
At least three syntheses of spirotryprostatin A have been reported to date, with each route using a different method to construct the spirooxindole core. The first of these syntheses was disclosed in 1998 by Edmondson and Danishefsky (Scheme 111),[233,234] and utilised an oxidative rearrangement of a fused indole **281** to form spirocycle **283** as the key step. This reaction is thought to occur *via* bromohydrin intermediate **282**, wherein the groups on the top (β) face direct bromination to the α-face. Stereospecific ring contraction then occurs resulting in bromide displacement and leading to the desired stereoisomer **283** in 46% yield with the core structure successfully assembled

(Scheme 111). The natural product **22** was then readily accessed in four straightforward chemical manipulations.



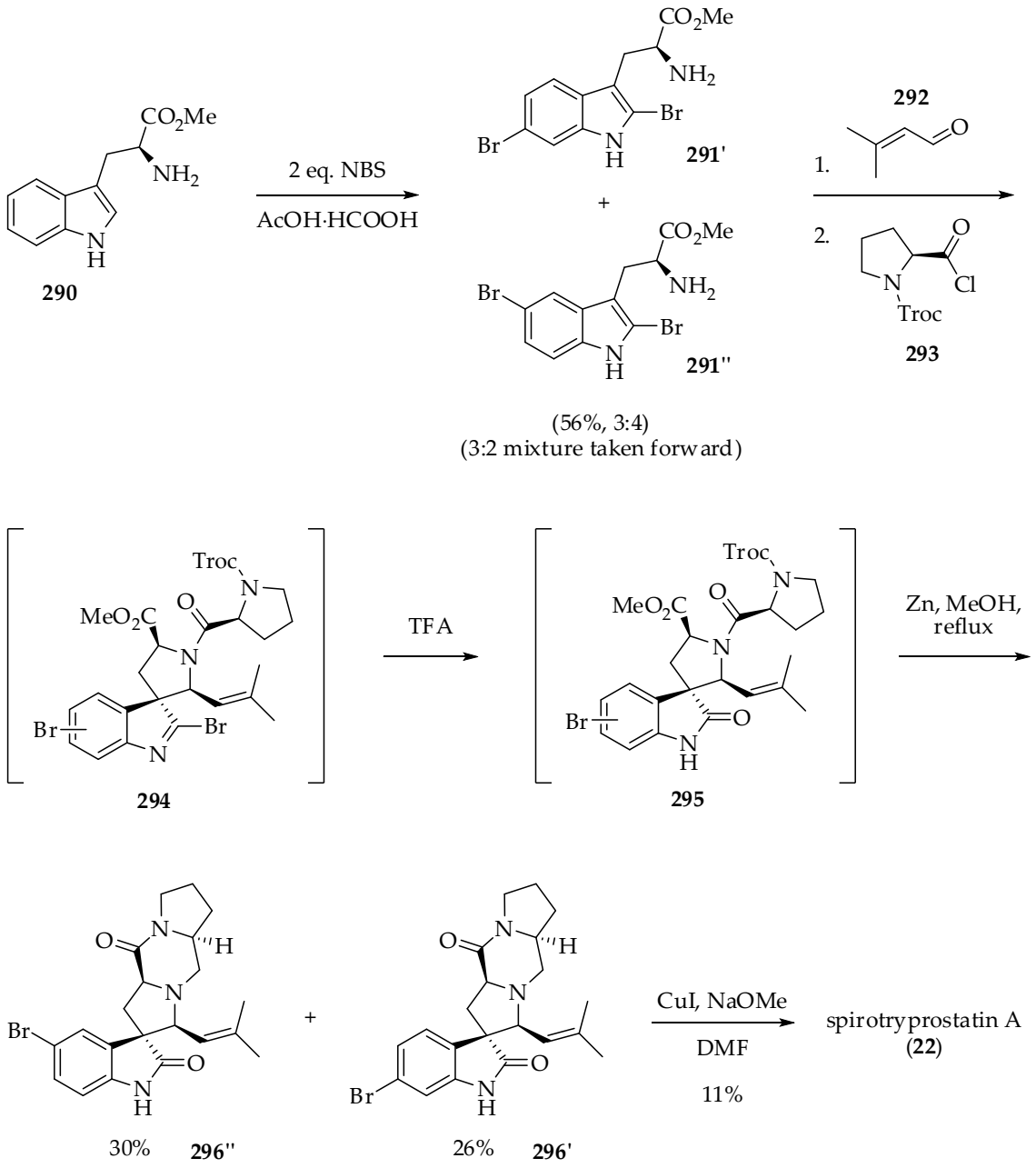
Scheme 111: Danishefsky's approach to the spirocyclic core of spirotryprostatin A

An alternative synthesis of spirotryprostatin A was reported in 2003 by Williams and co-workers.[235,236] Similar to the strategies discussed earlier in Chapter 4.3 (*vide supra,* page 81), they used a 1,3-dipolar cycloaddition reaction for the construction of the spirooxindole core. More specifically, starting with 3,3-disubstituted oxindole **284**, treatment with trifluoroacetic acid led to the *in situ* formation of unstable methylene oxindole **285** as a dipolarophile, whereas condensation of aldehyde **287** with chiral amine **286** formed azomethine ylide **288** as the desired dipole. Cycloaddition reaction between **285** and **288** afforded the desired product **289** in 44% yield and, remarkably, installed three new stereogenic centres with complete diastereocontrol. Subsequent cleavage of the chiral auxiliary, conjugation with a proline residue and double bond installation swiftly paved the way to spirotryprostatin A.



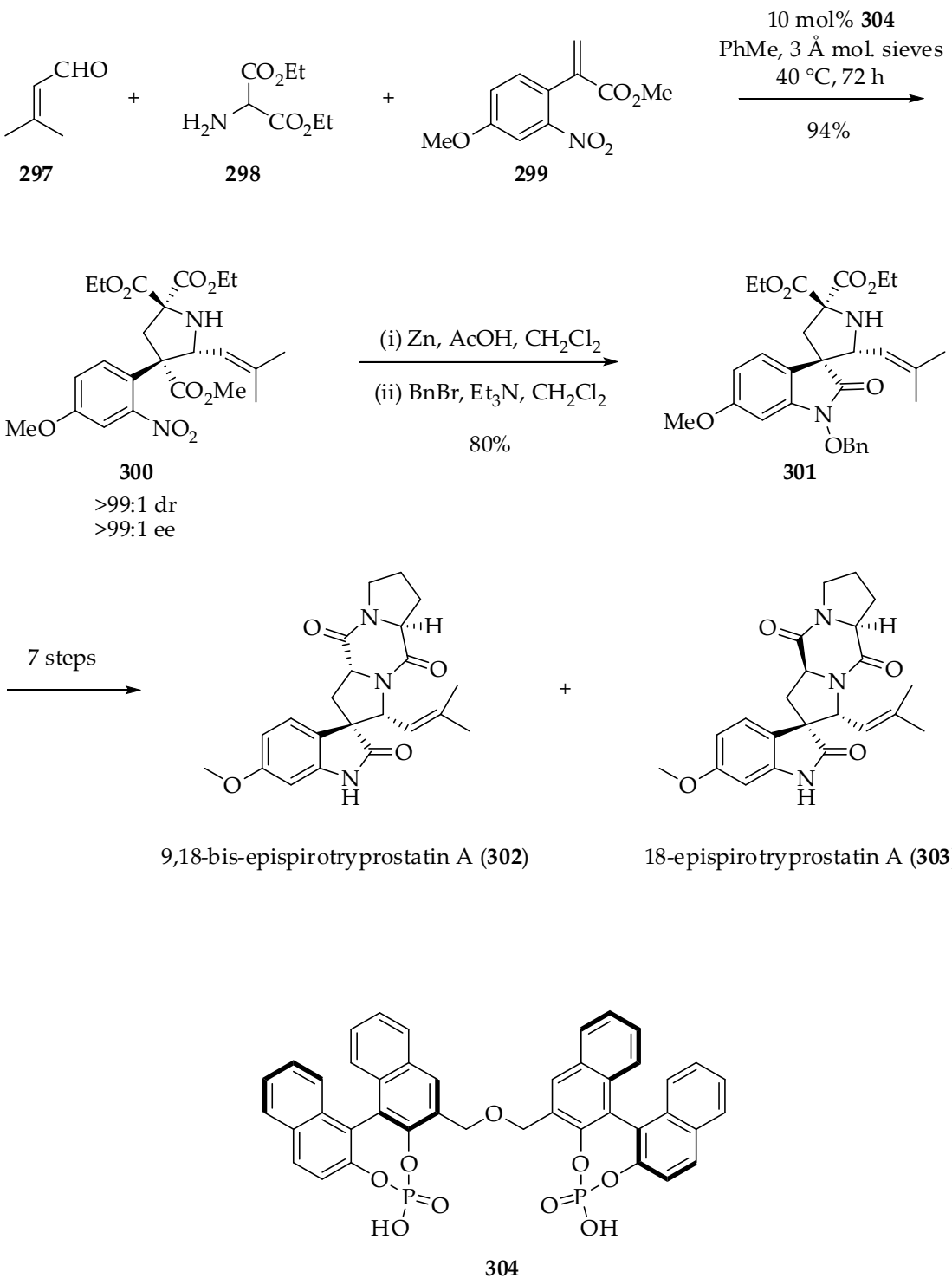
Scheme 112: Williams' approach to the spirocyclic core of spirotryprostatin A

The synthesis of spirotryprostatin A by Horne and co-workers was published in 2004 and focused on a stereoselective spirocyclisation strategy (Scheme 113).[237] Their venture began with the di-functionalisation of tryptophan methyl ester (**290**) with NBS. This step displayed only moderate selectivity, thus leaving the authors with a 3:2 mixture of regioisomeric indole bromides **291'** and **291''** to carry forward. The key step involves condensation of amines **291'/291''** with aldehyde **292** and activation of the resulting imine with proline-derived acyl chloride **293**, thus providing an electrophilic *N*-acyliminium ion and facilitating spirocyclization to **294**. TFA-assisted hydrolysis of the resulting haloindolenine intermediate **294** furnished a mixture of spirocyclic oxindoles **295**, which were subjected to zinc-mediated Troc-cleavage and lactamisation. Regioisomeric products **296'** and **296''** were now separable and the desired spirocycle **296'** was obtained in an overall yield of 26%, in a highly stereocontrolled manner (Scheme 113). This was then subjected to Cu-catalysed methoxylation conditions to furnish spirotryprostatin A (**22**) in 11% yield.



Scheme 113: Horne's approach to the spirocyclic core of spirotryprostatin A

More recently, Gong and co-workers, whilst not gaining access to spirotryprostatin A itself, instead synthesised two diastereomers of the natural product, **302** and **303** (Scheme 114). The group performed an enantioselective Brønsted acid-mediated 1,3-dipolar cycloaddition reaction of **299** with the azomethine ylide arising from condensation of **297** and **298**, to form the pyrrolidine portion in **300** with excellent diastereocontrol as a single enantiomer and diastereomer in high yield. The nitro group was then reduced to a hydroxylamine which underwent lactamisation to form **301** following benzyl protection.[238]

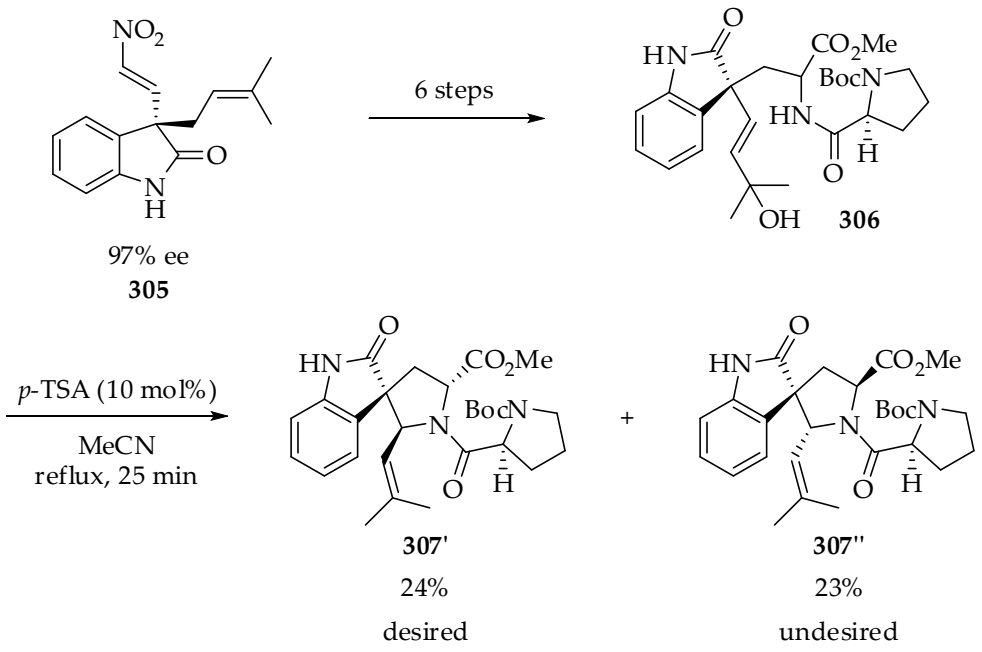


Scheme 114: Gong's approach to diastereomers of spirotryprostatin A

5.1.2 Previous syntheses of spirotryprostatin B

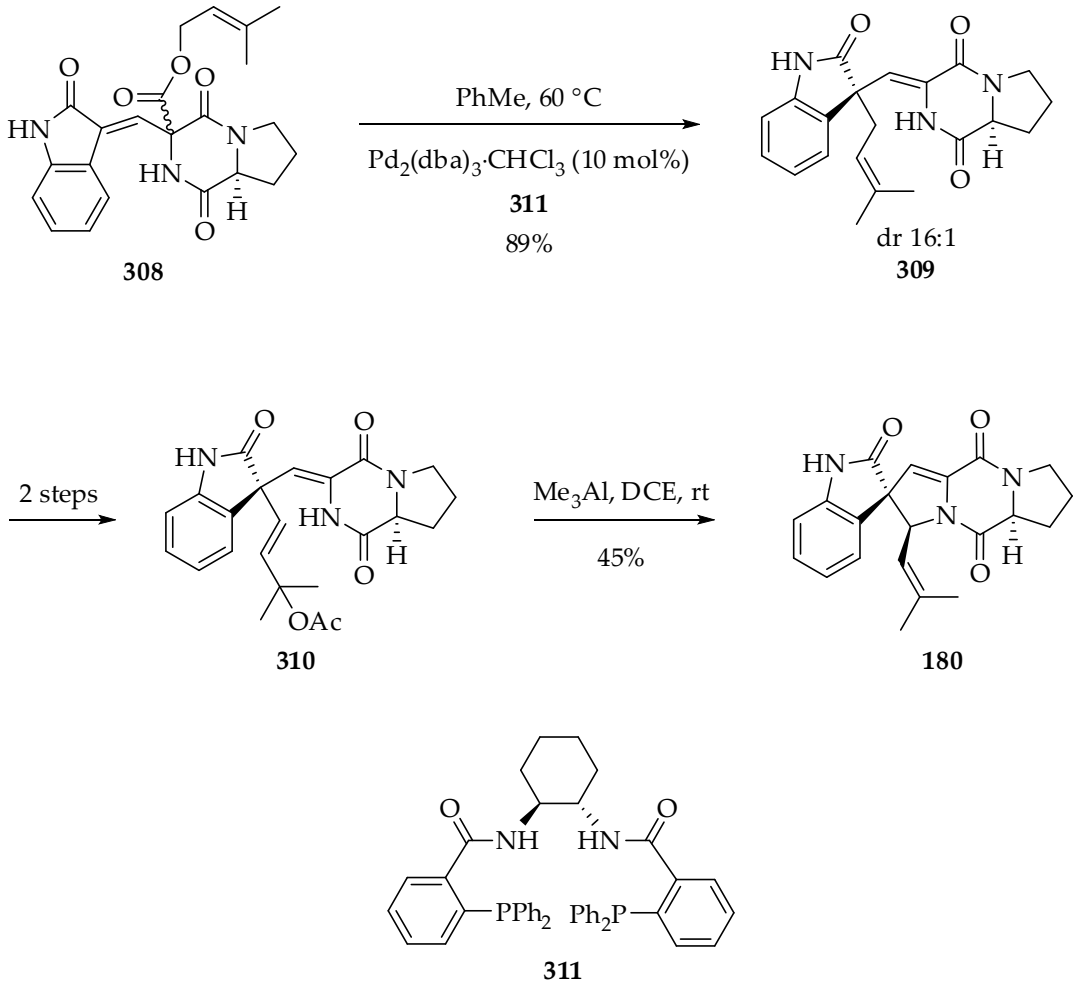
Spirotryprostatin B (**180**), on the other hand, has been a more frequent target for chemical synthesis than spirotryprostatin A, presumably due to its simpler structure. Several of the total syntheses of **180** make use of methods very similar to those seen in spirotryprostatin A synthesis, such as Williams' dipolar cycloaddition approach,[239] and Horne's Mannich-type reaction,[240] a similar version of which was used by Danishefsky.[241] Ganesan performed a biomimetic oxidative rearrangement *via* a bromohydrin,[242] much like Danishefsky's strategy for spirotryprostatin A. As previously mentioned, Carreira utilised the group's cyclopropanation ring expansion methodology for the synthesis of spirotryprostatin B, amongst other natural products (*vide supra*, Chapter 4.3.2),[205,206] whereas Overman effected cyclisation from a linear anilide precursor by means of an intramolecular Heck reaction.[243]

A more distinct synthesis of spirotryprostatin B was performed by Fuji and co-workers (Scheme 115). Their strategy commenced with oxindole **305**,[244] in which the quaternary stereocentre had been installed in high enantiomeric excess using the group's asymmetric nitro-olefination methodology. Following further manipulation to access allylic alcohol **306**, a catalytic amount of acid in refluxing acetonitrile promoted cyclisation and enabled rapid entry to spirocycle **307** (Scheme 115), albeit in low yield. The low efficiency of this reaction was attributed to the need to halt the reaction at 50% conversion in order to avoid deprotection of the Boc moiety, but, importantly, an unwanted diastereomer **307''** was also formed along with the desired compound **307'** as a 1:1 mixture.[245]



Scheme 115: Fuji's approach to spirotryprostatin B

In their synthesis, Trost and Stiles used a palladium-catalysed decarboxylative prenylation reaction to install the quaternary oxindole stereogenic centre. Pleasingly, the in presence of chiral phosphine ligand **311**, prenylation occurred regioselectively alpha- to the carbonyl of the oxindole with high stereocontrol. Following conversion of the prenyl side chain in **309** into allylic acetate **310**, stereoselective cyclisation was achieved using trimethylaluminum, which acted as both a Brønsted base to form an aluminium amide *in situ*, as well as a Lewis acid to activate the allylic acetate towards nucleophilic attack, thus furnishing spirotryprostatin B (**180**) in 45% yield (Scheme 116).[246]



308 **309** **310** **180** **311**

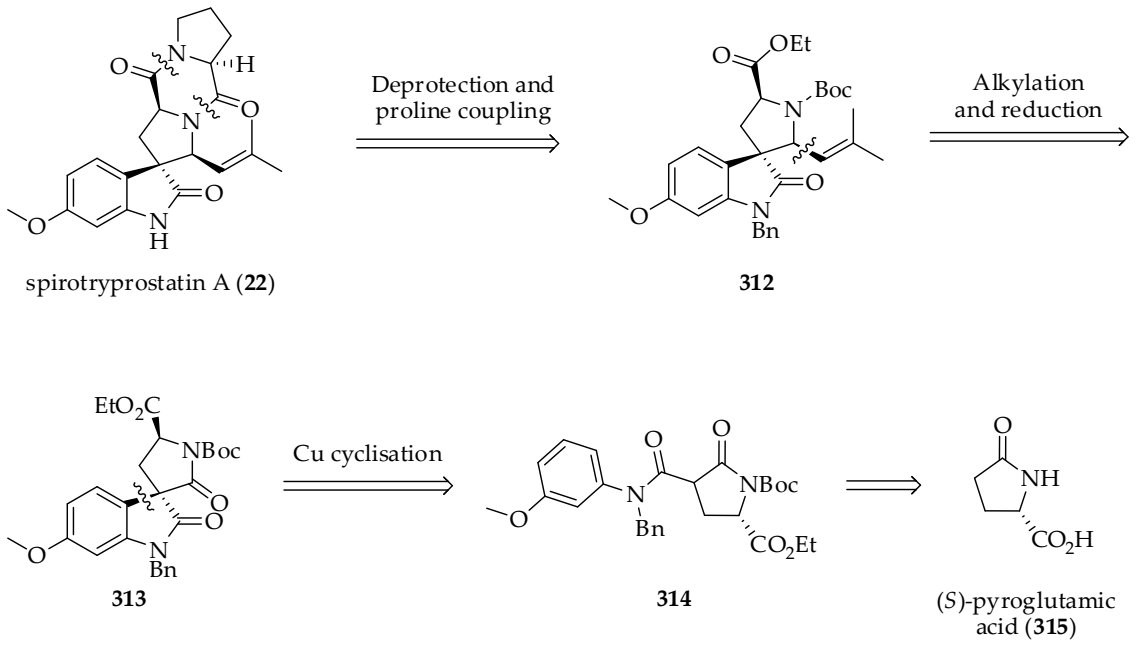
Scheme 116: Trost's approach to spirotryprostatin B

Despite the wealth of synthetic strategies towards the spirotryprostatins, we were now interested in showcasing our copper(II)-catalysed oxindole cyclisation method by applying it to a new synthesis of spirotryprostatin A (**22**). Our retrosynthetic strategy and preliminary results in this area are detailed in the following sections.

5.2 Results and discussion

5.2.1 Retrosynthesis of spirotryprostatin A

Retrosynthetically, an initial disconnection of the two amide bonds in spirotryprostatin A (**22**) gives a proline fragment and spirooxindole **312** (Scheme 117). We envisaged that the isobutylene side-chain in **312** could be introduced *via* selective addition of an appropriate nucleophile to the *N*-Boc-pyrrolidinone carbonyl in **313** and subsequent stereoselective reduction. Intermediate **313** will result from the copper(II)-catalysed cyclisation of anilide **314** as the key step, which could in turn be easily synthesised from inexpensive (*S*)-pyroglutamic acid (**315**). We aim to exploit the stereogenic centre from the chiral pool to set up two other stereocentres in the synthesis of spirotryprostatin A (**22**).

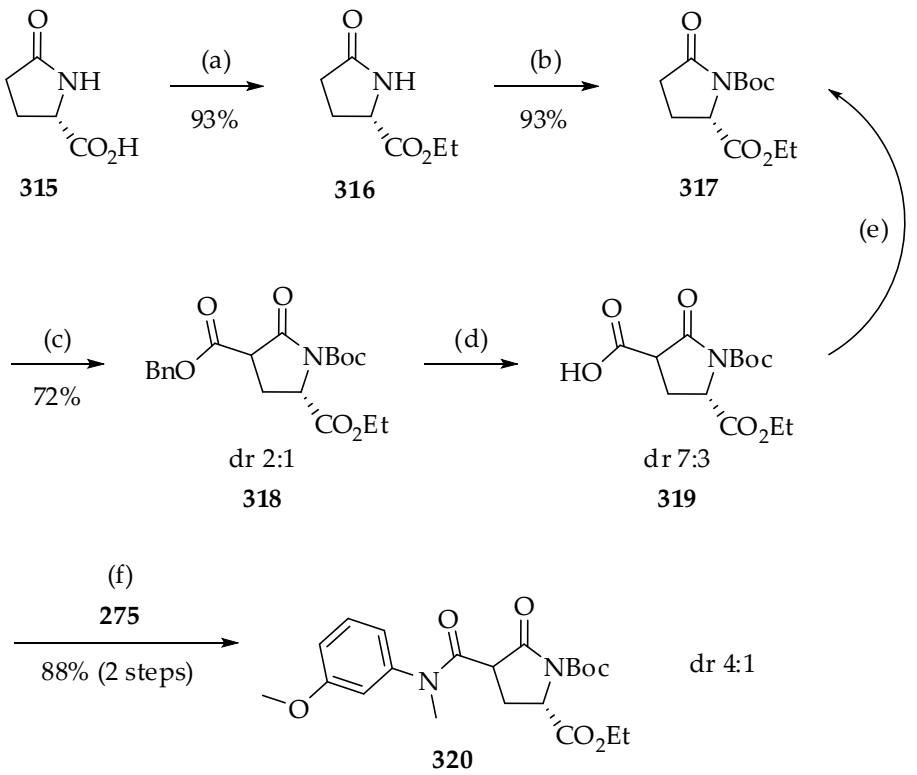


Scheme 117: Retrosynthesis of spirotryprostatin A (22)

We identified two potential elements for consideration and optimisation in the key copper-mediated cyclisation step of **314** to **313**: the regioselectivity of cyclisation, given that the methoxy substituent in anilide **314** is in the *meta*- position, as well as the diastereoselectivity of the cyclisation.

5.2.2 Initial steps

Initial work saw the synthesis of *m*-methoxy anilide **320** (Scheme 118). Following literature procedures, the first step was esterification of (*S*)-pyroglutamic acid (**315**),[247,248] followed by Boc-protection of the resultant ester **316** to give **317** in 86% yield over the two steps.[249] With *N*-protected lactam **317** in hand, the previously established route towards cyclisation precursors could now be applied. In this context, benzylcarboxylation under standard acylation conditions was achieved in 72% yield, providing dicarbonyl **318** as an inconsequential 2:1 mixture of diastereoisomers. This was followed by hydrogenolysis and amide coupling with the previously prepared methoxy-substituted aniline **275**, giving substrate **320** in 88% yield over the final two steps.



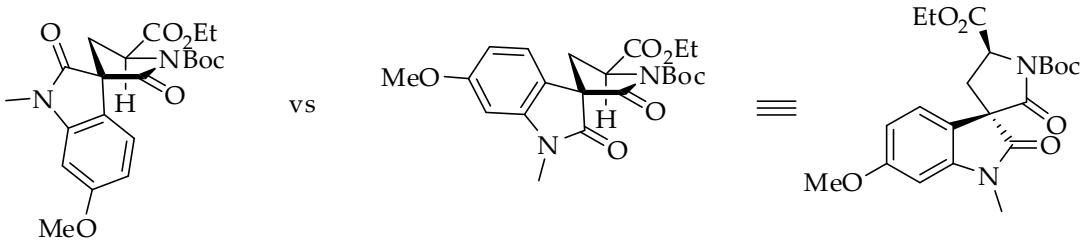
Reagents and conditions: (a) $SOCl_2$, EtOH, 0 °C to rt, 1 h; (b) Boc_2O, DMAP, Et_3N, CH_2Cl_2, rt, 12 h; (c) LiHMDS, CbzCl, THF, −78 °C, 1 h; (d) Pd/C, H_2, EtOAc, rt, 2 h; (e) MeCN:H_2O (99:1), reflux, 24 h; (f) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h.

Scheme 118: Synthesis of anilide substrate for cyclisation

There were initial concerns that, under the basic conditions of the benzylcarboxylation step, deprotonation of the acidic chiral proton alpha- to the pendent ester in **318** may

occur, resulting in epimerisation of the all-important chiral centre. To determine whether or not this was indeed the case, a sample of carboxylic acid **319** was subjected to decarboxylative conditions, thus reforming Boc-protected lactam **317** (Scheme 118). An $[\alpha]_D$ measurement of this material was obtained and compared to that of the original chiral material **317**. Pleasingly, a close match was observed, with experimental measurements of −36.4 (*c* 0.86, CH_2Cl_2) and −37.5 (*c* 0.86, CH_2Cl_2) respectively, confirming that no epimerisation had taken place. With concerns of stereochemistry quelled, and the final steps of substrate synthesis completed, attention could now be turned to the key cyclisation reaction.

It was our hope that the pre-existing stereogenic centre in **320**, derived from (*S*)-pyroglutamic acid, would result in substrate-controlled diastereoselectivity in the cyclisation reaction. Specifically, if the 5-membered lactam in product **321** adopts an envelope conformation, we would expect the thermodynamically more favoured product **321$_p$'** to be that in which both the ester group and the bulk of the oxindole moiety are in pseudo-equatorial positions (Figure 20). As the cyclisation reaction is performed at elevated temperature, we anticipated that the thermodynamic product would prevail, based on the assumption that the radical addition step onto the benzene ring is a reversible process.



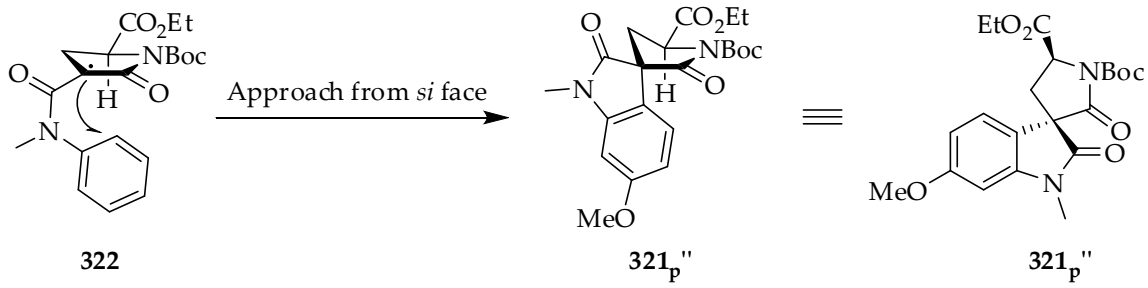
321$_p$''
Oxindole pseudo-axial
Unfavourable

321$_p$'
Both pseudo-equatorial
Favourable

321$_p$'

Figure 20: Expected thermodynamic product from Cu(II) cyclisation of 320

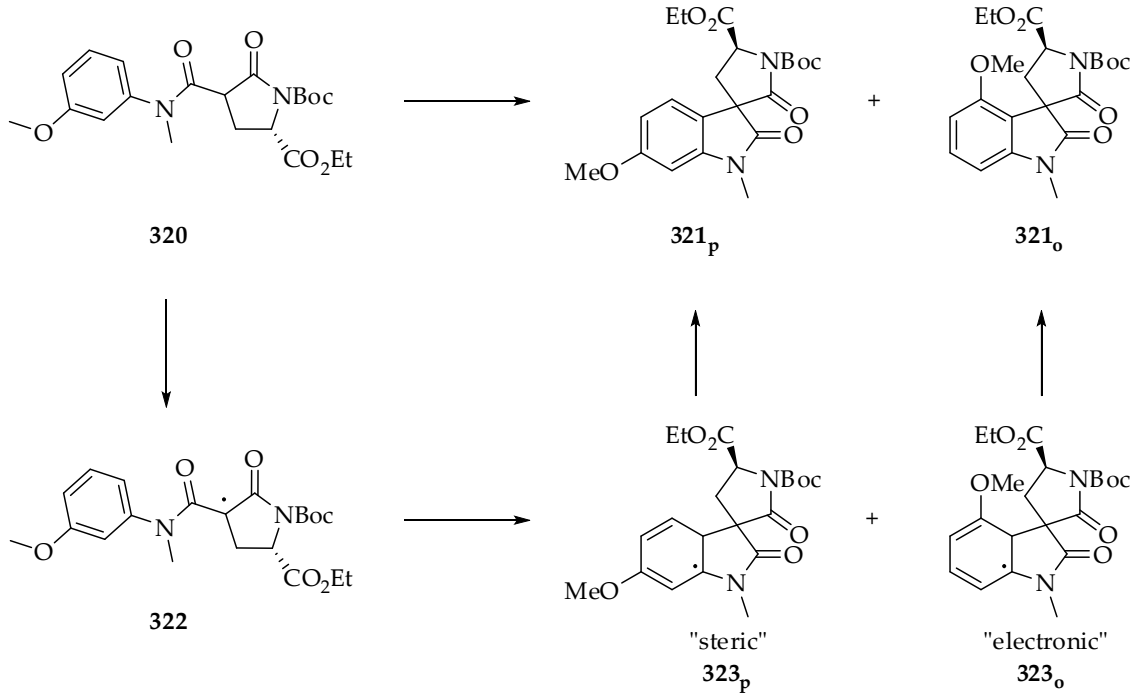
Alternatively, if the reaction proceeded under kinetic control, then the expected product **321$_p$''** would be that arising from formation of the new C–C bond anti- to the bulk of the CO_2Et group (Scheme 119), and provide the diastereomer with the incorrect stereochemical configuration at the quaternary carbon centre. We believed that due to the high temperature of the reaction, the kinetic control mechanism was unlikely.



322 **321_p''** **321_p''**

Scheme 119: Formation of expected kinetic product

In terms of regiochemistry, when the cyclisation precursor bears a *meta*-substituent, cyclisation can potentially yield two regioisomeric products: one arising from formation of the new bond at the carbon atom between the two substituents, and one resulting from radical addition to the position of the benzene ring furthest away from the methoxy substituent (Scheme 120). The former isomer **321_o** could be favoured based on electronic grounds as this leads to a more stabilised cyclohexadienyl radical intermediate **323_o**. On the other hand, addition *ortho*- to the substituent is the more sterically hindered position, suggesting that addition could take place *para*- to the substituent on steric grounds. We were excited to investigate which of the two isomers would be preferential in the spirotryprostatin A synthesis.

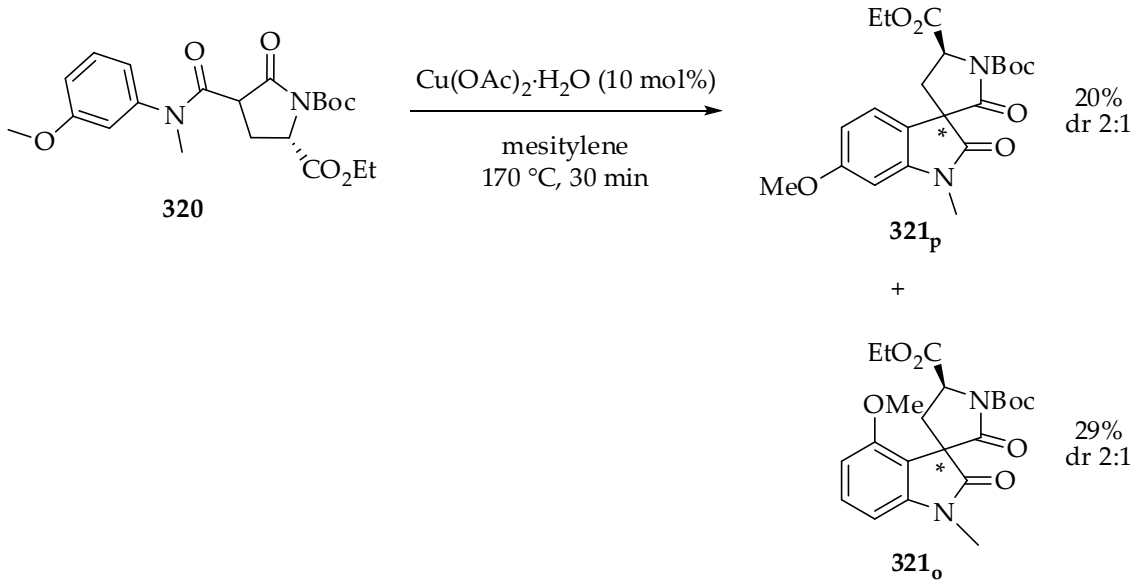


320 **321_p** **321_o**

322 **323_p** **323_o**

Scheme 120: Steric and electronic outcomes of the cyclisation reaction of *meta*-substituted substrate 320

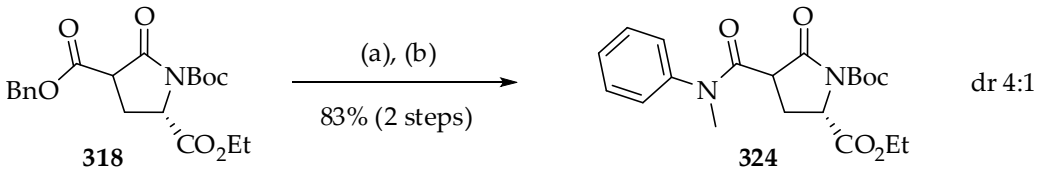
In our first attempt, cyclisation of *m*-methoxy-substituted anilide **320** resulted in the formation of oxindole **321** as an inseparable mixture of four compounds, namely regio- and stereoisomers, in a combined yield of 49%. A careful inspection of NMR data allowed us to establish that, interestingly, a 3:2 mixture of regioisomers $\mathbf{321_o}$ and $\mathbf{321_p}$ was obtained, with the minor compound $\mathbf{321_p}$ representing the desired isomer. Furthermore, the minor isomer was formed as a 2:1 mixture of diastereoisomers, although it was not possible to establish which of the two diastereoisomers was desired. It was clear that further investigation was essential.



Scheme 121: Cyclisation of *m*-methoxy anilide 320

5.2.3 Stereoselectivity study

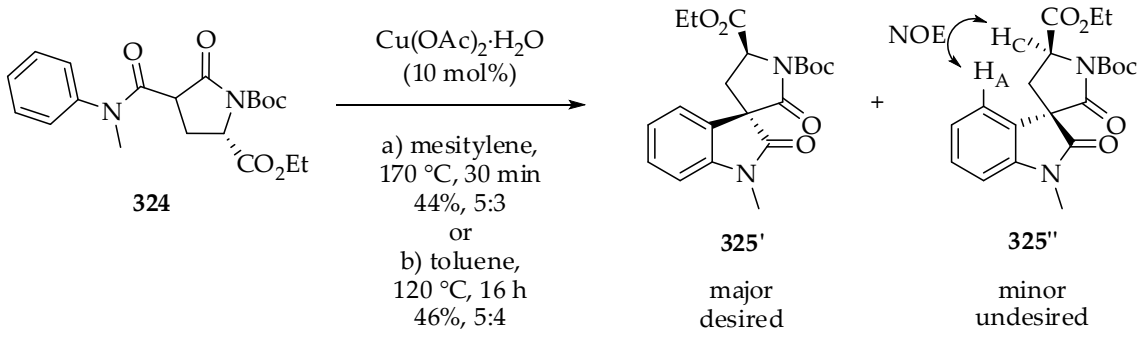
In order to facilitate the ease of data interpretation, our study began by examining the stereoselectivity of the reaction without the additional complexity of regioselectivity. Hence, our starting point was the reaction of unsubstituted substrate **324**. Using previously synthesised ester **318** (*vide supra,* Scheme 121), hydrogenolysis followed by amide coupling with *N*-methylaniline (**265**) furnished **324** in 83% yield over the two steps.



Reagents and conditions: (a) Pd/C, H_2, EtOAc, rt, 2 h; (b) 2-chloro-1-methylpyridinium iodide, Et_3N, **265**, CH_2Cl_2, 0 °C to rt, 16 h.

Scheme 122: Synthesis of unsubstituted substrate 324

Cyclisation of **324** under standard conditions (mesitylene, 170 °C, 30 min) provided a 5:3 mixture of diastereoisomers in 44% overall yield. At this point we were unable to ascertain which diastereoisomer was the major product, as the isomer mixture was inseparable and therefore NOE experiments were inconclusive. Nevertheless, irradiation of H_C showed a small enhancement of H_A in the minor diastereoisomer **325''** (Scheme 123), suggesting that the desired stereoisomer **325'**, with H_A and the ester group on the same face, could indeed be the major product.

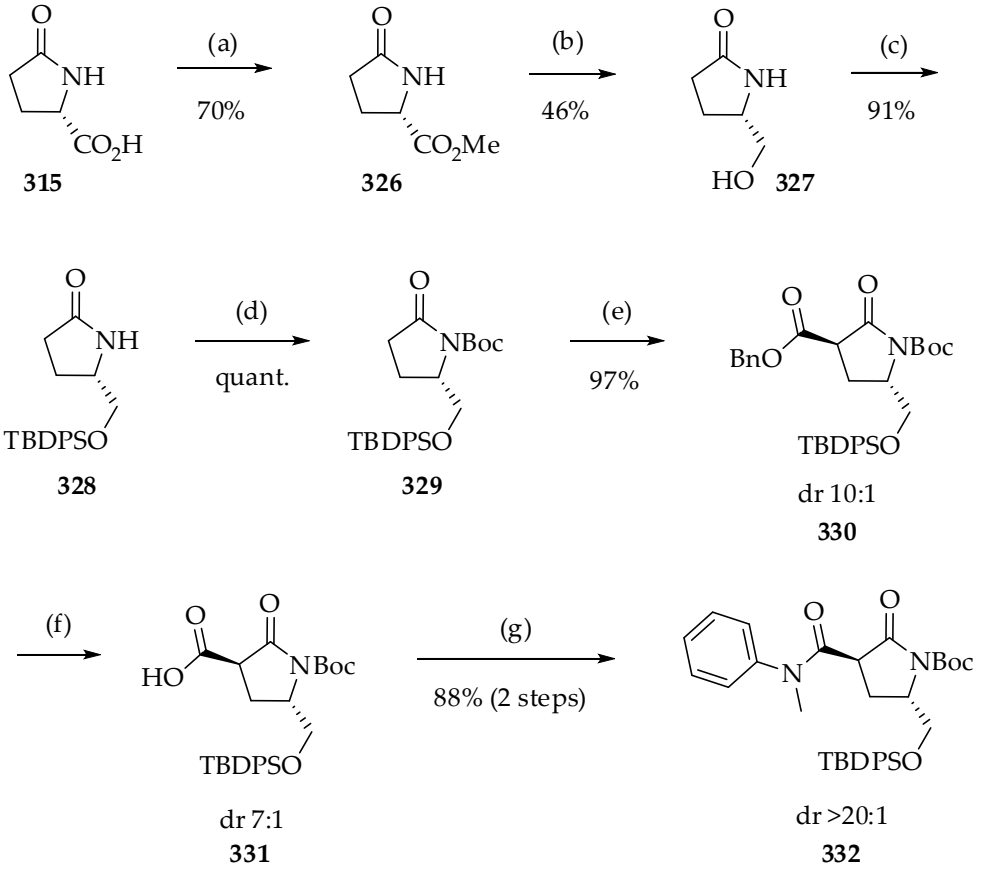


Scheme 123: Cyclisation of unsubstituted anilide 324

To investigate the effect of temperature, the cyclisation reaction was repeated in toluene at 120 °C, whereby only a slight change to both the yield and the diastereomeric ratio of products **325'** and **325''** was observed (Scheme 123).

As the size of the pendent side-chain on the pyrrolidone ring (ethyl ester in **324**) could also affect the stereoselectivity of cyclisation, we next sought to prepare a substrate with a larger side-chain and focused on *tert*-butyldiphenylsilyl (TBDPS)-protected primary alcohol **332** (Scheme 124).

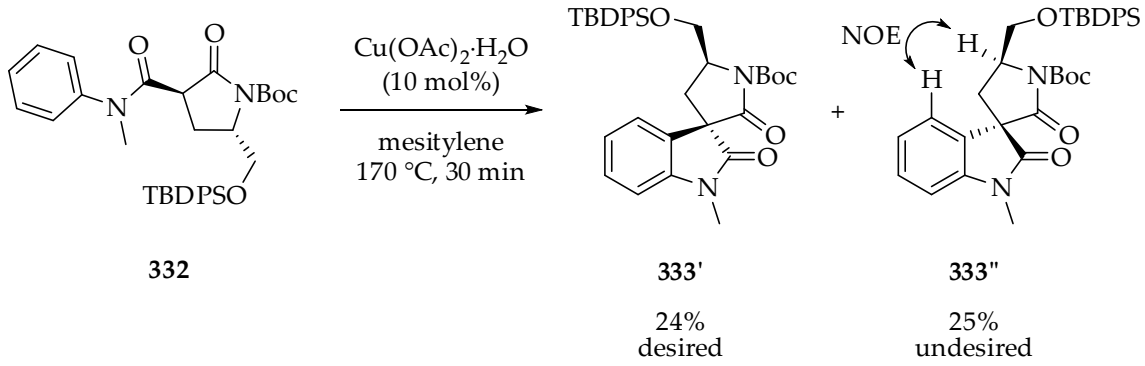
Thus, following literature precedent, ester **326** was obtained by esterification of (*S*)-pyroglutamic acid (**315**),[247,248] which was then reduced with sodium borohydride.[250] The resulting pyroglutamol (**327**),[251] was protected as a silyl ether **328** and further *N*-Boc protection provided lactam **329**,[251] ready for benzylcarboxylation. Following treatment of **329** with LiHMDS and CbzCl under standard conditions, **330** was obtained as an inconsequential 10:1 mixture of diastereoisomers. Finally, hydrogenolysis followed by amide coupling of **331** with *N*-methylaniline (**265**) cleanly gave *trans*-anilide **332** (Scheme 124).



Reagents and conditions: (a) $SOCl_2$, MeOH, −20 °C to rt, 1 h; (b) $NaBH_4$, EtOH, 0 °C, 2h; (c) TBDPSCl, imidazole, DMF, rt, 16 h; (d) Boc_2O, DMAP, MeCN, rt, 20 h; (e) LiHMDS, CbzCl, THF, −78 °C, 1 h; (f)) Pd/C, H_2, EtOAc, rt, 2 h; (g) 2-chloro-1-methylpyridinium iodide, **265**, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h.

Scheme 124: Second generation model substrate synthesis

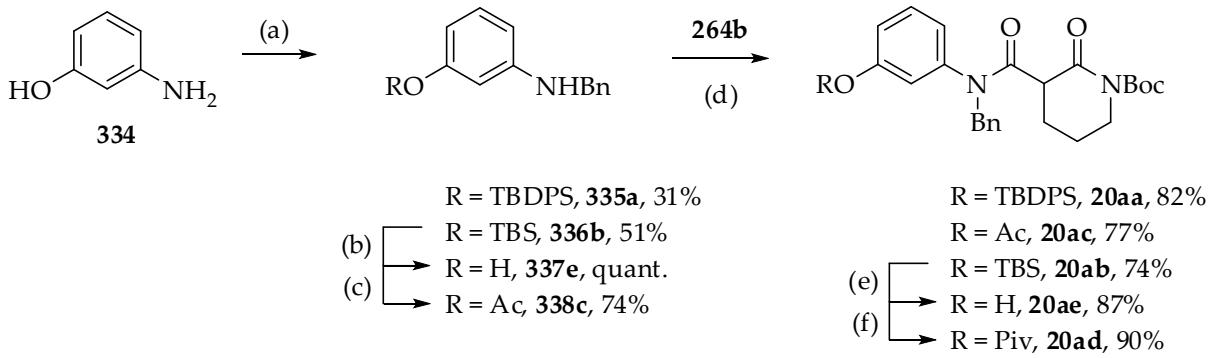
To our surprise, the cyclisation reaction of substrate **332** resulted in a completely non-selective reaction to provide a 1:1 mixture of diastereoisomers (Scheme 125), although these could now be separated and assigned by NOE studies.



Scheme 125: Cyclisation of TBDPS-protected substrate

5.2.4 Regioselectivity study

Having had little success with improving the stereoselectivity of the reaction, we turned our attention to examining the regioselectivity control elements in the cyclisation. We wished to explore whether, by altering steric and electronic properties of the substrates, the regioselectivity of the cyclisation could be improved. In order to investigate this effect without the additional complication of stereoselectivity, a range of *m*-hydroxy anilide cyclisation precursors (**20aa–ad**) were prepared, masked with a variety of oxygen protecting groups.



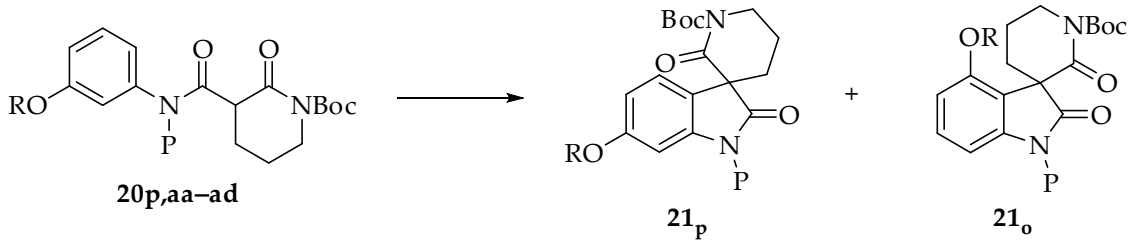
Reagents and conditions: (a) *i)* TBSCl or TBDPSCl, imidazole, DMF, rt, 4 h; *ii)* benzaldehyde, AcOH, MeOH, rt, 3h then $NaBH_4$, rt, 1 h; (b) TBAF, THF, rt, 3 h; (c) NaH, THF, 0 °C, 10 min, then Ac_2O, rt, 1 h; (d) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h, yields over 2 steps from **263b**; (e) TBAF, THF, rt, 1.5 h; (f) DMAP, Et_3N, PivCl, CH_2Cl_2, rt, 3 h

Scheme 126: Synthesis of substrates for regioselectivity study

Specifically, silyl protection of 3-aminophenol (**334**) followed by reductive amination with benzaldehyde gave the benzyl protected anilines **335a** and **335b**.[252] To access the acetoxy-protected phenol **336c**, **336b** was treated with tetrabutylammonium fluoride (TBAF) to remove the TBS moiety and then acylated. Amide coupling of **335a–c** with acid **264b** gave rise to substrates **20aa** to **20ac** in good yields. Desilylation of **20ab** followed by treatment with pivaloyl chloride then swiftly furnished **20d**. With these *meta*-substituted precursors in hand, investigation into the regioselectivity of the cyclisation commenced and the results of this study, together with a direct comparison to methoxy-substituted precursor **20p**, are shown in Table 23.

Initial investigation showed that by placing an electron withdrawing acetate group on the aromatic ring (Table 23, entry 2), the regioselectivity of the cyclisation is diminished in comparison to that of the electron-donating methoxy substrate (entry 1), thereby shifting the ratio towards the desired regioisomer $\mathbf{21_p}$.

Table 23: Results of cyclisation for regioselectivity study



Entry	R	P	$\mathbf{21_p}$:$\mathbf{21_o}$[a]	Yield of $\mathbf{21_p}$ [b]	Yield of $\mathbf{21_o}$ [b]
1	Me	Me	1 : 3	18	58[c]
2	Ac	Bn	1 : 1.6	15	24
3	Piv	Bn	1 : 1.7	15	25[c]
4	TBS	Bn	1 : 1.3	19[c]	26
5	**TBDPS**	**Bn**	**1.3 : 1**	**30**	**19**

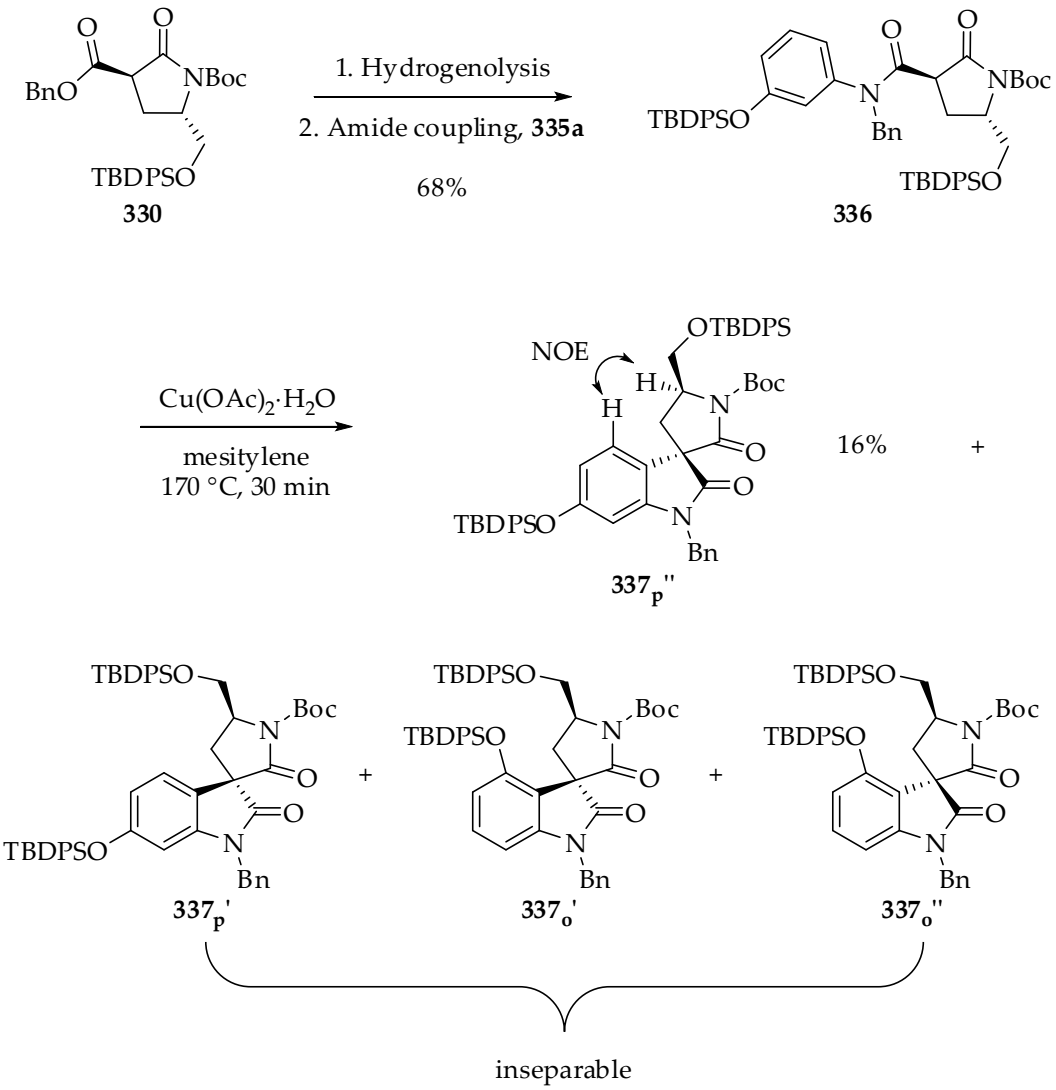
[a]Determined by ^{1}H NMR analysis of the unpurified product mixture; [b]Isolated yields; [c]Yields extrapolated; a small amount of Boc-protected lactam **262b** co-eluted with products during chromatography

Increasing the size of the protecting group to a pivaloyl, but maintaining its electron withdrawing nature, had little effect on the selectivity (entry 3). Unfortunately, in both cases, the use of acetate or pivaloyl electron-withdrawing groups resulted in a marked decrease in the yield of the reaction, an observation that had already been seen in previous studies (*vide supra*, Table 18).

In the case of the electron-donating silyl groups, the yields were moderate. TBS-protected substrate **20ab** gave nearly a 1:1 ratio of regioisomers (entry 4), and pleasingly, the use of bulky TBDPS group resulted in the desired isomer **20aa** being the major product (entry 5). Overall, we were able to override the electronic effects by making use of a large protecting group, thus giving rise to the desired regioisomer as the major product, although the selectivity and the yield were both still disappointing.

5.2.5 Continuation of synthesis

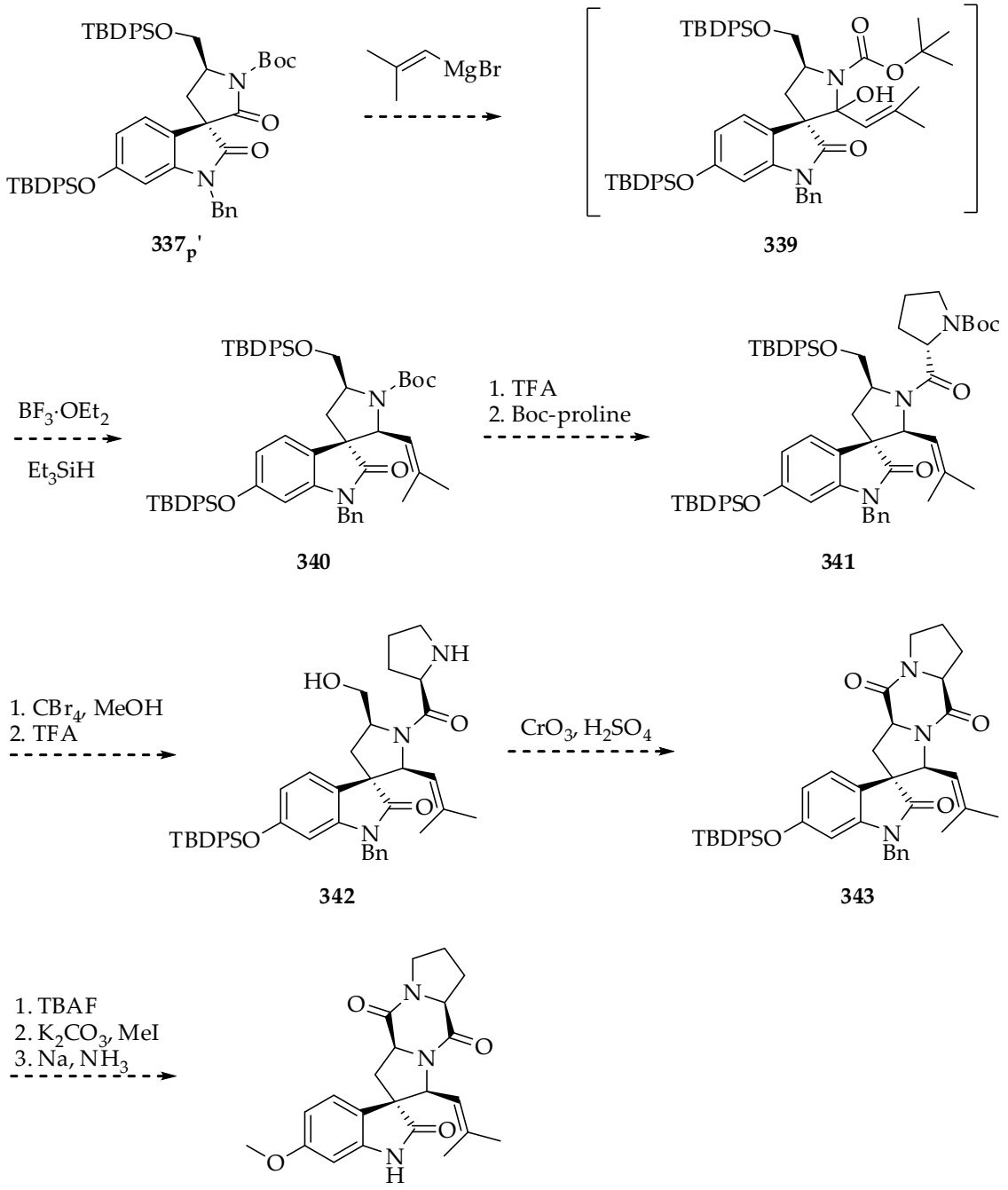
At this stage, we were interested in examining the cyclisation of a substrate containing both a TBDPS-protected *meta*-hydroxy aniline and a TBDPS-protected pendent primary alcohol functionality on the pyrrolidinone ring. Thus, cyclisation precursor **336** was prepared from ester **330** (Scheme 127). Cyclisation of this substrate afforded a complex mixture of stereo- and regioisomers (Scheme 127). One of these products was separated by chromatography and identified by NOE experiments as undesired diastereoisomer **337$_p$″**. In addition to 16% of isomer **337$_p$″**, an inseparable mixture of at least three further compounds was isolated (approx. 28% mass recovery). We had anticipated this mixture to potentially comprise of the remaining three isomers **337$_p$′**, **337$_o$′** and **337$_o$″**, however, due to the complexity of the NMR data, this conclusion was only tentative and the identities of the individual constituents of the mixture could not be conclusively established at this point.



Scheme 127: Synthesis and cyclisation of bis-OTBDPS substrate 336

5.3 Future work

The cyclisation step of this synthesis is evidently in need of further optimisation and this will be investigated in due course. If the efficiency and selectivity can be improved, spirotryprostatin A will be accessed *via* a synthetic plan as proposed in Scheme 128.



Scheme 128: Proposed forward synthesis of spirotryprostatin A

In this context, the carbonyl functionality of the pyrrolidinone amide in **337$_p$'** should possess increased electrophilicity compared to the amide in the oxindole unit due to the electron-withdrawing nature of the Boc group. This bias should enable addition of a nucleophile, such as a Grignard reagent, to install the isobutene side-chain.

Literature precedent shows that a nucleophilic addition/deoxygenation sequence can be used to convert *N*-Boc lactams into α-substituted *N*-Boc pyrrolidines respectively, *via* an *N*-acyliminium ion intermediate, with high stereselectivity.[253,254] We envisage using this nucleophilic addition/reductive deoxygenation sequence to convert **339** into **340**, with reduction occurring from the opposite face to the bulky OTBDPS side chain and installing the new stereogenic centre in **340** with the correct stereochemical configuration. Following this, *N*-Boc deprotection will allow coupling with *N*-Boc proline to form **341** (Scheme 128).

Selective primary TBDPS deprotection in the presence of a phenolic TBDPS function with carbon tetrabromide in refluxing methanol will provide **342** following Boc cleavage (Scheme 128).[255] Jones oxidation should then result in lactamisation directly from **342** to give **343**. In the final stages of the synthesis, desilylation and methylation will reveal the methoxy substituent, whereas single-electron reductive cleavage of the benzyl group[157,163] will provide the target natural product, spirotryprostatin A (**22**).

5.4 Summary

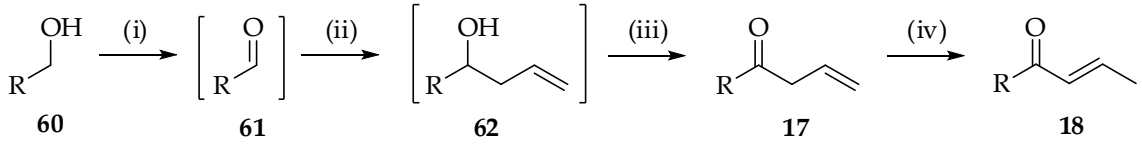
Preliminary studies towards the synthesis of spirotryprostatin A (**22**) *via* a copper(II)-catalysed radical cyclisation have been conducted. The stereochemistry of the cyclisation was investigated and it was found to be poor to moderate with the substrates utilised. Studies into the regioselectivity of the cyclisation showed that the ratio of regioisomeric products could be shifted towards the desired isomer by the use of a bulky silyl group, however both selectivity and yield were still disappointing and further optimisation of the cyclisation reaction is required.

Future work in the group will focus on continued optimisation of the copper(II) cyclisation reaction, followed by investigation into the subsequent steps of the proposed synthesis towards spirotryprostatin A (**22**).

Chapter 6 - Final conclusions and future work

6.1 Unsaturated ketones and elaeokanidine A

The aim of project I was to develop a telescoped procedure for the synthesis of β,γ- and α,β-unsaturated ketones **17** and **18** directly from primary alcohols **60**. A one-pot route to β,γ-unsaturated ketones was subsequently developed, utilising an oxidation/allylation/oxidation procedure, and has been demonstrated on a range of aromatic and aliphatic substrates. Allylic ketones **17** could then be easily transformed into the corresponding conjugated systems **18** by means of DBU-catalysed isomerisation (Scheme 129).



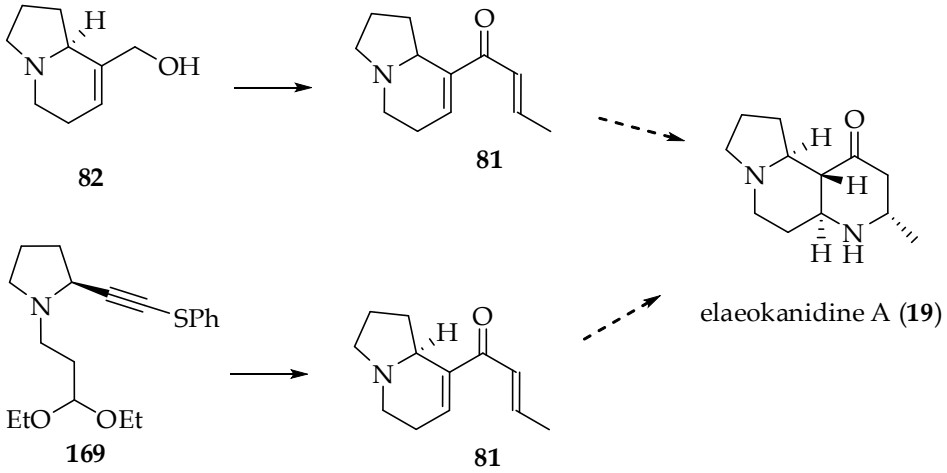
60 **61** **62** **17** **18**

Reagents and conditions: *i)* DMP (1.5–2.0 eq), CH_2Cl_2, rt, 1 h; *ii)* montmorillonite K10, potassium allyltrifluoroborate (**78**, 1.5–2.0 eq), rt, 1 h; *iii)* DMP (2.0–2.5 eq), rt, 1 h; *iv)* DBU (0.1 eq), Et_2O, 24 h

Scheme 129: Synthesis of β,γ- and α,β-unsaturated ketones 17 and 18 directly from primary alcohols 60

Future work in this area will address the inclusion of this isomerisation into the one-pot procedure, in addition to the application of this methodology to natural product synthesis.

We next sought to apply this methodology to the synthesis of elaeokanidine A (**19**), using alcohol **82** and dienone **81** as key intermediates. Following optimisation of the synthetic route, the construction of the indolizidine core was achieved, leading to the synthesis of alcohol **82**. Application of the O/A/O/I methodology was not as successful as anticipated, nevertheless access was gained to racemic **81** and the subsequent addition of ammonia was demonstrated, resulting in an inseparable mixture of diastereoisomers. An asymmetric route to **81** was developed by Cuthbertson by means of the cyclisation of acetal **169**, from which a sample enriched in elaeokanidine A (**19**) was obtained (Scheme 130).

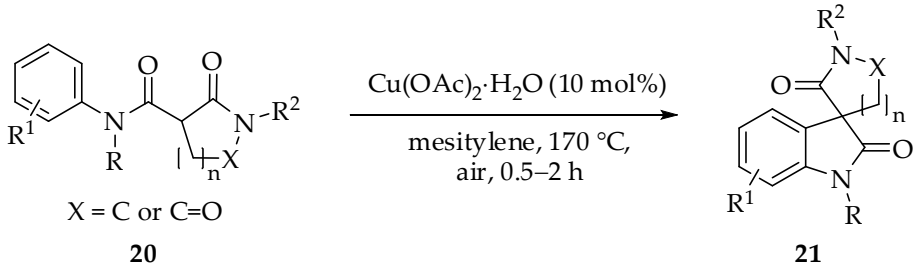


Scheme 130: Synthetic routes to dienone 81 and elaeokanidine A (19)

Future work will investigate the separation of the diastereoisomers resulting from ammonia addition, in order to obtain pure samples of elaeokanidine A (**19**).

6.2 Spirooxindoles and spirotryprostatin A

Building on previous work in the Taylor group concerning the synthesis of oxindoles, a simple and efficient route for the formation of lactam and imide-based spirocyclic oxindoles **21** has been developed. The key step in this process is the radical cyclisation of linear anilide precursors **20**, a reaction which is performed using just catalytic amounts of copper(II) under an air atmosphere (Scheme 131).

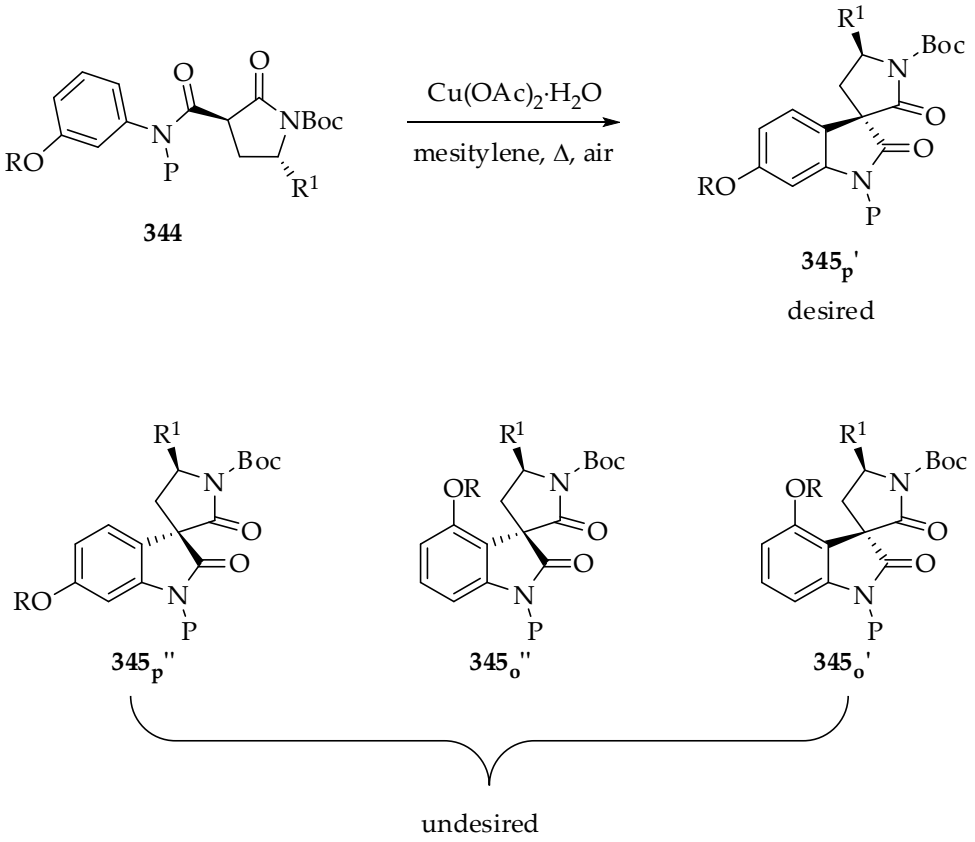


Scheme 131: Copper-catalysed cyclisation of linear anilides 20 to form spirooxindoles 21

The cyclisation has been demonstrated on a wide range of substrates with varying ring size, aromatic substituents and protecting groups, thus exemplifying the broad scope of this reaction. It was later found, by Franckevičius and Drouhin, that the cyclisation could be further improved by vigorously bubbling air through the reaction mixture,

and the utility of the reaction was demonstrated in a formal synthesis of the alkaloid horsfiline. Future work will look at the possibility of an enantioselective variant of the copper-catalysed cyclisation.

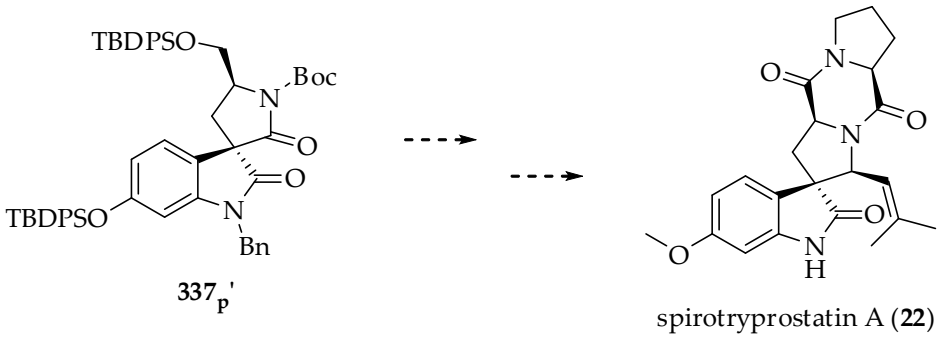
Preliminary studies towards the synthesis of spirotryprostatin A (**22**) have been launched, specifically investigating the stereo- and regioselectivity of the cyclisation of anilides **344** to give isomeric spirooxindoles **345** (Scheme 132).



Scheme 132: Stereo- and regioselectivity studies on the cyclisation reaction

Altering the steric bulk of R^1 had little effect on the stereoselectivity of the cyclisation reaction. The regioselectivity of the reaction initially favoured products $\mathbf{345_o}$, where the new bond is formed *ortho* to the aromatic substituent, presumably due to favourable electronics. With the use of a bulky TBDPS protecting group on the oxygen, the ratio of regioisomeric products arising from cyclisation was shifted to the desired isomer $\mathbf{345_p}$.

A route for the remainder of the synthesis of spirotryprostatin A (**22**) from spirocyclic oxindole $\mathbf{337_p'}$ has been proposed (Scheme 133). Future work will include optimisation of the cyclisation reaction and completion of the natural product synthesis.



337$_p$' spirotryprostatin A (**22**)

Scheme 133: Substrate 337$_p$′ for the proposed synthesis of spirotryprostatin A (22)

Chapter 7 – Experimental

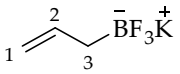
7.1 General Experimental

Except where specified, all reagents were purchased from commercial sources and were used without further purification. All procedures were carried out under an argon atmosphere, unless otherwise stated. Dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were dried using an Mbraun MPS solvent purification system. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl immediately before use. Petroleum ether (PE) refers to light petroleum ether, bp 40-60 °C. NH_3 refers to 35% aqueous ammonia. Et_2O* was prepared by shaking anhydrous diethyl ether with a quarter volume of 9:1 pH 10 carbonate buffer:diethylamine solution; the solvent was dried over Na_2SO_4. All aqueous solutions are saturated unless otherwise stated. Dess–Martin periodinane was synthesised using the procedures by Frigerio[55] (IBX) and Böckmann.[256] Flash column chromatography was performed using Fluka silica gel 60, 220–440 mesh at a medium positive pressure, unless otherwise stated. KF-SiO_2 refers to 10% w/w of finely ground KF and 90% w/w silica. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel F_{254} and visualised with ultraviolet light (254 nm), and staining with aqueous potassium permanganate or alcoholic anisaldehyde solutions as appropriate. R_f values are quoted to the nearest 0.05. Preparative thin layer chromatography was performed on glass sheets pre-coated with Analtech silica gel GF_{254} and visualised with ultraviolet light (254 nm). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a JEOL ECX 400 spectrometer or a JEOL ECS 400 spectrometer and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). The letters a and b following assignment indicates diastereotopic protons. Couplings are expressed as: s, singlet; d, doublet; t, triplet; q, quartet; quint., quintet; m, multiplet; br, broad; or combinations of these. Coupling constants are quoted to the nearest 0.5 Hz and are reported as measured splittings on each individual resonance. Where coincident coupling constants have been observed in the NMR spectrum, the apparent multiplicity of the proton resonance concerned is reported. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm), MeCN (δ_H = 1.94 ppm, quint.) or DMSO (δ_H = 2.50 ppm, quint.) was used as the internal reference. ^{13}C NMR

spectra were recorded on the same spectrometer at 100 MHz, using the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. ^{19}F NMR spectra were recorded at 300 MHz on a JEOL ECX 400 spectrometer. DEPT-135 and two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy were used as appropriate to aid in the assignment of ^{1}H and ^{13}C NMR spectra. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and the nearest 0.1 ppm for ^{13}C and ^{19}F. The atom numbering on the structures below is for assignment purposes and is independent of IUPAC nomenclature. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as thin film between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbencies are reported. Accurate mass data were recorded using a Bruker MicroTOF spectrometer. Elemental analysis was conducted on an Exeter Analytical, Inc. CE-440 Elemental Analyser with samples weighed using a Sartorius analytical balance. Crystallographic data was obtained using a SuperNova, Single source at offset, Eos diffractometer. References following compound names refer to literature procedures.

7.2 Unsaturated ketones

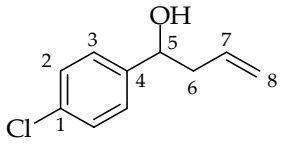
Potassium allyltrifluoroborate (78)[76]



To a solution of trimethylborate (5.57 mL, 50.0 mmol, 1.0 eq) in Et_2O (75 mL) cooled to −78 °C was added allylmagnesium bromide (1 M in Et_2O, 50.0 mL, 50.0 mmol, 1.0 eq) over 40 min *via* syringe pump. The reaction was stirred at –78 °C for 2 h then poured immediately onto 10% aq. HCl (50 mL) and the mixture was stirred vigorously at room temperature for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic extracts were concentrated *in vacuo*, and a solution of KHF_2 (3.5 M, 50.0 mL H_2O, 175 mmol) in water was added. The mixture was stirred at room temperature for 30 min before storing at 4 °C overnight. The resultant white solid was filtered, washed with Et_2O (50 mL) and dried *in vacuo* to

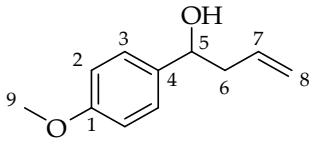
afford **78** (5.14 g, 69%) as a colourless powder, mp 259 °C – decomposition; δ_H (400 MHz, CD_3CN) 5.92 (1H, ddt, *J* = 17.5, 10.0, 8.0, H-2), 4.69 (1H, d, *J* = 17.5, H-1a), 4.61 (1H, d, *J* = 10.0, H-1b), 1.10–1.00 (2H, m, H-3); δ_F (300 MHz, CD_3CN) −140.0 (q, *J* = 58.0). Data consistent with the literature values.[76]

1-(4-Chlorophenyl)but-3-en-1-ol (62a)[76]



To a suspension of 4-chlorobenzaldehyde (60 mg, 0.43 mmol, 1.0 eq) and potassium allyltrifluoroborate (126 mg, 0.86 mmol, 2.0 eq) in CH_2Cl_2 (5 mL) was added boron trifluoride diethyl etherate (26 µL, 0.21 mmol, 0.5 eq). The reaction was stirred at room temperature overnight then quenched with aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to afford **62a** (73 mg, 0.40 mmol, 93%) as a colourless oil. R_f (1:4 EtOAc:Hexane) = 0.20; δ_H (400 MHz, $CDCl_3$) 7.34–7.28 (4H, m, H-2, H-3), 5.78 (1H, dddd, *J* = 11.0, 9.5, 7.5, 6.5, H-7), 5.19–5.14 (2H, m, H-8), 4.73 (1H, ddd, *J* = 8.0, 5.0, 3.0, H-5), 2.57–2.40 (2H, m, H-6), 2.06 (1H, d, *J* = 3.0, OH); δ_C (100 MHz, $CDCl_3$) 142.2 (C-1), 133.9 (C-7), 133.1 (C-4), 128.5 (C-2), 127.2 (C-3), 119.0 (C-8), 72.5 (C-5), 43.9 (C-6). Data consistent with the literature values.[257]

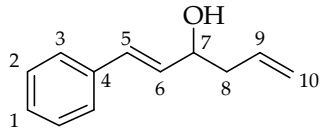
1-(4-Methoxyphenyl)but-3-en-1-ol (62c)



To a suspension of *p*-anisaldehyde (31 µL, 0.25 mmol, 1.0 eq), potassium allyltrifluoroborate (44 mg, 0.30 mmol, 1.2 eq) and montmorillonite K10 (50 mg) in CH_2Cl_2 (2 mL) was added acetic acid (159 µL, 2.8 mmol, 11.0 eq). The reaction mixture was stirred at room temperature for 15 min at which point the reaction was quenched

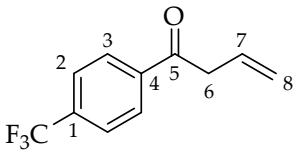
with aq. $NaHCO_3$ and stirred for 10 min. The mixture was filtered then diluted with CH_2Cl_2 (5 mL) and brine (5 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **62c** (38 mg, 0.21 mmol, 85%) as a colourless oil. R_f (1:9 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* = 8.5, H-2), 6.89 (2H, d, *J* = 8.5, H-3), 5.80 (1H, ddt, *J* = 17.0, 10.0, 7.0, H-7), 5.18–5.11 (2H, m, H-8), 4.69 (1H, t, *J* = 6.5, H-5), 2.96 (3H, s, H-9), 2.52–2.48 (2H, m, H-6), 2.01 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 159.0 (C-1), 136.0 (C-4), 134.6 (C-7), 127.0 (C-3), 118.2 (C-8), 113.7 (C-2), 72.9 (C-5), 55.3 (C-9), 43.7 (C-6). Data consistent with the literature values.[257]

(1*E*)-1-Phenylhexa-1,5-dien-3-ol (62h)



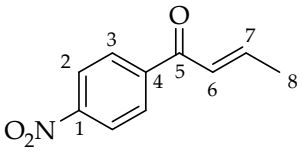
To a suspension of cinnamaldehyde (31 µL, 0.25 mmol, 1.0 eq), potassium allyltrifluoroborate (44 mg, 0.30 mmol, 1.2 eq) and montmorillonite K10 (50 mg) in CH_2Cl_2 (2 mL) was added acetic acid (159 µL, 2.8 mmol, 11.0 eq). The reaction mixture was stirred at room temperature for 15 min at which point the reaction was quenched with aq. $NaHCO_3$ and stirred for 10 min. The mixture was filtered then diluted with CH_2Cl_2 (5 mL) and brine (5 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **62h** (40 mg, 0.23 mmol, 92%) as a colourless oil. R_f (1:9 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 7.38 (2H, d, *J* = 7.0, H-3), 7.32 (2H, t, *J* = 7.0, H-2), 7.24 (1H, t, *J* = 7.0, H-1), 6.61 (1H, d, *J* = 16.0, H-5), 6.24 (1H, dd, *J* = 16.0, 6.0, H-6), 5.91–5.81 (1H, m, H-9), 5.22–5.17 (1H, m, H-10a), 5.17–5.14 (1H, m, H-10b), 4.39–4.33 (1H, m, H-7), 2.49–2.34 (2H, m, H-8), δ_C (100 MHz, $CDCl_3$) 136.6 (C-4), 134.0 (C-9), 131.5 (C-6), 130.4 (C-5), 128.6 (C-2), 127.7 (C-1), 126.5 (C-3), 118.6 (C-10), 71.7 (C-7), 42.0 (C-8). Data consistent with the literature values.[258]

1-(4-Trifluoromethylphenyl)but-3-en-1-one (17e)



To a suspension of 4-(trifluoromethyl)benzaldehyde (34 µL, 0.25 mmol) and potassium allyltrifluoroborate (39 mg, 0.26 mmol, 1.05 eq) in CH_2Cl_2 (2 mL) was added boron trifluoride diethyl etherate (15 µL, 0.13 mmol, 0.5 eq) and the mixture was stirred at room temperature for 10 min. Dess–Martin periodinane (127 mg, 0.30 mmol, 1.2 eq) was added and the mixture stirred for a further hour. The reaction was quenched with aq. $NaHCO_3$ (5 mL) and aq. $Na_2S_2O_3$ (5 mL) and stirred for 10 min before diluting with CH_2Cl_2 (5 mL) and brine (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic extracts then dried (Na_2SO_4) and concentrated *in vacuo* to afford **17e** (35 mg, 0.16 mmol, 65%) as an off-white waxy solid, which was used without further purification. R_f (1:9 EtOAc:PE) = 0.50; δ_H (400 MHz, $CDCl_3$) 8.07 (2H, d, *J* = 8.0) and 7.73 (2H, d, *J* = 8.0) (H-2, H-3), 6.07 (1H, ddt, *J* = 17.0, 10.5, 6.5, H-7), 5.27 (1H, dq, *J* = 10.5, 1.5, H-8a), 5.23 (1H, *J* = 17.0, 1.5, H-8b), 3.78 (2H, dt, *J* = 6.5, 1.5, H-6). Data consistent with the literature values.[48]

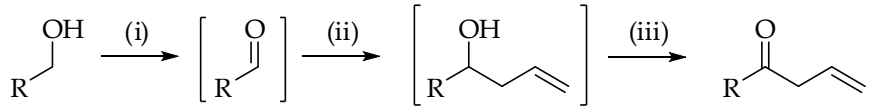
(2*E*)-1-(4-Nitrophenyl)but-2-en-1-one (18b)



To a suspsension of 4-nitrobenzaldehyde (38 mg, 0.25 mmol, 1.0 eq) and potassium allyltrifluoroborate (**78**, 39 mg, 0.26 mmol, 1.05 eq) in CH_2Cl_2 (2 mL) was added boron trifluoride diethyl etherate (15 µL, 0.13 mmol, 0.5 eq) and the mixture was stirred at room temperature for 10 min. Dess–Martin periodinane (127 mg, 0.30 mmol, 1.2 eq) was added and the mixture stirred for a further hour. The reaction was quenched with aq. $NaHCO_3$ (5 mL) and aq. $Na_2S_2O_3$ (5 mL) and stirred for 10 min before diluting with CH_2Cl_2 (5 mL) and brine (5 mL). The layers were separated and the aqueous layer was

extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **17b**. Flash column chromatography [KF-SiO_2, 1:9 EtOAc:PE] afforded **18b** as an off-white powdery solid (11 mg, 23%). R_f (1:9 EtOAc:PE) = 0.10; mp 68–71 °C (lit[259] 44 °C, MeOH-H_2O); ν_{max}/cm^{-1} (thin film) 1674, 1628, 1601, 1518, 1346; δ_H (400 MHz, $CDCl_3$) 8.32 (2H, d, *J* = 9.0, H-2), 8.05 (2H, d, *J* = 9.0, H-3), 7.14 (1H, dq, *J* = 15.0, 7.0, H-7), 6.86 (1H, dq, *J* = 15.0, 1.5, H-6), 2.05 (3H, dd, *J* = 7.0, 1.5, H-8); δ_C (100 MHz, $CDCl_3$) 189.2 (C-5), 150.0 (C-1), 147.5 (C-7), 142.8 (C-4), 129.4 (C-2), 127.2 (C-6), 123.7 (C-3), 18.8 (C-8); *m/z* (ESI) 192 $[MH]^+$; [HRMS (ESI): calcd for $C_{10}H_{10}NO_3$, 192.0655. Found: $[MH]^+$, 192.0648 (3.6 ppm error)]. NMR and MS data consistent with the literature values.[260]

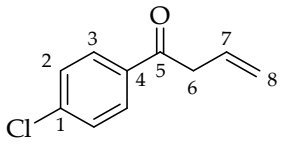
7.2.1 General procedure A – oxidation/allylation/oxidation of primary alcohols 60 to β,γ-unsaturated ketones 17



Reagents and conditions: *i)* DMP (1.5–2.0 eq), CH_2Cl_2, rt, 1 h; *ii)* montmorillonite K10, potassium allyltrifluoroborate (**78**, 1.5–2.0 eq), rt, 1 h; *iii)* Dess–Martin (2.0–2.5 eq), rt, 1 h

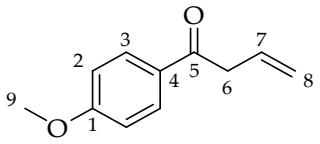
To the primary alcohol (0.25 mmol) in CH_2Cl_2 (5 mL) at room temperature was added Dess–Martin periodinane (1.5–2.0 eq, 0.25–0.50 mmol) and the mixture stirred for 1 h. Montmorillonite K10 (50 mg) was then added followed by potassium allyltrifluoroborate (73 mg, 0.49 mmol) and the mixture stirred for 1 h before adding a further portion of Dess–Martin periodinane (2.0–2.5 eq, 0.5–0.75 mmol). After 1 h, the reaction was quenched with aq. $NaHCO_3$ (5 mL) and aq. $Na_2S_2O_3$ (5 mL) and allowed to stir for 1h before diluting with brine (10 mL) and CH_2Cl_2 (10 mL). The mixture was filtered then the layers separated. The aqueous portion was further extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified on silica to afford the title compound.

1-(4-Chlorophenyl)but-3-en-1-one (17a)



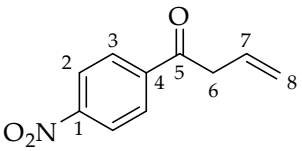
4-Chlorobenzyl alcohol (35 mg, 0.25 mmol), Dess–Martin periodinane (161 mg and 280 mg, 0.38 mmol and 0.66 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17a** (32 mg, 71%) as a white solid, mp 43–45 °C; R_f (1:4 EtOAc:Hexane) = 0.40; δ_H (400 MHz, $CDCl_3$) 7.91 (2H, d, *J* = 9.0), 7.44 (2H, d, *J* = 9.0) (H-2, H-3), 6.06 (1H, ddt, *J* = 17.0, 10.0, 6.5, H-7), 5.25 (1H, dq, *J* = 10.0, 1.5, H-8a), 5.21 (1H, dq, *J* = 17.0, 1.5, H-8b), 3.73 (2H, dt, *J* = 6.5, 1.5, H-6). Data consistent with the literature values.[261]

1-(4-Methoxyphenyl)but-3-en-1-one (17c)



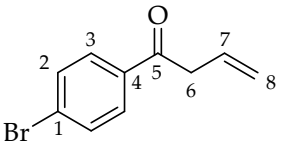
4-Methoxybenzyl alcohol (35 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 230 mg, 0.38 mmol and 0.54 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17c** (41 mg, 92%) as a white solid, mp 42–44 °C (lit[262] 41 °C); R_f (1:9 EtOAc:PE) = 0.20; δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* = 9.0, H-3), 6.93 (2H, d, *J* = 9.0, H-2), 6.07 (1H, ddt, *J* = 17.0, 10.5, 6.5, H-7), 5.21 (1H, dq, *J* = 10.5, 1.5, H-8a), 5.19 (1H, dq, *J* = 17.0, 1.5, H-8b), 3.87 (3H, s, H-9), 3.70 (2H, dt, *J* = 6.5, 1.5, H-6). Data consistent with the literature values.[262,263]

1-(4-Nitrophenyl)but-3-en-1-one (17b)



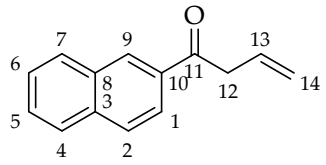
4-Nitrobenzyl alcohol (39 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 270 mg, 0.38 mmol and 0.64 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17b** (46 mg, 96%) as a white solid, mp 51–53 °C; R_f (1:9 EtOAc:PE) = 0.30; δ_H (400 MHz, $CDCl_3$) 8.32 (2H, d, *J* = 9.0, H-2), 8.12 (2H, d, *J* = 9.0, H-3), 6.07 (1H, ddt, *J* = 17.0, 10.5, 6.5, H-7), 5.29 (1H, dq, *J* = 10.5, 1.5, H-8a), 5.25 (1H, dq, *J* = 17.0, 1.5, H-8b), 3.81 (2H, dt, *J* = 6.5, 1.5, H-6). Data consistent with the literature values.[261]

1-(4-Bromophenyl)but-3-en-1-one (17d)



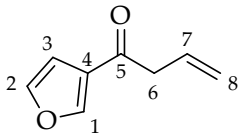
4-Bromobenzyl alcohol (47 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 270 mg, 0.38 mmol and 0.64 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17d** (48 mg, 85%) as a white solid, mp 39–41 °C; R_f (1:9 EtOAc:PE) = 0.60; δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* = 8.5), 7.60 (2H, d, *J* = 8.5) (H-2, H-3), 6.05 (1H, ddt, *J* = 17.0, 10.0, 6.5, H-7), 5.24 (1H, dq, *J* = 10.0, 1.5, H-8a), 5.21 (1H, dq, *J* = 17.0, 1.5, H-8b), 3.72 (2H, dt, *J* = 6.5, 1.5, H-6). Data consistent with the literature values.[264]

1-(Naphthalen-2-yl)but-3-en-1-one (17i)



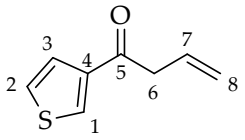
(2-Naphthyl)methanol (40 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 230 mg, 0.38 and 0.54 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17i** (37 mg, 75%) as a colourless oil. R_f (1:9 EtOAc:Hex) = 0.20; δ_H (400 MHz, $CDCl_3$) 8.49 (1H, m, H-9), 8.04 (1H, dd, *J* = 8.5, 2.0, H-1), 7.98–7.96 (1H, m H-4), 7.90 (1H, d, *J* = 8.5, H-2), 7.88 (1H, d, *J* = 8.0, H-7), 7.61 (1H, ddd, *J* = 8.0, 7.0, 1.5, H-6), 7.56 (1H, ddd, *J* = 8.0, 7.0, 1.5, H-5), 6.16 (1H, ddt, *J* = 16.5, 10.0, 6.5, H-13), 5.30–5.24 (2H, m, H-14), 3.90 (2H, dt, *J* = 6.5, 1.5, H-12); δ_C (100 MHz, $CDCl_3$) 198.0 (C-11), 135.6, 133.8 and 132.5 (C-3, C-8, C-10), 131.1 (C-13), 130.0 (C-9), 129.5 (C-4), 128.5 (C-2), 128.4 (C-6), 127.7 (C-7), 126.8 (C-5), 123.9 (C-1), 118.7 (C-14), 43.5 (C-12).

1-(Furan-3-yl)but-3-en-1-one (17f)



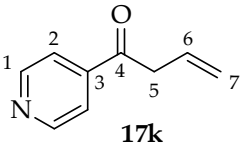
Furan-3-methanol (24 mg, 0.25 mmol), Dess–Martin periodinane (215 mg and 215 mg, 0.51 and 0.51 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (2.5 mL) were reacted according to general procedure A. The title compound **17f** was visible by crude ^{1}H NMR spectrum, but was not isolated as a pure product. δ_H (400 MHz, $CDCl_3$) 8.06 (1H, dd, *J* = 1.5, 1.0, H-1), 7.44 (1H, dd, *J* = 2.0, 1.5, H-2), 6.78 (1H, dd, *J* = 2.0, 1.0, H-3), 6.03 (1H, ddt, *J* = 17.0, 10.5, 7.0, H-7), 5.25–5.18 (2H, m, H-8), 3.53 (2H, dt, *J* = 7.0, 1.5, H-6).

1-(Thiophen-3-yl)but-3-en-1-one (17j)

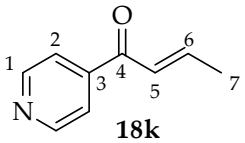


3-Thiophenemethanol (28 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 230 mg, 0.38 and 0.54 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17j** (29 mg, 76%) as a colourless oil. R_f (1:9 EA: Hexane) = 0.20; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, dd, *J* = 3.0, 1.0, H-1), 7.56 (1H, dd, *J* = 5.0, 1.0, H-2), 7.32 (1H, dd, *J* = 5.0, 3.0, H-3), 6.06 (1H, ddt, *J* = 17.0, 10.5, 7.0 H-7), 5.23 (1H, dq, *J* = 10.5, 1.5, H-8a), 5.21 (1H, dq, *J* = 17.0, 1.5, H-8b), 3.67 (2H, dt, *J* = 7.0, 1.5, H-6); δ_C (100 MHz, $CDCl_3$) 192.2 (C-5), 141.8 (C-4), 132.3 (C-1), 130.9 (C-7), 127.0 (C-2), 126.4 (C-3), 118.8 (C-8), 44.8 (C-6). Data consistent with the literature values.[49]

1-(Pyridin-4-yl)but-3-en-1-one (17k) and *(2E)*-1-(pyridin-4-yl)but-2-en-1-one (18k)



17k

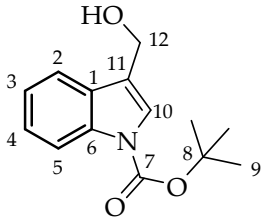


18k

3-Pyridylcarbinol (27 mg, 0.25 mmol), Dess–Martin periodinane (215 mg and 215 mg, 0.51 and 0.51 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A to afford 4:5 mixture of **17k** and **18k** (34 mg, corresponding to 15% of **17k,** 41%). Flash column chromatography [1:9 Acetone:CH_2Cl_2] afforded **18k** (17.5 mg, 76%) as a colourless oil. **17k:** The title compound was visible by crude ^{1}H NMR spectrum, but could not be isolated as a pure product as isomerisation occurs on silica. R_f(1:9 Acetone:CH_2Cl_2) = 0.40; δ_H (400 MHz, $CDCl_3$) 8.83 (2H, dd, *J* = 4.5, 1.5, H-1), 7.75 (2H, dd, *J* = 4.5, 1.5, H-2), 6.05 (1H, ddt, *J* = 17.0, 10.0, 6.5, H-6), 5.30–5.21 (2H, m, H-7),

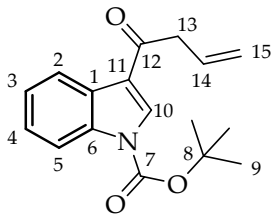
3.76 (2H, dt, *J* = 6.5, 1.5, H-5); **18k:** R_f (1:9 Acetone:CH_2Cl_2) = 0.30; δ_H (400 MHz, $CDCl_3$) 8.79 (2H, dd, *J* = 4.5, 1.5, H-1), 7.67 (2H, dd, *J* = 4.5, 1.5, H-2), 7.12 (1H, dq, *J* = 15.5, 7.0, H-6), 6.82 (1H, dq, *J* = 15.5, 1.5, H-5), 2.03 (3H, dd, *J* = 7.0, 1.5, H-7); δ_C (100 MHz, $CDCl_3$) 190.0 (C-4), 150.6 (C-1), 147.7 (C-6), 144.2 (C-3), 127.1 (C-5), 121.6 (C-2), 18.8 (C-7). Data consistent with the literature values.[265]

***tert*-Butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (60m)**



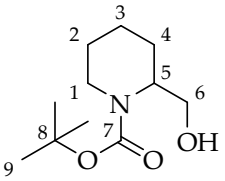
To a solution of indole-3-methanol (212 mg, 1.44 mmol) and 4-dimethylaminopyridine (194 mg, 1.58 mmol, 1.1 eq) in THF (10 mL) was added *tert*-butyldimethylsilyl chloride (238 mg, 1.58 mmol, 1.1 eq) and the reaction stirred for 2 h at room temperature. Di-*tert*-butyl dicarbonate (471 mg, 2.16 mmol, 1.5 eq) was added and the reaction stirred at room temperature for 16 h. Tetrabutylammonium fluoride (1 M solution in THF, 4.48 mL, 4.48 mmol) and 3 Å molecular sieves (200 mg) were added and the reaction stirred for 5.5 h at room temperature before removing the solvent *in vacuo*. Flash column chromatography [0–10% Acetone/CH_2Cl_2] afforded **60m** (211 mg, 59%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 8.14 (1H, br d, *J* = 7.5, H-5), 7.67–7.64 (1H, m, H-2), 7.59 (1H, br s, H-10), 7.34 (1H, ddd, *J* = 8.5, 7.5, 1.5, H-4), 7.27 (1H, ddd, *J* = 8.5, 7.5, 1.5, H-3), 4.85 (2H, s, H-12), 1.67 (9H, s, H-9); δ_C (100 MHz, $CDCl_3$) 149.7 (C-7), 135.8 (C-6), 129.1 (C-1), 124.7 (C-4), 123.7 (C-10), 122.7 (C-3), 120.4 (C-11), 119.3 (C-2), 115.3 (C-5), 83.8 (C-8), 57.2 (C-12), 28.2 (C-9). Data consistent with the literature values.[266]

tert-Butyl 3-but-3-enoyl-1H-indole-1-carboxylate (17m)



tert-Butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (**60m**, 63 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 280 mg, 0.38 mmol and 0.66 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.59 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [0–67% CH_2Cl_2:Hexane] afforded **17m** (21 mg, 31%) as a colourless solid, mp 99–101 °C; R_f (CH_2Cl_2) = 0.30; ν_{max}/cm^{-1} (neat) 2978, 2921, 1743, 1664, 1607, 1550; δ_H (400 MHz, $CDCl_3$) 8.39–8.36 (1H, m, H-4), 8.28 (1H, s, H-10), 8.11 (1H, dd, _J_ = 7.0, 1.5, H-5), 7.40–7.32 (2H, m, H-2, H-3), 6.17–6.06 (1H, m, H-14), 5.29–5.23 (2H, m, H-15), 3.69 (2H, dt, _J_ = 7.0, 1.5, H-13), 1.72 (9H, s, H-9); δ_C (100 MHz, $CDCl_3$) 194.0 (C-12), 149.1 (C-7), 135.5 (C-6), 132.1 (C-10), 131.3 (C-14), 127.5 (C-1), 125.5 (C-2), 124.4 (C-3), 122.7 (C-4), 119.8 (C-11), 118.6 (C-15), 114.9 (C-5), 85.5 (C-8), 45.0 (C-13), 28.1 (C-9); _m/z_ (ESI) 308 [MNa]$^+$; [HRMS (ESI): calcd for $C_{17}H_{19}NNaO_3$, 308.1257. Found: [MNa]$^+$, 308.1252 (1.9 ppm error)]. ^{1}H NMR data consistent with the literature values.[26]

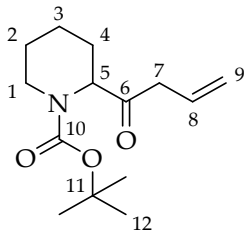
tert-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (60n)



To a solution of 2-piperidine methanol (150 mg, 1.28 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.73 mL, 4.56 mmol, 3.5 eq) and di-_tert_-butyl dicarbonate (360 mg, 1.56 mmol, 1.2 eq) and the reaction stirred at room temperature for 16 h. H_2O (3 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL) and the combined organic extracts were washed with H_2O (2 x 3 mL) and brine

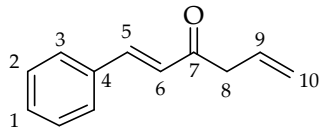
(3 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [1:9 Acetone:CH_2Cl_2] afforded **60n** (228 mg, 83%) as a colourless solid. Several peaks in the ^{1}H NMR experienced broadening as a result of the presence of rotamers associated with the carbamate. R_f (1:9 Acetone:CH_2Cl_2) = 0.30; δ_H (400 MHz, $CDCl_3$) 4.32–4.25 (1H, m, H-5), 3.93 (1H, br d, *J* = 12.0, H-1a), 3.81 (1H, ddd, *J* = 11.0, 9.0, 6.0, H-6a), 3.60 (1H, dt, *J* = 11.0, 6.0, H-6b), 2.86 (1H, br t, *J* = 12.0, H-1b), 1.71–1.51 (4H, m H-3, H-4), 1.50–1.36 (2H, m, H-2), 1.45 (9H, s, H-9). Data consistent with the literature values.[267]

***tert*-Butyl 2-but-3-enoylpiperidine-1-carboxylate (17n)**



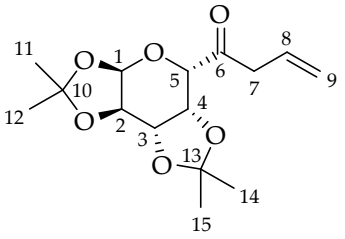
tert-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (**60n**, 54 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 280 mg, 0.38 mmol and 0.66 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17n** (40 mg, 63%) as a colourless oil. Several peaks in the ^{1}H NMR experienced broadening as a result of the presence of rotamers associated with the carbamate. R_f (1:9 EtOAc:Hexane) = 0.30; ν_{max}/cm^{-1} (neat) 2976, 2939, 2864, 1720, 1691, 1642; δ_H (400 MHz, $CDCl_3$) 5.92 (1H, ddt, *J* = 17.0, 10.0, 7.0, H-8), 5.18 (1H, br d, *J* = 10.0, H-9a), 5.13 (1H, dd, *J* = 17.0, 1.0, H-9b), 4.78 and 4.62 (1H, br s, H-5), 4.05 and 3.93 (1H, br s, H-1a), 3.24–3.20 (2H, m, H-7), 2.94–2.74 (1H, m, H-1b), 2.24–2.14 (1H, m, H-3a), 1.66–1.52 (3H, m, H-4a, H-3b, H-2a), 1.49 (9H, s, Boc), 1.42–1.32 (1H, m, H-2b), 1.32–1.22 (1H, m, H-4b); δ_C (100 MHz, $CDCl_3$) 207.8 (C-6), 155.7 and 155.1 (C-10), 130.4 (C-8), 118.7 (C-9), 80.1 (C-11), 61.0 and 59.9 (C-5), 43.8 (C-7), 42.8 and 41.7 (C-1), 28.3 (C-12), 25.0 (C-3), 24.9 (C-2), 20.5 (C-4); *m/z* (ESI) 276 $[MNa]^+$; [HRMS (ESI): calcd for $C_{14}H_{23}NNaO_3$, 276.1570. Found: $[MNa]^+$, 276.1573 (−0.4 ppm error)].

(1*E*)-1-Phenylhexa-1,5-dien-3-one (17h)



Cinnamyl alcohol (34 mg, 0.25 mmol), Dess–Martin periodinane (160 mg and 220 mg, 0.38 mmol and 0.52 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (5 mL) were reacted according to general procedure A. Flash column chromatography [1:9 EtOAc:Hexane] afforded **17h** (29 mg, 67%) as a colourless oil. R_f (1:9 EtOAc:PE) = 0.30; δ_H (400 MHz, $CDCl_3$) 7.59 (1H, d, *J* = 16.0, H-5), 7.56–7.53 (2H, m) and 7.40–7.37 (3H, m) (H-1, H-2, H-3), 6.77 (1H, d, *J* = 16.0, H-6), 6.02 (1H, ddt, *J* = 17.0, 10.0, 7.0, H-9), 5.25–5.18 (2H, m, H-10), 3.44 (2H, dt, *J* = 7.0, 1.5, H-8). δ_C (100 MHz, $CDCl_3$) 197.8 (C-7), 143.2 (C-5), 134.4 (C-4), 130.9 (C-9), 130.6 (C-1), 128.9, 128.3 (C-2, C-3), 125.4 (C-6), 118.9 (C-10), 45.9 (C-8). Data consistent with the literature values.[26]

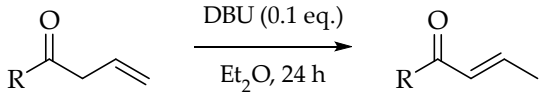
1-((3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-5-yl)but-3-en-1-one (17o)



1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose (64 mg, 0.25 mmol), Dess–Martin periodinane (200 mg and 260 mg, 0.47 mmol and 0.61 mmol), potassium allyltrifluoroborate (**78**, 73 mg, 0.49 mmol) and montmorillonite K10 (50 mg) in CH_2Cl_2 (2 mL) were reacted according to general procedure A. Flash column chromatography [0–5% Acetone:CH_2Cl_2] afforded **17o** (55 mg, 75%) as a colourless solid, mp 47–49 °C; R_f (CH_2Cl_2) = 0.15; ν_{max}/cm^{-1} (neat) 2988, 2936, 1723 (C=O), 1383; $[\alpha]_D^{20}$ –144 (*c* 0.405, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 5.97 (1H, ddt, *J* = 17.0, 10.5, 7.0, H-8), 5.64 (1H, d, *J* = 5.0, H-1), 5.20–5.08 (2H, m, H-9), 4.63 (1H, dd, *J* = 8.0, 2.5, H-3), 4.56 (1H, dd, *J* = 8.0, 2.0,

H-4), 4.35 (1H, dd, *J* = 5.0, 2.5, H-2), 4.22 (1H, d, *J* = 2.0, H-5), 3.50 (1H, ddt, *J* = 18.5, 7.0, 1.5, H-7a), 3.33 (1H, ddt, *J* = 18.5, 7.0, 1.5, H-7b), 1.49 (3H, s), 1.44 (3H, s), 1.33 (3H, s) and 1.30 (3H, s) (H-11, H-12, H-14, H-15); δ_C (100 MHz, $CDCl_3$) 207.2 (C-6), 130.0 (C-8), 118.7 (C-9), 109.6, 109.0 (C-10, C-13), 96.4 (C-1), 73.5 (C-5), 72.3 (C-4), 70.6 (C-3), 70.4 (C-2), 44.6 (C-7), 25.9, 25.8, 24.8, 24.2 (C-11, C-12, C-14, C-15); [HRMS (ESI): calcd for $C_{15}H_{22}NaO_6$, 321.1309. Found: $[MNa]^+$, 321.1317 (−2.7 ppm error)]; [Found C, 60.35%; H, 7.35%. $C_{15}H_{22}O_6$ requires C, 60.39%; H, 7.43%].

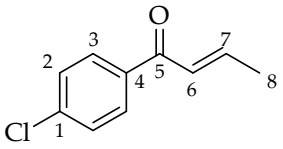
7.2.2 General procedure B – isomerisation of β,γ-unsaturated ketones 17 to α,β-unsaturated ketones 18



17 **18**

To the β,γ-unsaturated ketone **17** in Et_2O was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 eq) and the mixture stirred for 24 h at room temperature. The solvent was removed *in vacuo* and the residue purified on silica to afford the conjugated ketone **18**.

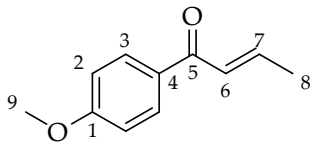
(2*E*)-1-(4-Chlorophenyl)but-2-en-1-one (18a)



1-(4-Chlorophenyl)but-3-en-1-one (**17a**, 15.0 mg, 0.08 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.25 µL, 0.008 mmol) in Et_2O (2 mL) were reacted according to general procedure B. Flash column chromatography [0−20% EtOAc/Hexane] afforded **18a** (14.2 mg, 95%) as a colourless solid, mp 39–41 °C; R_f (1:4 EtOAc:Hexane) = 0.30; ν_{max}/cm^{-1} (neat) 2968, 1671, 1622, 1587; δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.5) and 7.43 (2H, d, *J* = 8.5) (H-2, H-3), 7.08 (1H, dq, *J* = 15.0, 7.0, H-7), 6.86 (1H, dq, *J* = 15.0, 1.5, H-6), 2.00 (3H, dd, *J* = 7.0, 1.5, H-8);

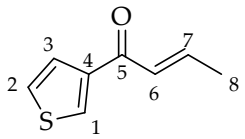
δ_C (100 MHz, $CDCl_3$) 189.4 (C-5), 145.6 (C-7), 139.0, 136.2 (C-1, C-4), 129.9, 128.9 (C-2, C-3), 127.0 (C-6), 18.6 (C-8); *m/z* (ESI) 181, 183 $[MH]^+$; [HRMS (ESI): calcd for $C_{10}H_{10}{}^{35}ClO$, 181.0415. Found: $[MH]^+$, 181.0416 (–0.5 ppm error)]. Compound previously reported, but no spectral data was provided.[268]

(2*E*)-1-(4-Methoxyphenyl)but-2-en-1-one (18c)



1-(4-Methoxyphenyl)but-3-en-1-one (**17c**, 15.0 mg, 0.09 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.25 µL, 0.008 mmol) in Et_2O (2 mL) were reacted according to general procedure B. Flash column chromatography [0−20% EtOAc/Hexane] afforded **18c** (14.4 mg, 96%) as a colourless solid. δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* = 9.0, H-3), 7.06 (1H, dq, *J* = 15.0, 6.5, H-7), 6.95 (2H, d, *J* = 9.0, H-2), 6.92 (1H, dd, *J* = 15.0, 1.5, H-6), 3.87 (3H, s, H-9), 1.99 (3H, dd, *J* = 6.5, 1.5, H-8). Data consistent with the literature values.[269]

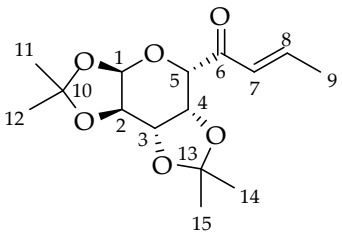
(2*E*)-1-(Thiophen-3-yl)but-2-en-1-one (18j)



1-(Thiophen-3-yl)but-3-en-1-one (**17j**, 23 mg, 0.15 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2 µL, 0.013 mmol) in Et_2O (2 mL) were reacted according to general procedure B. Flash column chromatography [1:9 EtOAc:Hexane] afforded **18j** (20 mg, 87%) as a colourless solid, mp 41–43 °C; R_f (1:9 EtOAc:Hexane) = 0.20; ν_{max}/cm^{-1} (neat) 3106, 3085, 3015, 2969, 1661, 1617, 1510; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, dd, *J* = 3.0, 1.0, H-1), 7.59 (1H, dd, *J* = 5.0, 1.0, H-2), 7.33 (1H, dd, *J* = 5.0, 3.0, H-3), 7.09 (1H, dq, *J* = 15.0, 7.0, H-7), 6.80 (1H, dq, *J* = 15.0, 1.5, H-6), 1.98 (3H, dd, *J* = 7.0, 1.5,

H-78); δ_C (100 MHz, $CDCl_3$) 184.0 (C-5), 144.2 (C-7), 142.7 (C-4), 131.9 (C-1), 128.0 (C-6), 127.4 (C-2), 126.3 (C-3), 18.5 (C-8); *m/z* (ESI) 153 $[MH]^+$, 175 $[MNa]^+$; [HRMS (ESI): calcd for C_8H_9OS, 153.0369. Found: $[MH]^+$, 153.0370 (–0.8 ppm error)].

(2*E*)-1-((3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-5-yl)but-2-en-1-one (18o)

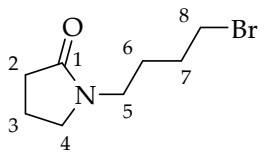


1-((3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-5-yl)but-3-en-1-one (**17o**, 25 mg, 0.08 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.25 µL, 0.008 mmol) in Et_2O (2 mL) were reacted according to general procedure B. Flash column chromatography [1:9 EtOAc:Hexane] afforded **18o** (17.6 mg, 70%, >20:1 *E*:*Z*) as a colourless solid, mp 101–103 °C; R_f (CH_2Cl_2) = 0.40; ν_{max}/cm^{-1} (neat) 2987, 2935, 1694, 1627; $[\alpha]_D^{20}$ –120 (*c* 0.45, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.04 (1H, dq, *J* = 15.5, 7.0, H-8), 6.64 (1H, dq, *J* = 15.5, 1.5, H-7), 5.67 (1H, d, *J* = 5.0, H-1), 4.64 (2H, t, *J* = 2.0, H-3 and 4), 4.37 (1H, dd, *J* = 5.0, 2.0, H-2), 4.31 (1H, d, *J* = 1.5, H-5), 1.91 (3H, dd, *J* = 7.0, 1.5, H-9), 1.51 (3H, s, H-11 or 12), 1.43 (3H, s, H-14 or 15), 1.34 (3H, s, H-11 or 12), 1.31 (3H, s, H-14 or 15); δ_C (100 MHz, $CDCl_3$) 196.3 (C-6), 144.4 (C-8), 126.8 (C-7), 109.7 (C-13), 108.9 (C-10), 96.5 (C-1), 73.1 (C-5), 72.4, 70.6 (C-3, C-4), 70.4 (C-2), 26.0 (C-11 or 12,), 25.8 (C-14 or 15), 24.8 (C-11 or 12), 24.3 (C-14 or 15), 18.5 (C-9); *m/z* (ESI) 299 $[MH]^+$, 321 $[MNa]^+$; [HRMS (ESI): calcd for $C_{15}H_{22}NaO_6$, 321.1309. Found: $[MNa]^+$, 321.1317 (–2.5 ppm error)].

7.3 Towards the synthesis of elaeokanidine A

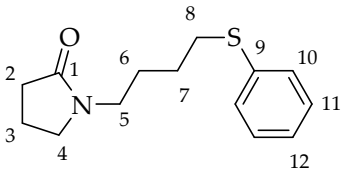
7.3.1 Pohmakotr's route

1-(4-Bromobutyl)pyrrolidin-2-one (134)[127]



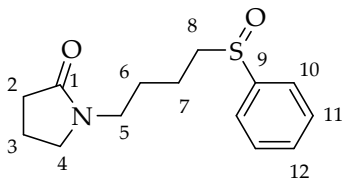
To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 660 mg, 16.5 mmol, 1.1 eq) in DMF (5 mL) was added dropwise a solution of pyrrolidinone (1.14 mL, 15.0 mmol, 1.0 eq) in DMF (15 mL) and the mixture stirred for 15 min. A solution of 1,4-dibromobutane (3.60 mL, 30.0 mmol, 2.0 eq) in DMF (5 mL) was added and the mixture was heated to 80 °C for 24 h. The reaction was cooled to room temperature and quenched with water (20 mL). The product was extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Flash column chromatography [Et_2O] afforded **134** (2.981 g, 90%) as a colourless oil. R_f (Et_2O) = 0.10; δ_H (400 MHz, $CDCl_3$) 3.43 (2H, t, *J* = 6.5, H-8), 3.37 (2H, t, *J* = 7.0, H-4), 3.30 (2H, t, *J* = 7.0, H-5), 2.37 (2H, t, *J* = 8.0, H-2), 2.02 (2H, tt, *J* = 8.0, 7.0, H-3), 1.87–1.80 (2H, m), 1.71-1.64 (2H, m) (H-6, H-7); δ_C (100 MHz, $CDCl_3$) 175.0 (C-1), 46.9 (C-4), 41.3 (C-5), 33.3 (C-8), 31.0 (C-2), 29.7, 25.7 (C-6, C-7), 17.8 (C-3). Data consistent with the literature values.[127]

1-(4-(Phenylthio)butyl)pyrrolidin-2-one (135)



To a solution of benzenethiol (103 µL, 1.0 mmol, 1.0 eq) and potassium hydroxide (56 mg, 1.0 mmol, 1.0 eq) in ethanol (6 mL) at room temperature was added dropwise 1-(4-bromobutyl)pyrrolidin-2-one (**134**, 221 mg, 1.0 mmol, 1.0 eq) as a solution in ethanol (2 mL). The reaction mixture was stirred for 18 h then the precipitate was removed *via* filtration and the filtrate was concentrated *in vacuo* to afford **135** (249 mg, quant.) as a yellow oil. R_f (EtOAc) = 0.20; δ_H (400 MHz, $CDCl_3$) 7.32–7.25 (4H, m, H-10, H-11), 7.19–7.14 (1H, m, H-12), 3.33 (2H, t, *J* = 7.0, H-4), 3.27 (2H, t, *J* = 7.0, H-5), 2.94 (2H, t, *J* = 7.0, H-8), 2.35 (2H, t, *J* = 8.0, H-2), 2.01–1.92 (2H, m, H-3), 1.70–1.88 (4H, m, H-6, H-7); δ_C (100 MHz, $CDCl_3$) 175.0 (C-1), 136.2 (C-9), 129.0, 128.8 (C-10, C-11), 125.8 (C-12), 46.9 (C-4), 41.7 (C-5), 33.0 (C-8), 30.9 (C-2), 26.0, 25.9 (C-6, C-7), 17.7 (C-3). Data consistent with the literature values.[126]

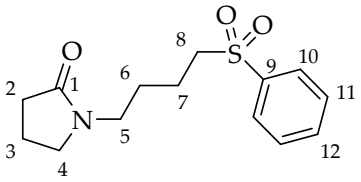
1-(4-(Phenylsulfinyl)butyl)pyrrolidin-2-one (127)[130]



Method 1: A solution of 1-(4-(phenylthio)butyl)pyrrolidin-2-one (**135**, 249 mg, 1.0 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) was cooled to –15 °C. A solution of *m*-CPBA (181 mg, 1.05 mmol, 1.05 eq) in CH_2Cl_2 (1 mL) was added dropwise and the reaction was stirred at this temperature for 1 h. Triethylamine (167 µL, 1.2 mmol, 1.2 eq) was added and the mixture stirred at room temperature for 16 h before pre-adsorbing onto silica. Flash column chromatography [1:9 MeOH:EtOAc] afforded **127** (248 mg, 93%) as a colourless oil; Method 2:[130] To a solution of sulfide **135** (100 mg, 0.40 mmol, 1.0 eq) in HFIP (0.5 mL) at room temperature was added aq. H_2O_2 (30%, 90 µL, 0.80 mmol, 2.0 eq) and stirred for 10 min. The reaction was quenched with aq. Na_2SO_3 (0.4 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **127** (106 mg, quant.) as a colourless oil. R_f (1:9 MeOH:EtOAc) = 0.10; δ_H (400 MHz, $CDCl_3$) 7.61 (2H, dd, *J* = 8.0, 1.5, H-10), 7.54–7.48 (3H, m, H-11, H-12), 3.33 (1H, m, H-4), 3.27 (2H, t, *J* = 7.0, H-5), 2.90–2.76 (2H, m, H-8), 2.37–2.31 (2H, m, H-2), 2.04–1.94 (2H, m, H-3), 1.81–1.56 (4H, m, H-6, H-7); δ_C (100 MHz, $CDCl_3$) 175.2 (C-1), 143.4 (C-9), 131.0

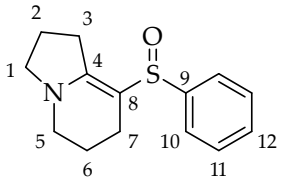
(C-12), 129.2 (C-11), 123.9 (C-10), 56.1 (C-8), 47.0 (C-4), 41.5 (C-5), 30.9 (C-2), 26.0, 19.2 (C-6, C-7), 17.8 (C-3); *m/z* (ESI) 266 $[MH]^+$; [HRMS (ESI): calc for $C_{14}H_{20}NO_2S$, 266.1209. Found: $[MH]^+$, 266.1204 (1.8 ppm error)]. Data consistent with the literature values.[126]

1-(4-(Phenylsulfonyl)butyl)pyrrolidin-2-one (136)



To a solution of 1-(4-(phenylthio)butyl)pyrrolidin-2-one (**135**, 106 mg, 0.43 mmol, 1.0 eq) in CH_2Cl_2 (4 mL) at 0 °C was added *m*-CPBA (255 mg, 1.48 mmol, 3.4 eq) and the mixture stirred for 16 h. Triethylamine (237 µL, 1.7 mmol, 4.0 eq) was added and the mixture stirred at room temperature for 1 h before pre-absorbing onto silica. Flash column chromatography [1:9 MeOH:EtOAc] afforded **136** (52 mg, 43%) as a colourless oil. R_f (1:9 MeOH:EtOAc) = 0.30; ν_{max}/cm^{-1} (neat) 2940, 1665, 1304, 1149; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, *J* = 7.0, H-10), 7.67–7.62 (1H, m, H-12), 7.56 (2H, dd, *J* = 8.0, 7.0, H-11), 3.32 (2H, t, *J* = 7.0, H-4), 3.24 (2H, t, *J* = 7.0, H-5), 3.12 (2H, t, *J* = 7.5, H-8), 2.35 (2H, t, *J* = 8.0, H-2), 1.98 (2H, tt, *J* = 8.0, 7.0, H-3), 1.75–1.59 (4H, m, H-6, H-7); δ_C (100 MHz, $CDCl_3$) 175.5 (C-1), 139.1 (C-9), 133.8 (C-12), 129.4 (C-11), 128.1 (C-10), 55.5 (C-8), 47.2 (C-4), 41.5 (C-5), 30.9 (C-2), 25.8 (C-7), 19.9 (C-6), 17.9 (C-3); *m/z* (ESI) 282 $[MH]^+$; [HRMS (ESI): calc for $C_{14}H_{20}NO_3S$, 282.1158. Found: $[MH]^+$, 282.1161 (–1.0 ppm error)].

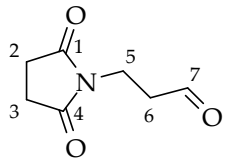
8-(Phenylsulfinyl)-1,2,3,5,6,7-hexahydroindolizine (128)[126]



To a solution of hexamethyldisilazide (212 µL, 1.02 mmol, 1.6 eq) in THF (8 mL) at −78 °C was added *n*-BuLi (1.7 M in hexanes, 0.56 mL, 0.96 mmol, 1.5 eq) and the mixture stirred for 30 min. To this LiHMDS solution was added dropwise a solution of 1-(4-(phenylsulfinyl)butyl)pyrrolidin-2-one (**127**, 169 mg, 0.64 mmol, 1.0 eq) in THF and the resulting mixture allowed to slowly warm to room temperature over 16 h. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) then dried (Na_2SO_4) and concentrated *in vacuo* to afford **128** (141 mg, 89%) as a colourless oil, R_f (1:9 MeOH:EtOAc) = 0.20; δ_H (400 MHz, $CDCl_3$) 7.57–7.53 (2H, m, H-10), 7.46–7.41 (2H, m, H-11), 7.38–7.34 (1H, m, H-12), 3.37–3.27 (2H, m) and 3.21–3.10 (2H, m) (H-1, H-5), 3.06 (1H, ddd, *J* = 12.0, 8.0, 4.0, H-3a), 2.93 (1H, m, H-3b), 2.30 (1H, m, H-7a), 2.04–1.97 (2H, m, H-2), 1.89–1.71 (2H, m, H-6), 1.60–1.51 (1H, m, H-7b). Data consistent with the literature values.[270]

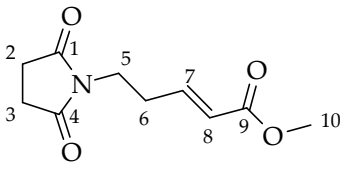
7.3.2 Taber's route

3-(2,5-Dioxopyrrolidin-1-yl)propanal (138)[100]



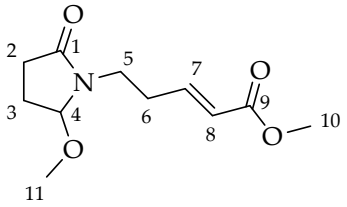
To a solution of sodium (50 mg, 2.15 mmol, 0.009 eq) in ethanol (50 mL) was added succinimide (**137**, 25 g, 253 mmol, 1.0 eq) to give a white suspension. Acrolein (16.9 mL, 253 mmol, 1.0 eq) was added *via* syringe pump over 2 h and the reaction was stirred for a further 3 h at room temperature. Glacial acetic acid (1 mL) was added and the mixture was concentrated *in vacuo* to give an oil which was pre-adsorbed onto silica. Flash column chromatography [5–20% acetone/$CHCl_3$] afforded the slightly impure aldehyde **138** (39.7 g) as a pale yellow viscous oil. R_f (1:9 MeOH:EtOAc) = 0.40; δ_H (400 MHz, $CDCl_3$) 9.72 (1H, t, *J* = 1.5, C-7), 3.81 (2H, t, *J* = 7.0, H-5), 2.73 (2H, td, *J* = 7.0, 1.5, H-6), 2.69 (4H, s, H-2, H-3); δ_C (100 MHz, $CDCl_3$) 199.4 (C-7), 176.9 (C-1, C-4), 41.3 (C-5), 32.3 (C-6), 28.0 (C-2, C-3). Data consistent with the literature values.[100]

Methyl (2*E*)-5-(2,5-dioxopyrrolidin-1-yl)pent-2-enoate (140)



To a solution of K_2CO_3 (9.18g, 66.5 mmol, 1.02 eq) in H_2O (50 mL) at 0 °C was added trimethyl phosphonoacetate (**139**, 11 mL, 68.0 mmol, 1.05 eq) and the mixture stirred at this temperature for 30 min. 3-(2,5-Dioxopyrrolidin-1-yl)propanal (**138**, 10.1 g, 64.1 mmol, 1.0 eq) was added as a solution in THF (50 mL) and the reaction was stirred at room temperature overnight (16 h). The mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to the afford **140** (13.2 g, 97% from **137**) as colourless needles. R_f (1:9 MeOH:EtOAc) = 0.60; mp 60–63 °C (lit[100] 64–65 °C); δ_H (400 MHz, $CDCl_3$) 6.83 (1H, dt, *J* = 16.0, 7.0, H-7), 5.84 (1H, dt, *J* = 16.0, 1.5, H-8), 3.70 (3H, s, Me), 3.63 (2H, t, *J* = 7.0, H-5), 2.70 (4H, s, H-2, H-3), 2.48 (2H, qd, *J* = 7.0, 1.5, H-6). Data consistent with the literature values.[100]

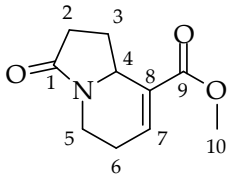
Methyl (2*E*)-5-(2-methoxy-5-oxopyrrolidin-1-yl)pent-2-enoate (125)



To a solution of methyl (2*E*)-5-(2,5-dioxopyrrolidin-1-yl)pent-2-enoate (**140**, 1.19 g, 5.62 mmol, 1.0 eq) in MeOH (15 mL) at 0 °C was added sodium borohydride (452 mg, 11.9 mmol, 2.2 eq) and the mixture was stirred at room temperature for 6 h. The reaction was quenched with aq. HCl (conc., 4.12 mL), diluted with H_2O (16.5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **125** (1.07 mg, 84%) as a colourless oil. R_f (1:9 MeOH:EtOAc) = 0.50; δ_H (400 MHz, $CDCl_3$) 6.90 (1H, dt, *J* = 16.0, 7.0, H-7), 5.87 (1H, dt, *J* = 16.0, 1.5, H-8), 4.89 (1H, dd, *J* = 6.0, 1.5, H-4), 3.71, (3H, s,

H-10), 3.61–3.53 (1H, m, H-5a), 3.31–3.23 (1H, m, H-5b), 3.25 (3H, s, H-11), 2.58–2.38 (3H, m, H-2a, H-6), 2.34–2.25 (1H, m, H-2b), 2.15–1.94 (2H, m, H-3); δ_C (100 MHz, $CDCl_3$) 175.1 (C-1), 166.6 (C-9), 145.5 (C-7), 122.7 (C-8), 90.3 (C-4), 52.7 (C-11), 51.5 (C-10), 30.6 (C-5), 29.2 (C-6), 28.8 (C-2), 23.6 (C-3). Data consistent with the literature values.[100]

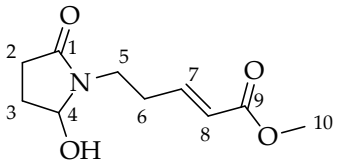
Methyl 3-oxo-1,2,3,5,6,8a-hexahydroindolizine-8-carboxylate (126)



To a solution of methyl (2*E*)-5-(2-methoxy-5-oxopyrrolidin-1-yl)pent-2-enoate (**125**, 2.28 g, 10.0 mmol, 1.0 eq) in CH_2Cl_2 (200 mL) at 0 °C was added dropwise $SnCl_4$ (2.93 mL, 25.0 mmol, 2.5 eq). The mixture was stirred at 0 °C for 30 min then heated to reflux and stirred at this temperature for 64 h. The reaction was then quenched with aq. NaOH (2 M, 80 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford crude methyl 7-chloro-3-oxooctahydroindolizine-8-carboxylate (**142**, 1.75 g) as a yellow oil which was used directly without further purification. To a solution of crude methyl 7-chloro-3-oxooctahydroindolizine-8-carboxylate (**142**, 1.75 g) in THF (30 mL) at room temperature was added DBU (1.47 mL, 9.83 mmol). The reaction was warmed to 60 °C and stirred at this temperature for 24 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with aq. HCl (10%, 20 mL) and H_2O (20 mL) then back-extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Flash column chromatography [1:9 acetone:CH_2Cl_2] afforded **126** (696 mg, 36% from **125**) as a colourless oil, R_f (1:9 acetone:CH_2Cl_2) = 0.25; δ_H (400 MHz, $CDCl_3$) 7.06 (1H, m, H-7), 4.44–4.36 (1H, m, H-4), 4.27 (1H, dd, *J* = 13.0, 6.5, H-5a), 3.77 (3H, s, H-10), 2.78–2.69 (1H, m, H-5b), 2.63 (1H, dddd, *J* = 12.5, 8.5, 7.0, 1.5, H-3a), 2.52–2.46 (1H, m, H-2a), 2.40 (1H, td, *J* = 9.5, 1.5, H-2b), 2.37-2.24 (2H, m, H-6) 1.60 (1H, ddt, *J* = 12.5, 11.0, 9.5, H-3b); δ_C (100 MHz, $CDCl_3$) 173.3 (C-1), 165.3 (C-9), 137.8 (C-7),

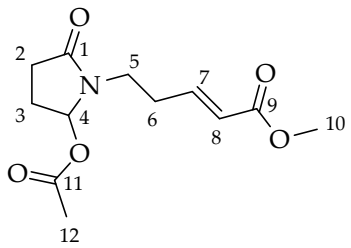
131.9 (C-8), 54.6 (C-4), 51.7 (C-10), 35.1 (C-5), 31.5 (C-2), 26.7 (C-3), 25.2 (C-6). Data consistent with the literature values.[100]

Methyl (2*E*)-5-(2-hydroxy-5-oxopyrrolidin-1-yl)pent-2-enoate (141)



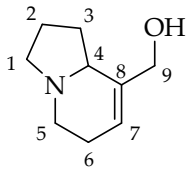
To a solution of methyl (2*E*)-5-(2,5-dioxopyrrolidin-1-yl)pent-2-enoate (**140**, 91 mg, 0.43 mmol, 1.0 eq) in MeOH (2 mL) cooled to 0 °C was added sodium borohydride (48 mg, 1.29 mmol, 3.0 eq) and the reaction was stirred at 0 °C for 2 h. The suspension was poured into a mixture of aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (10 mL). Once effervescence had ceased, the layers were separated and the aqueous layer further extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [1:4 Acetone:CH_2Cl_2] afforded **141** (30 mg, 33%) as a microcrystalline solid, R_f (1:9 Acetone:CH_2Cl_2) = 0.10; ν_{max}/cm^{-1} (thin film) 3175, 3003, 2933, 1722, 1657; mp 83–85 °C; δ_H (400 MHz, $CDCl_3$) 6.90 (1H, dt, *J* = 15.5, 7.0, H-7), 5.88 (1H, dt, *J* = 15.5, 1.5, H-8), 5.20 (1H, ddd, *J* = 8.5, 6.0, 2.0, H-4), 3.72 (3H, s, H-10), 3.57 (1H, dt, *J* = 14.0, 7.0, H-5a), 3.36 (1H, dt, *J* = 14.0, 7.0, H-5b), 3.29 (1H, d, *J* = 8.5, OH), 2.58–2.45 (3H, m, H-2a, H-6), 2.40–2.27 (2H, m, H-2b, H-3a), 1.93–1.84 (1H, m, H-3b); δ_C (100 MHz, $CDCl_3$) 174.9 (C-1), 166.9 (C-9), 145.8 (C-7), 122.7 (C-8), 83.5 (C-4), 51.6 (C-10), 38.7 (C-5), 30.7 (C-6), 28.8 (C-2), 28.3 (C-3); $[MNa]^+$; [HRMS (ESI): calc for $C_{10}H_{15}NNaO_4$, 236.0893 Found: $[MNa]^+$, 236.0895 (−0.6 ppm error)]. Data inconsistent with the literature values; this is discussed in Chapter 3.2.2.3).[100]

Methyl (2*E*)-5-(2-oxo-5-(prop-1-en-2-yloxy)pyrrolidin-1-yl)pent-2-enoate (154)



To a solution of methyl (2*E*)-5-(2-hydroxy-5-oxopyrrolidin-1-yl)pent-2-enoate (**141**, 72 mg, 0.34 mmol, 1.0 eq) and DMAP (4 mg, 0.03 mmol, 0.1 eq) in CH_2Cl_2 (4 mL) was added Et_3N (62 µL, 0.44 mmol, 1.3 eq) and acetic anhydride (36 µL, 0.38 mmol, 1.1 eq). The reaction was stirred at room temperature for 90 min then concentrated *in vacuo.* Flash column chromatography [1:9 Acetone:CH_2Cl_2] afforded **154** (6 mg, 0.02 mmol, 7%) as a colourless oil. R_f (1:9 Acetone:CH_2Cl_2) = 0.40; ν_{max}/cm^{-1} (thin film) 2952, 1713, 1660; δ_H (400 MHz, $CDCl_3$) 6.88 (1H, dt, *J* = 15.5, 7.0, H-7), 6.19 (1H, d, *J* = 5.5, H-4), 5.88 (1H, dt, *J* = 15.5, 1.5, H-8), 3.72 (3H, s, H-10), 3.62 (1H, dd, *J* = 14.0, 7.5, H-5a), 3.21 (1H, ddd, *J* = 14.0, 7.5, 6.0, H-5b), 2.62–2.41 (3H, m, H-2a, H-6), 2.39–2.26 (2H, m, H-3), 2.08 (3H, s, H-12), 2.05–1.98 (1H, m, H-2b); δ_C (100 MHz, $CDCl_3$) 175.8 (C-1), 170.8 (C-11), 166.5 (C-9), 144.9 (C-7), 123.0 (C-8), 84.7 (C-4), 51.5 (C-10), 39.6 (C-5), 30.5 (C-6), 28.2 (C-3), 26.0 (C-2), 21.1 (C-12); **154** was found to be unstable to ESI MS, resulting in elimination of acetate to give the acyliminium ion **143**. [M^+]; [HRMS (ESI): calc for $C_{10}H_{14}NO_3^+$, 196.0968 Found: [M^+], 196.0965 (1.5 ppm error)].

(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol (82)

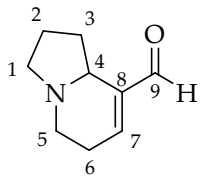


To a solution of methyl 3-oxo-1,2,3,5,6,8a-hexahydroindolizine-8-carboxylate (**126**, 86 mg, 0.44 mmol, 1.0 eq) in THF (2 mL) at –78 °C was added dropwise DIBAL-H (1 M in hexanes, 2.42 mL, 2.42 mmol, 5.5 eq) over 20 min. The reaction was stirred at −78 °C for 1 h then quenched with MeOH (4 mL) and H_2O (4 mL). After 10 min the resultant

gel was filtered through Celite, washed with EtOAc (5 mL) and acetone (5 mL) and the filtrate concentrated *in vacuo*. Flash column chromatography [Et_2O*] afforded **82** (51 mg, 76%) as a brown oil, R_f (Et_2O*) = 0.15; δ_H (400 MHz, $CDCl_3$) 5.71–5.67 (1H, m, H-7), 4.07 (2H, s, H-9), 3.19–3.12 (1H, m, H-4), 2.93 (1H, ddd, *J* = 10.0, 8.5, 4.0, H-1a), 2.83, (1H, dt, *J* = 11.0, 5.5, H-5a), 2.64 (1H, ddd, *J* = 10.0, 8.5, 7.5, H-1b), 2.54 (1H, ddd, *J* = 11.0, 7.0, 5.5, H-5b), 2.31–2.13 (2H, m, H-6), 2.08–1.99 (1H, m, H-3a), 1.96–1.84 (1H, m, H-2a), 1.81–1.70 (1H, m, H-2b), 1.60-1.50 (1H, dtd, *J* = 12.0, 10.5, 7.5, H-3b); δ_C (100 MHz, $CDCl_3$) 139.7 (C-8), 120.7 (C-7), 64.7 (C-9), 60.3 (C-4), 52.9 (C-1), 46.5 (C-5), 28.0 (C-3), 24.9 (C-6), 22.1 (C-2). Data consistent with the literature values.[100]

7.3.3 Continuation of synthesis

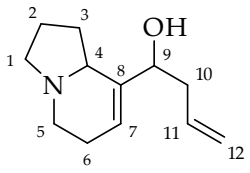
1,2,3,5,6,8a-Hexahydroindolizine-8-carbaldehyde (156)



To a solution of oxalyl chloride (206 µL, 2.43 mmol, 1.2 eq) in CH_2Cl_2 (2 mL) at −78 °C was added dropwise DMSO (345 µL, 4.86 mmol, 2.4 eq) and the colourless mixture stirred at this temperature for 30 min. A solution of (1,2,3,5,6,8a-hexahydroindolizin-8-yl)methanol (**82**, 310 mg, 2.03 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) cooled to –78 °C was added dropwise *via* cannula and the resultant solution was stirred at –78 °C for 30 min. Et_3N (1.41 mL, 10.1 mmol, 5.0 eq) was added and the reaction stirred at –78 °C for a further 30 min. The mixture was allowed to warm to room temperature and the reaction was stirred at this temperature for 2 h, then poured into aq. $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford **156** (224 mg, 73%) as a brown oil which was used in the next step without further purification. R_f (1:9:90 NH_3:MeOH:CH_2Cl_2) = 0.30; δ_H (400 MHz, $CDCl_3$) 9.41 (1H, s, H-9), 6.84 (1H, td, *J* = 4.0, 1.5, H-7), 3.43–3.36 (1H, m, H-4), 2.97–2.87 (2H, m, H-1a, H-5a), 2.72 (1H, ddd, *J* = 10.0, 8.5, 7.0, H-1b), 2.66–2.60 (1H, m, H-5b), 2.56–2.51 (1H, m, H-6a), 2.47–2.32 (2H, m, H-3a, H-6b), 1.92–1.75 (2H, m,

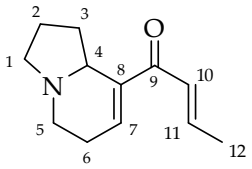
H-2), 1.50–1.39 (1H, m H-3b); δ_C (100 MHz, $CDCl_3$) 192.9 (C-9), 148.5 (C-7), 143.9 (C-8), 57.6 (C-4), 52.1 (C-1), 45.4 (C-5), 28.8 (C-3), 25.8 (C-6), 22.6 (C-2). Data consistent with the literature values.[100]

1-(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)but-3-en-1-ol (158)



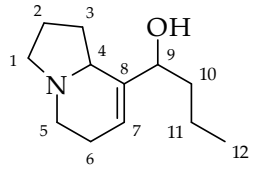
To a solution of 1,2,3,5,6,8a-hexahydroindolizine-8-carbaldehyde (**156**, 126 mg, 0.83 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) was added montmorillonite K10 (150 mg), potassium allyltrifluoroborate (148 mg, 1.00 mmol, 1.2 eq) and water (75 µL, 4.15 mmol, 5.0 eq). The reaction was stirred at room temperature for 30 min then filtered through a pad of Celite, washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Flash column chromatography [1:9:50 NH_3:MeOH:CH_2Cl_2] afforded **158** (72 mg, 45%, 1:1 mixture of diastereoisomers) as an orange oil, R_f (1:9:50 NH_3:MeOH:CH_2Cl_2) = 0.20; ν_{max}/cm^{-1} (thin film) 3368, 2912; δ_H (400 MHz, $CDCl_3$) 5.87–5.75 (1H, m, H-11), 5.76–5.73 (1H, m, H-7), 5.17–5.09 (2H, m, H-12), 4.17–4.13 (m) and 4.07 (dd, *J* = 8.0, 5.5) (1H, H-9), 3.22–3.15 (m) and 3.15–3.08 (m) (1H, H-4), 2.96 (1H, ddd, *J* = 10.5, 8.5, 3.5, H-1a), 2.86 (1H, dtd, *J* = 11.0, 5.5, 2.5, H-5a), 2.74–2.67 (1H, m, H-1b), 2.55 (1H, dddd, *J* = 11.0, 7.0, 5.5, 3.0, H-5b), 2.45–2.31 (2H, m, H-10), 2.30–2.20 (2H, m, H-6), 2.17–2.01 (1H, m, H-3a), 1.99–1.87 (1H, m, H-2a), 1.85–1.74 (1H, m, H-2b), 1.70–1.55 (1H, m, H-3b); δ_C (100 MHz, $CDCl_3$) 140.9 and 140.8 (C-8), 135.0 and 134.7 (C-7), 121.7 and 119.1 (C-11), 117.9 and 117.7 (C-12), 73.0 and 71.7 (C-9), 60.9 and 60.5 (C-4), 52.8 (C-1), 46.6 (C-5), 41.0 and 40.0 (C-10), 28.8 and 28.4 (C-3), 25.2 and 24.9 (C-6), 22.0 (C-2); [HRMS (ESI): calcd for $C_{12}H_{20}NO$, 194.1539. Found: $[MH]^+$, 194.1542 (−1.2 ppm error)].

(2*E*)-1-(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)but-2-en-1-one (81)



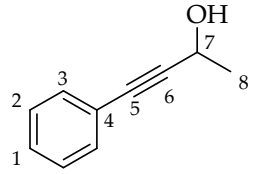
To a solution of oxalyl chloride (17 µL, 0.19 mmol, 1.2 eq) in CH_2Cl_2 (1 mL) at –78 °C was added dropwise DMSO (27 µL, 0.38 mmol, 2.4 eq) and the mixture stirred at this temperature for 30 min. A solution of 1-(1,2,3,5,6,8a-hexahydroindolizin-8-yl)but-3-en-1-ol (**158,** 31 mg, 0.16 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) cooled to –78 °C was added dropwise *via* cannula and the resultant solution was stirred at –78 °C for 30 min. Et_3N (112 µL, 0.80 mmol, 5.0 eq) was added and the reaction mixture stirred at –78 °C for a further 30 min. The mixture was allowed to warm to room temperature and the reaction was stirred at this temperature for 2 h then poured into aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Preparative TLC [500 µm, 1:9 MeOH:CH_2Cl_2] afforded **81** (8 mg, 26%) as a yellow oil, R_f (1:9 MeOH:CH_2Cl_2) = 0.30; ν_{max}/cm^{-1} (thin film) 2958, 2878, 2810, 1662, 1616; δ_H (400 MHz, $CDCl_3$) 6.87 (1H, dq, *J* = 15.0, 7.0, H-11), 6.83 (1H, td, *J* = 4.0, 1.5, H-7), 6.59 (1H, dq, *J* = 15.0, 1.5, H-10), 3.57–3.51 (1H, m, H-4), 2.96–2.86 (2H, m, H-1a, H-5a), 2.74 (1H, dt, *J* = 10.0, 8.0, H-1b), 2.64–2.57 (1H, m, H-5b), 2.54–2.44 (1H, m, H-6a), 2.40–2.27 (2H, m, H-3a, H-6b), 1.90 (3H, dd, *J* = 7.0, 1.5, H-12), 1.87–1.74 (2H, m, H-2), 1.44–1.33 (1H, m, H-3b); δ_C (100 MHz, $CDCl_3$) 190.6 (C-9), 142.8 (C-7), 142.2 (C-8), 136.9 (C-11), 126.9 (C-10), 58.9 (C-4), 52.5 (C-1), 45.3 (C-5), 29.1 (C-3), 25.4 (C-6), 22.3 (C-2), 18.4 (C-12); [HRMS (ESI): calcd for $C_{12}H_{18}NO$, 192.1383 Found: $[MH]^+$, 192.1386 (−1.4 ppm error)].

1-(1,2,3,5,6,8a-Hexahydroindolizin-8-yl)butan-1-ol (elaeokanine B, 89)



To a solution of 1,2,3,5,6,8a-hexahydroindolizine-8-carbaldehyde (**156**, 222 mg, 1.47 mmol, 1.0 eq) in THF (5 mL) at −10 °C was added propylmagnesium chloride (2 M in Et_2O, 1.47 mL, 2.94 mmol, 2 eq). The resultant mixture was stirred for 10 min at this temperature then allowed to warm to room temperature. The reaction was stirred at this temperature for a further 4 h, then quenched with H_2O (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (5mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [1:9:90 NH_3:MeOH:CH_2Cl_2] afforded **89** (70 mg, 24%, 1:1 mixture of diastereoisomers) as an orange oil, R_f (1:9:90 NH_3:MeOH:CH_2Cl_2) = 0.10; δ_H (400 MHz, $CDCl_3$) 5.73–5.69 (1H, m, H-7), 4.13–4.08 (m) and 4.04 (t, *J* = 7.0) (1H, H-9), 3.08–3.02 (m) and 3.02–2.95 (m) (1H, H-4), 2.96 (1H, ddd, *J* = 10.0, 8.5, 3.5, H-1a), 2.86 (1H, m, H-5a), 2.59 (1H, q, *J* = 9.0, H-1b), 2.47 (1H, m, H-5b), 2.30–1.24 (10H, m, H-2, H-3, H-6, H-10, H-11), 0.93 (3H, td, *J* = 7.0, 2.0, H-12); δ_C (100 MHz, $CDCl_3$) 142.4 and 141.8 (C-8), 121.8 and 118.7 (C-7), 74.4 and 72.8 (C-9), 60.9 and 60.7 (C-4), 53.0 and 52.9 (C-1), 46.9 and 46.8 (C-5), 38.8 and 37.5, 29.0 and 28.5, 25.6 and 25.4, 22.2 and 22.1, 19.4 and 19.0 (C-2, C-3, C-6, C-10, C-11), 14.1 (C-12); [HRMS (ESI): calc for $C_{12}H_{22}NO$, 196.1696 Found: $[MH]^+$, 196.1699 (−1.8 ppm error)]. Data consistent with the literature values.[103]

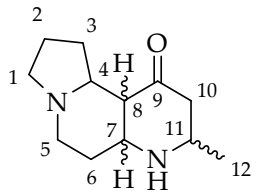
4-Phenylbut-3-yn-2-ol (166)[271]



To a solution of phenylacetylene (**165**, 70 mg, 0.69 mmol, 1.0 eq) in Et_2O (5 mL) at −78 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 0.42 mL, 0.69 mmol, 1.0 eq). The

resultant mixture was stirred at −78 °C for 15 min then allowed to warm to 0 °C. Acetaldehyde (42 µL, 0.75 mmol, 1.1 eq) was added dropwise and the reaction stirred at 0 °C for 2 h then quenched with aq. NH_4Cl (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **166** (68 mg, 68%) as a pale yellow oil. R_f(1:4 EtOAc:PE) = 0.30; δ_H (400 MHz, DMSO-d_6) 7.39–7.31 (5H, m, H-1, H-2, H-3), 5.44 (1H, d, *J* = 5.5, OH), 4.55 (1H, qd, *J* = 6.5, 5.5, H-7), 1.34 (1H, d, *J* = 6.5, H-8); δ_H (400 MHz, $CDCl_3$) 7.44–7.40 (2H, m), 7.32–7.28 (3H, m) (H-1, H-2, H-3), 4.76 (1H, dq, *J* = 6.5, 5.5, H-7), 1.88 (1H, d, *J* = 5.5, OH), 1.55 (3H, d, *J* = 6.5, H-8); δ_C (100 MHz, $CDCl_3$) 131.6 (C-2 or C-3), 128.4 (C-1), 128.3 (C-2 or C-3), 122.6 (C-4), 90.0 (C-6), 84.0 (C-5), 58.8 (C-7), 24.4 (C-8). Data consistent with the literature values.[271]

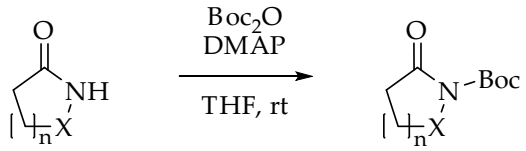
3-Methyldecahydropyrrolo[2,1-f][1,6]naphthyridin-1(10bH)-one (elaeokanidine A, 19, and 19a, 19b, 19c)



To a solution of (2*E*)-1-(1,2,3,5,6,8a-hexahydroindolizin-8-yl)but-2-en-1-one (4 mg, 0.02 mmol) in MeOH (0.2 mL) was added NH_3 (0.2 mL) and the reaction stirred at room temperature for 16 h. The solvent was removed *in vacuo* to afford **19, 19a, 19b** and **19c** (3.5 mg, 80%, 10:7:8:11 mixture of diastereoisomers) as a brown oil. δ_H (400 MHz, $CDCl_3$) 3.83–1.25 (16H, m, H-1, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-10, H-11), 1.22 (d, *J* = 6.0), 1.21 (d, *J* = 6.0), 1.16 (d, *J* = 7.0) and 1.15 (d, *J* = 7.0) (3H, H-12); [HRMS (ESI): calc for $C_{12}H_{21}N_2O$, 209.1648 Found: $[MH]^+$, 209.1654 (−2.5 ppm error)]. Data consistent with the literature values.[89]

7.4 Spirooxindoles

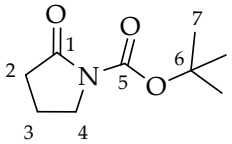
7.4.1 General procedure C – Boc protection of lactams and imides 261



261 **262**

To a solution of the amide/imide **261** (1.0 eq) in THF was added *N*,*N*-dimethylaminopyridine (0.1–1.1 eq) and di-*tert*-butyl dicarbonate (1.1–1.5 eq) and the mixture stirred at room temperature for 16 h before removing the solvent *in vacuo*. The residue was loaded onto a silica column and eluted with a petrol/ethyl acetate mixture to yield the Boc-protected amide/imide **262**. NB. Deviations from this procedure are noted.

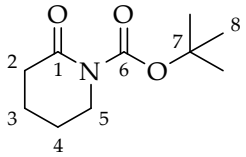
***tert*-Butyl 2-oxopyrrolidine-1-carboxylate (262a)[272]**



The title compound was prepared according to the procedure by Hara.[272] To a solution of pyrrolidinone (2.13 g, 25.0 mmol) in MeCN (12 mL) at 0 °C was added a solution of di-*tert*-butyl dicarbonate (5.73 g, 26.25 mmol) in MeCN (8 mL) followed by *N*,*N*-dimethylaminopyridine (305 mg, 2.50 mmol). The reaction was stirred at room temperature for 2.5 h then the solvent removed in vacuo and water (75 mL) added. The mixture was acidified to pH6–7 with 10% HCl followed by extraction with EtOAc (3 x 75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude compound. Flash column chromatography [50–100% EtOAc/PE] afforded **262a** (4.27 g, 92%) as a colourless oil. R_f (1:1 EtOAc:PE) = 0.40; δ_H (400 MHz, $CDCl_3$) 3.75–3.71 (2H, m, H-4), 2.51–2.47 (2H, m, H-2), 2.02–1.94 (2H, m,

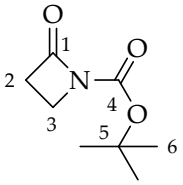
H-3), 1.51 (9H, s, H-7); δ_C (100 MHz, $CDCl_3$) 174.3 (C-1), 150.2 (C-5), 82.7 (C-6), 46.4 (C-4), 32.9 (C-2), 28.0 (C-7), 17.3 (C-3). Data consistent with the literature values.[272,273]

tert-Butyl 2-oxopiperidine-1-carboxylate (262b)



δ-Valerolactam (1.96 g, 19.8 mmol), di-*tert*-butyl dicarbonate (5.06 mg, 23.2 mmol) and *N*,*N*-dimethylaminopyridine (497 mg, 4.1 mmol) in THF (30 mL) were reacted according to general procedure C. Flash column chromatography [1:1 EtOAc:PE] afforded **262b** (3.93 mg, quant.) as a pale yellow oil. R_f (1:4 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 3.65–3.62 (2H, m, H-5), 2.51–2.47 (2H, m, H-2), 1.83–1.77 (4H, m, H-3, H-4), 1.51 (9H, s, H-8); δ_C (100 MHz, $CDCl_3$) 171.3 (C-1), 152.7 (C-6), 82.8 (C-7), 46.3 (C-5), 34.9 (C-2), 28.0 (C-8), 22.8 (C-3 or 4), 20.5 (C-3 or 4). Data consistent with the literature values.[273]

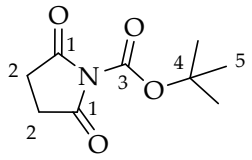
tert-Butyl 2-oxoazetidine-1-carboxylate (262d)



Azetidin-2-one (452 mg, 6.37 mmol), di-*tert*-butyl dicarbonate (2.08 g, 9.55 mmol) and *N*,*N*-dimethylaminopyridine (78 mg, 0.64 mmol) in THF (10 mL) were reacted according to general procedure C. Flash column chromatography [20–33% EtOAc/PE] afforded **262d** (956 mg, 87%) as a colourless oil, R_f (1:4 EtOAc:PE) = 0.20; δ_H (400 MHz, $CDCl_3$) 3.55 (2H, t, *J* = 5.0, H-3), 2.97 (2H, t, *J* = 5.0, H-2), 1.51 (9H, s, H-6); δ_C (100 MHz, $CDCl_3$) 164.6 (C-1), 148.0 (C-4), 83.2 (C-5), 37.7 (C-3), 36.1 (C-2), 28.0 (C-6); *m/z* (ESI) 194

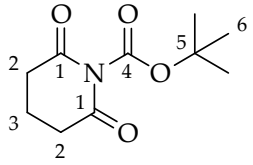
[MNa]$^+$; [HRMS (ESI): calcd for $C_8H_{13}NNaO_3$, 194.0788. Found: [MNa]$^+$, 194.0789 (−0.6 ppm error)]. Data consistent with the literature values.[274]

tert-Butyl 2,5-dioxopyrrolidine-1-carboxylate (262e)



Succinimide (396 mg, 4.0 mmol), di-*tert*-butyl dicarbonate (960 mg, 4.4 mmol) and *N*,*N*-dimethylaminopyridine (49 mg, 0.4 mmol) in THF (10 mL) were reacted according to general procedure C. Flash column chromatography [1:1 EtOAc:PE] afforded **262e** (723 mg, 91%) as a colourless microcrystalline solid, R_f (1:1 EtOAc:PE) = 0.40; mp 88–90 °C (lit[275] 86 °C) ; ν_{max}/cm^{-1} (neat) 2988, 2977, 2943, 1804, 1764, 1710; δ_H (400 MHz, $CDCl_3$) 2.77 (4H, s, H-2), 1.57 (9H, s, H-5); δ_C (100 MHz, $CDCl_3$) 172.8 (C-1), 146.5 (C-3), 86.3 (C-4), 28.5 (C-2), 27.7 (C-5); *m/z* (ESI) 222 [MNa]$^+$; [HRMS (ESI): calcd for $C_9H_{13}NNaO_4$, 222.0737. Found: [MNa]$^+$, 222.0736 (0.6 ppm error)]. Data consistent with the literature values.[275]

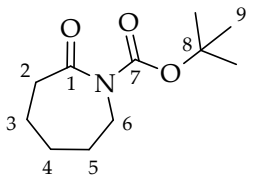
tert-Butyl 2,6-dioxopiperidine-1-carboxylate (262g)



Piperidine-2,6-dione (452 mg, 4.0 mmol), di-*tert*-butyl dicarbonate (960 mg, 4.4 mmol) and *N*,*N*-dimethylaminopyridine (49 mg, 0.4 mmol) in THF (10 mL) were reacted according to general procedure C. Flash column chromatography [1:1 EtOAc:PE] afforded **262g** (829 mg, 97%) as an off-white amorphous solid, mp 102–103 °C; R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (neat) 2986, 2941, 2902, 1776, 1726, 1691, 1461; δ_H (400 MHz, $CDCl_3$) 2.64 (4H, m, H-2), 2.00 (2H, m, H-3), 1.58 (9H, s, H-6); δ_C (100 MHz, $CDCl_3$) 170.1 (C-1), 148.9 (C-4), 86.3 (C-5), 31.8 (C-2), 27.4 (C-6), 17.1 (C-3);

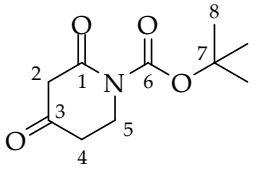
m/z (ESI) 236 $[MNa]^+$; [HRMS (ESI): calcd for $C_{10}H_{15}NNaO_4$, 236.0893. Found: $[MNa]^+$, 236.0891 (1.0 ppm error)]. Compound is known,[276] but no data is provided in the literature.

***tert*-Butyl 2-oxoazepane-1-carboxylate (262h)**



ε-Caprolactam (453 mg, 4.0 mmol), di-*tert*-butyl dicarbonate (960 mg, 4.4 mmol) and *N*,*N*-dimethylaminopyridine (538 mg, 4.4 mmol) in THF (10 mL) were reacted according to general procedure C. Flash column chromatography [1:1 EtOAc:PE] afforded **262h** (732 mg, 86%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.60; δ_H (400 MHz, $CDCl_3$) 3.77–3.74 (2H, m, H-6), 2.65–2.62 (2H, m, H-2), 1.79–1.70 (6H, m, H-3, H-4, H-5), 1.51 (9H, s, H-9); δ_C (100 MHz, $CDCl_3$) 175.7 (C-1), 152.9 (C-7), 82.7 (C-8), 46.1 (C-6), 39.5 (C-2), 29.2 (C-3 or 5), 28.6 (C-3 or 5), 28.0 (C-9), 23.5 (C-4). Data consistent with the literature values.[273]

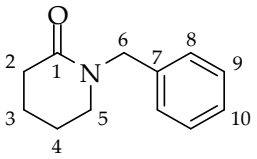
***tert*-Butyl 2,4-dioxopiperidine-1-carboxylate (262j)[223]**



The title compound was prepared according to the procedure by Vanotti.[223] To a solution of boc-β-alanine (2.50 g, 13.2 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (2.09 g, 14.5 mmol) and *N*,*N*-dimethylaminopyridine (2.42 g, 19.8 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide methiodide (4.70 g, 15.8 mmol) and the resultant mixture stirred at room temperature for 18 h. The reaction mixture was then washed with 5% $KHSO_4$ (4 x 50 mL), the

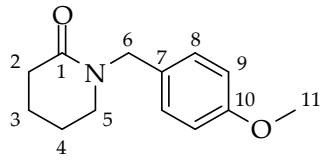
organic layer dried (Na_2SO_4) and concentrated *in vacuo* to give 4.24 g of a colourless solid. The solid was redissolved in EtOAc (60 mL) and heated to reflux for 7 h after which time the volume was reduced to approx. 15 mL and allowed to crystallize overnight. The solid was filtered and washed with cold EtOAc to afford **262j** (676 mg, 24%) as microcrystals. The filtrate was concentrated *in vacuo* and triturated with cold EtOAc to yield a further crop of the title compound, **262j** (1.05 g, 37%, total 61%) as an amorphous colourless solid, mp 104–106 °C; δ_H (400 MHz, $CDCl_3$) 4.09 (2H, t, *J* = 6.0, H-5), 3.50 (2H, s, H-2), 2.61 (2H, t, *J* = 6.0, H-4), 1.54 (9H, s, H-8); δ_C (100 MHz, $CDCl_3$) 202.1 (C-3), 165.3 (C-1), 151.2 (C-6), 84.2 (C-7), 52.2 (C-2), 40.6 (C-5), 38.2 (C-4), 27.9 (C-8). Data consistent with the literature values.[277]

1-Benzylpiperidin-2-one (262s)[227]



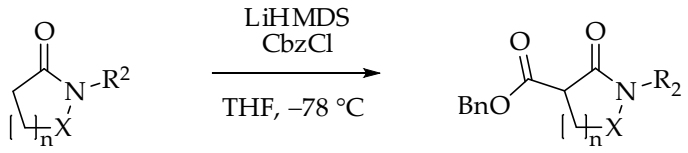
The title compound was prepared according to the procedure by Cossy.[227] To a stirred solution of *n*-butyllithium (1.6 M in hexanes, 6.5 mL, 10.45 mmol) in THF (30 mL) at −78 °C was added a solution of δ-valerolactam (942 mg, 9.50 mmol) in THF (10 mL) *via* cannula. After stirring for 20 min at −78 °C, benzyl bromide (1.13 mL, 9.50 mmol) was added and the solution slowly warmed to room temperature overnight (16 h). The reaction was quenched with aq. NH_4Cl (10 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [50–100% EtOAc/PE] afforded **262s** (585 mg, 33%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.15; δ_H (400 MHz, $CDCl_3$) 7.34–7.23 (5H, m, H-8, H-9, H-10), 4.60 (2H, s, H-6), 3.21–3.17 (2H, m H-5), 2.47 (2H, t, *J* = 6.5, H-2), 1.84–1.72 (4H, m, H-3 and 4); δ_C (100 MHz, $CDCl_3$) 169.8 (C-1), 137.3 (C-7), 128.5 (C-8), 128.0 (C-9), 127.3 (C-10), 50.0 (C-6), 47.2 (C-5), 32.4 (C-2), 23.2 (C-3 or 4), 21.4 (C-3 or 4). Data consistent with the literature values.[227]

1-(4-Methoxybenzyl)piperidin-2-one (262t)[228]



The title compound was prepared according to the procedure by Winter.[228] To a solution of δ-valerolactam (630 mg, 6.36 mL) in THF (30 mL) at 0 °C was added 4-methoxybenzylchloride (1.12 mL, 8.26 mmol) and sodium hydride (60% dispersion in mineral oil, 330 mg, 8.26 mmol) and the mixture heated to reflux for 24 h. After cooling, the reaction was quenched with H_2O (20 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [50–100% EtOAc/PE] afforded **262t** (1.31g, 94%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.20; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, d, *J* = 8.5, H-8), 6.84 (2H, d, *J* = 8.5, H-9), 4.52 (2H, s, H-6), 3.78 (3H, s, H-11), 3.18–3.15 (2H, m, H-5), 2.44 (2H, t, *J* = 6.5, H-2), 1.81–1.70 (4H, m, H-3, H-4); δ_C (100 MHz, $CDCl_3$) 169.7 (C-1), 158.9 (C-10), 129.4 (C-8), 113.9 (C-9), 55.2 (C-11), 49.4 (C-6), 47.0 (C-5), 32.4 (C-2), 23.1 (C-3 or 4), 21.3 (C-3 or 4), C-7 not visible due to broadening; *m/z* (ESI) 220 $[MH]^+$, 242 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{18}NO_2$, 220.1332. Found: $[MH]^+$, 220.1338 (−2.9 ppm error)]. Data consistent with the literature values.[228,278]

7.4.2 General procedure D – Benzylcarboxylation of *N*-protected lactams and imides 262

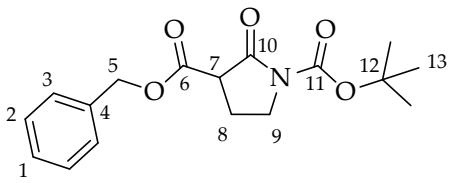


262 **263**

Based on the procedure by Bogle.[279] To a solution of amide/imide **262** in THF at −78 °C was added dropwise a solution of LiHMDS (2.1 eq, 1.0 M in THF) and the mixture stirred at −78 °C for 10 min. Benzylchloroformate (1.0 eq) was then added dropwise and the resulting mixture stirred at −78 °C for 1 h. The reaction was quenched at

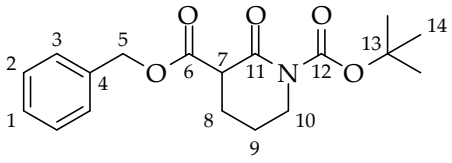
−78 °C with aq. NH_4Cl (10 mL) and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (3 x 25 mL), the combined organic extracts washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was loaded onto a silica column and eluted with an EtOAC/PE mixture to yield the ester **263**. NB. Deviations from this procedure are noted.

3-Benzyl 1-*tert*-butyl 2-oxopyrrolidine-1,3-dicarboxylate (263a)



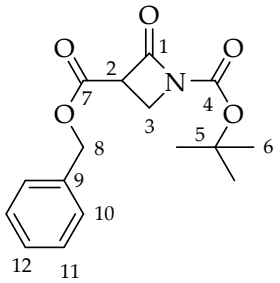
tert-Butyl 2,5-dioxopyrrolidine-1-carboxylate (**262a**, 558 mg, 3.0 mmol), LiHMDS (1 M in THF, 6.3 mL, 6.3 mmol) and benzylchloroformate (0.43 mL, 3.0 mmol) in THF (3 mL) were reacted according to general procedure D. Flash column chromatography [1:2 EtOAc:PE] afforded **263a** (602 mg, 63%) as a colourless solid, mp 74–76 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3066, 3034, 2980, 2935, 1787, 1756, 1729, 1498, 1478, 1455; δ_H (400 MHz, $CDCl_3$) 7.41–7.31 (5H, m, H-1, H-2, H-3), 5.21 (2H, s, H-5), 3.88 (1H, ddd, *J* = 11.0, 8.5, 5.0, H-9a), 3.70 (1H, ddd, *J* = 11.0, 8.0, 7.0, H-9b), 3.59 (1H, dd, *J* = 9.0, 7.5, H-7), 2.44–2.35 (1H, m, H-8a), 2.23 (1H, dddd, *J* = 13.0, 9.0, 8.0, 5.0, H-8b), 1.53 (9H, s, H-13); δ_C (100 MHz, $CDCl_3$) 168.6, 168.5 (C-6, C-10), 149.9 (C-11), 135.2 (C-4), 128.6 (C-2), 128.4 (C-1), 128.2 (C-3), 83.5 (C-12), 67.5 (C-5), 50.2 (C-7), 44.4 (C-9), 28.0 (C-13), 21.5 (C-8); *m/z* (ESI) 342 $[MNa]^+$; [HRMS (ESI): calcd for $C_{17}H_{21}NNaO_5$, 342.1312. Found: $[MNa]^+$, 342.1318 (−1.8 ppm error)]. Previously reported,[280] but no data is provided in the literature.

3-Benzyl 1-*tert*-butyl 2-oxopiperidine-1,3-dicarboxylate (263b)



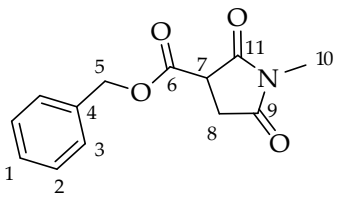
tert-Butyl 2-oxopiperidine-1-carboxylate (**262b**, 2.97 g, 14.9 mmol), LiHMDS (1 M in THF, 31.4 mL, 31.4 mmol) and benzylchloroformate (2.13 mL, 14.9 mmol) in THF (15 mL) were reacted according to general procedure D. Flash column chromatography [1:2 EtOAc:PE] afforded **263b** (4.71 g, 95%) as a colourless oil, R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (neat) 3065, 3034, 2979, 2941, 1771, 1741, 1721, 1498, 1479, 1456; δ_H (400 MHz, $CDCl_3$) 7.37–7.29 (5H, m, H-1, H-2, H-3), 5.22 (1H, d, *J* = 12.5, H-5a), 5.18 (1H, d, *J* = 12.5, H-5b), 3.68–3.64 (2H, m, H-10), 3.56 (1H, dd, *J* = 8.5, 7.0, H-7), 2.23–2.03 (2H, m, H-8), 1.98–1.89 (1H, m, H-9a), 1.85–1.75 (1H, m, H-9b), 1.52 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 169.7 (C-6), 167.2 (C-11), 152.5 (C-12), 135.4 (C-4), 128.5 (C-3), 128.2 (C-1), 128.1 (C-2), 83.3 (C-13), 67.1 (C-5), 51.4 (C-7), 45.7 (C-10), 27.9 (C-14), 24.2 (C-8), 20.9 (C-9); *m/z* (ESI) 356 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{23}NNaO_5$, 356.1468. Found: [MNa]$^+$, 356.1469 (−0.2 ppm error)]; [Found C, 64.71%; H, 6.90%; N, 4.14%. $C_{18}H_{23}NO_5$ requires C, 64.85%; H, 6.95%; N, 4.20%].

3-Benzyl 1-*tert*-butyl 2-oxoazetidine-1,3-dicarboxylate (263d)



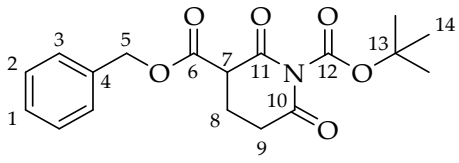
tert-Butyl 2-oxoazetidine-1-carboxylate (**262d**, 90 mg, 0.53 mmol), LiHMDS (1 M in THF, 1.11 mL, 1.11 mmol) and benzylchloroformate (0.075 mL, 0.53 mmol) in THF (2 mL) were reacted according to general procedure C. Flash column chromatography [1:4 EtOAc:PE] afforded **263d** (86 mg, 54%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (thin film) 3066, 3034, 2981, 2936, 1810, 1731, 1498, 1474, 1456; δ_H (400 MHz, $CDCl_3$) 7.39–7.34 (5H, m, H-10, H-11, H-12), 5.53 (2H, d, *J* = 1.0, H-8), 4.10 (1H, dd, *J* = 6.5, 3.5, H-2), 3.89 (1H, dd, *J* = 7.0, 3.5, H-3a), 3.71 (1H, dd, *J* = 7.0, 6.5, H-3b), 1.52 (9H, s, H-6); δ_C (100 MHz, $CDCl_3$) 165.7 (C-7), 158.8 (C-1), 147.6 (C-4), 134.9 (C-9), 128.6 (C-11), 128.6 (C-12), 128.3 (C-10), 84.0 (C-5), 67.8 (C-8), 53.1 (C-2), 41.1 (C-3), 27.9 (C-6); *m/z* (ESI) 328 [MNa]$^+$; [HRMS (ESI): calcd for $C_{16}H_{19}NNaO_5$, 328.1155. Found: [MNa]$^+$, 328.1158 (−0.9 ppm error)].

Benzyl 1-methyl-2,5-dioxopyrrolidine-3-carboxylate (263f)



1-Methylpyrrolidine-2,5-dione (1.13 g, 10.0 mmol), LiHMDS (1 M in THF, 21.0 mL, 21.0 mmol) and benzylchloroformate (1.43 mL, 10.0 mmol) in THF (40 mL) were reacted according to general procedure D. Flash column chromatography [1:2 EtOAc:PE] afforded **263f** (959 mg, 39%) as a colourless microcrystalline solid, mp 61–63 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3065, 3034, 2951, 1783, 1736, 1704, 1498; δ_H (400 MHz, $CDCl_3$) 7.38–7.30 (5H, m, H-1, H-2, H-3), 5.22 (2H, s, H-5), 3.80 (1H, dd, *J* = 9.5, 4.5, H-7), 3.08 (1H, dd, *J* = 18.0, 4.5, H-8a), 2.99 (3H, s, H-10), 2.87 (1H, dd, *J* = 18.0, 9.5, H-8b); δ_C (100 MHz, $CDCl_3$) 175.0, 172.0 (C-9, C-11), 167.3 (C-6), 134.7 (C-4), 128.6 (C-2), 128.5 (C-1), 128.2 (C-3), 68.0 (C-5), 46.3 (C-7), 32.0 (C-8), 25.3 (C-10); *m/z* (ESI) 270 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{13}NNaO_4$, 270.0737. Found: $[MNa]^+$, 270.0738 (−0.3 ppm error)].

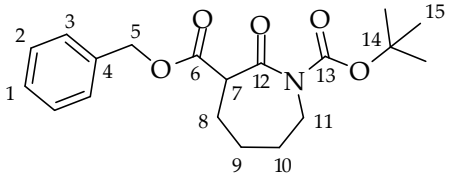
3-Benzyl 1-*tert*-butyl 2,6-dioxopiperidine-1,3-dicarboxylate (263g)



tert-Butyl 2,6-dioxopiperidine-1-carboxylate (**262g**, 638 mg, 2.99 mmol), LiHMDS (1 M in THF, 6.3 mL, 6.3 mmol) and benzylchloroformate (0.43 mL, 2.99 mmol) in THF (3 mL) were reacted according to general procedure D. Flash column chromatography [1:2 EtOAc:PE] afforded **263g** (394 mg, 38%) as a colourless oil, R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (neat) 3065, 3034, 2982, 2939, 1784, 1737, 1699, 1498, 1457; δ_H (400 MHz, $CDCl_3$) 7.38–7.33 (5H, m, C-1, C-2, C-3), 5.25 (1H, d, *J* = 12.0, H-5a), 5.21 (1H, d, *J* = 12.0, H-5b), 3.70 (1H, dd, *J* = 8.0, 5.0, H-7), 2.72 (1H, ddd, *J* = 18.0, 8.0, 5.0, H-9a), 2.66–2.57 (1H, m, H-9b), 2.40–2.31 (1H, m, H-8a), 2.24–2.15 (1H, m, H-8b), 1.57 (9H, s, H-14);

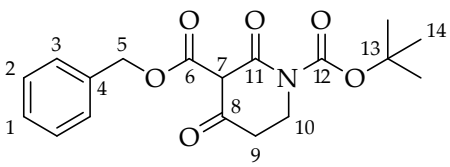
δ_C (100 MHz, $CDCl_3$) 169.1 (C-10), 167.6 (C-6), 166.2 (C-11), 148.2 (C-12), 135.0 (C-4), 128.8 (C-2), 128.7 (C-1), 128.3 (C-3), 86.9 (C-13), 68.0 (C-5), 48.4 (C-7), 29.8 (C-9), 27.5 (boc), 20.7 (C-8); *m/z* (ESI) 370 $[MNa]^+$; [HRMS (ESI): calcd for $C_{18}H_{21}NNaO_6$, 370.1261. Found: $[MNa]^+$, 370.1259 (0.6 ppm error)]

3-Benzyl 1-*tert*-butyl 2-oxoazepane-1,3-dicarboxylate (263h)



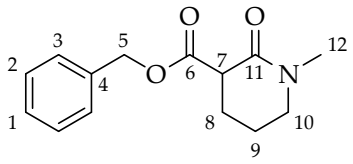
tert-Butyl 2-oxoazepane-1-carboxylate (**262h**, 568 mg, 2.66 mmol), LiHMDS (1 M in THF, 5.6 mL, 5.59 mmol) and benzylchloroformate (0.38 mL, 2.66 mmol) in THF (3 mL) were reacted according to general procedure D. Flash column chromatography [1:2 EtOAc:PE] afforded **263h** (377 mg, 41%) as a colourless oil, R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (neat) 3065, 3034, 2979, 2935, 2867, 1767, 1747, 1715, 1498, 1456; δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (5H, m, H-1, H-2, H-3), 5.23 (1H, d, *J* = 12.5, H-5a), 5.19 (1H, d, *J* = 12.5, H-5b), 4.13–4.06 (1H, m, H-11a), 3.78 (1H, dd, *J* = 10.5, 2.5, H-7), 3.36 (1H, dd, *J* = 15.5, 10.0, H-11b), 2.18-2.10 (1H, m, H-8a), 2.02–1.81 (3H, m, H-8b, H-9a, H-10a), 1.61–1.53 (2H, m, H-9b, H-10b), 1.51 (9H, s, H-15); δ_C (100 MHz, $CDCl_3$) 171.5 (C-12), 169.6 (C-6), 152.7 (C-13), 135.5 (C-4), 128.5, 128.4 (C-2, C-3), 128.3 (C-1), 83.4 (C-14), 67.1 (C-5), 54.4 (C-7), 45.5 (C-11), 27.9 (C-15), 27.9, 27.3 (C-9, C-10), 26.1 (C-8); *m/z* (ESI) 370 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{25}NNaO_5$, 370.1625. Found: $[MNa]^+$, 370.1624 (0.3 ppm error)].

3-Benzyl 1-*tert*-butyl 2,4-dioxopiperidine-1,3-dicarboxylate (263j)



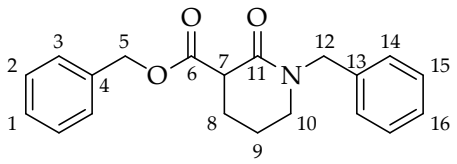
Based on the procedure by Asahi.[281] To a solution of *tert*-butyl 2,4-dioxopiperidine-1-carboxylate (**262j**, 675 mg, 3.17 mmol) in ethanol (25 mL) at 0 °C was added potassium carbonate (1.09 g, 7.92 mmol) and benzylchloroformate (0.48 mL, 5.33 mmol) and the mixture stirred at room temperature for 2.5 h. The reaction was quenched with 10% HCl (20 mL), extracted with CH_2Cl_2 (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [20–50% EtOAc/PE] afforded **263j** (391 mg, 36%) as a colourless oil which crystallised on standing, mp 70–71 °C; R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (thin film) 3112, 3065, 3051, 3012, 2981, 2968, 2931, 2915, 1768, 1712, 1695, 1682, 1652, 1590, 1501, 1464; δ_H (400 MHz, $CDCl_3$) 7.41–7.37 (5H, m, H-1, H-2, H-3), 6.00 (1H, t, *J* = 1.0, H-7), 5.23 (2H, s, H-5), 3.91 (2H, t, *J* = 6.5, H-10a), 2.64 (2H, td, *J* = 6.5, 1.0, H-9a), 1.53 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 164.0 (C-11), 162.7 (C-8), 152.2 (C-12), 150.8 (C-6), 134.0 (C-4), 129.1 (C-1), 128.8 (C-3), 128.6 (C-2), 111.2 (C-7), 83.2 (C-13), 70.9 (C-5), 42.4 (C-10), 28.0 (C-14), 27.2 (C-9); *m/z* (ESI) 370 $[MNa]^+$; [HRMS (ESI): calcd for $C_{18}H_{21}NNaO_6$, 370.1261. Found: $[MNa]^+$, 370.1246 (4.1 ppm error)].

Benzyl 1-methyl-2-oxopiperidine-3-carboxylate (263r)



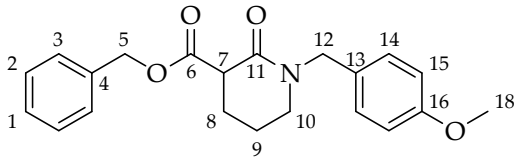
1-Methylpiperidin-2-one (544 mg, 4.81 mmol), LiHMDS (1 M in THF, 10.1 mL, 10.1 mmol) and benzylchloroformate (0.69 mL, 4.81 mmol) in THF (5 mL) were reacted according to general procedure D. Flash column chromatography [50–100% EtOAc/PE] afforded **263r** (475 mg, 40%) as a colourless oil, R_f (EtOAc) = 0.50; ν_{max}/cm^{-1} (thin film) 3063, 3033, 2945, 2872, 1737, 1644, 1500, 1454; δ_H (400 MHz, $CDCl_3$) 7.39–7.28 (5H, m, H-1, H-2, H-3), 5.22 (1H, d, *J* = 12.5, H-5a), 5.17 (1H, d, *J* = 12.5, H-5b), 3.46 (1H, dd, *J* = 7.5, 6.5, H-7), 3.36 (1H, ddd, *J* = 12.0, 8.0, 5.0, H-10a), 3.27 (1H, dt, *J* = 12.0, 5.5, H-10b), 2.97 (3H, s, H-12), 2.18-2.01 (2H, m, H-8), 1.99–1.90 (1H, m, H-9a), 1.82–1.72 (1H, m, H-9b); δ_C (100 MHz, $CDCl_3$) 171.0 (C-6), 165.6 (C-11), 135.7 (C-4), 128.5 (C-2), 128.2 (C-1), 128.1 (C-3), 66.9 (C-5), 49.7 (C-10), 49.1 (C-7), 35.0 (C-12), 25.3 (C-8), 20.9 (C-9); *m/z* (ESI) 270 $[MNa]^+$; [HRMS (ESI): calcd for $C_{14}H_{17}NNaO_3$, 270.1101. Found: $[MNa]^+$, 270.1111 (−3.7 ppm error)].

Benzyl 1-benzyl-2-oxopiperidine-3-carboxylate (263s)



1-Benzylpiperidin-2-one (**262s**, 585 mg, 3.09 mmol), LiHMDS (1 M in THF, 6.49 mL, 6.49 mmol) and benzylchloroformate (0.44 mL, 3.9 mmol) in THF (3 mL) were reacted according to general procedure D. Flash column chromatography [1:2 EtOAc] afforded **263s** (872 mg, 87%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (thin film) 3062, 3031, 2945, 2870, 1739, 1644, 1587, 1494, 1464, 1453; δ_H (400 MHz, $CDCl_3$) 7.40–7.22 (10H, m, H-1, H-2, H-3, H-14, H-15, H-16), 5.22 (2H, s, H-5), 4.77 (1H, d, *J* = 14.5, H-12a), 4.47 (1H, d, *J* = 14.5, H-12b), 3.56 (1H, dd, *J* = 7.0, 7.0, H-7), 3.28–3.16 (2H, m, H-10), 2.19–2.03 (2H, m, H-8), 1.93–1.84 (1H, m, H-9a), 1.77–1.67 (1H, m, H-9b); δ_C (100 MHz, $CDCl_3$) 171.0 (C-6), 165.7 (C-11), 136.7, 135.6 (C-4, C-13), 128.6, 128.5 (C-2, C-3, C-14 or C-15), 128.2 (C-1 or C-16), 128.1, 127.9 (C-2, C-3, C-14 or C-15), 127.4 (C-1 or C-16), 67.0 (C-5), 50.2 (C-12), 49.2 (C-7), 46.9 (C-10), 25.2 (C-8), 20.8 (C-9); *m/z* (ESI) 346 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{21}NNaO_3$, 346.1414. Found: $[MNa]^+$, 346.1417 (−1.0 ppm error)].

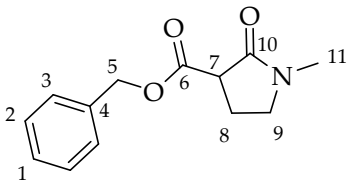
Benzyl 1-(4-methoxybenzyl)-2-oxopiperidine-3-carboxylate (263t)



1-(4-Methoxybenzyl)piperidin-2-one (**262t**, 738 mg, 3.37 mmol), LiHMDS (1 M in THF, 7.07 mL, 7.07 mmol) and benzylchloroformate (0.48 mL, 3.37 mmol) in THF (3.5 mL) were reacted according to general procedure D. Flash column chromatography [2:1 PE:EtOAc] afforded **263t** (790 mg, 66%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3064, 3033, 2941, 2870, 2837, 1736, 1642, 1585, 1512, 1493, 1463; δ_H (400 MHz, $CDCl_3$) 7.39-7.30 (5H, m, H-1, H-2, H-3), 7.17 (2H, d, *J* = 8.5, H-14), 6.79

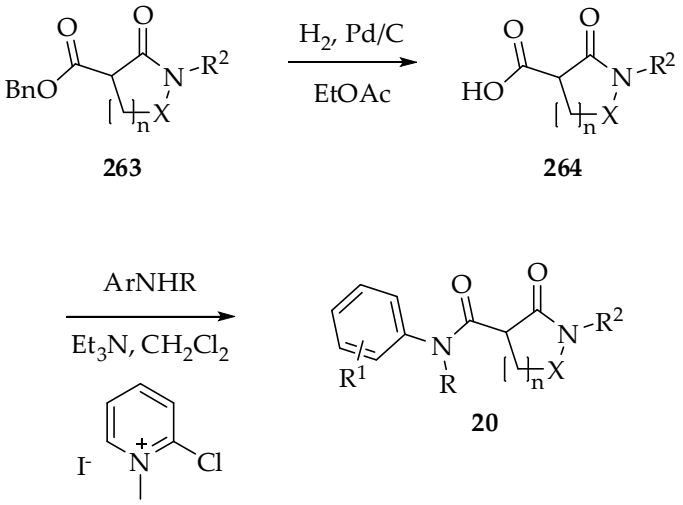
2H, d, *J* = 98.5, H-15), 5.22 (2H, s, H-5), 4.69 (1H, d, *J* = 14.5, H-12a), 4.40 (1H, d, *J* = 14.5, H-12b), 3.80 (3H, s, H-17), 3.56-3.52 (1H, m, H-7), 3.26-3.14 (2H, m, H-10), 2.18-2.02 (2H, m, H-8), 1.92-1.82 (1H, m, H-9a), 1.76-1.65 (1H, m, H-9b); δ_C (100 MHz, $CDCl_3$) 171.0 (C-6), 165.6 (C-11), 158.9 (C-16), 135.7 (C-4), 129.4 (C-14), 128.8 (C-13), 128.5 (C-2), 128.2 (C-1), 128.1 (C-3), 113.9 (C-15), 67.0 (C-5), 55.2 (C-17), 49.7 (C-12), 49.3 (C-7), 46.7 (C-10), 25.2 (C-8), 20.9 (C-9); *m/z* (ESI) 376 $[MNa]^+$; [HRMS (ESI): calcd for $C_{21}H_{23}NNaO_4$, 376.1519. Found: $[MNa]^+$, 376.1508 (3.1 ppm error)].

Benzyl 1-methyl-2-oxopyrrolidine-3-carboxylate (263x)



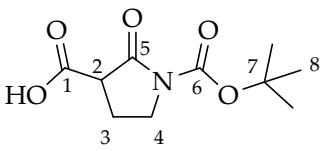
1-Methylpyrrolidin-2-one (1.04 g, 10.5 mmol), LiHMDS (1 M in THF, 22.0 mL, 22.0 mmol) and benzylchloroformate (1.49 mL, 10.5 mmol) in THF (10 mL) were reacted according to general procedure D. Flash column chromatography [50–100% EtOAc/PE] afforded **263x** (1.25 g, 47%) as a pale yellow oil, R_f (EtOAc) = 0.50; ν_{max}/cm^{-1} (thin film) 3064, 3033, 2953, 2885, 1736, 1687, 1499, 1455; δ_H (400 MHz, $CDCl_3$) 7.40–7.28 (5H, m, H-1, H-2, H-3), 5.20 (2H, s, H-5), 3.52–3.45 (2H, m, H-7, H-9a), 3.34 (1H, ddd, *J* = 9.5, 8.5, 6.0, H-9b), 2.87 (3H, s, H-11), 2.40 (1H, dddd, *J* = 13.0, 8.5, 6.5, 6.0, H-8a), 2.26 (1H, dddd, *J* = 13.0, 9.5, 8.5, 5.0, H-8b); δ_C (100 MHz, $CDCl_3$) 170.2, 169.5 (C-6, C-10), 135.5 (C-4), 128.5 (C-2), 128.2 (C-1), 128.0 (C-3), 67.1 (C-5), 48.2 (C-7), 47.8 (C-9), 30.0 (C-9), 22.2 (C-8); *m/z* (ESI) 256 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{15}NNaO_3$, 256.0944. Found: $[MNa]^+$, 256.0946 (−0.8 ppm error)].

7.4.3 General procedure E – Hydrogenolysis and amide coupling of esters 263



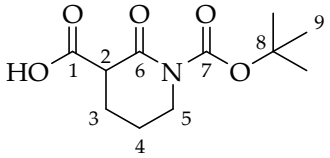
A solution of ester **263** in EtOAc in the presence of Pd/C was stirred under an atmosphere of H_2 (balloon) for 0.5–2 h. The mixture was filtered through celite, washed with EtOAc and concentrated *in vacuo* to afford the crude acid **264** which was used immediately in the next step. To a solution of the acid (1.0 eq) in CH_2Cl_2 at 0 °C was added the aniline (1.1 eq) and 2-chloro-1-methylpyridinium iodide (1.5 eq), followed by dropwise addition of triethylamine (5.0 eq) and the mixture stirred at room temperature for 16 h. The reaction was quenched with aq. HCl (10%, 5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was loaded onto a silica column and eluted with am EtOAc/PE mixture to yield the anilide **20**. NB. Deviations from this procedure are noted.

1-(*tert*-Butoxycarbonyl)-2-oxopyrrolidine-3-carboxylic acid (264a)



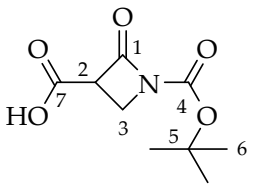
A solution of 3-benzyl 1-*tert*-butyl 2-oxopyrrolidine-1,3-dicarboxylate (**263a**, 576 mg, 1.81 mmol) in EtOAc (15 mL) was hydrogenolysed in the presence of 10% Pd/C (80 mg) for 2 h according to general procedure E to afford the crude title compound (412 mg) as a colourless amorphous solid, R_f (1:1 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 3.91 (1H, ddd, *J* = 11.5, 8.5, 3.5, H-4a), 3.70 (1H, ddd, *J* = 11.0, 9.0, 7.5, H-4b), 3.57 (1H, t, *J* = 10.0, H-2), 2.46–2.30 (2H, m, H-3), 1.54 (9H, s, H-8).

1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (264b)



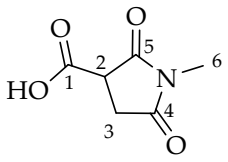
A solution of 3-benzyl 1-*tert*-butyl 2-oxopiperidine-1,3-dicarboxylate (**263b**, 2.40 g, 7.22 mmol) in EtOAc (60 mL) was hydrogenolysed in the presence of 10% Pd/C (320 mg) for 2 h according to general procedure E to afford the crude title compound (1.74 g) as a colourless amorphous solid, R_f (1:1 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 3.70 (2H, m, H-5), 3.42 (1H, dd, *J* = 9.5, 7.0, H-2), 2.31–2.21 (1H, m), 2.16–2.05 (1H, m), 2.02–1.93 (1H, m), 1.91–1.78 (1H, m) (H-3, H-4), 1.52 (9H, s, H-9).

1-(*tert*-Butoxycarbonyl)-2-oxoazetidine-3-carboxylic acid (264d)



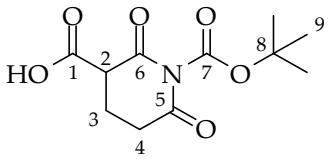
A solution of 3-benzyl 1-*tert*-butyl 2-oxoazetidine-1,3-dicarboxylate (**263d**, 359 mg, 1.18 mmol) in EtOAc (30 mL) was hydrogenolysed in the presence of 5% Pd/C (164 mg) for 1.5 h according to general procedure E to afford the crude title compound (244 mg). δ_H (400 MHz, $CDCl_3$) 8.20 (1H, br s, OH), 4.11 (1H, dd, *J* = 6.5, 3.5, H-2), 3.88 (1H, dd, *J* = 7.0, 3.5, H-3a), 3.74 (1H, dd, *J* = 7.0, 6.5, H-3b), 1.51 (9H, s, H-6).

1-Methyl-2,5-dioxopyrrolidine-3-carboxylic acid (264f)



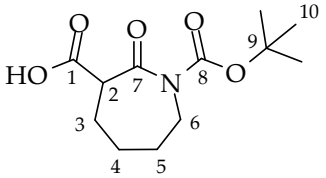
A solution of benzyl 1-methyl-2,5-dioxopyrrolidine-3-carboxylate (**263f**, 494 mg, 2.00 mmol) in EtOAc (20 mL) was hydrogenolysed in the presence of 5% Pd/C (426 mg) for 30 min according to general procedure E to afford the crude title compound (312 mg) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.82 (1H, br s, OH), 3.82 (1H, dd, *J* = 9.5, 5.0, H-2), 3.12 (1H, dd, *J* = 18.5, 5.0, H-3a), 3.01 (3H, s, H-6), 2.94 (1H, dd, *J* = 18.5, 9.5, H-3b).

1-(*tert*-Butoxycarbonyl)-2,6-dioxopiperidine-3-carboxylic acid (264g)



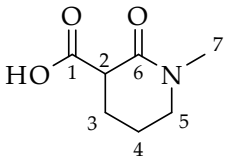
A solution of 3-benzyl 1-*tert*-butyl 2,6-dioxopiperidine-1,3-dicarboxylate (**263g**, 381 mg, 1.10 mmol) in EtOAc (10 mL) was hydrogenolysed in the presence of 10% Pd/C (50 mg) for 2 h according to general procedure E to afford the crude title compound (310 mg) as a colourless amorphous solid, R_f (1:1 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 3.63 (1H, dd, *J* = 8.0, 6.5, H-2), 2.86 (1H, dt, *J* = 18.0, 6.0, H-4a), 2.68 (1H, ddd, *J* = 18.0, 8.5, 6.0, H-4b), 2.37–2.31 (2H, m, H-3), 1.57 (9H, s, H-9).

1-(*tert*-Butoxycarbonyl)-2-oxoazepane-3-carboxylic acid (264h)



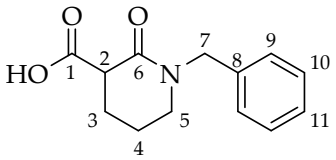
A solution of 3-benzyl 1-*tert*-butyl 2-oxoazepane-1,3-dicarboxylate (**263h**, 377 mg, 1.09 mmol) in EtOAc (10 mL) was hydrogenolysed in the presence of 10% Pd/C (50 mg) for 2 h according to general procedure E to afford the crude title compound (235 mg) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$) 4.20 (1H, dd, *J* = 15.5, 6.0, H-6a), 3.63 (1H, dd, *J* = 10.5, 2.0, H-2), 3.41 (1H, dd, *J* = 15.5, 10.5, H-6b), 2.39–2.32 (1H, m, H-3a), 2.08–1.51 (5H, m, H-3b, H-4, H-5), 1.54 (9H, s, H-10).

1-Methyl-2-oxopiperidine-3-carboxylic acid (264r)



A solution of benzyl 1-methyl-2-oxopiperidine-3-carboxylate (**263r**, 467 mg, 1.89 mmol) in EtOAc (20 mL) was hydrogenolysed in the presence of 10% Pd/C (90 mg) for 1 h according to general procedure E to afford the crude title compound (313 mg) as a colourless powder. δ_H (400 MHz, $CDCl_3$) 3.46–3.33 (2H, m, H-5), 3.20 (1H, dd, *J* = 10.5, 6.0, H-2), 3.03 (3H, s, H-7), 2.45–2.37 (1H, m, H-3 or 4), 2.07–1.96 (2H, m, H-3 and/or 4), 1.93–1.80 (1H, m, H-3 or 4). Previously reported, but no NMR data is provided in the literature.[282]

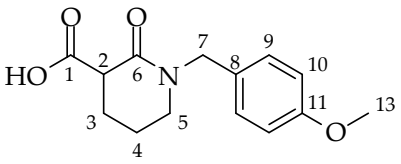
1-Benzyl-2-oxopiperidine-3-carboxylic acid (264s)



A solution of benzyl 1-benzyl-2-oxopiperidine-3-carboxylate (**263s**, 841 mg, 2.60 mmol) in EtOAc (25 mL) was hydrogenolysed in the presence of 10% Pd/C (115 mg) for 2 h according to general procedure E to afford the crude title compound (580 mg), R_f (1:1 EtOAc:PE) = 0.20; δ_H (400 MHz, $CDCl_3$) 7.38–7.22 (5H, m, H-9, H-10, H-11), 4.70

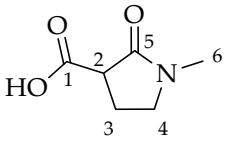
(1H, d, *J* = 14.5, H-7a), 4.57 (1H, d, *J* = 14.5, H-7b), 3.34–3.27 (3H, m, H-2, H-5), 2.34–2.35 (1H, m), 2.08–1.91 (2H, m), 1.86–1.74 (1H, m) (H-3, H-4).

1-(4-Methoxybenzyl)-2-oxopiperidine-3-carboxylic acid (264t)



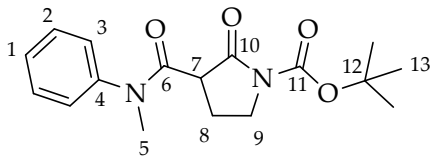
A solution of benzyl 1-(4-methoxybenzyl)-2-oxopiperidine-3-carboxylate (**263t**, 760 mg, 2.15 mmol) in EtOAc (20 mL) was hydrogenolysed in the presence of 10% Pd/C (95 mg) for 1.5 h according to general procedure E to afford the crude title compound (474 mg). δ_H (400 MHz, $CDCl_3$) 7.19 (2H, d, *J* = 8.5, H-9), 6.88 (2H, d, *J* = 8.5, H-10), 4.62 (1H, d, *J* = 14.5, H-7a), 4.51 (1H, d, *J* = 14.5, H-7b), 3.81 (3H, s, H-12), 3.32–3.24 (3H, m, H-2, H-5), 2.42–2.34 (1H, m), 2.06–1.89 (2H, m), 1.84–1.71 (1H, m) (H-3, H-4).

1-Methyl-2-oxopyrrolidine-3-carboxylic acid (264x)



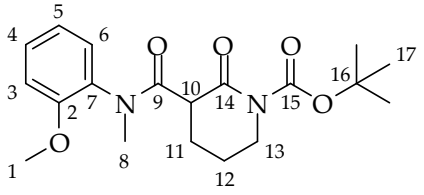
A solution of benzyl 1-methyl-2-oxopyrrolidine-3-carboxylate (**263x**, 1.23 g, 5.28 mmol) in EtOAc (55 mL) was hydrogenolysed in the presence of 5% Pd/C (450 mg) for 2 h according to general procedure E to afford the crude title compound (729 mg). δ_H (400 MHz, $CDCl_3$) 9.77 (1H, br s, OH), 3.47-3.41 (3H, m, H-2, H-4), 2.91 (3H, s, H-6), 2.42-2.33 (2H, m, H-3).

***tert*-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (20a)**



1-(*tert*-Butoxycarbonyl)-2-oxopyrrolidine-3-carboxylic acid (**264a**, 412 mg), *N*-methylaniline (0.21 mL, 1.98 mmol), 2-chloro-1-methylpyridinium iodide (689 mg, 2.70 mmol) and triethylamine (1.25 mL, 8.99 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20a** (556 mg, 97% over 2 steps) as a colourless foamy solid, mp 84–85 °C; R_f (1:1 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (neat) 3062, 2980, 2933, 1782, 1746, 1717, 1657, 1595, 1496, 1477, 1455; δ_H (400 MHz, $CDCl_3$) 7.45–7.33 (5H, m, H-1, H-2, H-3), 3.91 (1H, ddd, *J* = 10.5, 9.0, 4.0, H-9a), 3.56 (1H, t, *J* = 9.0, H-7), 3.52 (1H, dt, *J* = 10.5, 8.0, H-9b), 3.32 (3H, s, H-5), 2.47 (1H, ddd, *J* = 17.0, 13.0, 9.0, H-8a), 1.96 (1H, dddd, *J* = 13.0, 9.0, 8.0, 4.0, H-8b), 1.50 (9H, s, H-13); δ_C (100 MHz, $CDCl_3$) 170.3 (C-6), 168.7 (C-10), 149.9 (C-11), 143.3 (C-4), 129.8 (C-2), 128.1 (C-1), 127.6 (C-3), 83.0 (C-12), 47.4 (C-7), 44.9 (C-9), 37.8 (C-5), 27.9 (C-13), 22.2 (C-8); *m/z* (ESI) 341 $[MNa]^+$; [HRMS (ESI): calcd for $C_{17}H_{22}N_2NaO_4$, 341.1472. Found: $[MNa]^+$, 341.1475 (−1.0 ppm error)]; [Found C, 64.14%; H, 6.95%; N, 8.72%. $C_{17}H_{22}N_2O_4$ requires C, 64.13%; H, 6.97%; N, 8.80%].

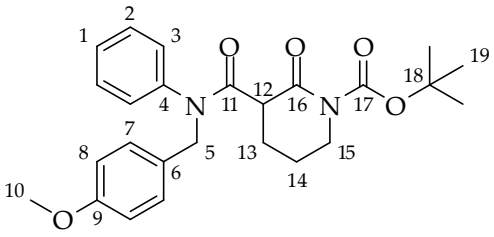
***tert*-Butyl 3-((2-methoxyphenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20b)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 421 mg), *N*-(2-methoxypheny)-*N*-methylamine (261 mg, 1.91 mmol), 2-chloro-1-methylpyridinium iodide (663 mg, 2.60 mmol) and triethylamine (1.21 mL, 8.66 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50%

EtOAc/PE] afforded **20b** (492 mg, 78% over 2 steps) as a colourless amorphous solid, mp 140–142 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (neat) 3066, 2940, 1768, 1716, 1657, 1597, 1501, 1460; δ_H (400 MHz, $CDCl_3$) 7.48 (1H, dd, *J* = 7.5, 1.5, H-6), 7.31 (1H, ddd, *J* = 8.0, 7.5, 1.5, H-4), 6.97 (1H, dd, *J* = 7.5, 1.5, H-5), 6.93 (1H, dd, *J* = 8.0, 1.5, H-3), 3.81 (3H, s, H-1), 3.65–3.53 (2H, m, H-13), 3.34 (1H, dd, *J* = 10.0, 7.0, H-10), 3.20 (3H, s, H-8), 2.14 (1H, dddd, *J* = 13.5, 11.5, 10.0, 4.0, H-11a), 1.96 (1H, ddt, *J* = 13.5, 9.5, 4.5, H-12a), 1.84–1.75 (1H, m, H-11b), 1.60–1.50 (1H, m, H-12b), 1.48 (9H, s, H-17); δ_C (100 MHz, $CDCl_3$) 170.6 (C-9), 168.2 (C-14), 154.9 (C-2), 152.5 (C-15), 132.1 (C-7), 130.1 (C-6), 129.5 (C-4), 121.4 (C-5), 111.5 (C-3), 82.9 (C-16), 55.4 (C-1), 48.4 (C-10), 46.5 (C-13), 36.2 (C-8), 27.9 (C-17), 25.1 (C-11), 21.5 (C-12); *m/z* (ESI) 385 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{26}N_2NaO_5$, 385.1734. Found: $[MNa]^+$, 385.1722 (3.1 ppm error)]; [Found C, 62.94%; H, 7.15%; N, 7.56%. $C_{19}H_{26}N_2O_5$ requires C, 62.97%; H, 7.23%; N, 7.73%].

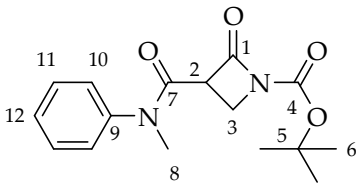
***tert*-Butyl 3-((4-methoxybenzyl)(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20c)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 402 mg), *N*-(4-methoxybenzyl)aniline (388 mg, 1.82 mmol), 2-chloro-1-methylpyridinium iodide (633 mg, 2.48 mmol) and triethylamine (1.15 mL, 8.27 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **20c** (629 mg, 86% over 2 steps) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (neat) 3063, 2977, 2936, 2838, 1768, 1716, 1655, 1613, 1594, 1513, 1494, 1457; δ_H (400 MHz, $CDCl_3$) 7.31–7.27 (3H, m, H-1, H-2 and/or H-3), 7.14 (2H, d, *J* = 9.0, H-7), 6.79 (2H, d, *J* = 9.0, H-8), 4.94 (1H, d, *J* = 14.5, H-5a), 4.78 (1H, d, *J* = 14.5, H-5b), 3.77 (3H, s, H-10), 3.62–3.58 (2H, m, H-15), 3.39 (1H, dd, *J* = 10.5, 7.0, H-12), 2.19 (1H, dddd, *J* = 13.5, 11.5, 10.5, 4.0, H-13a), 2.01–1.92 (1H, m, H-14a), 1.90–1.81 (1H, m, H-13b), 1.62–1.53 (1H, m, H-14b), 1.50 (9H, s, H-19), some aromatic peaks not visible due to broadening; δ_C (100 MHz, $CDCl_3$) 170.1 (C-11), 168.2 (C-16),

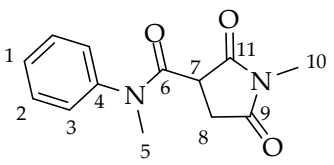
158.8 (C-9), 152.2 (C-17), 142.0 (C-4), 130.0 (C-7), 129.5 (C-2 or 3), 129.2 (C-6), 128.2 (C-1), 113.7 (C-8), 83.0 (C-18), 55.2 (C-10), 52.5 (C-5), 48.9 (C-12), 46.6 (C-15), 27.9 (C-19), 25.4 (C-13), 21.6 (C-14), some aromatic peaks not visible due to broadening; *m/z* (ESI) 461 $[MNa]^+$; [HRMS (ESI): calcd for $C_{25}H_{30}N_2NaO_5$, 461.2047. Found: $[MNa]^+$, 461.2036 (2.4 ppm error)].

tert-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxoazetidine-1-carboxylate (20d)



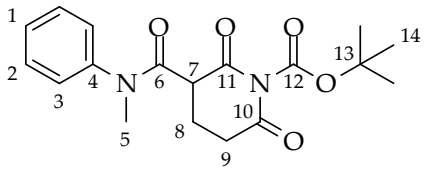
1-(*tert*-Butoxycarbonyl)-2-oxoazetidine-3-carboxylic acid (**264d**, 244 mg), *N*-methylaniline (0.14 mL, 1.29 mmol), 2-chloro-1-methylpyridinium iodide (450 mg, 1.77 mmol) and triethylamine (0.82 mL, 5.89 mmol) in CH_2Cl_2 (5 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **20d** (260 mg, 73% over 2 steps) as a colourless foam, R_f (1:2 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3063, 2979, 2935, 1805, 1724, 1656, 1595, 1497, 1474, 1457; δ_H (400 MHz, $CDCl_3$) 7.46–7.33 (5H, m, H-10, H-11, H-12), 4.01 (1H, dd, *J* = 6.0, 3.5, H-3a), 3.98 (1H, dd, *J* = 6.0, 3.5, H-2), 3.45 (1H, t, *J* = 6.0, H-3b), 3.33 (3H, s, H-8), 1.49 (9H, s, H-6); δ_C (100 MHz, $CDCl_3$) 164.6 (C-7), 160.8 (C-1), 147.7 (C-4), 142.4 (C-9), 129.9 (C-11), 128.3 (C-12), 127.5 (C-10), 83.5 (C-5), 51.6 (C-2), 41.7 (C-3), 37.7 (C-8), 27.9 (C-6); *m/z* (ESI) 327 $[MNa]^+$; [HRMS (ESI): calcd for $C_{16}H_{20}N_2NaO_4$, 327.1315. Found: $[MNa]^+$, 327.1314 (0.3 ppm error)].

_N_,1-Dimethyl-2,5-dioxo-_N_-phenylpyrrolidine-3-carboxamide (20f)



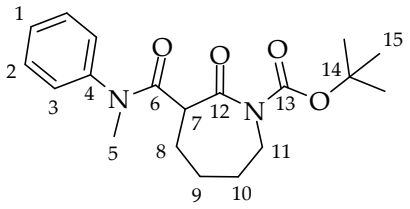
1-Methyl-2,5-dioxopyrrolidine-3-carboxylic acid (**264f**, 312 mg), *N*-methylaniline (0.24 mL, 2.20 mmol), 2-chloro-1-methylpyridinium iodide (765 mg, 3.00 mmol) and triethylamine (1.4 mL, 10.0 mmol) in CH_2Cl_2 (20 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20f** (437 mg, 89% over 2 steps) as a colourless amorphous solid, mp 99–101 °C; R_f (1:1 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 2946, 1778, 1703, 1654, 1496; δ_H (400 MHz, $CDCl_3$) 7.49–7.36 (5H, m, H-1, H-2, H-3), 3.78 (1H, dd, *J* = 9.0, 5.0, H-7), 3.35 (3H, s, H-5), 3.10 (1H, dd, *J* = 18.0, 5.0, H-8a), 2.96 (3H, s, H-10), 2.63 (1H, dd, *J* = 18.0, 9.0, H-8b); δ_C (100 MHz, $CDCl_3$) 175.9 (C-11), 174.2 (C-9), 167.5 (C-6), 142.9 (C-4), 130.0 (C-2), 128.5 (C-1), 127.7 (C-3), 43.8 (C-7), 38.0 (C-5), 33.3 (C-8), 25.2 (C-10); *m/z* (ESI) 269 [MNa]$^+$; [HRMS (ESI): calcd for $C_{13}H_{14}N_2NaO_3$, 269.0897. Found: [MNa]$^+$, 269.0896 (0.1 ppm error)].

***tert*-Butyl 3-(methyl(phenyl)carbamoyl)-2,6-dioxopiperidine-1-carboxylate (20g)**



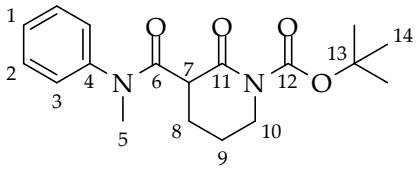
1-(*tert*-Butoxycarbonyl)-2,6-dioxopiperidine-3-carboxylic acid (**264g**, 304 mg), *N*-methylaniline (0.14 mL, 1.30 mmol), 2-chloro-1-methylpyridinium iodide (452 mg, 1.77 mmol) and triethylamine (0.82 mL, 5.90 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20g** (295 mg, 78% over 2 steps) as a sticky colourless oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (neat) 3061, 2982, 2937, 1782, 1734, 1698, 1659, 1595, 1496, 1457; δ_H (400 MHz, $CDCl_3$) 7.47–7.28 (5H, m, H-1, H-2, H-3), 3.53 (1H, dd, *J* = 9.5, 5.5, H-7), 3.33 (3H, s, H-5), 2.90–2.84 (1H, m, H-9a), 2.45–2.30 (2H, m, H-8a, H-9b), 1.97–1.91 (1H, m, H-8b), 1.54 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 169.4 (C-10), 167.7 (C-6), 167.5 (C-11), 148.4 (C-12), 143.1 (C-4), 130.2 (C-2), 128.6 (C-1), 127.2 (C-3), 86.5 (C-13), 45.4 (C-7), 37.7 (C-5), 30.1 (C-9), 27.3 (C-14), 21.0 (C-8); *m/z* (ESI) 369 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{22}N_2NaO_5$, 369.1421. Found: [MNa]$^+$, 369.1420 (0.3 ppm error)].

***tert*-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxoazepane-1-carboxylate (20h)**



1-(*tert*-Butoxycarbonyl)-2-oxoazepane-3-carboxylic acid (**264h**, 235 mg), *N*-methylaniline (0.11 mL, 1.00 mmol), 2-chloro-1-methylpyridinium iodide (348 mg, 1.37 mmol) and triethylamine (0.63 mL, 4.55 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20h** (225 mg, 60% over 2 steps) as a colourless amorphous solid, mp 70–71 °C; R_f (1:1 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (neat) 3061, 2934, 2869, 1766, 1714, 1688, 1596, 1495, 1455; δ_H (400 MHz, $CDCl_3$) 7.40–7.29 (3H, m), 7.22–7.19 (2H, m) (H-1, H-2, H-3), 4.00 (1H, dd, *J* = 15.5, 6.5, H-11a), 3.48 (1H, dd, *J* = 10.5, 2.0, H-7), 3.29 (3H, s, H-5), 2.55 (1H, dd, *J* = 15.5, 10.5, H-11b), 2.11–2.05 (1H, m, H-8a), 1.90–1.69 (3H, m, H-8b, H-9a, H-10a), 1.50 (9H, s, H-15), 1.42–1.27 (2H, m, H-9b, H-10b); δ_C (100 MHz, $CDCl_3$) 172.5, 169.1 (C-6, C-12), 153.0 (C-13), 143.3 (C-4), 129.7 (C-2), 128.1 (C-1), 127.7 (C-3), 83.0 (C-14), 51.8 (C-7), 45.0 (C-11), 37.5 (C-5), 28.0 (C-15), 27.8, 27.6 (C-9, C-10), 26.8 (C-8); *m/z* (ESI) 369 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{26}N_2NaO_4$, 369.1785. Found: $[MNa]^+$, 369.1775 (2.8 ppm error)].

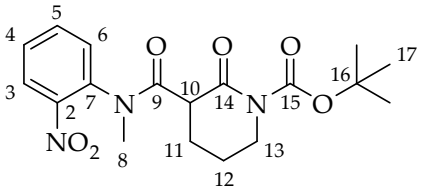
***tert*-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20i)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 485 mg), *N*-methylaniline (0.24 mL, 2.20 mmol), 2-chloro-1-methylpyridinium iodide (765 mg, 3.00 mmol) and triethylamine (1.4 mL, 10.0 mmol) in CH_2Cl_2 (20 mL) were reacted according to general procedure E. Flash column chromatography [33–50% EtOAc/PE] afforded **20i** (529 mg, 80% over 2 steps) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.30;

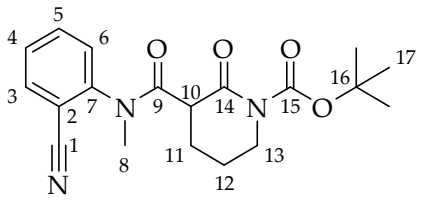
ν_{max}/cm^{-1} (neat) 3061, 2979, 2968, 1768, 1716, 1658, 1595, 1496, 1478, 1457; δ_H (400 MHz, $CDCl_3$) 7.41–7.29 (5H, m, H-1, H-2, H-3), 3.59–3.55 (2H, m, H-10), 3.42 (1H, dd, *J* = 10.5, 7.0, H-7), 3.28 (3H, s, H-5), 2.18-2.08 (1H, m, H-8a), 1.98–1.90 (1H, m, H-9a), 1.87–1.79 (1H, m, H-8b), 1.59–1.50 (1H, m, H-9b), 1.47 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 170.0 (C-6), 168.2 (C-11), 152.4 (C-12), 143.7 (C-4), 129.8 (C-2), 128.0 (C-1), 127.3 (C-3), 83.0 (C-13), 48.5 (C-7), 46.4 (C-10), 37.5 (C-5), 27.8 (C-14), 25.3 (C-8), 21.5 (C-9); *m/z* (ESI) 333 [MH]$^+$, 355 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{25}N_2O_4$, 333.1809. Found: [MH]$^+$, 333.1811 (−0.7 ppm error)].

tert-Butyl 3-(methyl(2-nitrophenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20k)



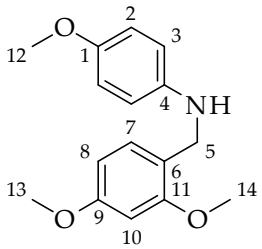
1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 494 mg), 2-nitro-*N*-methylaniline (340 mg, 2.24 mmol), 2-chloro-1-methylpyridinium iodide (778 mg, 3.05 mmol) and triethylamine (1.41 mL, 10.2 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **20k** (296 mg, 37% over 2 steps) as an orange powder, mp 140–142 °C; R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (neat) 3071, 2978, 2936, 1767, 1718, 1665, 1603, 1530, 1485, 1458; δ_H (400 MHz, $CDCl_3$) 7.93 (1H, dd, *J* = 8.0, 1.5, H-3), 7.87–7.84 (1H, m, H-6), 7.68 (1H, ddd, *J* = 8.0, 7.5, 1.5, H-5), 7.54 (1H, ddd, *J* = 8.0, 7.5, 1.5, H-4), 3.60 (2H, dd, *J* = 9.5, 4.0, H-13), 3.22 (1H, dd, *J* = 10.0, 6.5, H-10), 3.22 (3H, s, H-8), 2.29–2.18 (1H, m, H-11a), 2.03–1.92 (2H, m, H-11b, H-12a), 1.65–1.52 (1H, m, H-12b), 1.48 (9H, s, H-17); δ_C (100 MHz, $CDCl_3$) 169.7 (C-9), 168.0 (C-14), 151.9 (C-15), 146.6 (C-2), 136.6 (C-7), 134.5 (C-5), 132.5 (C-6), 129.6 (C-4), 124.9 (C-3), 83.2 (C-16), 49.1 (C-10), 46.8 (C-13), 37.3 (C-8), 27.9 (C-17), 24.9, 21.5; *m/z* (ESI) 400 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{23}N_3NaO_4$, 400.1479. Found: [MNa]$^+$, 400.1477 (1.4 ppm error)].

***tert*-Butyl 3-((2-cyanophenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20l)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 220 mg), 2-(methylamino)benzonitrile (131 mg, 1.00 mmol), 2-chloro-1-methylpyridinium iodide (346 mg, 1.36 mmol) and triethylamine (0.63 mL, 4.53 mmol) in CH_2Cl_2 (12 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20l** (258 mg, 77% over 2 steps) as a colourless amorphous solid, mp 134–136 °C; R_f (1:1 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3071, 2978, 2938, 2230, 1767, 1717, 1663, 1595, 1489, 1454; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* = 8.0, 1.0, H-6), 7.73 (1H, dd, *J* = 7.5, 1.5, H-3), 7.68 (1H, td, *J* = 8.0, 1.5, H-5), 7.48 (1H, td, *J* = 7.5, 1.0, H-4), 3.62–3.58 (2H, m, H-13), 3.34 (3H, s, H-8), 3.20 (1H, dd, *J* = 10.0, 6.5, H-10), 2.30–2.20 (1H, m, H-11a), 2.05–1.96 (2H, m, H-11b, H-12a), 1.64–1.53 (1H, m, H-12b), 1.48 (9H, s, H-17); δ_C (100 MHz, $CDCl_3$) 169.6 (C-9), 167.7 (C-14), 151.9 (C-15), 146.3 (C-7), 134.8 (C-5), 133.6 (C-3), 130.6 (C-6), 128.9 (C-4), 115.8 (C-1), 112.1 (C-2), 83.2 (C-16), 48.8 (C-10), 46.7 (C-13), 37.2 (C-8), 27.9 (C-17), 25.3 (C-11), 21.4 (C-12); *m/z* (ESI) 380 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{23}N_3NaO_4$, 380.1581. Found: $[MNa]^+$, 380.1568 (3.4 ppm error)].

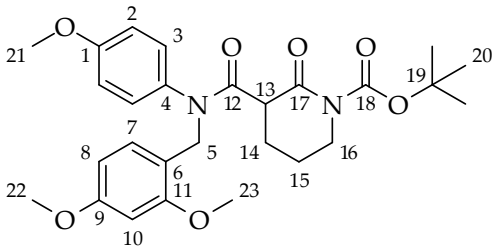
***N*-(2,4-Dimethoxybenzyl)-4-methoxyaniline (273)**



The title compound was prepared by Johannes Klein, based on the procedure by Trost.[158] To 4-methoxyaniline (2.46 g, 20.0 mmol) and 2,4-dimethoxybenzaldehyde (3.33 g, 20.0 mmol) was added glacial acetic acid (10 mL) and the mixture heated to

100 °C for 1 h. The solvent was removed under reduced pressure, the residue re-dissolved in EtOH (20 mL), cooled to 0 °C and $NaBH_4$ (1.29 g, 34.0 mmol) was added portionwise. The reaction was stirred for 30 min at 0 °C and 30 min at room temperature before quenching with 2M NaOH (50 mL) and extracting with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from EtOH afforded **273** (3.53 g, 64%) as pale brown needles, mp 72–74 °C (lit[283] 72-73 °C); δ_H (400 MHz, $CDCl_3$) 7.20 (1H, d, *J* = 8.0, H-7), 6.78 (2H, d, *J* = 9.0, H-2), 6.64 (2H, d, *J* = 9.0, H-3), 6.49 (1H, d, *J* = 2.5, H-10), 6.44 (1H, dd, *J* = 8.0, 2.5, H-8), 4.22 (2H, s, H-5), 3.84 (3H, s, H-14), 3.80 (3H, s, H-13), 3.75 (3H, s, H-12); δ_C (100 MHz, $CDCl_3$) 160.1 (C-9), 158.4 (C-11), 152.0 (C-1), 142.7 (C-4), 129.7 (C-7), 119.9 (C-6), 114.7 (C-2), 114.4 (C-3), 103.7 (C-8), 98.5 (C-10), 55.7 (C-12), 55.3, 55.3 (C-13, C-14), 44.1 (C-5). Data consistent with the literature values.[158,283]

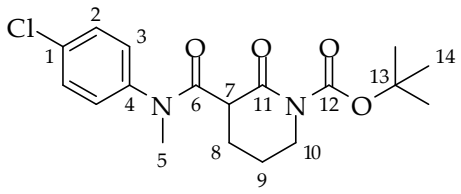
***tert*-Butyl 3-((2,4-dimethoxybenzyl)(4-methoxyphenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20m)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 479 mg), *N*-(2,4-dimethoxybenzyl)-4-methoxyaniline (**273**, 592 mg, 2.17 mmol), 2-chloro-1-methylpyridinium iodide (754 mg, 2.96 mmol) and triethylamine (1.37 mL, 9.86 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **20m** (761 mg, 74% over 2 steps) as an off-white sticky foam, R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (neat) 3056, 2938, 2837, 1767, 1716, 1654, 1614, 1589, 1511, 1458; δ_H (400 MHz, $CDCl_3$) 7.30 (1H, d, *J* = 8.5, H-7), 6.78–6.74 (2H, m, H-2), 6.43 (1H, dd, *J* = 8.5, 2.5, H-8), 6.31 (1H, d, *J* = 2.5, H-10), 4.94 (1H, d, *J* = 14.5, H-5a), 4.79 (1H, d, *J* = 14.5, H-5b), 3.77 (3H, s), 3.76 (3H, s) (H-21, H-22), 3.61 (2H, dd, *J* = 8.0, 4.5, H-16), 3.57 (3H, s, H-23), 3.44 (1H, dd, *J* = 10.0, 7.0, H-13), 2.23–2.12 (1H, m, H-14a), 2.00–1.93 (1H, m, H-15a), 1.90–1.81 (1H, m, H-14b), 1.63–1.53

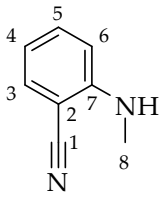
(1H, m, H-15b), 1.50 (9H, s, H-20), H-3 not visible due to broadening; δ_C (100 MHz, $CDCl_3$) 170.3 (C-12), 168.4 (C-17), 160.0 (C-9), 158.8 (C-1), 158.3 (C-11), 152.2 (C-18), 135.0 (C-4), 130.8 (C-7), 117.6 (C-6), 114.2 (C-2), 104.1 (C-8), 98.1 (C-10), 82.9 (C-19), 55.3 (C-22), 55.2 (C-21), 55.1 (C-23), 48.8 (C-13), 47.2 (C-5), 46.6 (C-16), 27.9 (C-20), 25.4 (C-14), 21.6 (C-15), C-3 not visible due to broadening; *m/z* (ESI) 499 $[MH]^+$; [HRMS (ESI): calcd for $C_{27}H_{35}N_2O_7$, 499.2439. Found: $[MH]^+$, 499.2423 (3.4 ppm error)].

***tert*-Butyl 3-((4-chlorophenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20n)**



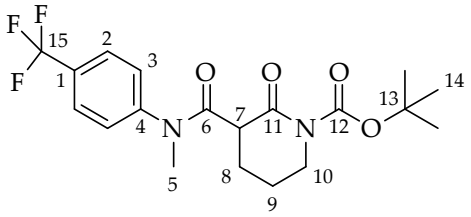
1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 541 mg), 4-chloro-*N*-methylaniline (0.30 mL, 2.45 mmol), 2-chloro-1-methylpyridinium iodide (852 mg, 3.34 mmol) and triethylamine (1.55 mL, 11.1 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20n** (618 mg, 78% over 2 steps) as a colourless microcrystalline solid, mp 103–104 °C; R_f (1:1 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3091, 3064, 2978, 2937, 1768, 1716, 1659, 1592, 1490, 1457; δ_H (400 MHz, $CDCl_3$) 7.39–7.28 (4H, m, H-2, H-3), 3.61 (2H, dd, *J* = 8.0, 4.5, H-10), 3.41 (1H, dd, *J* = 10.5, 7.0, H-7), 3.27 (3H, s, H-5), 2.16 (1H, dddd, *J* = 13.5, 11.5, 10.5, 4.0, H-8a), 2.01–1.93 (1H, m, H-9a), 1.88–1.80 (1H, m, H-8b), 1.65–1.52 (1H, m, H-9b), 1.49 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 169.9 (C-6), 168.1 (C-11), 152.3 (C-12), 142.3 (C-4), 134.0 (C-1), 130.0 (C-2), 128.9 (C-3), 83.2 (C-13), 48.5 (C-7), 46.5 (C-10), 37.6 (C-5), 27.9 (C-14), 25.3 (C-8), 21.5 (C-9); *m/z* (ESI) 389 $[MNa]^+$; [HRMS (ESI): calcd for $C_{18}H_{23}{}^{35}ClN_2NaO_4$, 389.1239. Found: $[MNa]^+$, 389.1239 (–0.1 ppm error)].

2-(Methylamino)benzonitrile (270)[224]



The title compound was prepared according to the procedure by González.[224] To a solution of 2-aminobenzonitrile (288 mg, 2.44 mmol) and pyridine (0.68 mL, 8.48 mmol) in dioxane (30 mL) at room temperature was added copper(II) acetate (1.10 g, 6.06 mmol). The mixture was stirred at room temperature for 15 min then methylboronic acid (362 mg, 6.06 mmol) added and the reaction heated to reflux for 4 h. After cooling, the mixture was filtered through a pad of celite and the solvent removed *in vacuo*. Flash column chromatography [0–15% EtOAc/PE] afforded **270** (131 mg, 41%) as a colourless microcrystalline solid, mp 61–62 °C (lit[284] 62–64 °C); R_f (1:4 EtOAc:PE) = 0.40; δ_H (400 MHz, $CDCl_3$) 7.41 (1H, ddd, *J* = 8.5, 7.5, 1.5, H-5), 7.38 (1H, ddd, *J* = 7.5, 1.5, 0.5, H-3), 6.67 (1H, td, *J* = 7.5, 1.0, H-4), 6.65 (1H, br d, *J* = 8.5, H-6), 4.64 (1H, br s, NH), 2.92 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 151.1 (C-7), 134.3 (C-5), 132.6 (C-3), 118.0 (C-1), 116.3 (C-4), 110.0 (C-6), 95.5 (C-2), 30.0 (C-8). Data consistent with the literature values.[224,284]

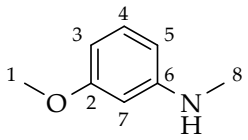
***tert*-Butyl 3-(methyl(4-(trifluoromethyl)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20o)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 456 mg), 4-(trifluoromethyl)-*N*-methylaniline (0.29 mL, 2.06 mmol), 2-chloro-1-methylpyridinium iodide (718 mg, 2.81 mmol) and triethylamine (1.31 mL, 9.38 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column

chromatography [1:1 EtOAc:PE] afforded **20o** (622 mg, 80% over 2 steps) as a colourless powder, mp 103–105 °C; R_f (1:1 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3073, 2979, 2938, 1768, 1718, 1662, 1612, 1517, 1477, 1459; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* = 8.0, H-2), 7.52 (2H, d, *J* = 8.0, H-3), 3.62 (2H, dd, *J* = 7.5, 4.5, H-10), 3.40 (1H, dd, *J* = 10.0, 7.0, H-7), 3.32 (3H, s, H-5), 2.25–2.13 (1H, m, H-8a), 2.02–1.94 (1H, m, H-9a), 1.91–1.80 (1H, m, H-8b), 1.66–1.54 (1H, m, H-9b), 1.50 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 169.7 (C-6), 168.0 (C-11), 152.2 (C-12), 146.9 (C-4), 130.0 (q, *J* = 33.0, C-1), 127.9 (C-3), 127.0 (C-2), 123.5 (q, *J* = 272.5, C-15), 83.2 (C-13), 48.6 (C-7), 46.5 (C-10), 37.6 (C-5), 27.9 (C-14), 25.3 (C-8), 21.4 (C-9); δ_F (376 MHz, $CDCl_3$) −62.5 (3F); *m/z* (ESI) 423 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{23}F_3N_2NaO_4$, 423.1502. Found: $[MNa]^+$, 423.1509 (−1.5 ppm error)].

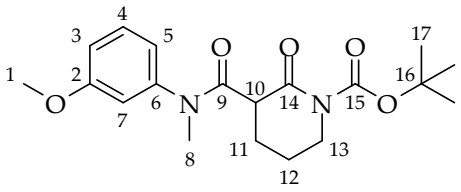
3-Methoxy-*N*-methylaniline (275)[225]



The title compound was prepared according to the procedure by Teichert.[225] To a suspension of NaOMe (2.18 g, 40.6 mmol) in MeOH (12 mL) at room temperature was added 3-methoxyaniline (0.91 mL, 8.12 mmol). The resulting brown suspension was poured into a suspension of paraformaldehyde (340 mg, 11.4 mmol) in MeOH (8 mL). The mixture was stirred at room temperature for 6 h. Sodium borohydride (306 mg, 8.12 mmol) was added slowly and the reaction heated to reflux for 2 h then stirred at room temperatre for 12 h. The reaction was quenched with aq. NaOH (2 M, 10 mL) and H_2O (10 mL), and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [1:4 EtOAc:PE] afforded **275** (707 mg, 76%) as a brown liquid, R_f (1:4 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3411, 2991, 2934, 2904, 2834, 2810, 1616, 1512, 1499, 1463; δ_H (400 MHz, $CDCl_3$) 7.10 (1H, t, *J* = 8.0, H-4), 6.29 (1H, ddd, *J* = 8.0, 2.5, 0.5, H-3), 6.24 (1H, ddd, *J* = 8.0, 2.5, 0.5, H-5), 6.17 (1H, t, *J* = 2.5, H-7), 3.79 (3H, s, H-1), 2.83 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 160.8 (C-2), 150.7 (C-6), 129.9 (C-4), 105.7 (C-5), 102.3 (C-3), 98.3 (C-7), 55.1 (C-1), 30.7 (C-8); *m/z* (ESI) 138 $[MH]^+$; [HRMS (ESI): calcd for $C_8H_{12}NO$,

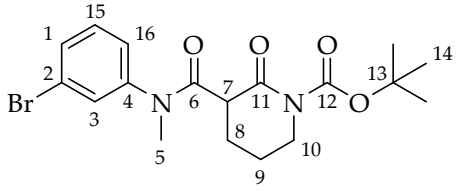
138.0913. Found: [MH]$^+$, 138.0916 (−2.1 ppm error)]. NMR data consistent with the literature values.[285]

***tert*-Butyl 3-((3-methoxyphenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20p)**



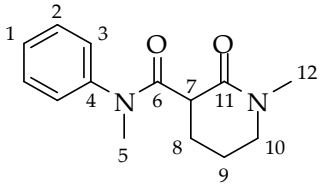
1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 456 mg), 3-methoxy-*N*-methylaniline (290 mg, 2.12 mmol), 2-chloro-1-methylpyridinium iodide (737 mg, 2.89 mmol) and triethylamine (1.34 mL, 9.63 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [1:1 EtOAc:PE] afforded **20p** (532 mg, 76% over 2 steps) as an off-white sticky oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3065, 2977, 2939, 2839, 1768, 1717, 1657, 1600, 1489, 1458; δ_H (400 MHz, $CDCl_3$) 7.29 (1H, t, *J* = 8.0, H-4), 6.94–6.86 (3H, m, H-3, H-5, H-7), 3.80 (3H, s, H-1), 3.63-3.58 (2H, m, H-13), 3.48 (1H, dd, *J* = 10.5, 7.0, H-10), 3.29 (3H, s, H-8), 2.21–2.11 (1H, m, H-11a), 2.00–1.92 (1H, m, H-12a), 1.91–1.80 (1H, m, H-11b), 1.65–1.52 (1H, m, H-12b), 1.49 (9H, s, H-17); δ_C (100 MHz, $CDCl_3$) 170.0 (C-9), 168.3 (C-14), 160.5 (C-2), 152.6 (C-15), 144.9 (C-6), 130.5 (C-4), 119.3 (C-5), 114.1 (C-3), 112.7 (C-7), 83.0 (C-16), 55.4 (C-1), 48.7 (C-10), 46.5 (C-13), 37.5 (C-8), 27.9 (C-17), 25.5 (C-11), 21.6 (C-12); *m/z* (ESI) 385 [MNa]$^+$; [HRMS (ESI): calcd for $C_{19}H_{26}N_2NaO_5$, 385.1734. Found: [MNa]$^+$, 385.1735 (−0.4 ppm error)].

***tert*-Butyl 3-((3-bromophenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20q)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 416 mg), *N*-methyl-3-bromoaniline (350 mg, 1.88 mmol), 2-chloro-1-methylpyridinium iodide (655 mg, 2.57 mmol) and triethylamine (1.19 mL, 8.56 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **20q** (296 mg, 42% over 2 steps) as a colourless amorphous solid, mp 113–115 °C; R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (neat) 3062, 2977, 2934, 1768, 1717, 1660, 1587, 1569, 1476; δ_H (400 MHz, $CDCl_3$) 7.52–7.48 (2H, m, H-1, H-16), 7.35 (1H, br s, H-3), 7.31–7.28 (1H, m, H-15), 3.62 (2H, dd, *J* = 7.5, 4.5, H-10), 3.42 (1H, dd, *J* = 10.5, 7.0, H-7), 3.29 (3H, s, H-5), 2.23–2.12 (1H, m, H-8a), 2.02–1.94 (1H, m, H-9a), 1.92–1.83 (1H, m, H-8b), 1.67–1.59 (1H, m, H-9b), 1.51 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 169.8 (C-6), 168.1 (C-11), 152.4 (C-12), 145.0 (C-4), 131.4 (C-15), 131.1, 130.5 (C-1, C-16), 126.4 (C-3), 123.0 (C-2), 83.2 (C-13), 48.6 (C-7), 46.5 (C-10), 37.7 (C-5), 27.9 (C-14), 25.4 (C-8), 21.5 (C-9); *m/z* (ESI) 433, 435 $[MNa]^+$; [HRMS (ESI): calcd for $C_{18}H_{23}{}^{79}BrN_2NaO_4$, 433.0733. Found: $[MNa]^+$, 433.0724 (2.2 ppm error)]; [Found C, 52.27%; H, 5.57%; N, 6.60%. $C_{18}H_{23}BrN_2O_4$ requires C, 52.56%; H, 5.64%; N, 6.81%].

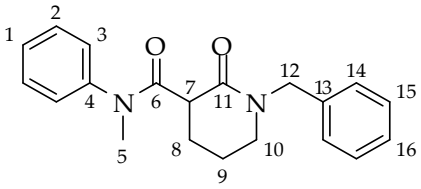
_N_,1-dimethyl-2-oxo-_N_-phenylpiperidine-3-carboxamide (20r)



1-Methyl-2-oxopiperidine-3-carboxylic acid (**264r**, 291 mg), *N*-methylaniline (0.22 mL, 2.04 mmol), 2-chloro-1-methylpyridinium iodide (708 mg, 2.78 mmol) and triethylamine (1.29 mL, 9.25 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [0–10% MeOH/EtOAc] afforded **20r** (472 mg, quant. over 2 steps) as an off-white microcrystalline solid, mp 113–115 °C; R_f (EtOAc) = 0.10; ν_{max}/cm^{-1} (thin film) 3058, 2942, 2871, 1654, 1634, 1594, 1496; δ_H (400 MHz, $CDCl_3$) 7.41–7.25 (5H, m, H-1, H-2, H-3), 3.40–3.32 (2H, m, H-7, H-10a), 3.28 (3H, s, H-5), 3.13 (1H, dddd, *J* = 12.0, 5.0, 4.0, 1.5, H-10b), 2.89 (3H, s, H-12), 2.11 (1H, dddd, *J* = 13.0, 12.0, 10.0, 3.0, H-8a), 1.98–1.90 (1H, m, H-9a), 1.84–1.76 (1H, m, H-8b), 1.60–1.48 (1H, m, H-9b); δ_C (100 MHz, $CDCl_3$) 171.1 (C-6), 167.0 (C-11), 144.1

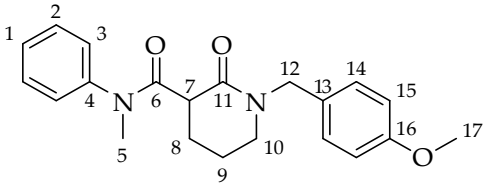
(C-4), 129.7 (C-2), 127.7 (C-1), 127.5 (C-3), 49.7 (C-10), 45.9 (C-7), 37.5 (C-5), 34.8 (C-12), 25.7 (C-8), 21.3 (C-9); *m/z* (ESI) 269 $[MNa]^+$; [HRMS (ESI): calcd for $C_{14}H_{18}N_2NaO_2$, 269.1260. Found: $[MNa]^+$, 269.1258 (0.9 ppm error)].

1-Benzyl-*N*-methyl-2-oxo-*N*-phenylpiperidine-3-carboxamide (20s)



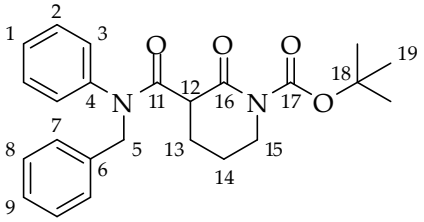
1-Benzyl-2-oxopiperidine-3-carboxylic acid (**264s**, 580 mg), *N*-methylaniline (0.30 mL, 2.74 mmol), 2-chloro-1-methylpyridinium iodide (952 mg, 3.73 mmol) and triethylamine (1.73 mL, 12.45 mmol) in CH_2Cl_2 (20 mL) were reacted according to general procedure E. Flash column chromatography [50–75% EtOAc/PE] afforded **20s** (770 mg, 92% over 2 steps) as a pale yellow oil which crystallised on standing, mp 84–86 °C; R_f (1:1 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3064, 3037, 2963, 2935, 2874, 1735, 1632, 1595, 1494; δ_H (400 MHz, $CDCl_3$) 7.46–7.21 (10H, m, H-1, H-2, H-3, H-14, H-15, H-16), 4.63 (1H, d, *J* = 15.0, H-12a), 4.54 (1H, d, *J* = 15.0, H-12b), 3.47 (1H, dd, *J* = 9.0, 6.5, H-7), 3.34 (3H, s, H-5), 3.28 (1H, ddd, *J* = 12.0, 10.0, 4.5, H-10a), 3.12–3.06 (1H, m, H-10b), 2.12 (1H, dddd, *J* = 12.5, 11.5, 9.0, 3.0, H-8a), 1.99–1.91 (1H, m, H-9a), 1.84 (1H, dddd, *J* = 12.5, 6.5, 3.0, 1.0, H-8b), 1.58–1.47 (1H, m, H-9b); δ_C (100 MHz, $CDCl_3$) 171.3 (C-6), 167.3 (C-11), 144.1 (C-4), 136.8 (C-13), 129.8, 128.6, 127.8, 127.8, 127.6, 127.2 (C-1, C-2, C-3, C-14, C-15, C-16), 50.3 (C-12), 47.1 (C-10), 46.0 (C-7), 37.6 (C-5), 25.9 (C-8), 21.3 (C-9); *m/z* (ESI) 345 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{22}N_2NaO_2$, 345.1573. Found: $[MNa]^+$, 345.1576 (–0.7 ppm error)].

1-(4-Methoxybenzyl)-*N*-methyl-2-oxo-*N*-phenylpiperidine-3-carboxamide (20t)



1-(4-Methoxybenzyl)-2-oxopiperidine-3-carboxylic acid (**264t**, 474 mg), *N*-methylaniline (0.21 mL, 1.98 mmol), 2-chloro-1-methylpyridinium iodide (689 mg, 2.70 mmol) and triethylamine (1.25 mL, 9.00 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [50–75% EtOAc/PE] afforded **20t** (578 mg, 81% over 2 steps) as an off-white crystalline solid, mp 141–143 °C; R_f (1:1 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (thin film) 3059, 3035, 2936, 2868, 2836, 1656, 1635, 1595, 1512, 1495, 1463; δ_H (400 MHz, $CDCl_3$) 7.45–7.32 (5H, m, H-1, H-2, H-3), 7.17 (2H, d, *J* = 8.5, H-14), 6.83 (2H, d, *J* = 8.5, H-15), 4.56 (1H, d, *J* = 14.5, H-12a), 4.46 (1H, d, *J* = 14.5, H-12b), 3.77 (3H, s, H-17), 3.45 (1H, dd, *J* = 9.0, 6.5, H-7), 3.33 (3H, s, H-5), 3.24 (1H, ddd, *J* = 12.0, 10.0, 4.5, H-10a), 3.10–3.03 (1H, m, H-10b), 2.09 (1H, dddd, *J* = 12.5, 11.5, 9.0, 3.0, H-8a), 1.97–1.88 (1H, m, H-9a), 1.85–1.77 (1H, m, H-8b), 1.55–1.44 (1H, m, H-9b); δ_C (100 MHz, $CDCl_3$) 171.4 (C-6), 167.1 (C-11), 158.8 (C-16), 144.1 (C-4), 129.8 (C-2), 129.2 (C-14), 128.9 (C-13), 127.8 (C-1), 127.5 (C-3), 113.9 (C-15), 55.2 (C-17), 49.7 (C-12), 46.8 (C-10), 46.0 (C-7), 37.6 (C-5), 25.8 (C-8), 21.3 (C-9); *m/z* (ESI) 353 $[MH]^+$; [HRMS (ESI): calcd for $C_{21}H_{25}N_2O_3$, 353.1860. Found: $[MH]^+$, 353.1859 (0.3 ppm error)].

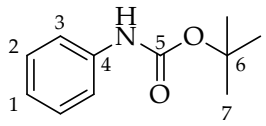
***tert*-Butyl 3-(benzyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20u)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 483 mg), *N*-benzyl-*N*-phenylamine (401 mg, 2.19 mmol), 2-chloro-1-methylpyridinium iodide (760 mg, 2.98 mmol) and triethylamine (1.38 mL, 9.94 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **20u** (647 mg, 77% over 2 steps) as a colourless oil which crystallised on standing, mp 95–97 °C; R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (neat) 3062, 3031, 2979, 2936, 1768, 1714, 1659, 1595, 1495, 1480, 1455; δ_H (400 MHz, $CDCl_3$) 7.38–7.19 (10H, m, H-1, H-2, H-3, H-7, H-8, H-9), 5.01 (1H, d, *J* = 14.5, H-5a), 4.85 (1H, d, *J* = 14.5, H-5b), 3.61 (2H, dd, *J* = 8.5, 4.5, H-15), 3.42 (1H, dd, *J* = 10.5, 7.0, H-12), 2.20 (1H, dddd, *J* = 13.5, 11.5, 10.5, 4.0, H-13a), 2.01–1.93 (1H, m, H-14a), 1.92–1.84 (1H, m, H-13b), 1.63–1.52 (1H,

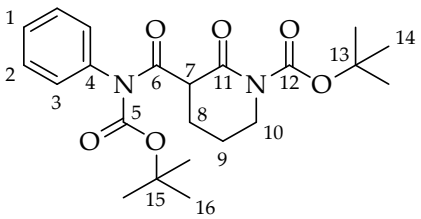
m, H-14b), 1.50 (9H, s, H-19); δ_C (100 MHz, $CDCl_3$) 170.2 (C-11), 168.2 (C-16), 152.2 (C-17), 142.0 (C-4), 136.9 (C-6), 129.6, 128.5, 128.3, 128.2, 127.2 (five of C-1, C-2, C-3, C-7, C-8, C-9), 83.0 (C-18), 53.2 (C-5), 48.8 (C-12), 46.5 (C-15), 27.9 (C-19), 25.4 (C-13), 21.5 (C-14), one aromatic peak not visible due to broadening; *m/z* (ESI) 431 $[MNa]^+$; [HRMS (ESI): calcd for $C_{24}H_{22}N_2NaO_4$, 431.1941. Found: $[MNa]^+$, 431.1935 (2.5 ppm error)].

tert-Butyl phenylcarbamate (279)[229]



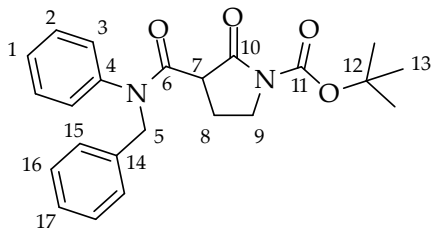
The title compound was prepared based on the procedure by Peterson.[229] To a suspension of aniline (1.0 mL, 11.0 mmol) and potassium carbonate (3.07 g, 22.2 mmol) in THF:H_2O (1:1, 50 mL) was added di-*tert*-butyl dicarbonate (2.87, 13.2 mmol) and the mixture stirred at room temperature for 7 h. The mixture was separated and the aqueous phase extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [10–20% EtOAc/hexane] afforded **279** (1.98, 94%) as a colourless microcrystalline solid, mp 132–134 °C (lit[286] 132–133 °C); R_f (1:4 EtOAc:PE) = 0.50; δ_H (400 MHz, $CDCl_3$) 7.38–7.26 (4H, m, H-2, H-3), 7.05–7.00 (1H, m, H-1), 1.51 (9H, s, H-7); δ_C (100 MHz, $CDCl_3$) 152.7 (C-5), 138.3 (C-4), 129.0 (C-2), 123.0 (C-1), 118.5 (C-3), 80.5 (C-6), 28.3 (C-7). Data consistent with the literature values.[286,287]

***tert*-Butyl 3-(*tert*-butoxycarbonyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20v)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 369 mg), *tert*-butyl phenylcarbamate (**279**, 322 mg, 1.67 mmol), 2-chloro-1-methylpyridinium iodide (581 mg, 2.28 mmol) and triethylamine (1.06 mL, 7.59 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [33–50% EtOAc/PE afforded **20v** (390 mg, 61% over 2 steps) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (neat) 3064, 3040, 2978, 2937, 1771, 1729, 1723, 1717, 1597, 1492, 1476, 1457; δ_H (400 MHz, $CDCl_3$) 7.40–7.35 (2H, m, H-2), 7.33–7.28 (1H, m, H-1), 7.20–7.16 (2H, m, H-3), 4.63 (1H, dd, *J* = 11.0, 7.0, H-7), 3.79 (1H, ddd, *J* = 13.5, 9.0, 4.5, H-10a), 3.74–3.65 (1H, m, H-10b), 2.33–2.10 (2H, m, H-8), 2.04–1.78 (2H, m, H-9), 1.52 (9H, s, H-14), 1.33 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 172.5 (C-6), 168.5 (C-11), 152.9 (C-5), 152.4 (C-12), 138.8 (C-4), 128.8 (C-2), 128.2 (C-3), 127.7 (C-1), 83.4, 83.0 (C-13, C-15), 52.4 (C-7), 45.9 (C-10), 28.0 (C-14), 27.7 (C-16), 24.2 (C-8), 21.6 (C-9); *m/z* (ESI) 441 [MNa]$^+$; [HRMS (ESI): calcd for $C_{22}H_{30}N_2NaO_6$, 441.1996. Found: [MNa]$^+$, 441.1996 (0.1 ppm error)].

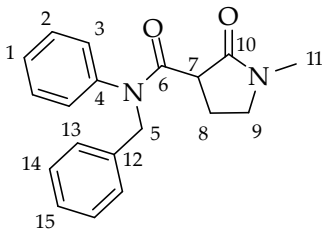
***tert*-Butyl 3-(benzyl(phenyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (20w)**



1-(*tert*-Butoxycarbonyl)-2-oxopyrrolidine-3-carboxylic acid (**264a**, 344 mg), *N*-benzylaniline (302 mg, 1.65 mmol), 2-chloro-1-methylpyridinium iodide (574 mg, 2.25 mmol) and triethylamine (1.05 mL, 7.50 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [1:2 EtOAc:PE] afforded **20w** (379 mg, 64% over 2 steps) as a sticky yellow oil, R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3063, 3031, 2933, 1782, 1746, 1717, 1657, 1595, 1495, 1454; δ_H (400 MHz, $CDCl_3$) 7.34–7.19 (10H, m, H-1, H-2, H-3, H-15, H-16, H-17), 5.07 (1H, d, *J* = 14.5, H-5a), 4.81 (1H, d, *J* = 14.5, H-5b), 3.92 (1H, ddd, *J* = 10.5, 9.0, 4.0, H-9a), 3.53 (1H, t, *J* = 9.0, H-7), 3.52 (1H, dt, *J* = 10.5, 8.0, H-9b), 2.51 (1H, dtd, *J* = 13.0, 9.0, 8.0, H-8a), 1.98 (1H, dddd, *J*= 13.0, 9.0, 8.0, 4.0, H-8b), 1.50 (9H, s, H-13); δ_C (100 MHz, $CDCl_3$) 170.3 (C-10), 168.8 (C-6), 149.8 (C-11), 141.5 (C-4), 136.6 (C-14), 129.6, 128.5,

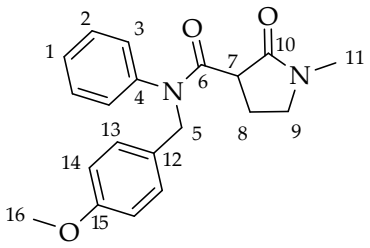
128.4 (three of C-2, C-3, C-15, C-16), 128.3, 127.3 (C-1, C-17), 83.0 (C-12), 53.4 (C-5), 47.6 (C-7), 44.9 (C-9), 27.9 (C-13), 22.1 (C-8), one aromatic peak not visible due to broadening; *m/z* (ESI) 417 $[MNa]^+$; [HRMS (ESI): calcd for $C_{23}H_{26}N_2NaO_4$, 417.1785. Found: $[MNa]^+$, 414.1786 (−0.4 ppm error)].

_N_-Benzyl-1-methyl-2-oxo-_N_-phenylpyrrolidine-3-carboxamide (20x)



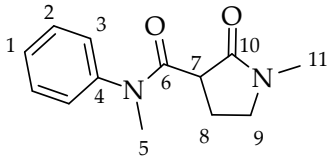
1-Methyl-2-oxopyrrolidine-3-carboxylic acid (**264x**, 226 mg), *N*-benzylaniline (319 mg, 1.74 mmol), 2-chloro-1-methylpyridinium iodide (605 mg, 2.37 mmol) and triethylamine (1.01 mL, 7.90 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [50–100% EtOAc/PE] afforded **20x** (472 mg, 94% over 2 steps) as an off-white microcrystalline solid, mp 176–178 °C; R_f (EtOAc) = 0.40; ν_{max}/cm^{-1} (thin film) 3062, 3033, 3007, 2988, 2959, 2931, 2879, 1686, 1650, 1593, 1560, 1496, 1455; δ_H (400 MHz, $CDCl_3$) 7.34–7.18 (10H, m, H-1, H-2, H-3, H-13, H-14, H-15), 5.03 (1H, d, *J* = 14.5, H-5a), 4.85 (1H, d, *J* = 14.5, H-5b), 3.50 (1H, td, *J* = 9.0, 4.0, H-9a), 3.43 (1h, dd, *J* = 9.0, 4.0, H-7), 3.22 (1H, ddd, *J* = 9.0, 8.5, 7.0, H-9b), 2.82 (4H, s, H-11), 2.53–2.44 (1H, m, H-8a), 2.00 (1H, dddd, *J* = 12.5, 9.0, 8.5, 4.0, H-8b); δ_C (100 MHz, $CDCl_3$) 171.2 (C-10), 170.5 (C-6), 141.9 (C-4), 137.0 (C-12), 129.4, 128.5, 128.4 (three of C-2, C-3, C-13, C-14), 128.0, 127.3 (C-1, C-15), 53.4 (C-5), 47.9 (C-9), 45.6 (C-7), 29.9 (C-11), 23.0 (C-8), one aromatic peak not visible due to broadening; *m/z* (ESI) 309 $[MH]^+$, 331 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{21}N_2O_2$, 309.1598. Found: $[MH]^+$, 309.1590 (2.3 ppm error)].

_N_-(4-Methoxybenzyl)-1-methyl-2-oxo-_N_-phenylpyrrolidine-3-carboxamide (20y)



1-Methyl-2-oxopyrrolidine-3-carboxylic acid (**264x**, 226 mg), *N*-(4-methoxybenzyl)aniline (370 mg, 1.74 mmol), 2-chloro-1-methylpyridinium iodide (605 mg, 2.37 mmol) and triethylamine (1.01 mL, 7.90 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [50–100% EtOAc/PE] afforded **20y** (480 mg, 87% over 2 steps) as an off-white powder, mp 126–128 °C; R_f (EtOAc) = 0.20; ν_{max}/cm^{-1} (thin film) 3060, 3037, 2997, 2932, 2885, 2836, 1690, 1649, 1613, 1594, 1512, 1495, 1454; δ_H (400 MHz, $CDCl_3$) 7.35–7.10 (5H, m, H-1, H-2, H-3), 7.13 (2H, d, *J* = 8.5, H-13), 6.78 (2H, d, *J* = 8.5, H-14), 4.96 (1H, d, *J* = 14.5, H-5a), 4.79 (1H, d, *J* = 14.5), 3.75 (3H, s, H-16), 3.48 (1H, td, *J* = 9.0, 4.0, H-9a), 3.39 (1H, dd, *J* = 9.0, 7.0, H-7), 3.21 (1H, ddd *J* = 9.0, 8.5, 7.0, H-9b), 2.82 (3H, s, H-11), 2.47 (1H, ddt, *J* = 13.0, 9.0, 7.0, H-8a), 1.99 (1H, dddd, *J* = 13.0, 9.0, 8.5, 4.0, H-8b); δ_C (100 MHz, $CDCl_3$) 171.2 (C-10), 170.3 (C-6), 158.8 (C-15), 141.8 (C-4), 129.9 (C-13), 129.4 (C-2), 129.1 (C-12), 128.8, 128.0 (C-1, C-3), 113.7 (C-14), 55.1 (C-16), 52.7 (C-5), 47.9 (C-9), 45.6 (C-7), 29.8 (C-11), 23.0 (C-8); *m/z* (ESI) 339 $[MH]^+$, 361 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{23}N_2O_3$, 339.1703. Found: $[MH]^+$, 339.1701 (0.7 ppm error)].

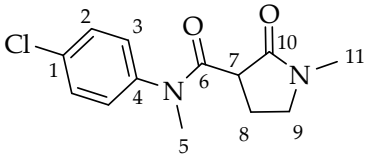
_N_,1-Dimethyl-2-oxo-_N_-phenylpyrrolidine-3-carboxamide (20z)



1-Methyl-2-oxopyrrolidine-3-carboxylic acid (**264x**, 646 mg), *N*-methylaniline (0.55 mL, 5.04 mmol), 2-chloro-1-methylpyridinium iodide (1.79 g, 7.00 mmol) and triethylamine (3.29 mL, 23.6 mmol) in CH_2Cl_2 (100 mL) were reacted according to general procedure

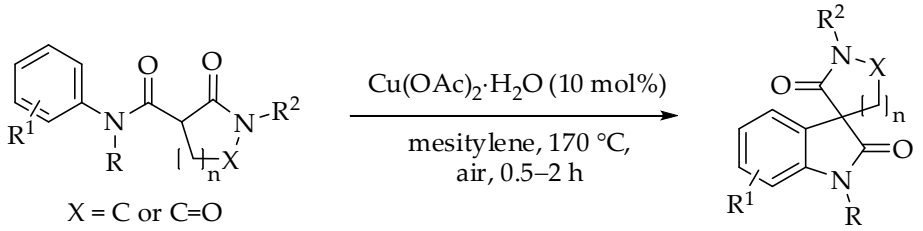
E. Flash column chromatography [49:1 EtOAc:MeOH] afforded **20z** (810 mg, 74% over 2 steps) as an off-white microcrystalline solid, mp 120–122 °C; R_f (EtOAc) = 0.20; ν_{max}/cm^{-1} (thin film) 2988, 2941, 2889, 1686, 1638, 1592, 1497, 1450; δ_H (400 MHz, $CDCl_3$) 7.44–7.30 (5H, m, H-1, H-2, H-3), 3.52–3.43 (2H, m, H-7, H-9a), 3.32 (3H, s, H-5), 3.25–3.18 (1H, m, H-9b), 2.82 (3H, s, H-11), 2.45 (1H, dq, *J* = 13.5, 7.0, H-8a), 2.04–1.94 (1H, m, H-8b); δ_C (100 MHz, $CDCl_3$) 171.3 (C-10), 170.4 (C-6), 143.6 (C-4), 129.7 (C-2), 127.9 (C-1), 127.7 (C-3), 47.9 (C-9), 45.3 (C-7), 37.7 (C-5), 29.8 (C-11), 23.1 (C-8); *m/z* (ESI) 255 [MNa]$^+$; [HRMS (ESI): calcd for $C_{13}H_{16}N_2NaO_2$, 255.1104. Found: [MNa]$^+$, 255.1101 (1.1 ppm error)].

_N_-(4-Chlorophenyl)-_N_,1-dimethyl-2-oxopyrrolidine-3-carboxamide (20za)



1-Methyl-2-oxopyrrolidine-3-carboxylic acid (**264x**, 235 mg), 4-chloro-*N*-methylaniline (0.14 mL, 1.81 mmol), 2-chloro-1-methylpyridinium iodide (629 mg, 2.47 mmol) and triethylamine (1.14 mL, 8.22 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [50–100% EtOAc/PE] afforded **20za** (303 mg, 67% over 2 steps) as an off-white amorphous solid, mp 96–98 °C; R_f (EtOAc) = 0.30; ν_{max}/cm^{-1} (thin film) 3055, 2949, 2884, 1686, 1654, 1591, 1491, 1453; δ_H (400 MHz, $CDCl_3$) 7.42–7.34 (4H, m, H-2, H-3), 3.47 (1H, td, *J* = 9.0, 4.0, H-9a), 3.42 (1H, dd, *J* = 9.0, 7.0, H-7), 3.27 (3H, s, H-5), 3.22 (1H, ddd, *J* = 9.0, 8.5, 7.0, H-9b), 2.80 (3H, s, H-11), 2.44 (1H, ddt, *J* = 13.0, 9.0, 7.0, H-8a), 1.97 (1H, dddd, *J* = 13.0, 9.0, 8.5, 4.0, H-8b); δ_C (100 MHz, $CDCl_3$) 171.0 (C-10), 170.1 (C-6), 142.0 (C-4), 133.7 (C-1), 129.8, 129.1 (C-2, C-3), 47.9 (C-9), 45.2 (C-7), 37.7 (C-5), 29.8 (C-11), 22.9 (C-8); *m/z* (ESI) 267, 269 [MH]$^+$, 289, 291 [MNa]$^+$; [HRMS (ESI): calcd for $C_{13}H_{16}{}^{35}ClN_2O_2$, 267.0895. Found: [MH]$^+$, 267.0899 (−1.4 ppm error)].

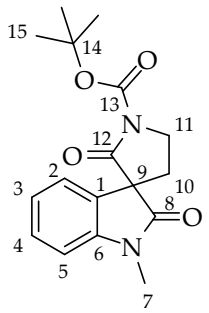
7.4.4 General procedure F – Cyclisation of anilides 20



20 **21**

To the linear amide **20** (1.0 eq) was added $Cu(OAc)_2 \cdot H_2O$ (0.1 eq) and mesitylene. A reflux condenser was fitted and the reaction carried out under an air atmosphere. The flask was lowered into an oil bath, pre-heated to 170 °C, and the reaction stirred at 170 °C for 0.5–2 h. After allowing to cool to room temperature, the solvent was removed *in vacuo*. The residue was loaded onto a silica column and eluted with an EtOAc/PE mixture to yield the spirooxindole **21**.

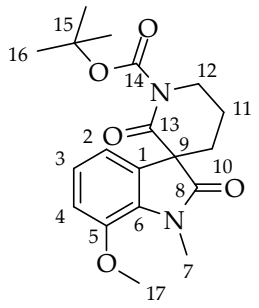
***tert*-Butyl 1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (21a)**



tert-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (**20a**, 127 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [1:3 EtOAc:PE] afforded a mixture of spirocycle **21a** and lactam **262a** (83 mg, corresponding to 73 mg of pure **21a**, 58%) as a colourless amorphous solid. A small sample of pure **21a** was isolated for full characterisation, mp 150–152 °C; R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3058, 2980, 2935, 1783, 1750, 1716, 1613, 1494, 1472; δ_H (400 MHz, $CDCl_3$) 7.33 (1H, td, *J* = 8.0, 1.0, H-4), 7.17 (1H, d, *J* = 7.5, 1.0, H-2), 7.08 (1H, td, *J* = 7.5, 1.0, H-3), 6.86 (1H, br d, *J* = 8.0, H-5), 4.18 (1H, ddd, *J* = 10.5,

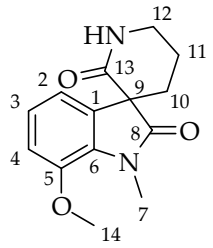
8.0, 7.0, H-11a), 3.98 (1H, ddd, *J* = 10.5, 8.5, 4.5, H-11b), 3.20 (3H, s, H-7), 2.62 (1H, ddd, *J* = 13.0, 8.0, 4.5, H-10a), 2.36 (1H, ddd, *J* = 13.0, 8.5, 7.0, H-10b), 1.53 (9H, s, H-15); δ_C (100 MHz, $CDCl_3$) 174.2 (C-8), 169.3 (C-12), 150.0 (C-13), 144.3 (C-6), 129.4 (C-4), 128.6 (C-1), 123.2, 123.1 (C-2, C-3), 108.6 (C-5), 83.6 (C-14), 59.4 (C-9), 44.1 (C-11), 28.1 (C-10), 27.9 (C-15), 26.5 (C-7); *m/z* (ESI) 339 $[MNa]^+$; [HRMS (ESI): calcd for $C_{17}H_{20}N_2NaO_4$, 339.1315. Found: $[MNa]^+$, 339.1318 (−0.9 ppm error)].

tert-Butyl 7-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21b)



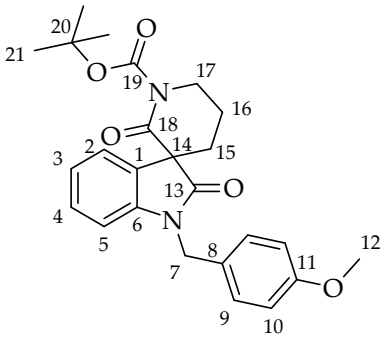
tert-Butyl 3-((2-methoxyphenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20b**, 139 mg, 0.38 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded a mixture of spirocycle **21b** and lactam **262b** (71 mg, corresponding to 67 mg of **21b**, 48%) as an off-white amorphous solid. A small sample of pure **21b** was isolated for full characterisation, mp 104–106 °C; R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (neat) 2977, 2939, 1768, 1718, 1613, 1598, 1493, 1473; δ_H (400 MHz, $CDCl_3$) 7.00 (1H, dd, *J* = 8.0, 7.5, H-3), 6.90–6.86 (2H, m, H-2, H-4), 3.89–3.83 (2H, m, H-12), 3.84 (3H, s, H-17), 3.49 (3H, s, H-7), 2.42–2.27 (2H, m, H-10a, H-11a), 2.14–1.96 (2H, m, H-10b, H-11b), 1.47 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.5 (C-8), 167.5 (C-13), 153.3 (C-14), 145.5 (C-5), 133.2 (C-1), 131.8 (C-6), 123.4 (C-3), 115.8 (C-2), 112.8 (C-4), 83.4 (C-15), 58.2 (C-9), 55.9 (C-17), 47.1 (C-12), 32.3 (C-10), 29.9 (C-7), 27.9 (C-16), 19.4 (C-11); *m/z* (ESI) 383 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{24}N_2NaO_5$, 383.1577. Found: $[MNa]^+$, 383.1569 (2.8 ppm error)].

7-Methoxy-1-methylspiro[indoline-3,3'-piperidine]-2,2'-dione (266b)



tert-Butyl 3-((2-methoxyphenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20b**, 143 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [1:4 EtOAc:PE → 1:9 MeOH:EtOAc] afforded **266b** (17 mg, 16%) as a pale brown amorphous solid, mp 184–188 °C; R_f (EtOAc) = 0.20; ν_{max}/cm^{-1} (neat) 3299, 3072, 2943, 1707, 1665, 1614, 1597, 1491, 1465 ; δ_H (400 MHz, $CDCl_3$) 7.00 (1H, dd, *J* = 8.0, 7.5, H-3), 6.91–6.86 (2H, m, H-2, H-4), 6.65 (1H, br s, NH), 3.84 (2H, s, H-14), 3.60–3.50 (2H, m, H-12), 3.50 (3H, s, H-7), 2.39–2.24 (2H, m, H-10a, H-11a), 2.08–1.94 (2H, m, H-10b, H-11b); δ_C (100 MHz, $CDCl_3$) 176.1 (C-8), 168.6 (C-13), 145.4 (C-5), 133.4 (C-1), 132.0 (C-6), 123.3 (C-3), 115.6 (C-2), 112.7 (C-4), 55.9 (C-14), 55.5 (C-9), 42.7 (C-12), 31.7 (C-10), 29.9 (C-7), 18.6 (C-11); *m/z* (ESI) 283 $[MNa]^+$; [HRMS (ESI): calcd for $C_{14}H_{16}N_2NaO_3$, 283.1053. Found: $[MNa]^+$, 293.1054 (−0.0 ppm error)].

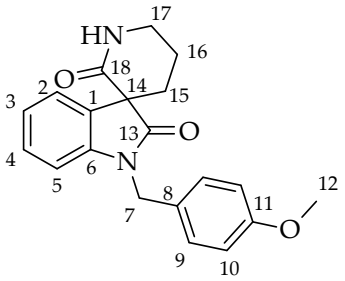
***tert*-Butyl 1-(4-methoxybenzyl)-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21c)**



tert-Butyl 3-((4-methoxybenzyl)(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20c**, 169 mg, 0.39 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in

mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] gave a mixture of spirocycle **21c** and lactam **262b** (88 mg, corresponding to 81 mg of **21c**, 48%) as an off-white powder. A small sample of pure **21c** was isolated for full characterisation, mp 164–166 °C; R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (neat) 3057, 2978, 2934, 1767, 1719, 1610, 1513, 1488, 1466; δ_H (400 MHz, $CDCl_3$) 7.30 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-2), 7.24 (2H, d, *J* = 9.0, H-9), 7.18 (1H, td, *J* = 7.5, 1.0, H-4), 7.01 (1H, td, *J* = 7.5, 1.0, H-3), 6.84 (2H, d, *J* = 9.0, H-10), 6.71 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-5), 4.87 (2H, d, *J* = 3.0, H-7), 3.93–3.89 (2H, m, H-17), 3.76 (3H, s, H-12), 2.46–2.33 (2H, m, H-15a, H-16a), 2.22–2.11 (1H, m, H-16b), 2.09–2.02 (1H, m, H-15b), 1.50 (9H, s, H-21); δ_C (100 MHz, $CDCl_3$) 175.6 (C-13), 167.5 (C-18), 159.0 (C-11), 152.9 (C-19), 143.0 (C-6), 131.9 (C-1), 128.8 (C-4), 128.4 (C-9), 127.3 (C-8), 123.1 (C-2), 122.8 (C-3), 114.2 (C-10), 109.8 (C-5), 83.5 (C-20), 58.2 (C-14), 55.2 (C-12), 47.2 (C-17), 43.3 (C-7), 32.1 (C-15), 27.9 (C-21), 19.5 (C-16); *m/z* (ESI) 459 [MNa]$^+$; [HRMS (ESI): calcd for $C_{25}H_{28}N_2NaO_5$, 459.1890. Found: [MNa]$^+$, 459.1896 (−1.4 ppm error)].

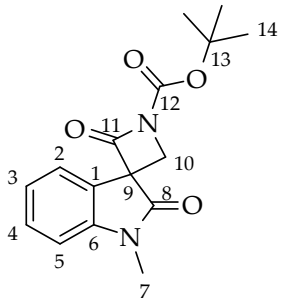
1-(4-Methoxybenzyl)spiro[indoline-3,3'-piperidine]-2,2'-dione (266c)



tert-Butyl 3-((4-methoxybenzyl)(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20c**, 169 mg, 0.39 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [1:4 EtOAc:PE → 1:9 MeOH:EtOAc] afforded **266c** (20 mg, 15%) as an off-white amorphous solid, mp 221–223 °C; R_f (1:1 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (neat) 3301, 3061, 2935, 1712, 1664, 1610, 1513, 1488, 1465; δ_H (400 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 7.5, 1.0, H-2), 7.25 (2H, d, *J* = 9.0, H-9), 7.18 (1H, td, *J* = 7.5, 1.0, H-4), 7.01 (1H, td, *J* = 7.5, 1.0, H-3), 6.84 (2H, d, *J* = 9.0, H-10), 6.72 (1H, d, *J* = 7.5, H-5), 6.64 (1H, br s, NH), 4.89 (2H, s, H-7), 3.76 (3H, s, H-12), 3.63–3.50 (2H, m, H-17), 2.42–2.30 (2H, m, H-15a, H-16a), 2.15–2.01 (2H, m, H-15b, H-16b); δ_C (100 MHz, $CDCl_3$) 176.2 (C-13), 168.4 (C-

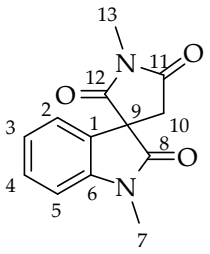
18), 158.9 (C-11), 143.2 (C-6), 132.2 (C-1), 128.6 (C-4), 128.3 (C-9), 127.5 (C-8), 122.9 (C-2), 122.7 (C-3), 114.1 (C-10), 109.6 (C-5), 55.5 (C-14), 55.2 (C-12), 43.2 (C-7), 42.8 (C-17), 31.4 (C-15), 18.8 (C-16); *m/z* (ESI) 359 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{20}N_2NaO_3$, 359.1366. Found: $[MNa]^+$, 359.1356 (2.9 ppm error)].

***tert*-Butyl 1'-methyl-2,2'-dioxospiro[azetidine-3,3'-indoline]-1-carboxylate (21d)**



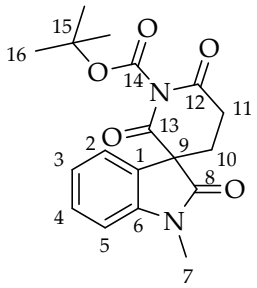
tert-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxoazetidine-1-carboxylate (**20d**, 88 mg, 0.29 mmol) and copper(II) acetate monohydrate (6 mg, 0.03 mmol) in mesitylene (6 mL) were reacted for 2 h according to general procedure F. Flash column chromatography [1:4 EtOAc:PE] afforded a mixture of spirocycle **21d** and lactam **262d** (25 mg, corresponding to 23 mg of pure **21d**, 26%) as a colourless oil, R_f (1:2 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3061, 2979, 2937, 1810, 1721, 1657, 1614, 1484, 1471; δ_H (400 MHz, $CDCl_3$) 7.37 (1H, td, *J* = 8.0, 1.0, H-4), 7.34 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-2), 7.11 (1H, td, *J* = 7.5, 1.0, H-3), 6.87 (1H, br d, *J* = 8.0, H-5), 4.11 (1H, d, *J* = 6.5, H-10a), 3.86 (1H, d, *J* = 6.5, H-10b), 3.23 (3H, s, H-7), 1.57 (9H, s, H-14); δ_C (100 MHz, $CDCl_3$) 170.9 (C-8), 160.5 (C-11), 147.5 (C-12), 144.4 (C-6), 130.1 (C-4), 129.9 (C-1), 123.4, 123.2 (C-2, C-3), 108.9 (C-5), 84.4 (C-13), 63.1 (C-9), 47.8 (C-10), 28.0 (C-14), 26.7 (C-7); *m/z* (ESI) 325 $[MNa]^+$; [HRMS (ESI): calcd for $C_{16}H_{18}N_2NaO_4$, 325.1159. Found: $[MNa]^+$, 325.1155 (1.2 ppm error)].

1,1'-Dimethylspiro[indoline-3,3'-pyrrolidine]-2,2',5'-trione (21f)



N,1-Dimethyl-2,5-dioxo-*N*-phenylpyrrolidine-3-carboxamide (**20f**, 98 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1.5 h according to general procedure F. Flash column chromatography [20–33% EtOAc/PE] afforded **21f** (68 mg, 70%) as an off-white amorphous solid, mp 156–159 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 2939, 1783, 1703, 1613, 1494, 1471; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, ddd, *J* = 8.0, 6.0, 3.0, H-4), 7.13–7.10 (1H, m, H-2, H-3), 6.93 (1H, br d, *J* = 8.0, H-5), 3.32 (1H, d, *J* = 18.0, H-10a), 3.27 (3H, s, H-7), 3.11 (3H, s, H-13), 2.97 (1H, d, *J* = 18.0, H-10b); δ_C (100 MHz, $CDCl_3$) 174.8, 173.4 (C-11, C-12), 173.2 (C-8), 144.5 (C-6), 130.0 (C-4), 127.4 (C-1), 123.6, 122.6 (C-2, C-3), 109.1 (C-5), 56.4 (C-9), 38.6 (C-10), 27.0 (C-7), 26.0 (C-13); *m/z* (ESI) 267 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{12}N_2NaO_3$, 267.0740. Found: $[MNa]^+$, 267.0738 (0.9 ppm error)].

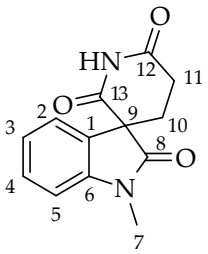
***tert*-Butyl 1-methyl-2,2',6'-trioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21g)**



tert-Butyl 3-(methyl(phenyl)carbamoyl)-2,6-dioxopiperidine-1-carboxylate (**20g**, 114 mg, 0.33 mmol) and copper(II) acetate monohydrate (7 mg, 0.035 mmol) in toluene (7 mL) were heated to 120 °C for 12 h. After cooling to room temperature, the solvent was removed *in vacuo*. Flash column chromatography [20–33% EtOAc/PE] afforded **21g** (51 mg, 45%) as an off-white amorphous solid, mp 122–123 °C; R_f (1:1 EtOAc:PE) =

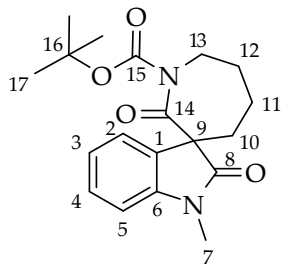
0.50; ν_{max}/cm^{-1} (thin film) 3061, 2982, 2938, 1781, 1735, 1693, 1613, 1495, 1472; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, td, *J* = 8.0, 1.0, H-4), 7.24 (1H, dd, *J* = 7.5, H-2), 7.13 (1H, td, *J* = 7.5, 1.0, H-3), 6.92 (1H, br d, *J* = 8.0, H-5), 3.40 (1H, ddd, *J* = 18.0, 9.0, 6.5, H-11a), 3.25 (3H, s, H-7), 2.87 (1H, dt, *J* = 18.0, 6.0, H-11b), 2.36–2.31 (2H, m, H-10), 1.54 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 172.5 (C-8), 169.3 (C-12), 166.8 (C-13), 148.2 (C-14), 143.8 (C-6), 129.9 (C-4), 127.8 (C-1), 123.6 (C-2), 123.4 (C-3), 109.1 (H-5), 86.8 (C-15), 54.8 (C-9), 27.8 (C-11), 27.4 (C-16), 26.7 (C-7), 26.6 (C-10); *m/z* (ESI) 367 $[MNa]^+$; [HRMS (ESI): calcd for $C_{18}H_{20}N_2NaO_5$, 367.1264. Found: $[MNa]^+$, 367.1262 (0.6 ppm error)].

1-Methylspiro[indoline-3,3'-piperidine]-2,2',6'-trione (266g)



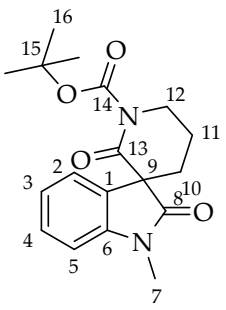
tert-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20g**, 132 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [1:2 EtOAc:PE → 3:17 MeOH:EtOAc] afforded **266g** (39 mg, 42%) as a pale brown amorphous solid, mp 220 °C - decomposition; R_f (1:1 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3211, 3097, 1725, 1697, 1611, 1495, 1471, 1451; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, br s, NH), 7.40 (1H, td, *J* = 8.0, 1.0, H-4), 7.21 (1H, dd, *J* = 7.5, 1.0, H-2), 7.13 (1H, td, *J* = 7.5, 1.0, H-3), 6.93 (1H, br d, *J* = 8.0, H-5), 3.34 (1H, ddd, *J* = 18.0, 9.5, 6.0, H-11a), 3.26 (3H, s, H-7), 2.83 (1H, dt, *J* = 18.0, 6.0, H-10b), 2.42–2.28 (2H, m, H-10); δ_C (100 MHz, $CDCl_3$) 172.9 (C-8), 171.5 (C-12), 168.7 (C-13), 143.9 (C-6), 129.8 (C-4), 128.1 (C-1), 123.4, 123.4 (C-2, C-3), 109.1 (C-5), 54.9 (C-9), 27.7 (C-11), 27.5 (C-10), 26.7 (C-7); *m/z* (ESI) 267 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{12}N_2NaO_3$, 267.0740. Found: $[MNa]^+$, 267.0740 (−0.1 ppm error)].

tert-Butyl 1'-methyl-2,2'-dioxospiro[azepane-3,3'-indoline]-1-carboxylate (21h)



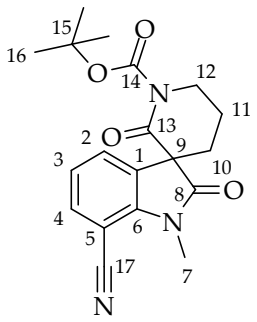
tert-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxoazepane-1-carboxylate (**20h**, 99 mg, 0.29 mmol) and copper(II) acetate monohydrate (6 mg, 0.03 mmol) in mesitylene (6 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–33% EtOAc/PE] afforded **21h** (63 mg, 64%) as an off-white amorphous solid, mp 139–141 °C; R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (neat) 3056, 2977, 2935, 1762, 1710, 1610, 1494, 1472; δ_H (400 MHz, $CDCl_3$) 7.30 (1H, td, _J_ = 8.0, 1.0, H-4), 7.26–7.23 (1H, m, H-2), 7.07 (1H, td, _J_ = 7.5, 1.0, H-3), 6.84 (1H, d, _J_ = 8.0, H-5), 4.23 (1H, ddd, _J_ = 14.5, 9.0, 2.5, H-13a), 3.93 (1H, ddd, _J_ = 14.5, 7.0, 2.5, H-13b), 3.22 (3H, s, H-7), 2.25–1.80 (6H, m, H-10, H-11, H-12), 1.45 (9H, s, H-17); δ_C (100 MHz, $CDCl_3$) 174.7 (C-8), 173.4 (C-14), 153.3 (C-15), 143.0 (C-6), 133.1 (C-1), 128.6 (C-4), 123.4 (C-2), 122.9 (C-3), 108.5 (C-5), 82.6 (C-16), 62.5 (C-9), 43.0 (C-13), 33.1 (C-10), 27.9 (C-17), 26.5 (C-7), 26.4 (C-11), 21.8 (C-12); _m/z_ (ESI) 367 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{24}N_2NaO_4$, 367.1628. Found: $[MNa]^+$, 367.1631 (−0.7 ppm error)]; [Found C, 66.12%; H, 7.05%; N, 7.92%. $C_{19}H_{24}N_2O_4$ requires C, 66.26%; H, 7.02%; N, 8.13%].

tert-Butyl 1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21i)



tert-Butyl 3-(methyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20i**, 132 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–33% EtOAc/PE] afforded **20i** (74 mg, 56%) as an off-white powder, mp 132–134 °C; R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3058, 2979, 2937, 1768, 1720, 1610, 1494, 1471; δ_H (400 MHz, $CDCl_3$) 7.30–7.25 (2H, m, H-4, H-2), 7.03 (1H, td, *J* = 7.5, 1.0, H-3), 6.83 (1H, br d, *J* = 8.0, H-5), 3.89–3.80 (2H, m, H-12), 3.18 (3H, s, H-7), 2.37–2.27 (2H, m, H-10a, H-11a), 2.15–2.06 (1H, m, H-11b), 2.02–1.95 (1H, m, H-10b), 1.44 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.3 (C-8), 167.4 (C-13), 153.0 (C-14), 143.8 (C-6), 131.7 (C-1), 128.8 (C-4), 123.0 (C-2), 122.7 (C-3), 108.6 (C-5), 83.3 (C-15), 58.1 (C-9), 47.0 (C-12), 31.9 (C-10), 27.8 (C-16), 26.4 (C-7), 19.3 (C-11); *m/z* (ESI) 353 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{22}N_2NaO_4$, 353.1472. Found: [MNa]$^+$, 353.1475 (−0.9 ppm error)].

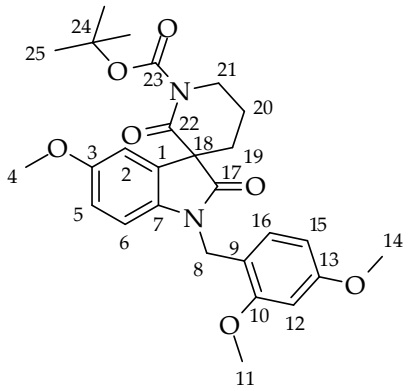
***tert*-Butyl 7-cyano-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21l)**



tert-Butyl 3-((2-cyanophenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20l**, 86 mg, 0.24 mmol) and copper(II) acetate monohydrate (5 mg, 0.025 mmol) in mesitylene (5 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded a mixture of spirocycle **21l** and lactam **262b** (20 mg, corresponding to 16 mg of pure **21l**, 19%) as off-white dendrites. A small sample of pure **21l** was isolated for full characterisation, mp 155–157 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 2979, 2941, 2226, 1768, 1725, 1598, 1475; δ_H (400 MHz, $CDCl_3$) 7.52 (1H, dd, *J* = 8.0, 1.0, H-4), 7.45 (1H, dd, *J* = 7.5, 1.0, H-2), 7.11 (1H, dd, *J* = 8.0, 7.5, H-3), 3.97–3.84 (2H, m, H-12), 3.59 (3H, s, H-7), 2.53–2.28 (2H, m,

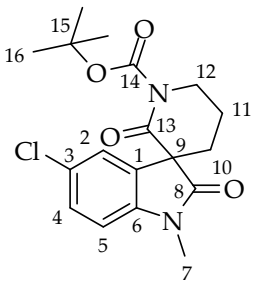
H-10a, H-11a), 2.12–2.00 (2H, m, H-10b, H-11b), 1.48 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.1 (C-8), 166.3 (C-13), 152.8 (C-14), 145.8 (C-6), 133.4 (C-1), 133.3 (C-4), 127.2 (C-2), 122.9 (C-3), 116.7 (C-17), 93.9 (C-5), 84.0 (C-15), 57.0 (C-9), 47.0 (C-12), 32.0 (C-10), 28.3 (C-7), 27.9 (C-16), 19.3 (C-11); *m/z* (ESI) 378 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{21}N_3NaO_4$, 378.1424. Found: $[MNa]^+$, 378.1406 (4.9 ppm error)].

***tert*-Butyl 1-(2,4-dimethoxybenzyl)-5-methoxy-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21m)**



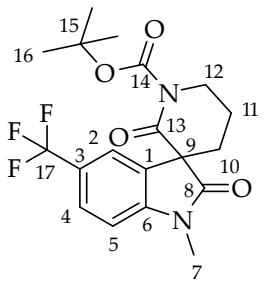
tert-Butyl 3-((2,4-dimethoxybenzyl)(4-methoxyphenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20m**, 175 mg, 0.35 mmol) and copper(II) acetate monohydrate (7 mg, 0.035 mmol) in mesitylene (7 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–50% EtOAc/PE] afforded **21m** (110 mg, 63%) as a pale yellow oil, R_f (1:1 EtOAc:PE) = 0.60; ν_{max}/cm^{-1} (thin film) 3079, 2975, 2938, 2837, 1768, 1718, 1614, 1592, 1508, 1497, 1458; δ_H (400 MHz, $CDCl_3$) 7.09 (1H, d, *J* = 8.5, H-16), 6.88 (1H, dd, *J* = 2.5, 0.5, H-2), 6.70 (1H, dd, *J* = 8.5, 2.5, H-5), 6.66 (1H, dd, *J* = 8.5, 0.5, H-6), 6.44 (1H, d, *J* = 2.5, H-12), 6.39 (1H, dd, *J* = 8.5, 2.5, H-15), 4.84 (2H, s, H-8), 3.90 (2H, t, *J* = 6.0, H-21), 3.84 (3H, s, H-11), 3.75 (3H, s, H-14), 3.74 (3H, s, H-4), 2.44–2.35 (2H, m, H-19a, H-20a), 2.16–2.01 (2H, m, H-19b, H-20b), 1.48 (9H, s, H-25); δ_C (100 MHz, $CDCl_3$) 175.3 (C-17), 167.5 (C-22), 160.2 (C-13), 157.9 (C-10), 155.8 (C-3), 152.9 (C-23), 136.7 (C-7), 133.0 (C-1), 128.9 (C-16), 115.7 (C-9), 112.7 (C-5), 110.9 (C-2), 110.0 (C-6), 104.3 (C-15), 98.3 (C-12), 83.4 (C-24), 58.6 (C-18), 55.8 (C-4), 55.3, 55.3 (C-11, C-14), 47.2 (C-21), 38.3 (C-8), 32.2 (C-19), 27.9 (C-25), 19.5 (C-20); *m/z* (ESI) 519 $[MNa]^+$; [HRMS (ESI): calcd for $C_{27}H_{32}N_2NaO_7$, 519.2102. Found: $[MNa]^+$, 519.2091 (2.0 ppm error)].

***tert*-Butyl 5-chloro-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21n)**



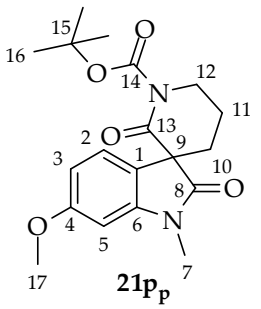
tert-Butyl 3-((4-chlorophenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20n**, 149 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [1:1 EtOAc:PE] afforded **21n** (92 mg, 62%) as a colourless microcrystalline solid, mp 133–135 °C; R_f (1:1 EtOAc:PE) = 0.45; ν_{max}/cm^{-1} (thin film) 3068, 2978, 2937, 1768, 1721, 1608, 1491; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, dd, *J* = 8.0, 2.0, H-4), 7.26 (1H, d, *J* = 2.0, H-2), 6.78 (1H, d, *J* = 8.0, H-5), 3.90–3.86 (2H, m, H-12), 3.20 (3H, s, H-7), 2.44–2.29 (2H, m, H-10a, H-11a), 2.14–1.97 (2H, m, H-10b, H-11b), 1.48 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 174.9 (C-8), 166.8 (C-13), 152.9 (C-14), 142.5 (C-6), 133.2 (C-1), 128.8 (C-4), 128.0 (C-3), 123.7 (C-2), 109.5 (C-5), 83.7 (C-15), 58.2 (C-9), 47.0 (C-12), 31.9 (C-10), 27.9 (C-16), 26.7 (C-7), 19.4 (C-11); *m/z* (ESI) 387, 389 $[MNa]^+$; [HRMS (ESI): calcd for $C_{18}H_{21}{}^{35}ClN_2NaO_4$, 387.1082. Found: $[MNa]^+$, 387.1066 (4.1 ppm error)].

***tert*-Butyl 1-methyl-2,2'-dioxo-5-(trifluoromethyl)spiro[indoline-3,3'-piperidine]-1'-carboxylate (21o)**

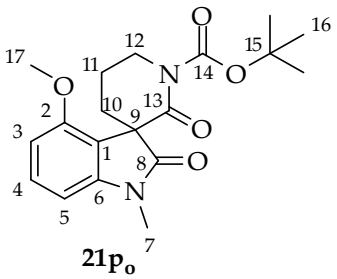


tert-Butyl 3-(methyl(4-(trifluoromethyl)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20o**, 160 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded a mixture of spirocycle **21o** and lactam **262b** (59 mg, corresponding to 51 mg of pure **21o**, 32%) as off-white dentrites. A small sample of pure **21o** was isolated for full characterisation, mp 142–144 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3077, 2980, 2939, 1770, 1723, 1621, 1507, 1476, 1451; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, br d, *J* = 8.0, H-4), 7.50–7.49 (1H, m, H-2), 6.93 (1H, d, *J* = 8.0, H-5), 3.91 (2H, t, *J* = 6.0, H-12), 3.25 (3H, s, H-7), 2.49–2.30 (2H, m, H-10a, H-11a), 2.15–2.02 (2H, m, H-10b, H-11b), 1.48 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.3 (C-8), 166.7 (C-13), 152.8 (C-14), 147.0 (C-6), 132.3 (C-1), 126.8 (q, *J* = 4.0, C-4), 125.1 (q, *J* = 33.0, C-3), 124.2 (q, *J* = 271.5, C-17), 120.2 (q, *J* = 4.0, C-2), 108.4 (C-5), 83.8 (C-15), 58.0 (C-9), 47.0 (C-12), 31.9 (C-10), 27.9 (C-16), 26.8 (C-7), 19.5 (C-11); δ_F (376 MHz, $CDCl_3$) −61.3 (3F); *m/z* (ESI) 421 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{21}F_3N_2NaO_4$, 421.1346. Found: $[MNa]^+$, 421.1356 (−2.5 ppm error)].

***tert*-Butyl 6-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate ($21p_p$) and *tert*-butyl 4-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate ($21p_o$)**



$21p_p$

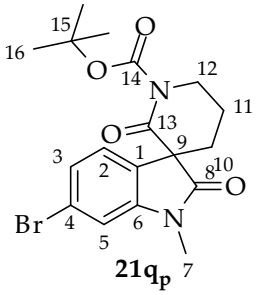


$21p_o$

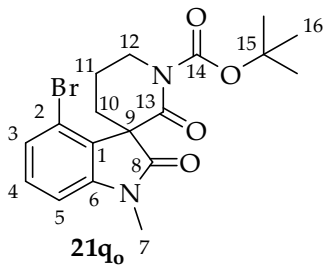
tert-Butyl 3-((3-methoxyphenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20p**, 143 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded **$21p_p$** (26 mg, 18%) as an off-white amorphous solid, as well as a mixture of spirocycle **$21p_o$** and lactam **262b**

(89 mg, corresponding to 82.5 mg of pure **21p$_o$**, 58%; a small sample of pure **21p$_o$** was isolated for full characterisation) as an off-white amorphous solid. **21p$_p$**: mp 145–147 °C; R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3075, 2977, 2938, 2840, 1768, 1723, 1623, 1507, 1473, 1457; δ_H (400 MHz, $CDCl_3$) 7.19 (1H, d, *J* = 8.5, H-2), 6.55 (1H, dd, *J* = 8.5, 2.5, H-3), 6.44 (1H, d, *J* = 2.5, H-5), 3.93–3.82 (2H, m, H-12), 3.82 (3H, s, H-17), 3.20 (3H, s, H-7), 2.37–2.29 (2H, m, H-10a, H-11a), 2.18–2.06 (1H, m, H-11b), 2.00–1.93 (1H, m, H-10b), 1.47 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.9 (C-8), 167.9 (C-13), 160.7 (C-4), 153.3 (C-14), 145.3 (C-6), 123.9 (C-1), 123.8 (C-2), 106.5 (C-3), 96.7 (C-5), 83.4 (C-15), 57.8 (C-9), 55.6 (C-17), 47.1 (C-12), 32.1 (C-10), 27.9 (C-16), 26.6 (C-7), 19.5 (C-11); *m/z* (ESI) 383 [MNa]$^+$; [HRMS (ESI): calcd for $C_{19}H_{24}N_2NaO_5$, 383.1577. Found: [MNa]$^+$, 383.1569 (2.3 ppm error)]; **21p$_o$**; mp 117–119 °C; R_f (1:1 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 2976, 2938, 1768, 1716, 1610, 1476; δ_H (400 MHz, $CDCl_3$) 7.25 (1H, dd, *J* = 8.5, 8.0, H-4), 6.61 (1H, d, *J* = 8.5, H-5), 6.49 (1H, dd, *J* = 8.0, 0.5, H-3), 4.03 (1H, dtd, *J* = 12.5, 4.5, 2.0, H-12a), 3.82 (3H, s, H-17), 3.71 (1H, ddd, *J* = 12.5, 11.0, 3.5, H-12b), 3.17 (3H, s, H-7), 2.58–2.47 (1H, m, H-11a), 2.43–2.36 (1H, m, H-10a), 2.07–1.94 (2H, m, H-10b, H-11b), 1.49 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.9 (C-8), 167.1 (C-13), 154.6 (C-2), 153.3 (C-14), 145.2 (C-6), 130.1 (C-4), 118.1 (C-1), 106.3 (C-5), 101.8 (C-3), 83.1 (C-15), 57.2 (C-9), 55.6 (C-17), 47.1 (C-12), 30.0 (C-10), 28.0 (C-16), 26.7 (C-7), 19.9 (C-11); *m/z* (ESI) 383 [MNa]$^+$; [HRMS (ESI): calcd for $C_{19}H_{24}N_2NaO_5$, 383.1577. Found: [MNa]$^+$, 383.1566 (3.0 ppm error)].

***tert*-Butyl 6-bromo-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21q$_p$) and *tert*-butyl 4-bromo-1-methyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21q$_o$)**



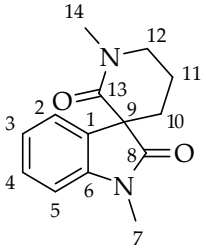
21q$_p$



21q$_o$

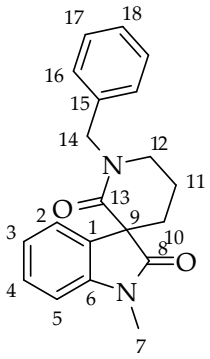
tert-Butyl 3-((3-bromophenyl)(methyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20q**, 69 mg, 0.17 mmol) and copper(II) acetate monohydrate (3.4 mg, 0.017 mmol) in mesitylene (3.4 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded a mixture of spirocycle **21q$_p$** and lactam **262b** (19 mg, corresponding to 18 mg of pure **21q$_p$**, 25%; a small sample of pure **21q$_p$** was isolated for full characterisation) as an off-white powder, as well as **21q$_o$** (30 mg, 44%) as off-white crystals (dendrites). **21q$_p$**: mp 171–173 °C; R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3068, 2978, 2937, 1768, 1722, 1603, 1493; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, dd, *J* = 8.0, 1.5, H-3), 7.15 (1H, d, *J* =8.0, H-2), 7.01 (1H, d, *J* = 1.5, H-5), 3.90–3.86 (2H, m, H-12), 3.21 (3H, s, H-7), 2.43–2.29 (2H, m, H-10a, H-11a), 2.16–1.96 (2H, m, H-10b, H-11b), 1.48 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.2 (C-8), 167.0 (C-13), 153.0 (C-14), 145.3 (C-6), 130.6 (C-1), 125.6 (C-3), 124.4 (C-2), 122.6 (C-4), 112.2 (C-5), 83.7 (C-15), 57.9 (C-9), 47.1 (C-12), 31.9 (C-10), 28.0, 27.9 (C-16), 26.7 (C-7), 19.4 (C-11); *m/z* (ESI) 431, 433 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{21}{}^{79}BrN_2NaO_4$, 431.0577. Found: [MNa]$^+$, 431.0579 (−0.4 ppm error)]; **21q$_o$**: mp 144–146 °C; R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (thin film) 3070, 2978, 2935, 1769, 1720, 1605, 1457; δ_H (400 MHz, $CDCl_3$) 7.19–7.13 (2H, m, H-3, H-4), 6.77 (1H, dd, *J* = 6.5, 2.5, H-5), 4.14–4.08 (1H, m, H-12a), 3.78–3.70 (1H, m, H-12b), 3.18 (3H, s, H-7), 2.74–5.59 (2H, m, H-10a, H-11a), 2.02–1.95 (2H, m, H-10b, H-11b), 1.50 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 174.9 (C-10), 165.5 (C-13), 153.0 (C-14), 145.7 (C-6), 130.8 (C-1), 130.2 (C-4), 126.6 (C-3), 118.3 (C-2), 107.4 (C-5), 83.5 (C-15), 59.0 (C-9), 46.7 (C-12), 29.2 (C-10), 27.9 (C-16), 26.7 (C-7), 19.5 (C-11); *m/z* (ESI) 431, 433 [MNa]$^+$; [HRMS (ESI): calcd for $C_{18}H_{21}{}^{79}BrN_2NaO_4$, 431.0577. Found: [MNa]$^+$, 431.0586 (−2.1 ppm error)].

1,1'-Dimethylspiro[indoline-3,3'-piperidine]-2,2'-dione (21r)



N,1-Dimethyl-2-oxo-*N*-phenylpiperidine-3-carboxamide (**20r**, 99 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [EtOAc] afforded **21r** (64 mg, 65%) as an off-white amorphous solid, mp 198–200 °C; R_f (EtOAc) = 0.10; ν_{max}/cm^{-1} (thin film) 3042, 2948, 2923, 2885, 2861, 1710, 1634, 1607, 1493, 1468, 1454; δ_H (400 MHz, $CDCl_3$) 7.29 (1H, td, *J* = 7.5, 1.0, H-4), 7.25 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-2), 7.03 (1H, td, *J* = 7.5, 1.0, H-3), 6.86–6.83 (1H, m, H-5), 3.61–3.48 (2H, m, H-12), 3.23 (3H, s, H-7), 3.01 (3H, s, H-14), 2.40–2.30 (2H, m, H-10a, H-11a), 2.19–2.09 (1H, m, H-11b), 2.04–1.96 (1H, m, H-10b); δ_C (100 MHz, $CDCl_3$) 176.3 (C-8), 166.3 (C-13), 144.1 (C-6), 132.5 (C-1), 128.6 (C-4), 122.8 (C-2), 122.6 (C-3), 108.5 (C-5), 55.7 (C-9), 50.2 (C-12), 35.6 (C-14), 31.6 (C-10), 26.5 (C-7), 19.1 (C-11); *m/z* (ESI) 267 $[MNa]^+$; [HRMS (ESI): calcd for $C_{14}H_{16}N_2NaO_2$, 267.1104. Found: $[MNa]^+$, 267.1101 (1.3 ppm error)].

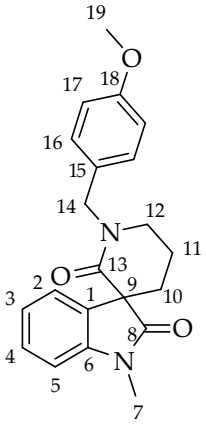
1'-Benzyl-1-methylspiro[indoline-3,3'-piperidine]-2,2'-dione (21s)



1-Benzyl-*N*-methyl-2-oxo-*N*-phenylpiperidine-3-carboxamide (**21s**, 124 mg, 0.39 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [1:1 EtOAc:PE] afforded **21s** (79 mg, 64%) as an off-white amorphous solid, mp 134–136 °C; R_f (1:1 EtOAc:PE) = 0.25; ν_{max}/cm^{-1} (thin film) 3058, 3029, 2939, 2864, 1714, 1640, 1610, 1492, 1469; δ_H (400 MHz, $CDCl_3$) 7.37–7.27 (6H, m, H-4, H-16, H-17, H-18), 7.26 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-2), 7.06 (1H, td, *J* = 7.5, 1.0, H-3), 6.89–6.86 (1H, m, H-5), 4.77 (1H, d, *J* = 14.5, H-14a), 4.51 (1H, d, *J* = 14.5, H-14b), 3.51–3.40 (2H, m, H-12), 3.26 (3H, s, H-7), 2.40–2.26 (2H, m, H-10a, H-11a), 2.12–1.97 (2H, m, H-10b, H-11b); δ_C (100 MHz, $CDCl_3$) 176.3 (C-8), 166.5 (C-13), 144.2 (C-6), 136.8 (C-15), 132.7

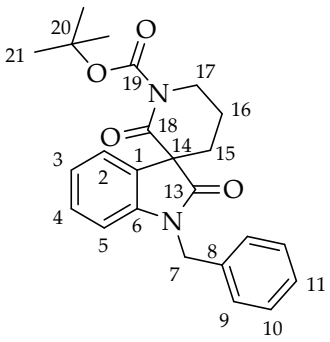
(C-1), 128.7 (C-4, C-17), 128.0 (C-16), 127.4 (C-18), 122.7, 122.6 (C-2, C-3), 108.5 (C-5), 55.8 (C-9), 50.7 (C-14), 47.4 (C-12), 31.6 (C-10), 26.5 (C-7), 19.1 (C-11); *m/z* (ESI) 343 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{20}N_2NaO_2$, 343.1417. Found: $[MNa]^+$, 343.1408 (2.7 ppm error)].

1'-(4-Methoxybenzyl)-1-methylspiro[indoline-3,3'-piperidine]-2,2'-dione (21t)



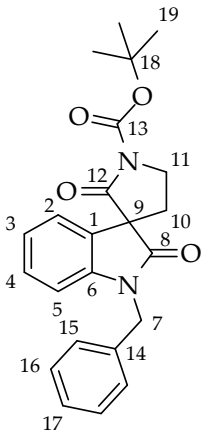
1-(4-Methoxybenzyl)-*N*-methyl-2-oxo-*N*-phenylpiperidine-3-carboxamide (**21t**, 127 mg, 0.36 mmol) and copper(II) acetate monohydrate (7 mg, 0.035 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [1:1 EtOAc:PE] afforded **21t** (81 mg, 64%) as an off-white amorphous solid, mp 133–135 °C; R_f (1:1 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3056, 2937, 2863, 2837, 1713, 1638, 1611, 1512, 1492, 1467; δ_H (400 MHz, $CDCl_3$) 7.31 (1H, td, *J* = 7.5, 1.0, H-4), 7.24–7.19 (3H, m, H-2, H-16), 7.05 (1H, td, *J* = 7.5, 1.0, H-3), 6.89–6.85 (3H, m, H-5, H-17), 4.71 (1H, d, *J* = 14.5, H-14a), 4.43 (1H, d, *J* = 14.5, H-14b), 3.80 (3H, s, H-19), 3.49–3.39 (2H, m, H-12), 3.25 (3H, s, H-7), 2.38–2.24 (2H, m, H-10a, H-11a), 2.10–1.95 (2H, m, H-10b, H-11b); δ_C (100 MHz, $CDCl_3$) 176.4 (C-8), 166.3 (C-13), 159.0 (C-18), 144.2 (C-6), 132.8 (C-1), 129.4 (C-16), 129.0 (C-15), 128.6 (C-4), 122.7, 122.6 (C-2, C-3), 114.0 (C-17), 108.5 (C-5), 55.8 (C-9), 55.2 (C-19), 50.1 (C-14), 47.1 (C-12), 31.6 (C-10), 26.5 (C-7), 19.1 (C-11); *m/z* (ESI) 373 $[MNa]^+$; [HRMS (ESI): calcd for $C_{21}H_{22}N_2NaO_3$, 373.1523. Found: $[MNa]^+$, 373.1505 (4.7 ppm error)].

tert-Butyl 1-benzyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21u)



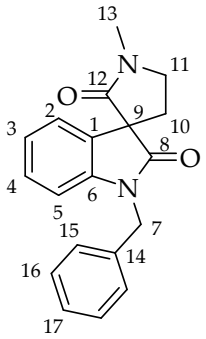
tert-Butyl 3-(benzyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20u**, 162 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded a mixture of spirocycle **21u** and lactam **262b** (106 mg, corresponding to 83 mg of pure **21u**, 51%) as an off-white amorphous solid. A small sample of pure **21u** was isolated for full characterisation, mp 162–164 °C; R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (thin film) 3062, 3031, 2978, 2935, 1768, 1718, 1609, 1489, 1466, 1456; δ_H (400 MHz, $CDCl_3$) 7.33–7.22 (6H, m, H-2, H-9, H-10, H-11), 7.17 (1H, td, _J_ = 8.0, 1.0, H-4), 7.02 (1H, td, _J_ = 8.0, 1.0, H-3), 6.69 (1H, br d, _J_ = 8.0, H-5), 4.94 (2H, d, _J_ = 1.0, H-7), 3.95–3.87 (2H, m, H-17), 2.47–2.33 (2H, m, H-15a, H-16a), 2.23–2.04 (2H, m, H-15b, H-16b), 1.50 (9H, s, H-21); δ_C (100 MHz, $CDCl_3$) 175.7 (C-13), 167.5 (C-18), 152.9 (C-19), 143.0 (C-6), 135.3 (C-8), 131.9 (C-1), 128.8 (C-4), 128.8 (C-10), 127.5 (C-11), 127.0 (C-9), 123.2 (C-2), 122.8 (C-3), 109.7 (C-5), 83.5 (C-20), 58.3 (C-14), 47.2 (C-17), 43.8 (C-7), 32.1 (C-15), 27.9 (C-21), 19.5 (C-16); _m/z_ (ESI) 429 $[MNa]^+$; [HRMS (ESI): calcd for $C_{24}H_{26}N_2NaO_4$, 429.1785. Found: $[MNa]^+$, 429.1791 (−1.3 ppm error)].

tert-Butyl 1-benzyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (21w)



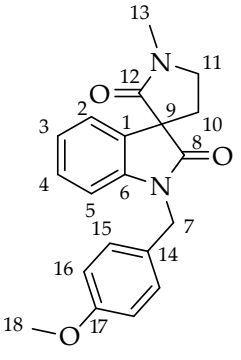
tert-Butyl 3-(benzyl(phenyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (**20w**, 120mg, 0.30 mmol) and copper(II) acetate monohydrate (6 mg, 0.03 mmol) in mesitylene (6 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–30% EtOAc/PE] afforded **21w** (66 mg, 55%) as a colourless amorphous solid, mp 175–177 °C; R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3061, 2962, 2931, 2872, 1783, 1749, 1718, 1612, 1490, 1467, 1456; δ_H (400 MHz, $CDCl_3$) 7.34–7.23 (5H, m, H-15, H-16, H-17), 7.21 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-2), 7.19 (1H, td, *J* = 7.5, 1.0, H-4), 7.04 (1H, td, *J* = 7.5, 1.0, H-3), 6.69 (1H, br d, *J* = 7.5, H-5), 5.02 (1H, d, *J* = 16.0, H-7a), 4.82 (1H, d, *J* = 16.0, H-7b), 4.21 (1H, ddd, *J* = 10.5, 8.0, 7.0, H-11a), 4.01 (1H, ddd, *J* = 10.5, 8.5, 5.0, H-11b), 2.70 (1H, ddd, *J* = 13.0, 8.0, 5.0, H-10a), 2.41 (1H, ddd, *J* = 13.0, 8.5, 7.0, H-10b), 1.55 (9H, s, H-19); δ_C (100 MHz, $CDCl_3$) 174.5 (C-8), 169.3 (C-12), 150.0 (C-13), 143.4 (C-6), 135.0 (C-14), 129.3 (C-4), 128.9 (C-16), 128.8 (C-1), 127.6 (C-17), 127.0 (C-15), 123.2 (C-3), 123.1 (C-2), 109.7 (C-5), 83.7 (C-18), 59.5 (C-9), 44.2 (C-11), 44.0 (C-7), 28.2 (C-10), 28.0 (C-19); *m/z* (ESI) 415 $[MNa]^+$; [HRMS (ESI): calcd for $C_{23}H_{24}N_2NaO_4$, 415.1628. Found: $[MNa]^+$, 415.1618 (2.5 ppm error)]; [Found C, 69.82%; H, 6.20%; N, 6.81%. $C_{23}H_{24}N_2O_4$ requires C, 70.39%; H, 6.16%; N, 7.14%].

1-Benzyl-1'-methylspiro[indoline-3,3'-pyrrolidine]-2,2'-dione (21x)



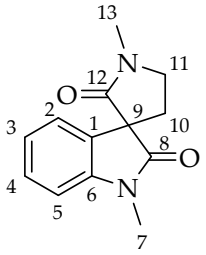
N-Benzyl-1-methyl-2-oxo-*N*-phenylpyrrolidine-3-carboxamide (**20x**, 123 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [50–75% EtOAc/PE] afforded **21x** (71 mg, 58%) as an off-white amorphous solid, mp 151–153 °C; R_f (EtOAc) = 0.50; ν_{max}/cm^{-1} (thin film) 3059, 3031, 2932, 2885, 1714, 1690, 1611, 1490, 1466, 1455; δ_H (400 MHz, $CDCl_3$) 7.33–7.21 (5H, m, H-15, H-16, H-17), 7.19–7.15 (2H, m, H-2, H-4), 7.03 (1H, ddd, *J* = 8.0, 7.0, 1.0, H-3), 6.69 (1H, dd, *J* = 8.0, 1.0, H-5), 5.02 (1H, d, *J* = 16.0, H-7a), 4.84 (1H, d, *J* = 16.0 H-7b), 3.82 (1H, dd, *J* = 9.5, 8.5, 6.0, H-11a), 3.62 (1H, ddd, *J* = 9.5, 8.5, 4.5, H-11b), 3.00 (3H, s, H-13), 2.76 (1H, ddd, *J* = 13.0, 8.5, 4.5, H-10a), 2.45 (1H, ddd, *J* = 13.0, 8.5, 6.0, H-10b); δ_C (100 MHz, $CDCl_3$) 175.9 (C-8), 170.4 (C-12), 143.5 (C-6), 135.3 (C-14), 129.9 (C-1), 128.9 (C-4), 128.8 (C-16), 127.5 (C-17), 127.0 (C-15), 123.0 (C-3), 122.8 (C-2), 109.5 (C-5), 57.8 (C-9), 47.2 (C-11), 43.9 (C-7), 30.5 (C-13), 29.3 (C-10); *m/z* (ESI) 307 $[MH]^+$, 329 $[MNa]^+$; [HRMS (ESI): calcd for $C_{19}H_{18}N_2NaO_2$, 329.1260. Found: $[MNa]^+$, 329.1255 (1.6 ppm error)].

1-(4-Methoxybenzyl)-1'-methylspiro[indoline-3,3'-pyrrolidine]-2,2'-dione (21y)



N-(4-Methoxybenzyl)-1-methyl-2-oxo-*N*-phenylpyrrolidine-3-carboxamide (**20y**, 135 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [50–100% EtOAc/PE] afforded **21y** (74 mg, 55%) as an off-white microcrystalline solid, mp 140–142 °C; R_f (EtOAc) = 0.30; ν_{max}/cm^{-1} (thin film) 3058, 2997, 2935, 2837, 1712, 1692, 1612, 1586, 1514, 1489, 1466; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* = 9.0, H-15), 7.17 (1H, td, *J* = 7.5, 1.5, H-4), 7.15 (1H, ddd, *J* = 7.5, 1.5, 0.5, H-2), 7.02 (1H, td, *J* = 7.5, 1.0, H-3), 6.84 (2H, d, *J* = 9.0, H-16), 6.71 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-5), 4.95 (1H, d, *J* = 15.5, H-7a), 4.77 (1H, d, *J* = 15.5, H-7b), 3.81 (1H, ddd, *J* = 9.5, 8.5, 6.0, H-11a), 3.75 (3H, s, H-18), 3.61 (1H, ddd, *J* = 9.5, 8.5, 4.5, H-11b), 2.99 (3H, s, H-13), 2.74 (1H, ddd, *J* = 13.0, 8.5, 4.5, H-10a), 2.43 (1H, ddd, *J* = 13.0, 8.5, 6.0, H-10b); δ_C (100 MHz, $CDCl_3$) 175.8 (C-8), 170.5 (C-12), 158.9 (C-17), 143.5 (C-6), 130.0 (C-1), 128.8 (C-4), 128.4 (C-15), 127.3 (C-14), 123.0 (C-3), 122.7 (C-2), 114.2 (C-16), 109.5 (C-5), 57.8 (C-9), 55.2 (C-18), 47.2 (C-11), 43.3 (C-7), 30.5 (C-13), 29.3 (C-10); *m/z* (ESI) 337 $[MH]^+$, 359 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{21}N_2O_3$, 337.1547. Found: $[MH]^+$, 337.1547 (−0.0 ppm error)].

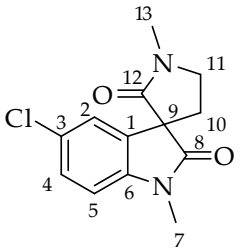
1,1'-Dimethylspiro[indoline-3,3'-pyrrolidine]-2,2'-dione (21z)



N,1-Dimethyl-2-oxo-*N*-phenylpyrrolidine-3-carboxamide (**20z**, 82 mg, 0.35 mmol) and copper(II) acetate monohydrate (7 mg, 0.035 mmol) in mesitylene (7 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [EtOAc] afforded **21z** (47 mg, 58%) as a colourless microcrystalline solid, mp 163–165 °C; R_f (EtOAc) = 0.30; ν_{max}/cm^{-1} (thin film) 3059, 2998, 2935, 2878, 1718, 1682, 1611, 1495, 1471; δ_H (400 MHz, $CDCl_3$) 7.31 (1H, td, *J* = 7.5, 1.0, H-4), 7.15 (1H, dd, *J* = 7.5, 1.0, H-2), 7.07 (1H, td, *J* = 7.5, 1.0, H-3), 6.86 (1H, br d, *J* = 7.5, H-5), 3.79 (1H, ddd, *J* = 9.5, 8.5, 6.0, H-11a), 3.59 (1H, ddd, *J* = 9.5, 8.5, 4.5, H-11b), 3.22 (3H, s, H-7), 2.98 (3H, s, H-13), 2.68

(1H, ddd, *J* = 13.0, 8.5, 4.5, H-10a), 2.39 (1H, ddd, *J* = 13.0, 8.5, 6.0, H-10b); δ_C (100 MHz, $CDCl_3$) 175.7 (C-8), 170.4 (C-12), 144.5 (C-6), 129.9 (C-1), 129.0 (C-4), 123.0 (C-3), 122.8 (C-2), 108.5 (C-5), 57.8 (C-9), 47.2 (C-11), 30.5 (C-13), 29.5 (C-10), 26.5 (C-7); *m/z* (ESI) 231, $[MH]^+$, 253 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{14}N_2NaO_2$, 253.0947. Found: $[MNa]^+$, 253.0948 (−0.3 ppm error)]; [Found C, 67.74%; H, 6.13%; N, 11.96%. $C_{13}H_{14}N_2O_2$ requires C, 67.81%; H, 6.13%; N, 12.17%].

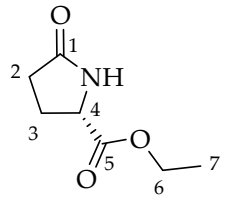
5-Chloro-1,1'-dimethylspiro[indoline-3,3'-pyrrolidine]-2,2'-dione (21za)



N-(4-Chlorophenyl)-*N*,1-dimethyl-2-oxopyrrolidine-3-carboxamide (**20za**, 106 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 1 h according to general procedure F. Flash column chromatography [EtOAc] afforded **21za** (69 mg, 66%) as an off-white powder, mp 171–173 °C; R_f (EtOAc) = 0.30; ν_{max}/cm^{-1} (thin film) 3064, 2941, 2888, 1718, 1691, 1610, 1491, 1468, 1450; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, dd, *J* = 8.5, 2.0, H-4), 7.13 (1H, d, *J* = 2.0, H-2), 6.78 (1H, d, *J* = 8.5, H-5), 3.78 (1H, ddd, *J* = 9.5, 8.5, 6.0, H-11a), 3.58 (1H, ddd, *J* = 9.5, 8.5, 4.5, H-11b), 3.20 (3H, s, H-7), 2.98 (3H, s, H-13), 2.68 (1H, ddd, *J* = 13.0, 8.5, 4.5, H-10a), 2.37 (1H, ddd, *J* = 13.0, 8.5, 6.0, H-10b); δ_C (100 MHz, $CDCl_3$) 175.2 (C-8), 169.8 (C-12), 143.1 (C-6), 131.4 (C-1), 128.9 (C-4), 128.3 (C-3), 123.4 (C-2), 109.4 (C-5), 57.8 (C-9), 47.1 (C-11), 30.6 (C-13), 29.3 (C-10), 26.7 (C-7); *m/z* (ESI) 287, 289 $[MNa]^+$; [HRMS (ESI): calcd for $C_{13}H_{13}{}^{35}ClN_2NaO_2$, 287.0558. Found: $[MNa]^+$, 287.0548 (3.3 ppm error)]; [Found C, 58.94%; H, 5.07%; N, 10.15%. $C_{13}H_{13}ClN_2O_2$ requires C, 58.99%; H, 4.95%; N, 10.58%].

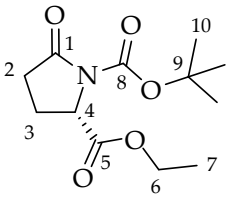
7.5 Towards the synthesis of spirotryprostatin A

(*S*)-Ethyl 5-oxopyrrolidine-2-carboxylate (316)



The title compound was prepared based on the procedures by Kamimura[247] and Williams.[248] To a solution of (*S*)-pyroglutamic acid (**315**, 5.00 g, 38.8 mmol) in EtOH (70 mL) at 0 °C was added thionyl chloride (2.83 mL, 38.8 mmol) dropwise. The reaction was stirred at 0 °C for 10 min then allowed to warm to room temperature and stirred at this temperature for 1 h. After dilution with H_2O (20 mL), $NaHCO_3$ (12 g) was added slowly and the resulting suspension filtered. The filtrate was concentrated *in vacuo* to approx. half the original volume then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **316** (5.67 g, 93%) as colourless prisms, mp 52–54 °C (lit[288] 53–54 °C); R_f (EtOAc) = 0.30; $[\alpha]_D^{20}$ +6.9 (*c* 1.00, MeOH) [lit[289] $[\alpha]_D$ +6.3 (*c* 1.00, EtOH)]; δ_H (400 MHz, $CDCl_3$) 6.53 (1H, br s, NH), 4.23 (1H, dd, *J* = 8.5, 5.0, H-4), 4.21 (2H, q, *J* = 7.0, H-6), 2.51–2.41 (1H, m, H-3a), 2.41–2.30 (2H, m, H-2), 2.25–2.16 (1H, m, H-3b), 1.28 (3H, t, *J* = 7.0, H-7). Data consistent with the literature values.[248,289]

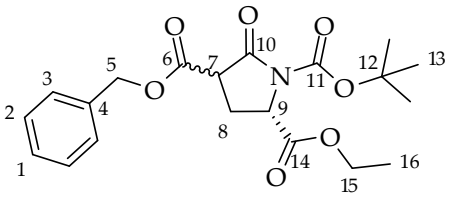
(*S*)-1-*tert*-Butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (317)



The title compound was prepared based on the procedure by Flynn.[249] To a solution of (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (**316**, 5.57 g, 35.5 mmol) in CH_2Cl_2 (100 mL) was added *N*,*N*-dimethylaminopyridine (440 mg, 3.60 mmol), di-*tert*-butyl dicarbonate

(15.75 g, 72.2 mmol) and triethylamine (15.2 mL, 109 mmol). The reaction was stirred at room temperature for 12 h then concentrated *in vacuo*. Flash column chromatography [1:1 EtOAc:PE] afforded **317** (8.50 g, 93%) as off-white needles, mp 53–54 °C (lit[290] 53–54 °C); R_f (1:1 EtOAc:PE) = 0.40; $[\alpha]_D^{20}$ −37.5 (*c* 0.86, CH_2Cl_2) [lit[290] $[\alpha]_D$ −39.8 (*c* 0.5, MeOH); lit[291] $[\alpha]_D$ −34.9 (*c* 0.81, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 4.58 (1H, dd, *J* = 9.5, 3.0, H-4), 4.23 (2H, q, *J* = 7.0, H-6), 2.62 (1H, ddd, *J* = 17.5, 10.0, 9.5, H-2a), 2.48 (1H, ddd, *J* = 17.5, 9.5, 3.5, H-2b), 2.36–2.25 (1H, m, H-3a), 2.02 (1H, tdd, *J* = 9.5, 6.5, 3.5, H-3b), 1.48 (9H, s, H-10), 1.28 (3H, t, *J* = 7.0, H-7); δ_C (100 MHz, $CDCl_3$) 173.4 (C-1), 171.3 (C-5), 149.2 (C-8), 83.5 (C-9), 61.6 (C-6), 58.9 (C-4), 31.1 (C-2), 27.8 (C-10), 21.5 (C-3), 14.1 (C-7). Data consistent with the literature values.[290]

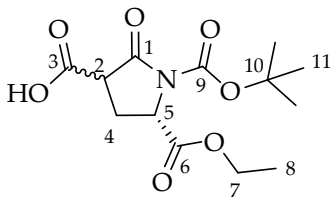
(*S*)-4-Benzyl 1-*tert*-butyl 2-ethyl 5-oxopyrrolidine-1,2,4-tricarboxylate (318)



(*S*)-1-*tert*-Butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (**317**, 8.28 g, 32.2 mmol), LiHMDS (1 M in THF, 67.7 mL, 67.7 mmol) and benzylchloroformate (4.60 mL, 32.2 mmol) in THF (30 mL) were reacted according to general procedure D. Flash column chromatography [20–33% EtOAc/PE] afforded **318** (9.13 g, 72%, 2:1 mixture of diastereoisomers) as a pale yellow oil, R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (thin film) 3065, 3034, 2981, 2937, 2362, 2341, 1796, 1740, 1498, 1475, 1457; δ_H (400 MHz, $CDCl_3$, minor diastereoisomer starred) 7.39–7.28 (5H and 5H*, m, H-1, H-1*, H-2, H-2*, H-3, H-3*), 5.21 (2H, s, H-5), 5.18 (2H*, d, *J* = 3.5, H-5*), 4.64 (1H, dd, *J* = 9.5, 2.5, H-9), 4.60–4.56 (1H*, m, H-9*), 4.25–4.07 (2H and 2H*, m, H-15, H-15*), 3.72 (1H, dd, *J* = 10.5, 9.0, H-7), 3.60–3.56 (1H*, m, H-7*), 2.73 (1H, ddd, *J* = 13.5, 10.5, 9.5, H-8a), 2.55–2.51 (2H*, m H-8a*, H-8b*), 2.24 (1H, ddd, *J* = 13.5, 9.0, 2.5, H-8b), 1.47 (9H and 9H*, s, H-13, H-13*), 1.27 (3H, t, *J*= 7.0, H-16), 1.23 (3H*, t, *J* = 7.0, H-16*); δ_C (100 MHz, $CDCl_3$, minor diastereoisomer starred) 170.7 (C-14), 170.2 (C-14*), 167.8, 167.7 (C-6, C-10), 167.4, 167.1 (C-6*, C-10*), 149.0 (C-11*), 148.9 (C-11), 135.12 (C-4*), 135.0 (C-4), 128.5 (C-2), 128.5 (C-2*), 128.4 (C-1), 128.3 (C-1*), 128.2 (C-3), 128.1 (C-3*), 84.1 (C-12), 84.0 (C-12*), 67.6

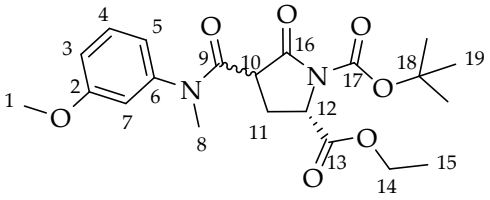
(C-5), 61.9 (C-15), 61.7 (C-15*), 57.5 (C-9*), 57.1 (C-9), 48.7 (C-7*), 48.4 (C-7), 27.8 (C-13), 25.3 (C-8), 24.6 (C-8*), 14.1 (C-16), 14.0 (C-16*); *m/z* (ESI) 414 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{25}NNaO_7$, 414.1523. Found: $[MNa]^+$, 414.1524 (−0.1 ppm error)].

(*S*)-1-(*tert*-Butoxycarbonyl)-5-(ethoxycarbonyl)-2-oxopyrrolidine-3-carboxylic acid (319)



A solution of (*S*)-4-benzyl 1-*tert*-butyl 2-ethyl 5-oxopyrrolidine-1,2,4-tricarboxylate (**318**, 2.37 g, 6.07 mmol) in EtOAc (60 mL) was hydrogenolysed in the presence of 10% Pd/C (290 mg) for 2 h according to general procedure E to afford the crude title compound (1.73 g, 7:3 mixture of diastereoisomers) as a colourless oil, R_f(1:1 EtOAc:PE) = 0.10; δ_H (400 MHz, $CDCl_3$, minor diastereoisomer starred) 8.01 (1H, br s, OH), 4.66 (1H, dd, *J* = 9.5, 2.0, H-5), 4.60 (1H*, dd, *J* = 9.0, 5.0, H-5*), 4.25 (2H, q, *J* = 7.0, H-7), 3.69 (1H, dd, *J* = 11.0, 9.0, H-2), 3.60 (1H*, dd, *J* = 10.0, 6.0, H-2*), 2.67 (1H, ddd, *J* = 13.5, 11.0, 9.5, H-4a), 2.61 (1H*, ddd, *J* = 13.5, 10.0, 9.0, H-4a*), 2.50 (1H*, ddd, *J* = 13.5, 6.0, 5.0, H-4b*), 2.36 (1H, ddd, *J* = 13.5, 9.0, 2.0, H-4b), 1.50 (9H, s, H-11), 1.49 (9H*, s, H-11*), 1.30 (3H, t, *J* = 7.0, H-8), 1.28 (3H, t, *J* = 7.0, H-8*).

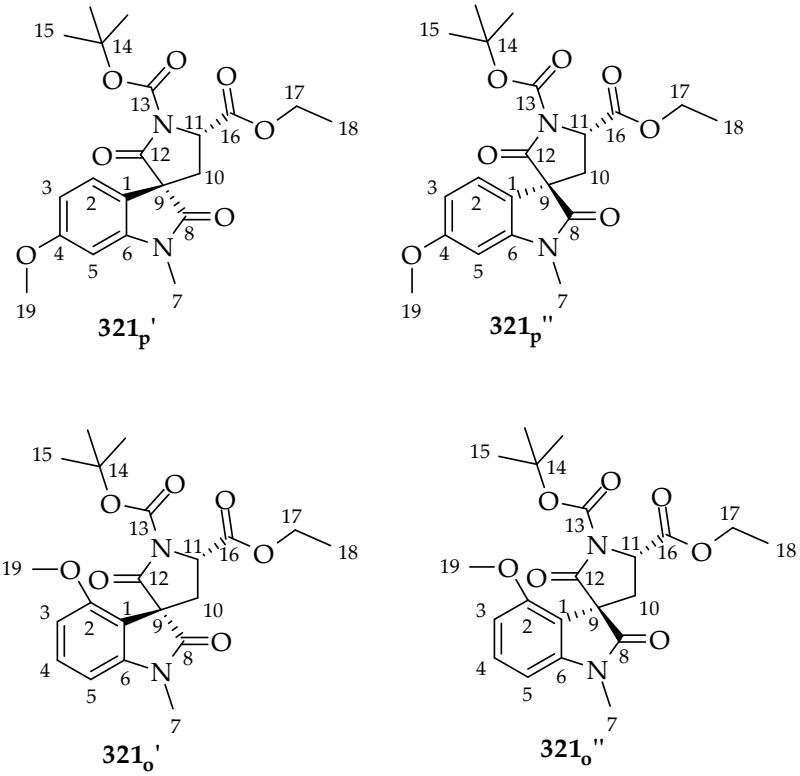
(*S*)-1-*tert*-Butyl 2-ethyl 4-((3-methoxyphenyl)(methyl)carbamoyl)-5-oxopyrrolidine-1,2-dicarboxylate (320)



(*S*)-1-(*tert*-Butoxycarbonyl)-5-(ethoxycarbonyl)-2-oxopyrrolidine-3-carboxylic acid (**319**, 453 mg), 3-methoxy-*N*-methylaniline (225 mg, 1.64 mmol), 2-chloro-1-

methylpyridinium iodide (575 mg, 2.26 mmol) and triethylamine (1.05 mL, 7.52 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–50% EtOAc/PE] afforded **320** (587 mg, 88% over 2 steps, 4:1 mixture of diastereoisomers) as a pale yellow sticky oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3071, 2980, 2938, 2839, 1791, 1747, 1722, 1659, 1601, 1498, 1456; δ_H (400 MHz, $CDCl_3$, minor diastereoisomer starred) 7.30 (1H and 1H*, t, *J* = 8.0, H-4, H-4*), 6.95 (2H, v br s, H-5, H-7), 6.89 (1H and 1H*, dd, *J* = 8.0, 2.5, H-3, H-3*), 4.67 (1H, dd, *J* = 10.0, 2.5, H-12), 4.45 (1H*, dd, *J* = 9.0, 6.5, H-12*), 4.30–4.22 (2H*, m, H-14*), 4.15 (1H, dq, *J* = 11.0, 7.0, H-14a), 4.10 (1H, dq, *J* = 11.0, 7.0, H-14b), 3.82 (3H and 3H*, s, H-1, H-1*), 3.70 (1H, t, *J* = 9.0, H-10), 3.62 (1H*, dd, *J* = 9.0, 7.5, H-10*), 3.31 (3H, s, H-8), 3.29 (3H*, s, H-8*), 2.84 (1H, dt, *J* = 13.5, 10.0, H-11a), 2.53 (1H*, ddd, *J* = 13.0, 7.5, 7.0, H-11a*), 2.33 (1H*, dt, *J* = 13.0, 9.0, H-11b*), 1.97 (1H, ddd, *J* = 13.5, 9.0, 2.5, H-11b), 1.47 (9H and 9H*, s, H-19, H-19*), 1.30 (3H*, t, *J* = 7.0, H-15*), 1.18 (3H, t, *J* = 7.0, H-15); δ_C (100 MHz, $CDCl_3$, minor diastereoisomer starred) 171.1 (C-13), 170.1 (C-13*), 169.7 (C-16), 169.2 (C-16*), 167.8 (C-9), 167.2 (C-9*), 160.5 (C-2, C-2*), 149.0 (C-17*), 148.8 (C-17), 144.1 (C-6*), 143.9 (C-6), 130.5 (C-4), 130.4 (C-4*), 119.3 (br, C-5, C-5* or C-7, C-7*), 114.2 (br, C-3, C-3*), 113.1 (C-5* or C-7*), 112.8 (C-5 or C-7), 83.7 (C-18), 83.6 (C-18*), 61.6 (C-14*), 61.5 (C-14), 57.6 (C-12*), 57.4 (C-12), 55.4 (C-1, C-1*), 46.1 (C-10*), 45.7 (C-10), 37.8 (C-8, C-8*), 27.7 (C-19, C-19*), 26.1 (C-11), 25.7 (C-11*), 14.0 (C-15*), 13.9 (C-15); *m/z* (ESI) 443 $[MNa]^+$; [HRMS (ESI): calcd for $C_{21}H_{28}N_2NaO_7$, 443.1789. Found: $[MNa]^+$, 443.1797 (−1.8 ppm error)].

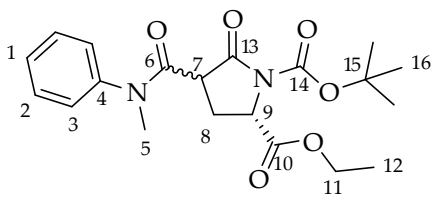
(3*S*,5'*S*)-1'-*tert*-Butyl 5'-ethyl 6-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (321$_p$′), (3*R*,5'*S*)-1'-*tert*-butyl 5'-ethyl 6-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (321$_p$′′), (3*S*,5'*S*)-1'-*tert*-butyl 5'-ethyl 4-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (321$_o$′) and (3*R*,5'*S*)-1'-*tert*-butyl 5'-ethyl 4-methoxy-1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (321$_o$′′)



(*S*)-1-*tert*-Butyl 2-ethyl 4-((3-methoxyphenyl)(methyl)carbamoyl-5-oxopyrrolidine-1,2-dicarboxylate (**320**, 162 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 45 min according to general procedure F Flash column chromatography [20–33% EtOAc/PE] afforded an inseparable mixture of **321$_p$**′, **321$_p$**″, **321$_o$**′, **321$_o$**″, and lactam **317** (95 mg, corresponding to 32.5 mg of **321$_o$**, 20%; 21 mg of **321$_p$**, 13%; 14 mg of **321$_o$***, 9%; 11.5 mg of **321$_p$***, 7%) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 2980, 2938, 2843, 1792, 1748, 1722, 1612, 1508, 1475; δ_H (400 MHz, $CDCl_3$, minor diastereoisomers starred) 7.31–7.25 (1H$_o$, 1H$_o$*, m, H$_o$-4, H$_o$-4*), 7.17 (1H$_p$, d, *J* = 8.5, H$_p$-2), 7.05 (1H$_p$*, d, *J* = 8.5, H$_p$-2*), 6.61 (1H$_o$*, d, *J* = 8.5, H$_o$-3*), 6.61 (1H$_o$, d, *J* = 8.5, H$_o$- 3), 6.56 (1H$_p$*, dd, *J* = 8.5, 2.0, H$_p$-3*), 6.55 (1H$_p$, dd, *J* = 8.5, 2.0, H$_p$-3), 6.51 (1H$_o$, 1H$_o$*, d, *J* = 8.0, H$_o$-5, H$_o$-5*), 6.43

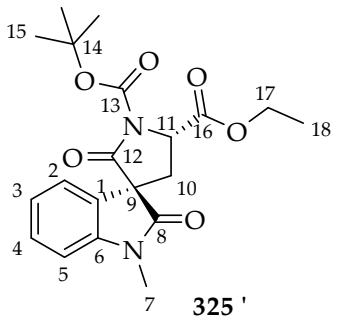
($1H_p$, d, J = 2.0, H_p-5), 6.42 ($1H_p$*, d, J = 2.0, H_p-5*), 4.99 ($1H_o$*, dd, J = 9.0, 8.0, H_o-11*), 4.93 ($1H_o$, dd, J = 9.5, 6.0, H_o-11), 4.92 ($1H_p$, dd, J = 9.5, 5.0, H_p-11), 4.88 ($1H_p$*, dd, J = 9.5, 4.5, H_p-11*), 4.37–4.25 ($2H_p$, $2H_p$*, $2H_o$ and $2H_o$*, m, H_p-17, H_p-17*, H_o-17, H_o-17*), 3.82 ($3H_o$, s, H_o-19), 3.81 ($3H_p$*, s, H_p-19*), 3.81 ($3H_p$, s, H_p-19), 3.79 ($3H_o$*, s, H_o-19*), 3.19 ($3H_p$, s, H_p-7), 3.17 ($3H_o$, s, H_o-7), 3.17 ($3H_o$*, s, H_o-7*), 3.16 ($3H_p$*, s, H_p-7*), 2.98 ($1H_p$, dd, J = 14.0, 9.5, H_p-10a), 2.84 ($1H_o$, dd, J = 13.5, 9.5, H_o-10a), 2.77 ($1H_p$*, dd, J = 13.5, 4.5, H_p-10a*), 2.70 ($1H_o$*, dd, J = 13.0, 8.0, H_o-10a*), 2.68–2.61 ($1H_o$*, $1H_p$*, m, H_o-10b*, H_p-10b*), 2.84 ($1H_o$, dd, J = 13.5, 6.0, H_o-10b), 2.23 ($1H_p$, dd, J = 14.0, 5.0, H_p-10b), 1.52 ($9H_o$, s, H_o-15), 1.52 ($9H_p$*, s, H_p-15*), 1.51 ($9H_o$*, s, H_o-15*), 1.50 ($9H_p$, s, H_p-15), 1.35–1.23 ($3H_p$, $3H_p$*, $3H_o$ and $3H_o$*, m, H_p-18, H_p-18*, H_o-18, H_o-18*); δ_C (100 MHz, $CDCl_3$, minor diastereoisomers starred) 174.7, 174.4 (C_p-8, C_o-8*), 173.8 (C_p-8*), 173.6 (C_o-8), 171.5 (C_p-16), 170.5 (C_o-16*), 170.4 (C_o-16), 169.9 (C_p-16*), 168.8 (C_p-12), 168.6 (C_p-12*), 168.3 (C_o-12), 168.2 (C_o-12*), 161.2 (C_p-4*), 161.1 (C_p-4), 155.4 (C_o-2*), 155.0 (C_o-2), 149.4 (C_o-13), 149.3, 149.0 (C_o-13*, C_p-13*), 148.9 (C_p-13), 145.7, 145.6, 145.6 and 145.5 (C_o-6, C_p-6, C_o-6*, C_p-6*), 131.0 (C_o-4*), 130.8 (C_o-4), 124.5 (C_p-2), 123.4 (C_p-2*), 120.3 (C_p-1*), 120.2 (C_p-1), 114.4 (C_o-1), 113.0 (C_o-1*), 107.1 (C_p-3), 106.9 (C_p-3*), 106.2 (C_o-3*), 106.0 (C_o-3), 102.0 (C_o-5), 101.8 (C_o-5*), 96.7 (C_p-5*), 96.6 (C_p-5), 84.2, 84.1 and 83.8 (C_p-14, C_o-14*, C_p-14*), 83.8 (C_o-14), 61.9, 61.8, 61.4 and 61.3 (C_o-17, C_p-17, C_o-17*, C_p-17*), 58.2, 58.0, 57.7, 57.6 (C_o-9, C_p-9, C_o-9*, C_p-9*), 57.4 (C_o-11), 56.8, 56.7 (C_o-11*, C_p-11*), 56.5 (C_p-11), 55.5, 55.5 and 55.4 (C_o-19, C_p-19, C_o-19*, C_p-19*), 31.5 (C_p-10*), 31.3 (C_p-10), 29.4 (C_o-10), 28.3 (C_o-10*), 27.8, 27.7 and 27.7 (C_o-15, C_p-15, C_o-15*, C_p-15*), 26.8 (C_o-7), 26.7 (C_o-7*), 26.7 (C_p-7), 26.6 (C_p-7*), 14.1 and 14.0 (C_o-18, C_p-18, C_o-18*, C_p-18*); *m/z* (ESI) 441 $[MNa]^+$; [HRMS (ESI): calcd for $C_{21}H_{26}N_2NaO_7$, 441.1632. Found: $[MNa]^+$, 441.1632 (0.0 ppm error)].

(*S*)-1-*tert*-Butyl 2-ethyl 4-(methyl(phenyl)carbamoyl)-5-oxopyrrolidine-1,2-dicarboxylate (324)

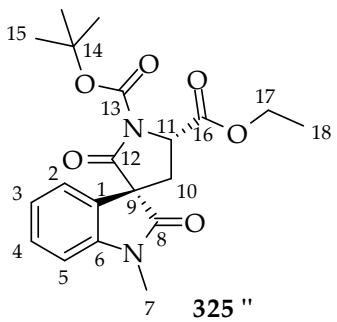


(*S*)-1-(*tert*-Butoxycarbonyl)-5-(ethoxycarbonyl)-2-oxopyrrolidine-3-carboxylic acid (**319**, 467 mg), *N*-methylaniline (0.18 mL, 1.71 mmol), 2-chloro-1-methylpyridinium iodide (593 mg, 2.33 mmol) and triethylamine (1.08 mL, 7.75 mmol) in CH_2Cl_2 (10 mL) were reacted according to general procedure E. Flash column chromatography [20–30% EtOAc/PE] afforded **324** (524 mg, 82% over 2 steps, 4:1 mixture of diastereoisomers) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3063, 2981, 2937, 1792, 1748, 1722, 1659, 1595, 1496, 1456; δ_H (400 MHz, $CDCl_3$, minor diastereoisomer starred) 7.44–7.32 (5H and 5H*, m, H-1, H-1*, H-2, H-2*, H-3, H-3*), 4.65 (1H, dd, *J* = 10.0, 2.5, H-9), 4.43 (1H*, dd, *J* = 9.0, 7.0, H-9*), 4.30–4.21 (2H*, m, H-11*), 4.13 (1H, dq, *J* = 11.0, 7.0, H-11a), 4.08 (1H, dq, *J* = 11.0, 7.0, H-11b), 3.66 (1H, dd, *J* = 10.0, 9.0, H-7a), 3.58 (1H*, dd, *J* = 9.5, 8.0, H-7*), 3.32 (3H, s, H-5), 3.30 (3H*, s, H-5*), 2.86 (1H, dt, *J* = 13.5, 10.0, H-8a), 2.55 (1H*, dd, *J* = 13.0, 8.0, 7.0, H-8a*), 2.32 (1H*, dt, *J* = 13.0, 9.0, H-8b*), 1.97 (1H, ddd, *J* = 13.5, 9.0, 2.5, H-8b), 1.47 (9H, 9H*, s, H-16, H-16*), 1.30 (3H*, t, *J* = 7.0, H-12*), 1.16 (3H, t, *J* = 7.0, H-12); δ_C (100 MHz, $CDCl_3$, minor diastereoisomer starred) 171.1 (C-10), 170.2 (C-10*), 169.7 (C-13), 169.2 (C-13*), 167.9 (C-6), 167.3 (C-6*), 149.1 (C-14*), 148.9 (C-14) 143.1 (C-4*), 143.0 (C-4), 129.9 (C-2), 129.8 (C-2*), 128.3 (C-1), 128.2 (C-1*), 127.4 (C-3, C-3*), 83.8 (C-15), 83.8 (C-15*), 61.6 (C-11*), 61.6 (C-11), 57.6 (C-9*), 57.4 (C-9), 46.1 (C-7*), 45.7 (C-7), 38.0 (C-5, C-5*), 27.8 (C-16, C-16*), 26.1 (C-8), 25.7 (C-8*), 14.1 (C-12*), 14.0 (C-12); *m/z* (ESI) 413 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{26}N_2NaO_6$, 413.1683. Found: $[MNa]^+$, 413.1686 (−0.7 ppm error)].

(3R,5'S)-1'-*tert*-Butyl 5'-ethyl 1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (325′) and (3S,5'S)-1'-*tert*-butyl 5'-ethyl 1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1',5'-dicarboxylate (325′′)



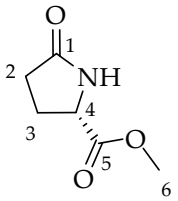
325 '



325 ''

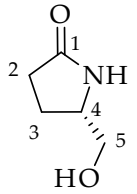
(*S*)-1-*tert*-Butyl 2-ethyl 4-(methyl(phenyl)carbamoyl)-5-oxopyrrolidine-1,2-dicarboxylate (**324**, 156 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 45 min according to general procedure F. Flash column chromatography [20–33% EtOAc/PE] afforded an inseparable mixture of **325′**, **325′′** and lactam **317** (90 mg, corresponding to 67.5 mg of **325′** and **325′′**, 44%, 5:3 dr; minor diastereoisomer was tentatively assigned as **325′′** due to a small NOE enhancement between H-2* and H-11*) as a pale yellow oil, R_f (1:1 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3057, 2981, 2937, 1793, 1750, 1720, 1612, 1494, 1473; δ_H (400 MHz, $CDCl_3$, minor diastereoisomer starred) 7.34 (1H*, td, *J* = 7.5, 1.0, H-4*), 7.33 (1H, dd, *J* = 7.5, 1.0, H-4), 7.29 (1H, dd, *J* = 7.5, 1.0, H-2), 7.17 (1H*, dd, *J* = 7.5, 1.0, H-2*), 7.08 (1H*, dd, *J* = 7.5, 1.0, H-3*), 7.08 (1H, dd, *J* = 7.5, 1.0, H-3), 6.86 (1H, br d, *J* = 7.5, H-5*), 6.86 (1H, br d, *J* = 7.5, H-5*), 4.95 (1H, dd, *J* = 10.0, 5.0, H-11), 4.91 (1H*, dd, *J* = 9.5, 4.5, H-11*), 4.38–4.27 (2H, 2H*, m, H-17, H-17*), 3.22 (3H, s, H-7), 3.19 (3H*, s, H-7*), 3.01 (1H, dd, *J* = 14.0, 10.0, H-10a), 2.80 (1H*, dd, *J* = 13.5, 4.5, H-10a*), 2.69 (1H*, dd, *J* = 13.5, 9.5, H-10b*), 2.28 (1H, dd, *J* = 14.0, 5.0, H-10b), 1.52 (9H*, s, H-15*), 1.50 (9H, s, H-15), 1.34 (3H, t, *J*= 7.0, H-18), 1.33 (3H*, t, *J*= 7.0, H-18*); δ_C (100 MHz, $CDCl_3$, minor diastereoisomer starred) 174.2 (C-8), 173.2 (C-8*), 171.5 (C-16), 169.9 (C-16*), 168.5 (C-12), 168.3 (C-12*), 149.3 (C-13*), 148.9 (C-13), 144.4 (C-6*), 144.2 (C-6), 129.7 (C-4*), 129.6 (C-4), 128.4 (C-1*), 128.3 (C-1), 123.8 (C-2), 123.4 (C-3), 123.1 (C-3*), 122.7 (C-2*), 108.7 (C-5*), 108.6 (C-5), 84.3 (C-14), 84.2 (C-14*), 62.0 (C-17*), 61.9 (C-17), 58.7 (C-9*), 58.5 (C-9), 56.8 (C-11*), 56.6 (C-11), 31.4 (C-10*), 31.2 (C-10), 27.7 (C-15*), 27.7 (C-15), 26.7 (C-7), 26.6 (C-7*), 14.1, 14.0 (C-18, C-18*); *m/z* (ESI) 411 $[MNa]^+$; [HRMS (ESI): calcd for $C_{20}H_{24}N_2NaO_6$, 411.1527. Found: $[MNa]^+$, 411.1517 (2.2 ppm error)].

(*S*)-Methyl 5-oxopyrrolidine-2-carboxylate (326)



The title compound was prepared based on the procedures by Kamimura[247] and Williams.[248] To a solution of (S)-pyroglutamic acid (**315,** 5.00 g, 38.8 mmol) in MeOH (70 mL) at 0 °C was added thionyl chloride (2.83 mL, 38.8 mmol) dropwise. The reaction was stirred at 0 °C for 10 min then allowed to warm to room temperature and stirred at this temperature for 1 h. After dilution with H_2O (20 mL), $NaHCO_3$ (12 g) was added slowly and the resulting suspension filtered. The filtrate was concentrated *in vacuo* to approx. half the original volume then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **326** (3.85 g, 70%) as a colourless oil, R_f (EtOAc) = 0.20; $[\alpha]_D^{20}$ −2.9 (*c* 0.83, CH_2Cl_2) [lit[292] $[\alpha]_D$ −2.3 (*c* 1.0, CH_2Cl_2)]; δ_H (400 MHz, $CDCl_3$) 6.59 (1H, br s, NH), 4.25 (1H, dd, *J* = 9.0, 5.5, H-4), 3.76 (3H, s, H-6), 2.52–2.17 (4H, m, H-2, H-3); δ_C (100 MHz, $CDCl_3$) 177.9 (C-1), 172.4 (C-5), 55.3 (C-4), 52.5 (C-6), 29.2 (C-2), 24.7 (C-3). Data consistent with the literature values.[292,293]

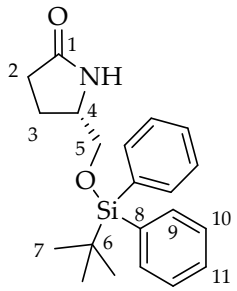
(*S*)-5-(Hydroxymethyl)pyrrolidin-2-one (327)[250]



The title compound was prepared according to the procedure by Otsuka.[250] To a solution of (*S*)-methyl 5-oxopyrrolidine-2-carboxylate (**326**, 3.84 g, 26.8 mmol) in EtOH (40 mL) at 0 °C was slowly added sodium borohydride (1.01 g, 27.3 mmol). The reaction stirred at room temperature for 2 h before acidification with conc. aq. HCl (3 mL) and concentrated *in vacuo*. The residue was suspended in $CHCl_3$ (20 mL), filtered through celite and the filtrate concentrated *in vacuo*. Flash column chromatography [5–10% MeOH/$CHCl_3$] afforded **327** (1.44 g, 46%) as colourless prisms, mp 65–67 °C (lit[294] 68–69 °C); R_f (1:9 MeOH:$CHCl_3$) = 0.20; $[\alpha]_D^{20}$ +39.1 (*c* 0.31, MeOH) [lit[250] $[\alpha]_D$ +34.5 (*c* 1.04, EtOH); lit[295] $[\alpha]_D$ +25 (*c* 0.35, MeOH)]; δ_H (400 MHz, $CDCl_3$) 7.46 (1H, br s, NH), 4.55 (1H, t, *J* = 6.0, OH), 3.81–3.74 (1H, m, H-4), 3.64 (1H, ddd, *J* = 11.5, 5.5, 3.0, H-5a), 3.43 (1H, dt, *J* = 11.5, 6.5, H-5b), 2.40–2.26 (2H, m, H-2), 2.14 (1H, dddd, *J* = 13.0, 9.0, 8.0, 7.0, H-3a), 1.77 (1H, dddd, *J* = 13.0, 9.5, 7.5, 5.5, H-3b);

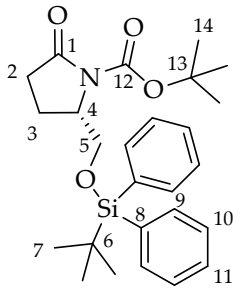
δ_C (100 MHz, $CDCl_3$) 179.4 (C-1), 65.7 (C-5), 56.5 (C-4), 30.3 (C-2), 22.5 (C-3). Data consistent with the literature values.[250,294]

(*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)pyrrolidin-2-one (328)[251]



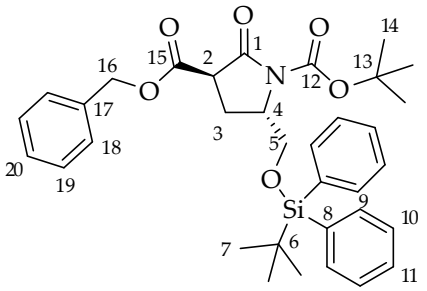
The title compound was prepared according to the procedure by Zanardi.[251] To a solution of (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**327**, 1.38 g, 12.0 mmol) in DMF (30 mL) was added imidazole (982 mg, 14.4 mmol) followed by *tert*-butyldiphenylsilylchloride (3.73 mL, 14.4 mmol). The reaction was stirred at room temperature for 16 h then quenched with aq. NH_4Cl (80 mL) and extracted with EtOAc (2 x 40 mL). The combined organic extracts were washed with H_2O (2 x 40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [EtOAc] afforded **328** (3.81 g, 91%) as a colourless oil, R_f (EtOAc) = 0.50; $[\alpha]_D^{20}$ +14.5 (*c* 0.565, $CHCl_3$) [lit[251] $[\alpha]_D$ +15.4 (*c* 0.9, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 7.65–7.62 (4H, m, H-9), 7.47–7.37 (6H, m, H-10, H-11), 5.85 (1H, br s, NH), 3.84–3.77 (1H, m, H-4), 3.62 (1H, dd, *J* = 10.5, 4.0, H-5a), 3.51 (1H, dd, *J* = 10.5, 7.5, H-5b), 2.35–2.30 (2H, m, H-2), 2.18–2.09 (1H, m, H-3a), 1.76–1.67 (1H, m, H-3b), 1.05 (9H, s, H-7); δ_C (100 MHz, $CDCl_3$) 177.8 (C-1), 135.5 (C-9), 132.9 (C-8), 129.9 (C-11), 127.8 (C-10), 67.5 (C-5), 55.6 (C-4), 29.7 (C-2), 26.8 (C-7), 22.7 (C-3), 19.1 (C-6). Data consistent with the literature values.[251]

(*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (329)[251]



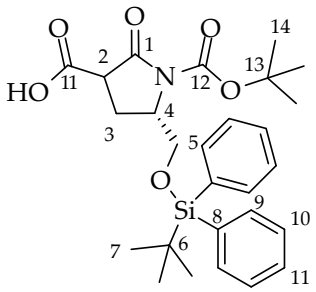
The title compound was prepared according to the procedure by Zanardi.[251] To a solution of (*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)pyrrolidin-2-one (**328**, 3.78 g, 10.7 mmol) in MeCN (40 mL) was added di-*tert*-butyl dicarbonate (2.55 g, 11.8 mmol) and *N*,*N*-dimethylaminopyridine (130 mg, 1.07 mmol). The reaction was stirred at room temperature for 20 h, then concentrated *in vacuo*. Flash column chromatography [1:3 EtOAc:PE] afforded **329** (4.87, quant.) as a colourless oil which crystallised on standing, mp 107–108 °C (lit[296] 106–108 °C); R_f (1:1 EtOAc:PE) = 0.60; $[\alpha]_D^{20}$ −38.7 (*c* 0.995, $CHCl_3$) [lit[297] $[\alpha]_D$ −38.4 (*c* 1.30, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 7.65–7.59 (4H, m, H-9), 7.46–7.35 (6H, m, H-10, H-11), 4.23–4.18 (1H, m, H-4), 3.89 (1H, dd, *J* = 10.5, 4.0, H-5a), 3.70 (1H, dd, *J* = 10.5, 2.5, H-5b), 2.79 (1H, dt, *J* = 17.5, 10.5, H-2a), 2.43 (1H, ddd, *J* = 17.5, 9.0, 3.0, H-2b), 2.20–2.09 (2H, m, H-3), 1.43 (9H, s, H-14), 1.04 (9H, s, H-7); δ_C (100 MHz, $CDCl_3$) 175.0 (C-1), 149.8 (C-12), 135.5 (C-9), 135.5 (C-9), 133.0 (C-8), 132.6 (C-8), 129.8 (C-11), 129.8 (C-11), 127.8 (C-10), 127.8 (C-10), 82.7 (C-13), 64.9 (C-5), 58.8 (C-4), 32.3 (C-2), 28.0 (C-14), 26.8 (C-7), 21.1 (C-3), 19.1 (C-6). Data consistent with the literature values.[251,296]

(5*S*)-3-Benzyl 1-*tert*-butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-2-oxopyrrolidine-1,3-dicarboxylate (330)



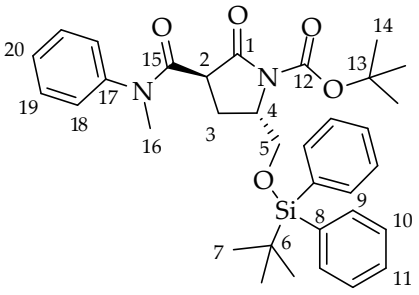
(*S*)-*tert*-Butyl 2-((*tert*-butyldiphenylsilyloxy)methyl)-5-oxopyrrolidine-1-carboxylate (**329**, 4.65 g, 10.25 mmol), LiHMDS (1 M in THF, 21.5 mL, 21.5 mmol) and benzylchloroformate (1.46 mL, 10.25 mmol) in THF (20 mL) were reacted according to general procedure D. Flash column chromatography [1:9 EtOAc:PE] afforded **330** (5.85 g, 91%, 10:1 mixture of diastereoisomers; major diastereoisomer was tentatively assigned as **330** due to a lack of NOE enhancement between H-2 and H-4) as a colourless oil, R_f (1:4 EtOAc:PE) = 0.40; $[\alpha]_D^{20}$ −23.7 (*c* 1.10, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3071, 3050, 3034, 2959, 2932, 2889, 2859, 1788, 1757, 1733, 1456; δ_H (400 MHz, $CDCl_3$, major diastereoisomer quoted) 7.62–7.56 (4H, m, H-9), 7.45–7.30 (11H, m, H-10, H-11, H-18, H-19, H-20), 5.23 (2H, s, H-16), 4.27–4.22 (1H, m, H-4), 3.94 (1H, dd, *J* = 11.0, 9.0, H-2), 3.91 (1H, dd, *J* = 10.5, 4.0, H-5a), 3.68 (1H, dd, *J* = 10.5, 2.5, H-5b), 2.59 (1H, ddd, *J* = 13.0, 11.0, 9.0, H-3a), 2.29 (1H, ddd, *J* = 13.0, 9.0, 1.0, H-3b), 1.44 (9H, s, H-14), 1.04 (9H, s, H-7); δ_C (100 MHz, $CDCl_3$, major diastereoisomer quoted) 169.1 (C-15), 169.0 (C-1), 149.4 (C-12), 135.6 (C-17), 135.4 (C-9), 135.4 (C-9), 132.7 (C-8), 132.4 (C-8), 129.9 (C-11), 129.9 (C-11), 128.5 (C-18), 128.2 (C-20), 128.0 (C-19), 127.8 (C-10), 127.8 (C-10), 83.3 (C-13), 67.3 (C-16), 64.8 (C-5), 57.0 (C-4), 49.7 (C-2), 27.9 (C-14), 26.8 (C-7), 25.4 (C-3), 19.1 (C-6); *m/z* (ESI) 610 $[MNa]^+$; [HRMS (ESI): calcd for $C_{34}H_{41}NNaO_6Si$, 610.2595. Found: $[MNa]^+$, 610.2596 (−0.2 ppm error)]. Enantiomer is reported in the literature.[298]

(5*S*)-1-(*tert*-Butoxycarbonyl)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (331)



A solution of (5*S*)-3-benzyl 1-*tert*-butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-2-oxopyrrolidine-1,3-dicarboxylate (**330**, 2.01 g, 3.43 mmol) in EtOAc (35 mL) was hydrogenolysed in the presence of 5% Pd/C (290 mg) for 18 h according to general procedure E to afford the crude title compound (1.76 g, 7:1 mixture of diastereoisomers) as a colourless oil. δ_H (400 MHz, $CDCl_3$, major diastereoisomer quoted) 7.62–7.56 (4H, m, H-9), 7.48–7.36 (6H, m, H-10, H-11), 4.27–4.23 (1H, m, H-4), 3.98 (1H, dd, *J* = 11.0, 3.0, H-5a), 3.94 (1H, dd, *J* = 11.5, 9.5, H-2), 3.71 (1H, dd, *J* = 11.0, 2.0, H-5b), 2.56–2.40 (2H, m, H-3), 1.46 (9H, s, H-14), 1.04 (9H, s, H-7). Enantiomer is reported in the literature.[298]

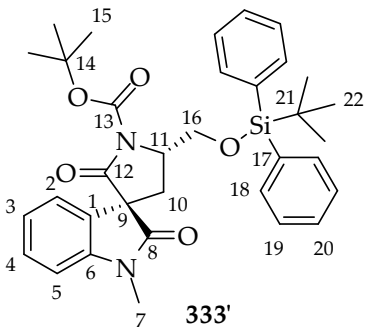
(5*S*)-*tert*-Butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-3-(methyl(phenyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (332)



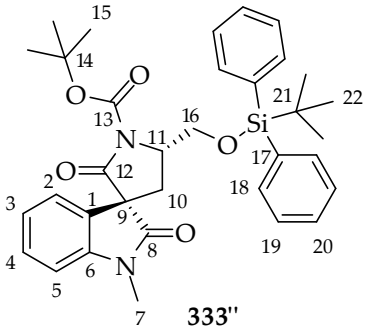
((5S)-1-(*tert*-Butoxycarbonyl)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (**331**, 872 mg), *N*-methylaniline (0.21 mL, 1.93 mmol), 2-chloro-1-methylpyridinium iodide (670 mg, 2.63 mmol) and triethylamine (1.22 mL, 8.76 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column

chromatography [10–20% EtOAc/PE] afforded **332** (903 mg, 88% over 2 steps, >20:1 dr; major diastereoisomer tentatively assigned as **332** due to a lack of NOE enhancement between H-2 and H-4) as a colourless sticky foam, R_f (1:4 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (thin film) 3070, 3052, 2959, 2932, 2858, 1785, 1746, 1716, 1655, 1595, 1567, 1496, 1472, 1459; $[\alpha]_D^{20}$ +48.6 (*c* 1.03, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.49–7.22 (15H, m, H-9, H-10, H-11, H-18, H-19, H-20), 4.25–4.20 (1H, m, H-4), 3.92 (1H, dd, *J* = 9.5, 10.0, H-2), 3.80 (1H, dd, *J* = 10.5, 3.0, H-5a), 3.48 (1H, dd, *J* = 10.5, 2.0, H-5b), 3.33 (3H, s, H-16), 2.80 (1H, dt, *J* = 12.5, 10.0, H-3a), 2.07–2.00 (1H, ddd, *J* = 12.5, 9.5, 1.0, H-3b), 1.42 (9H, s, H-14), 0.71 (9H, s, H-7); δ_C (100 MHz, $CDCl_3$) 170.9 (C-1), 169.3 (C-15), 149.4 (C-12), 143.3 (C-17), 135.3 (C-9), 132.7 (C-8), 132.2 (C-8), 129.9 (one of C-11, C-18, C-19), 129.7 (one of C-11, C-18, C-19), 128.1 (C-20), 127.7 (C-10), 127.7 (C-10), 127.5 (one of C-11, C-18, C-19), 82.9 (C-13), 64.9 (C-5), 57.2 (C-4), 47.3 (C-2), 38.3 (C-16), 27.9 (C-14), 26.6 (C-7), 26.1 (C-3), 18.7 (C-6); *m/z* (ESI) 609 $[MNa]^+$; [HRMS (ESI): calcd for $C_{34}H_{42}N_2NaO_5Si$, 609.2755. Found: $[MNa]^+$, 609.2756 (−0.1 ppm error)].

(3*R*,5'*S*)-*tert*-Butyl 5'-((*tert*-butyldiphenylsilyloxy)methyl)-1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (333′) and (3*S*,5'*S*)-*tert*-butyl 5'-((*tert*-butyldiphenylsilyloxy)methyl)-1-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (333′′)



333'

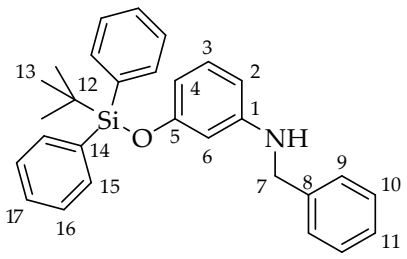


333''

(5S)-*tert*-Butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-3-(methyl(phenyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (**332**, 235 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [1:4 EtOAc/PE] afforded **333′** (56 mg, 24%) as a yellow oil, as well as an inseparable mixture of

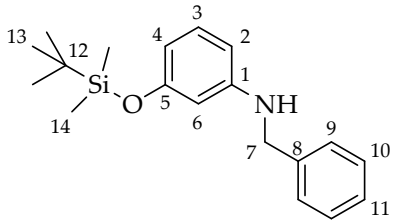
spirocycle **333''** and lactam **329** (81 mg, corresponding to 58 mg of **333''**, 25%) as an off-white sticky foam. **333'**: R_f (1:4 EtOAc:PE) = 0.15; ν_{max}/cm^{-1} (thin film) 3071, 3053, 2959, 2933, 2889, 2858, 1786, 1749, 1718, 1614, 1494, 1471; $[\alpha]_D^{20}$ −10.6 (*c* 0.78, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.66–7.63 (4H, m, H-18), 7.47–7.36 (6H, m, H-19, H-20), 7.31 (1H, td, *J* = 7.5, 1.0, H-4), 7.06 (1H, dd, *J* = 7.5, 1.0, H-2), 6.98 (1H, td, *J* = 7.5, 1.0, H-3), 6.85 (1H, br d, *J* = 7.5, H-5), 4.59 (1H, dddd, *J* = 8.0, 7.0, 5.5, 2.5, H-11), 4.14 (1H, dd, *J* = 10.5, 5.5, H-16a), 3.93 (1H, dd, *J* = 10.5, 2.5, H-16b), 3.20 (3H, s, H-7), 2.64 (1H, dd, *J* = 13.5, 8.0, H-10a), 2.58 (1H, dd, *J* = 13.5, 7.0, H-10b), 1.44 (9H, s, H-15), 1.09 (9H, s, H-22); δ_C (100 MHz, $CDCl_3$) 175.0 (C-8), 169.8 (C-12), 149.7 (C-13), 144.6 (C-6), 135.6 (C-18), 135.5 (C-18), 133.0 (C-17), 132.9 (C-17), 129.9 (C-20), 129.9 (C-20), 129.2 (C-4), 128.8 (C-1), 127.8 (C-19), 127.8 (C-19), 123.7 (C-2), 123.2 (C-3), 108.5 (C-5), 83.6 (C-14), 63.7 (C-16), 58.9 (C-9), 56.2 (C-11), 30.2 (C-10), 27.9 (C-15), 26.9 (C-22), 26.6 (C-7), 19.4 (C-21); Stereochemistry assigned based on a lack of NOE enhancement between H-2 and H-11; *m/z* (ESI) 607 $[MNa]^+$; [HRMS (ESI): calcd for $C_{34}H_{40}N_2NaO_5Si$, 607.2599. Found: $[MNa]^+$, 607.2610 (−1.9 ppm error)]; **333''**: R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3071, 3051, 2959, 2932, 2892, 2857, 1785, 1751, 1719, 1612, 1494, 1472; δ_H (400 MHz, $CDCl_3$) 7.71–7.68 (4H, m, H-18), 7.46–7.35 (6H, m, H-19, H-20), 7.32 (1H, td, *J* = 7.5, 1.0, H-4), 7.18 (1H, ddd, *J* = 7.5, 1.0, 0.5, H-2), 7.07 (1H, td, *J* = 7.5, 1.0, H-3), 6.85 (1H, br d, *J* = 7.5, H-5), 4.44 (1H, tdd, *J* = 8.5, 5.0, 3.5, H-11), 4.27 (1H, dd, *J* = 9.5, 8.5, H-16a), 4.09 (1H, dd, *J* = 9.5, 3.5, H-16b), 3.24 (3H, s, H-7), 2.94 (1H, dd, *J* = 14.0, 5.0, H-10a), 2.46 (1H, dd, *J* = 14.0, 8.5, H-10b), 1.40 (9H, s, H-15), 1.08 (9H, s, H-22); δ_C (100 MHz, $CDCl_3$) 174.0 (C-8), 169.8 (C-12), 149.6 (C-13), 144.3 (C-6), 135.6 (C-18), 135.6 (C-18), 133.4 (C-17), 133.2 (C-17), 130.1 (C-1), 129.7 (C-20), 129.3 (C-4), 127.7 (C-19), 123.0 (C-2), 122.6 (C-3), 108.5 (C-5), 83.7 (C-14), 64.1 (C-16), 58.8 (C-9), 56.5 (C-11), 30.5 (C-10), 27.8 (C-15), 26.8 (C-22), 26.7 (C-7), 19.3 (C-21); Stereochemistry assigned based on an NOE enhancement between H-2 and H-11; *m/z* (ESI) 607 $[MNa]^+$; [HRMS (ESI): calcd for $C_{34}H_{40}N_2NaO_5Si$, 607.2599. Found: $[MNa]^+$, 607.2593 (0.9 ppm error)].

_N_-Benzyl-3-(*tert*-butyldiphenylsilyloxy)aniline (335a)



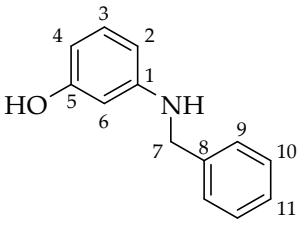
The title compound was prepared based on the procedure by Hennessy.[252] To 3-aminophenol (**334,** 2.18 g, 20.0 mmol), imidazole (1.77 g, 26.0 mmol) and *tert*-butyldiphenylsilyl chloride (5.72 mL, 22.0 mmol) was added DMF (8 mL) and the mixture was stirred at room temperature for 4 h. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H_2O (5 x 10 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to afford 3-(*tert*-butyldimethylsilyloxy)aniline (7.82 g). The crude residue was re-dissolved in MeOH (20 mL), and benzaldehyde (2.14 mL, 21.0 mmol) and acetic acid (3 drops) were added. The mixture was stirred at room temperature for 3 h. Sodium borohydride (760 mg, 20.0 mmol) was added in very small portions and the mixture stirred at room temperature for 1 h. The solvent was removed *in vacuo*, and the residue diluted with H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [1:49 EtOAc:PE] afforded **335a** (2.69 g, 31%) as a yellow oil, R_f (1:4 EtOAc:PE) = 0.70; ν_{max}/cm^{-1} (thin film) 3419, 3069, 3049, 3028, 2999, 2957, 2930, 2891, 2857, 1600, 1493, 1472, 1453; δ_H (400 MHz, $CDCl_3$) 7.75–7.72 (4H, m, H-15), 7.45–7.23 (11H, m, H-9, H-10, H-11, H-16, H-17), 6.89 (1H, t, *J* = 8.0, H-3), 6.21–6.16 (2H, m, H-2, H-4), 6.12 (1H, t, *J* = 2.0, H-6), 4.11 (2H, s, H-7), 3.66 (1H, br s, NH), 1.10 (9H, s, H-13); δ_C (100 MHz, $CDCl_3$) 156.7 (C-5), 149.2 (C-1), 139.3 (C-8), 135.5 (C-15), 133.2 (C-14), 129.7 (C-17), 129.6 (C-3), 128.5 (C-10), 127.6 (C-16), 127.5 (C-9), 127.1 (C-11), 109.2 (C-4), 106.3 (C-2), 104.3 (C-6), 48.2 (C-7), 26.5 (C-13), 19.4 (C-12); *m/z* (ESI) 438 $[MH]^+$; [HRMS (ESI): calcd for $C_{29}H_{32}NOSi$, 438.2248. Found: $[MH]^+$, 438.2263 (−3.4 ppm error)].

_N_-Benzyl-3-(_tert_-butyldimethylsilyloxy)aniline (335b)[252]



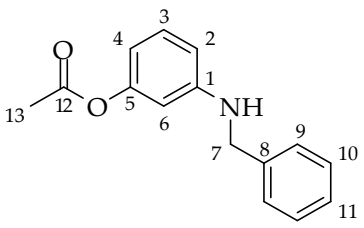
The title compound was prepared according to the procedure by Hennessy.[252] To 3-aminophenol (**334,** 545 mg, 5.00 mmol), imidazole (442 mg, 6.50 mmol) and *tert*-butyldimethylsilyl chloride (831 mg, 5.50 mmol) was added DMF (3 mL) and the mixture was stirred at room temperature for 4 h. The reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with H_2O (5 x 5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to afford 3-(*tert*-butyldimethylsilyloxy)aniline (1.01 g). The crude residue was re-dissolved in MeOH (5 mL), and benzaldehyde (0.48 mL, 4.71 mmol) and acetic acid (3 drops) were added. The mixture was stirred at room temperature for 3 h. Sodium borohydride (170 mg, 4.48 mmol) was added in very small portions and the mixture stirred at room temperature for 1 h. The solvent was removed *in vacuo*, and the residue diluted with H_2O (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [1:49 EtOAc:PE] afforded **335b** (793 mg, 51%) as a pale yellow oil, R_f (1:4 EtOAc:PE) = 0.70; δ_H (400 MHz, $CDCl_3$) 7.42–7.28 (5H, m, H-9, H-10, H-11), 7.05 (1H, t, *J* = 8.0, H-3), 6.30 (1H, ddd, *J* = 8.0, 2.0, 1.0, H-2), 6.26 (1H, ddd, *J* = 8.0, 2.0, 1.0, H-4), 6.17 (1H, t, *J* = 2.0, H-6), 4.33 (2H, s, H-7), 4.02 (1H, br s, NH), 1.00 (9H, s, H-13), 0.19 (6H, s, H-14); δ_C (100 MHz, $CDCl_3$) 156.7 (C-5), 149.4 (C-1), 139.4 (C-8), 129.8 (C-3), 128.6 (C-10), 127.5 (C-9), 127.2 (C-11), 109.4 (C-4), 106.5 (C-2), 104.7 (C-6), 48.3 (C-7), 25.7 (C-13), 18.2 (C-12), −4.5 (C-14); *m/z* (ESI) 314 $[MH]^+$; [HRMS (ESI): calcd for $C_{19}H_{28}NNOSi$, 314.1935. Found: $[MH]^+$, 314.1931 (1.2 ppm error)]. Data consistent with the literature values.[252]

3-(Benzylamino)phenol (335e)



To a solution of *N*-benzyl-3-(*tert*-butyldimethylsilyloxy)aniline (**335b**, 292 mg, 0.93 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1 M in THF, 1.03 mL, 1.03 mmol) and the reaction stirred at room temperature for 3 h. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [1:4 EtOAc:PE] afforded **335e** (185 mg, quant.) as a brown oil, R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3409, 3335, 3085, 3060, 3029, 2927, 2852, 1602, 1511, 1496, 1471, 1452; δ_H (400 MHz, $CDCl_3$) 7.38-7.33 (4H, m, H-9, H-10), 7.31–7.27 (1H, m, H-11), 7.03 (1H, t, *J* = 8.0, H-3), 6.24 (1H, ddd, *J* = 8.0, 2.0, 1.0, H-2), 6.19 (1H, ddd, *J* = 8.0, 2.0, 1.0, H-4), 6.12 (1H, t, *J* = 2.0, H-6), 4.30 (2H, s, H-7); δ_C (100 MHz, $CDCl_3$) 156.7 (C-5), 149.7 (C-1), 139.2 (C-8), 130.2 (C-3), 128.6 (C-10), 127.5 (C-9), 127.2 (C-11), 105.9 (C-2), 104.6 (C-4), 99.7 (C-6), 48.2 (C-7); *m/z* (ESI) 200 $[MH]^+$; [HRMS (ESI): calcd for $C_{13}H_{14}NO$, 200.1070. Found: $[MH]^+$, 200.1069 (0.5 ppm error)]. Data consistent with the literature values.[299]

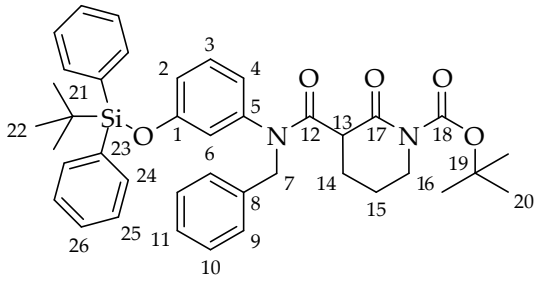
3-(Benzylamino)phenyl acetate (335c)



To a suspension of sodium hydride (60% in mineral oil, 38 mg, 0.92 mmol) in THF (3.5 mL) at 0 °C was added a solution of 3-(benzylamino)phenol (**335e**, 166 mg, 0.83 mmol) in THF (1.5 mL) *via* syringe and the mixture stirred at 0 °C for 10 min. Acetic anhydride (0.083 mL, 0.88 mmol) was added and the mixture stirred at room

temperature for 1 h. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [1:9 EtOAc:PE] afforded **335c** (148 mg, 74%) as a colourless oil, R_f (1:4 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3414, 3084, 3061, 3029, 2924, 2849, 1761, 1741, 1614, 1588, 1509, 1495, 1452; δ_H (400 MHz, $CDCl_3$) 7.38–7.27 (5H, m, H-9, H-10, H-11), 7.16 (1H, t, *J* = 8.0, H-3), 6.50 (1H, ddd, *J* = 8.0, 2.0, 0.5, H-2), 6.44 (1H, ddd, *J* = 8.0, 2.0, 1.0, H-4), 6.36 (1H, t, *J* = 2.0, H-6), 4.31 (2H, br s, H-7), 4.12 (1H, br s, NH), 2.27 (3H, s, H-13); δ_C (100 MHz, $CDCl_3$) 169.5 (C-12), 151.8 (C-5), 149.3 (C-1), 138.9 (C-8), 129.9 (C-3), 128.6 (C-10), 127.5 (C-9), 127.3 (C-11), 110.5 (C-2), 110.3 (C-4), 105.7 (C-6), 48.2 (C-7), 21.2 (C-13); *m/z* (ESI) 242 $[MH]^+$; [HRMS (ESI): calcd for $C_{15}H_{16}NO_2$, 242.1176. Found: $[MH]^+$, 242.1181 (−2.1 ppm error)].

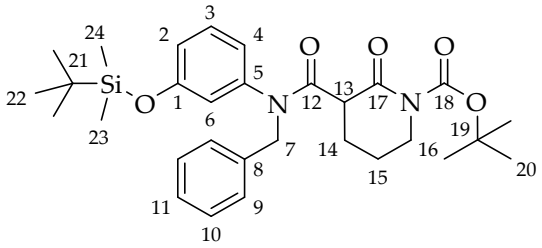
***tert*-Butyl 3-(benzyl(3-(*tert*-butyldiphenylsilyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20aa)**



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 513 mg), *N*-benzyl-3-(*tert*-butyldiphenylsilyloxy)aniline (812 mg, 1.86 mmol), 2-chloro-1-methylpyridinium iodide (646 mg, 2.79 mmol) and triethylamine (1.2 mL, 9.30 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [20–33% EtOAc/PE] afforded **20aa** (1.04 g, 82% over 2 steps) as an off-white sticky foam, R_f (1:4 EtOAC:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3070, 3030, 2958, 2933, 2894, 2859, 1769, 1717, 1657, 1593, 1485, 1457; δ_H (400 MHz, $CDCl_3$) 7.65–7.62 (4H, m, H-24), 7.47–7.32 (6H, m, H-25, H-26), 7.21–7.16 (3H, m, H-10, H-11), 7.11–7.07 (2H, m, H-9), 7.00 (1H, t, *J* = 8.0, H-3), 6.74 (2H, v br s, H-2, H-4), 6.42 (1H, v br s, H-6), 4.84 (1H, br d, *J* = 14.0, H-7a), 4.52 (1H, v br s, H-7b), 3.57 (2H, dd, *J* = 7.5, 4.5, H-16), 3.29 (1H, dd, *J* = 10.0, 7.0, H-13), 2.02–1.84 (2H, m, H-14a, H-15a), 1.60–1.41 (2H, m, H-14b, H-15b), 1.50 (9H, s,

H-20), 1.06 (9H, s, H-22); δ_C (100 MHz, $CDCl_3$) 170.0 (C-12), 168.0 (C-17), 156.3 (C-1), 152.3 (C-18), 142.5 (C-5), 136.8 (C-8), 135.4 (C-24), 132.3 (C-23), 132.3 (C-23), 130.0 (C-3), 130.0 (C-26), 128.5 (C-9), 128.2 (C-10), 127.8 (C-25), 127.8 (C-25), 127.1 (C-11), 119.9 (C-2 or C-4), 83.0 (C-19), 52.9 (C-7), 48.7 (C-13), 46.4 (C-16), 27.9 (C-20), 26.4 (C-22), 25.3 (C-14), 21.5 (C-15), 19.3 (C-21), some aromatic peaks not visible due to broadening; *m/z* (ESI) 685 $[MNa]^+$; [HRMS (ESI): calcd for $C_{40}H_{46}N_2NaO_5Si$, 685.3068. Found: $[MNa]^+$, 685.3069 (−0.2 ppm error)].

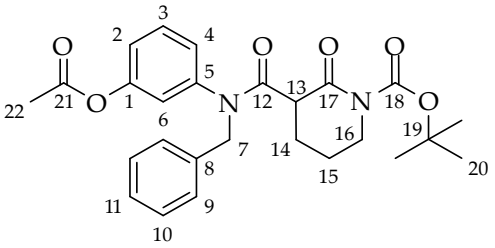
tert-Butyl 3-(benzyl(3-(_tert_-butyldimethylsilyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20ab)



1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 298 mg), *N*-benzyl-3-(*tert*-butyldimethylsilyloxy)aniline (423 mg, 1.23 mmol), 2-chloro-1-methylpyridinium iodide (470 mg, 1.84 mmol) and triethylamine (0.85 mL, 6.14 mmol) in CH_2Cl_2 (5 mL) were reacted according to general procedure E. Flash column chromatography [1:3 EtOAc:PE] afforded **20ab** (466 mg, 74% over 2 steps) as a colourless oil, R_f (1:2 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3064, 3030, 2955, 2931, 2896, 2859, 1771, 1718, 1659, 1592, 1485, 1459; δ_H (400 MHz, $CDCl_3$) 7.28–7.18 (5H, m, H-9, H-10, H-11), 7.15 (1H, t, *J* = 8.0, H-3), 6.80 (1H, v br s, H-4 or H-6), 6.77 (1H, ddd, *J* = 8.0, 2.5, 1.0, H-2), 6.55 (1H, v br s, H-4 or H-6), 4.95 (1H, v br s, H-7a), 4.84 (1H, v br s, H-7b), 3.63–3.55 (2H, m, H-16), 3.47 (1H, dd, *J* = 10.5, 7.0, H-13), 2.25–2.15 (1H, m, H-14a), 1.98 (1H, ddd, *J* = 14.0, 9.5, 5.0, H-15a), 1.94–1.84 (1H, m, H-14b), 1.64–1.53 (1H, m, H-15b), 1.50 (9H, s, H-20), 0.91 (9H, s, H-22), 0.07 (3H, s, H-23), 0.06 (3H, s, H-24); δ_C (100 MHz, $CDCl_3$) 170.1 (C-12), 168.0 (C-17), 156.4 (C-1), 152.3 (C-18), 142.9 (C-5), 137.0 (C-8), 130.2 (C-3), 128.6, 128.4 (C-9, C-10), 127.3 (C-11), 120.3 (C-2), 83.0 (C-19), 53.0 (C-7), 48.8 (C-13), 46.4 (C-16), 27.9 (C-20), 25.6 (C-22), 25.4 (C-14), 21.5 (C-15), 18.1 (C-21), −4.6 (C-23), −4.6 (C-24), some aromatic peaks not visible due to broadening; *m/z* (ESI) 561

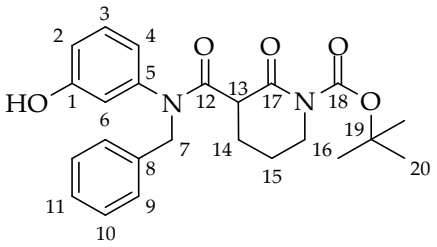
[MNa]$^+$; [HRMS (ESI): calcd for $C_{30}H_{42}N_2NaO_5Si$, 561.2755. Found: [MNa]$^+$, 561.2750 (0.9 ppm error)].

***tert*-Butyl 3-((3-acetoxyphenyl)(benzyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20ac)**



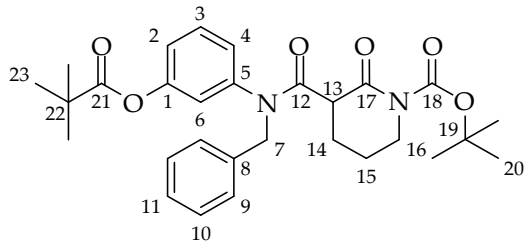
1-(*tert*-Butoxycarbonyl)-2-oxopiperidine-3-carboxylic acid (**264b**, 111 mg), 3-(benzylamino)phenyl acetate (121 mg, 0.50 mmol), 2-chloro-1-methylpyridinium iodide (174 mg, 0.68 mmol) and triethylamine (0.32 mL, 2.28 mmol) in CH_2Cl_2 (5 mL) were reacted according to general procedure E. Flash column chromatography [2:3 EtOAc:PE] afforded **20ac** (158 mg, 77% over 2 steps) as a colourless oil, R_f (1:1 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3063, 3030, 2978, 2936, 1767, 1719, 1656, 1601, 1486, 1456; δ_H (400 MHz, $CDCl_3$) 7.29 (1H, t, *J* = 8.0, H-3), 7.28–7.18 (5H, m, H-9, H-10, H-11), 7.06 (1H, v br s, H-4 or H-6), 7.04 (1H, dd, *J* = 8.0, 2.0, H-2), 6.95 (1H, v br s, H-4 or H-6), 5.00 (1H, d, *J* = 14.5, H-7a), 4.83 (1H, d, *J* = 14.5, H-7b), 3.63–3.58 (2H, m, H-16), 3.46 (1H, dd, *J* = 10.5, 6.5, H-13), 2.25 (3H, s, H-22), 2.24–2.14 (1H, m, H-14a), 2.01–1.85 (2H, m, H-14b, H-15a), 1.67–1.57 (1H, m, H-15b), 1.49 (9H, s, H-20); δ_C (100 MHz, $CDCl_3$) 170.1 (C-12), 168.9 (C-21), 168.2 (C-17), 152.0 (C-18), 151.0 (C-1), 142.8 (C-5), 136.7 (C-8), 130.2 (C-3), 128.5, 128.4 (C-9, C-10), 127.3 (C-11), 121.6 (C-2), 83.0 (C-19), 53.1 (C-7), 48.8 (C-13), 46.5 (C-16), 27.9 (C-20), 25.3 (C-14), 21.5 (C-15), 21.0 (C-22), some aromatic peaks not visible due to broadening; *m/z* (ESI) 489 [MNa]$^+$; [HRMS (ESI): calcd for $C_{26}H_{30}N_2NaO_6$, 489.1996. Found: [MNa]$^+$, 489.1993 (0.7 ppm error)].

***tert*-Butyl 3-(benzyl(3-hydroxyphenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20ae)**



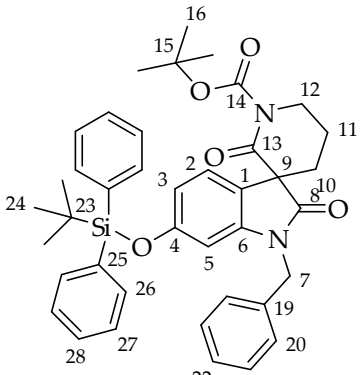
To a solution of *tert*-butyl 3-(benzyl(3-(*tert*-butyldimethylsilyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20ab**, 184 mg, 0.43 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1 M in THF, 0.38 mL, 0.38 mmol) and the reaction stirred at room temperature for 1.5 h. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [2:3 EtOAc:PE] afforded **20ae** (126 mg, 87%) as a colourless amorphous solid, mp 141–142 °C; R_f (2:3 EtOAc:PE) = 0.10; ν_{max}/cm^{-1} (thin film) 3390, 3065, 3031, 2979, 2939, 1763, 1718, 1652, 1605, 1592, 1486, 1457; δ_H (400 MHz, $CDCl_3$) 7.54 (1H, br s, OH), 7.24–7.15 (5H, m, H-9, H-10, H-11), 7.10 (1H, t, *J* = 8.0, H-3), 6.80 (1H, v br s, H-4 or H-6), 6.83 (1H, ddd, *J* = 8.0, 2.5, 1.0, H-2), 6.61 (1H, v br s, H-4 or H-6), 4.98 (1H, d, *J* = 15.0, H-7a), 4.80 (1H, d, *J* = 15.0, H-7b), 3.60 (2H, dd, *J* = 7.5, 4.5, H-16), 3.53 (1H, dd, *J* = 10.5, 6.5, H-13), 2.23–2.12 (1H, m, H-14a), 1.98–1.86 (2H, m, H-14b, H-15a), 1.63–1.52 (1H, m, H-15b), 1.48 (9H, s, H-20); δ_C (100 MHz, $CDCl_3$) 170.4 (C-12), 168.8 (C-17), 157.4 (C-1), 152.0 (C-18), 142.7 (C-5), 136.8 (C-8), 130.3 (C-3), 128.4, 128.3 (C-9, C-10), 127.2 (C-11), 115.8 (C-2), 83.3 (C-19), 53.1 (C-7), 49.1 (C-13), 46.7 (C-16), 27.9 (C-20), 25.4 (C-14), 21.5 (C-15), some aromatic peaks not visible due to broadening; *m/z* (ESI) 447 $[MNa]^+$; [HRMS (ESI): calcd for $C_{24}H_{28}N_2NaO_5$, 447.1890. Found: $[MNa]^+$, 447.1871 (4.5 ppm error)].

***tert*-Butyl 3-(benzyl(3-(pivaloyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20ad)**

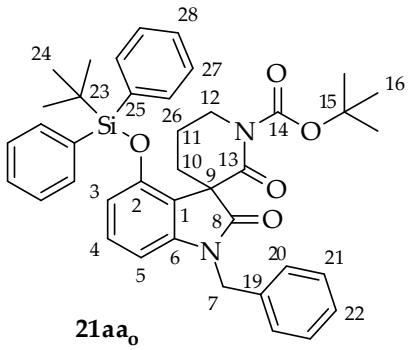


To a solution of *tert*-butyl 3-(benzyl(3-hydroxyphenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20ae**, 103 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was added *N*,*N*-dimethylaminopyridine (3 mg, 0.024 mmol), triethylamine (0.10 mL, 0.73 mmol) and trimethylacetyl chloride (0.06 mL, 0.48 mmol). The reaction was stirred at room temperature for 3 h then quenched with 10% HCl (2 mL) and the layers separated. The organic layer was washed with aq. $NaHCO_3$ (5 mL) and brine (5 mL) then dried (Mg_2SO_4) and concentrated *in vacuo*. Flash column chromatography [1:2 EtOAc:PE] afforded **20ad** (111 mg, 90%) as a colourless foam, R_f (2:3 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3064, 3030, 2976, 2935, 2875, 1753, 1718, 1656, 1601, 1482, 1457; δ_H (400 MHz, $CDCl_3$) 7.29–7.19 (6H, m, H-3, H-9, H-10, H-11), 7.01 (1H, ddd, *J* = 8.0, 2.0, 1.0, H-2), 6.70 (1H, v br s), 6.90 (1H, v br s) (H-4, H-6), 4.98 (1H, br s, H-7a), 4.86 (1H, br s, H-7b), 3.65–3.60 (2H, m, H-16), 3.48 (1H, dd, *J* = 10.0, 7.0, H-13), 2.25–2.15 (1H, m, H-14a), 2.01–1.84 (2H, m, H-14b, H-15a), 1.67–1.55 (1H, m, H-15b), 1.50 (9H, s, H-20), 1.32 (9H, s, H-23); δ_C (100 MHz, $CDCl_3$) 176.6 (C-21), 170.1 (C-12), 168.2 (C-17), 152.1 (C-18), 151.6 (C-1), 142.8 (C-5), 136.7 (C-8), 130.1 (C-3), 128.6, 128.4 (C-9, C-10), 127.3 (C-11), 121.5 (C-2), 83.0 (C-19), 53.1 (C-7), 48.9 (C-13), 46.5 (C-16), 39.1 (C-22), 27.9 (C-20), 27.0 (C-23), 25.3 (C-14), 21.5 (C-15), some aromatic peaks not visible due to broadening; *m/z* (ESI) 531 $[MNa]^+$; [HRMS (ESI): calcd for $C_{29}H_{36}N_2NaO_6$, 531.2466. Found: $[MNa]^+$, 531.2463 (0.5 ppm error)].

***tert*-Butyl 1-benzyl-6-(*tert*-butyldiphenylsilyloxy)-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate ($21aa_p$) and *tert*-butyl 1-benzyl-4-(*tert*-butyldiphenylsilyloxy)-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate ($21aa_o$)**



$21aa_p$

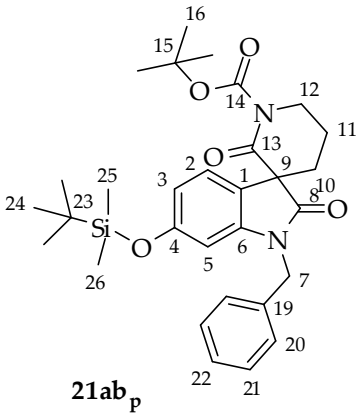


$21aa_o$

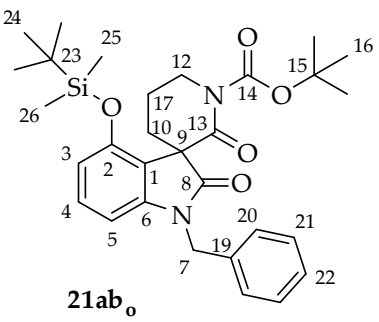
tert-Butyl 3-(benzyl(3-(*tert*-butyldiphenylsilyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20aa**, 265 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [10–20% EtOAc/PE] afforded **$21aa_p$** (78 mg, 30%) as a colourless powder, and **$21aa_o$** (49 mg, 19%) as an off-white amorphous solid. **$21aa_p$**: mp 169–170 °C; R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3071, 3031, 2959, 2933, 2895, 2859, 1768, 1723, 1616, 1499, 1473, 1456; δ_H (400 MHz, $CDCl_3$) 7.63–7.59 (4H, m, H-26), 7.45–7.39 (2H, m, H-28), 7.36–7.30 (4H, m, H-27), 7.21–7.18 (3H, m, H-21, H-22), 7.05–7.02 (2H, m, H-20), 7.02 (1H, d, *J* = 8.0, H-2), 6.42 (1H, dd, *J* = 8.0, 2.0, H-3), 6.11 (1H, d, *J* = 2.0, H-5), 4.67 (1H, d, *J* = 15.5, H-7a), 4.57 (1H, d, *J* = 15.5, H-7b), 3.91–3.78 (2H, m, H-12), 2.36 (1H, ddd, *J* = 13.5, 10.0, 3.5, H-10a), 2.31–2.21 (1H, m, H-11a), 2.15–2.05 (1H, m, H-11b), 1.95 (1H, ddd, *J* = 13.5, 7.0, 3.5, H-10b), 1.48 (9H, s, H-16), 1.02 (9H, s, H-24); δ_C (100 MHz, $CDCl_3$) 176.1 (C-8), 167.8 (C-13), 156.3 (C-4), 152.8 (C-14), 143.8 (C-6), 135.4 (C-26), 135.2 (C-19), 132.6 (C-25), 130.0, 130.0 (C-28), 128.6 (C-21), 127.8, 127.8 (C-27), 127.4 (C-22), 127.0 (C-20), 124.0 (C-1), 123.7 (C-2), 113.5 (C-3), 102.3 (C-5), 83.4 (C-15), 57.9 (C-9), 47.2 (C-12), 43.8 (C-7), 32.1 (C-10), 27.9 (C-16), 26.5 (C-24), 19.5, 19.4 (C-11, C-23); *m/z* (ESI) 683 $[MNa]^+$; [HRMS (ESI): calcd for $C_{40}H_{44}N_2NaO_5Si$, 683.2912. Found: $[MNa]^+$, 683.2912 (−0.1 ppm error)]; **$21aa_o$**: mp 151–153 °C; R_f (1:4 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3071, 3053, 3031, 2957, 2932, 2897, 2859, 1770, 1715, 1698, 1608, 1494, 1468; δ_H (400 MHz, $CDCl_3$)

7.75–7.68 (4H, m, H-26), 7.47–7.20 (11H, m, H-20, H-21, H-22, H-27, H-28), 6.65 (1H, t, *J* = 8.5, 8.0, H-4), 6.25 (1H, dd, *J* = 8.0, 0.5, H-5), 6.01 (1H, dd, *J* = 8.5, 0.5, H-3), 5.03 (1H, d, *J* = 16.0, H-7a), 4.67 (1H, d, *J* = 16.0, H-7b), 4.19–4.13 (1H, m, H-12a), 3.77 (1H, td, *J* = 12.5, 4.0, H-12b), 3.00–2.88 (1H, m, H-11a), 2.82 (1H, td, *J* = 13.0, 3.0, H-10a), 2.17–2.11 (1H, m, H-10b), 2.02–1.95 (1H, m, H-11b), 1.47 (9H, s, H-16), 1.02 (9H, s, H-24); δ_C (100 MHz, $CDCl_3$) 175.7 (C-8), 166.2 (C-13), 153.2 (C-14), 150.9 (C-2), 144.4 (C-6), 135.7 (C-19), 135.4, 135.1 (C-26), 132.2, 130.9 (C-25), 130.0, 130.0 (C-28), 129.0 (C-4), 128.8 (C-21), 128.0, 127.9 (C-27), 127.5 (C-22), 127.1 (C-20), 119.5 (C-1), 114.7 (C-3), 102.6 (C-5), 83.1 (C-15), 57.0 (C-9), 47.2 (C-12), 43.9 (C-7), 29.6 (C-10), 27.9 (C-16), 26.1 (C-24), 19.0 (C-23), 18.5 (C-11); *m/z* (ESI) 683 $[MNa]^+$; [HRMS (ESI): calcd for $C_{40}H_{44}N_2NaO_5Si$, 683.2912. Found: $[MNa]^+$, 683.2889 (3.3 ppm error)].

***tert*-Butyl 1-benzyl-6-(*tert*-butyldimethylsilyloxy)-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate ($\mathbf{21ab_p}$) and *tert*-butyl 1-benzyl-4-(*tert*-butyldimethylsilyloxy)-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate ($\mathbf{21ab_o}$)**



$\mathbf{21ab_p}$

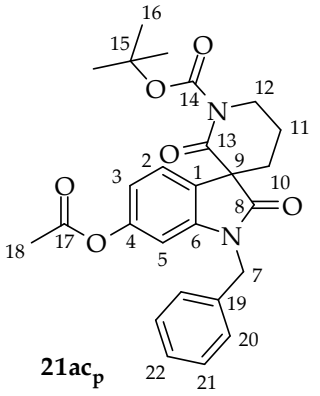


$\mathbf{21ab_o}$

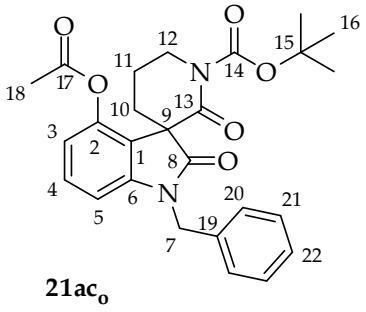
tert-Butyl 3-(benzyl(3-(*tert*-butyldimethylsilyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20ab**, 215 mg, 0.40 mmol) and copper(II) acetate monohydrate (8 mg, 0.04 mmol) in mesitylene (8 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–33% EtOAc/PE] afforded a mixture of $\mathbf{21ab_p}$ and lactam **262b** (54 mg, corresponding to 41 mg of pure $\mathbf{21ab_p}$, 19%; a small sample of pure $\mathbf{21ab_p}$ was isolated for full characterisation) as an off-white amorphous solid, and $\mathbf{21ab_o}$ (56 mg, 26%) as an off-white amorphous solid. $\mathbf{21ab_p}$: mp 136–138 °C; R_f (1:4 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3063, 3032, 2954, 2932, 2896, 2859, 1770,

1720, 1615, 1499, 1473, 1457; δ_H (400 MHz, $CDCl_3$) 7.32–7.20 (5H, m, H-20, H-21, H-22), 7.12 (1H, d, *J* = 8.0, H-2), 6.43 (1H, dd, *J* = 8.0, 2.0, H-3), 6.13 (1H, d, *J* = 2.0, H-5), 4.92 (1H, d, *J* = 16.0, H-7a), 4.85 (1H, d, *J* = 16.0, H-7b), 3.94–3.81 (2H, m, H-12), 2.41 (1H, ddd, *J* = 13.5, 10.5, 3.5, H-10a), 2.35–2.26 (1H, m, H-11a), 2.20–2.09 (1H, m, H-11b), 2.01 (1H, ddd, *J* = 13.5, 6.5, 3.5, H-10b), 1.49 (9H, s, H-16), 0.88 (9H, s, H-24), 0.03 (3H, s, H-25), 0.02 (3H, s, H-26); δ_C (100 MHz, $CDCl_3$) 176.1 (C-8), 167.8 (C-13), 156.3 (C-4), 152.7 (C-14), 143.9 (C-6), 135.2 (C-19), 128.8 (C-21), 127.5 (C-22), 127.0 (C-20), 124.3 (C-1), 123.7 (C-2), 113.6 (C-3), 102.9 (C-5), 83.3 (C-15), 57.9 (C-9), 47.2 (C-12), 43.8 (C-7), 32.1 (C-10), 27.9 (C-16), 25.5 (C-24), 19.5 (C-11), 18.1 (C-23), −4.7 (C-25, C-26); *m/z* (ESI) 559 $[MNa]^+$; [HRMS (ESI): calcd for $C_{30}H_{40}N_2NaO_5Si$, 559.2599. Found: $[MNa]^+$, 559.2597 (0.3 ppm error)]; **21ab$_o$**: mp 159–161 °C; R_f (1:4 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3063, 3032, 2957, 2931, 2896, 2858, 1771, 1714, 1696, 1606, 1495, 1468; δ_H (400 MHz, $CDCl_3$) 7.32–7.21 (5H, m, H-20, H-21, H-22), 7.02 (1H, t, *J* = 8.5, 8.0, H-4), 6.50 (1H, dd, *J* = 8.5, 0.5, H-3), 6.31 (1H, dd, *J* = 8.0, 0.5, H-5), 4.91 (1H, d, *J* = 16.0, H-7a), 4.81 (1H, d, *J* = 16.0, H-7b), 4.13–4.06 (1H, m, H-12a), 3.69 (1H, td, *J* = 12.5, 4.0, H-12b), 2.85-2.72 (1H, m, H-11a), 2.56 (1H, td, *J* = 13.0, 3.5, H-10a), 2.07–2.00 (1H, m, H-10b), 1.95 (1H, dtt, *J* = 11.5, 4.0, 3.5, H-11b), 1.50 (9H, s, H-16), 0.98 (9H, s, H-24), 0.29 (3H, s, H-25), 0.24 (3H, s, H-26); δ_C (100 MHz, $CDCl_3$) 175.8 (C-8), 166.3 (C-13), 153.0 (C-14), 151.2 (C-2), 144.6 (C-6), 135.6 (C-19), 129.5 (C-4), 128.7 (C-21), 127.4 (C-22), 126.9 (C-20), 120.2 (C-1), 113.3 (C-3), 102.6 (C-5), 83.0 (C-15), 56.9 (C-9), 47.2 (C-12), 43.8 (C-7), 29.5 (C-10), 27.9 (C-16), 25.8 (C-24), 18.9 (C-11), 18.2 (C-23), −3.8, −4.1 (C-25, C-26); *m/z* (ESI) 559 $[MNa]^+$; [HRMS (ESI): calcd for $C_{30}H_{40}N_2NaO_5Si$, 559.2599. Found: $[MNa]^+$, 559.2591 (1.5 ppm error)].

tert-Butyl 6-acetoxy-1-benzyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21ac$_p$) and _tert_-butyl 4-acetoxy-1-benzyl-2,2'-dioxospiro[indoline-3,3'-piperidine]-1'-carboxylate (21ac$_o$)



21ac$_p$

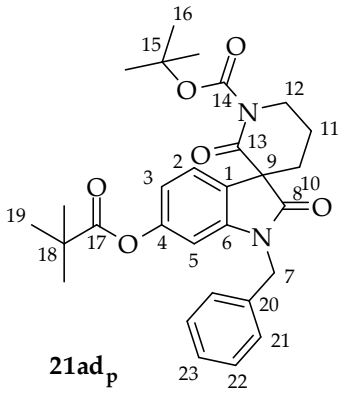


21ac$_o$

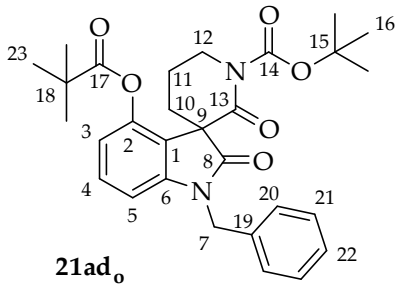
tert-Butyl 3-((3-acetoxyphenyl)(benzyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20ac**, 129 mg, 0.28 mmol) and copper(II) acetate monohydrate (6 mg, 0.03 mmol) in mesitylene (6 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [20–33% EtOAc/PE] afforded **21ac$_p$** (19 mg, 15%) as an off-white amorphous solid, and **21ac$_o$** (31 mg, 24%) as an off-white amorphous solid. **21ac$_p$**: mp 154–156 °C; R_f (1:2 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3064, 3032, 2978, 2935, 1767, 1721, 1615, 1497, 1455; δ_H (400 MHz, $CDCl_3$) 7.33–7.23 (6H, m, H-2, H-20, H-21, H-22), 6.73 (1H, dd, *J* = 8.0, 2.0, H-3), 6.43 (1H, d, *J* = 2.0, H-5), 4.97 (1H, d, *J* = 16.0, H-7a), 4.83 (1H, d, *J* = 16.0, H-7b), 3.92–3.86 (2H, m, H-12), 2.45–2.31 (2H, m, H-10a, H-11a), 2.22 (3H, s, H-18), 2.19–2.01 (2H, m, H-10b, H-11b), 1.49 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.8 (C-8), 169.2 (C-17), 167.2 (C-13), 152.7 (C-14), 151.1 (C-4), 144.1 (C-6), 134.8 (C-19), 129.0 (C-1), 128.9 (C-21), 127.6 (C-22), 126.9 (C-20), 123.8 (C-2), 115.5 (C-3), 104.0 (C-5), 83.6 (C-15), 58.0 (C-9), 47.2 (C-12), 43.9 (C-7), 32.0 (C-10), 27.9 (C-16), 21.1 (C-18), 19.5 (C-11); *m/z* (ESI) 487 $[MNa]^+$; [HRMS (ESI): calcd for $C_{26}H_{28}N_2NaO_6$, 487.1840. Found: $[MNa]^+$, 487.1827 (2.5 ppm error)]; **21ac$_o$**: mp 155–157 °C; R_f (1:2 EtOAc:PE) = 0.20; ν_{max}/cm^{-1} (thin film) 3063, 3032, 2980, 2935, 1771, 1718, 1621, 1470, 1455; δ_H (400 MHz, $CDCl_3$) 7.32–7.23 (5H, m, H-20, H-21, H-22), 7.16 (1H, dd, *J* = 8.5, 8.0, H-4), 6.86 (1H, d, *J* = 8.5, H-3), 6.54 (1H, d, *J* = 8.0, H-5), 4.93 (1H, d, *J* = 16.0, H-7a), 4.82 (1H, d, *J* = 16.0, H-7b), 4.09 (1H, dt, *J* = 12.0, 4.0, H-12a), 3.67 (1H, ddd, *J* = 12.0, 11.0, 4.0, H-12b), 2.66–2.55 (1H, m, H-11a), 2.25 (3H, s, H-18), 2.23–2.19 (2H, m, H-10), 2.04–1.95 (1H, m, H-11b), 1.50 (9H, s, H-16); δ_C (100 MHz, $CDCl_3$) 175.4 (C-8), 167.9 (C-17), 166.4 (C-13), 152.9 (C-14), 146.0 (C-2), 144.5 (C-6), 135.1

(C-19), 129.7 (C-4), 128.8 (C-21), 127.6 (C-22), 127.0 (C-20), 122.6 (C-1), 117.0 (C-3), 107.0 (C-5), 83.6 (C-15), 57.1 (C-9), 47.3 (C-12), 44.0 (C-7), 31.0 (C-10), 27.9 (C-16), 20.9 (C-18), 19.7 (C-11); *m/z* (ESI) 487 $[MNa]^+$; [HRMS (ESI): calcd for $C_{26}H_{28}N_2NaO_6$, 487.1840. Found: $[MNa]^+$, 487.1837 (0.6 ppm error)].

***tert*-Butyl 1-benzyl-2,2'-dioxo-6-(pivaloyloxy)spiro[indoline-3,3'-piperidine]-1'-carboxylate ($21ad_p$) and *tert*-butyl 1-benzyl-2,2'-dioxo-4-(pivaloyloxy)spiro[indoline-3,3'-piperidine]-1'-carboxylate ($21ad_o$)**



$21ad_p$

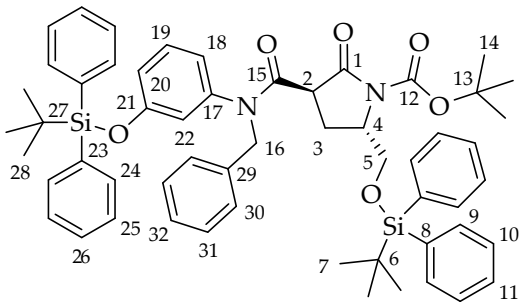


$21ad_o$

tert-Butyl 3-(benzyl(3-(pivaloyloxy)phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (**20ad**, 88 mg, 0.17 mmol) and copper(II) acetate monohydrate (3.5 mg, 0.018 mmol) in mesitylene (4 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [15–20% EtOAc/PE] afforded **$21ad_p$** (13 mg, 15%) as an off-white amorphous solid, and a mixture of spirocycle **$21ad_o$** and lactam **262b** (25.5 mg, corresponding to 21.5 mg of pure **$21ad_o$**, 25%; a small sample of pure **$21ad_o$** was isolated for full characterisation) as an off-white amorphous solid. **$21ad_p$**: mp 175–176 °C; R_f (1:2 EtOAc:PE) = 0.40; ν_{max}/cm^{-1} (thin film) 3064, 3032, 2977, 2934, 2872, 1750, 1723, 1615, 1497, 1480, 1455; δ_H (400 MHz, $CDCl_3$) 7.35–7.23 (6H, m, H-2, H-21, H-22, H-23), 6.71 (1H, dd, *J* = 8.0, 2.0, H-3), 6.43 (1H, d, *J* = 2.0, H-5), 4.99 (1H, d, *J* = 16.0, H-7a), 4.85 (1H, d, *J* = 16.0, H-7b), 3.95–3.85 (2H, m, H-12), 2.46–2.30 (2H, m, H-10a, H-11a), 2.21–2.03 (2H, m, H-10b, H-11b), 1.50 (9H, s, H-16), 1.30 (9H, s, H-19); δ_C (100 MHz, $CDCl_3$) 176.8 (C-17), 175.9 (C-8), 167.3 (C-13), 152.8 (C-14), 151.7 (C-4), 144.2 (C-6), 135.0 (C-20), 128.9 (C-22), 128.8 (C-1), 127.6 (C-23), 126.8 (C-21), 123.8 (C-2), 115.5 (C-3), 103.8 (C-5), 83.6 (C-15), 58.0 (C-9), 47.2 (C-12), 43.8 (C-7), 39.1 (C-18), 32.0 (C-10), 27.9 (C-16), 27.0 (C-19), 19.5 (C-11); *m/z* (ESI) 529 $[MNa]^+$; [HRMS (ESI): calcd for

$C_{29}H_{35}N_2NaO_6$, 529.2309. Found: $[MNa]^+$, 529.2298 (2.1 ppm error)]; **21ad$_o$**: mp 166–168 °C; R_f (1:2 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3063, 3032, 2977, 2935, 2873, 1759, 1718, 1621, 1604, 1470, 1456; δ_H (400 MHz, $CDCl_3$) 7.33–7.24 (5H, m, H-20, H-21, H-22), 7.16 (1H, dd, *J* = 8.5, 8.0, H-4), 6.79 (1H, dd, *J* = 8.5, 0.5, H-3), 6.53 (1H, dd, *J* = 8.0, 0.5, H-5), 4.94 (1H, d, *J* = 16.0, H-7a), 4.85 (1H, d, *J* = 16.0, H-7b), 4.13–4.06 (1H, m, H-12a), 3.68–3.61 (1H, m, H-12b), 2.88–2.75 (1H, m, H-11a), 2.31–2.22 (1H, m, H-10a), 2.15–2.09 (1H, m, H-10b), 1.97–1.89 (1H, m, H-11b), 1.50 (9H, s, H-16), 1.33 (9H, s, H-23); δ_C (100 MHz, $CDCl_3$) 175.9 (C-17), 175.0 (C-8), 166.0 (C-13), 153.0 (C-14), 146.7 (C-2), 144.4 (C-6), 135.1 (C-19), 129.7 (C-4), 128.8 (C-21), 127.6 (C-22), 126.9 (C-20), 122.1 (C-1), 116.9 (C-3), 106.6 (C-5), 83.4 (C-15), 56.9 (C-9), 47.2 (C-12), 43.9 (C-7), 39.3 (C-18), 30.5 (C-10), 27.9 (C-16), 27.0 (C-23), 18.4 (C-11); *m/z* (ESI) 529 $[MNa]^+$; [HRMS (ESI): calcd for $C_{29}H_{35}N_2NaO_6$, 529.2309. Found: $[MNa]^+$, 529.2323 (−2.6 ppm error)].

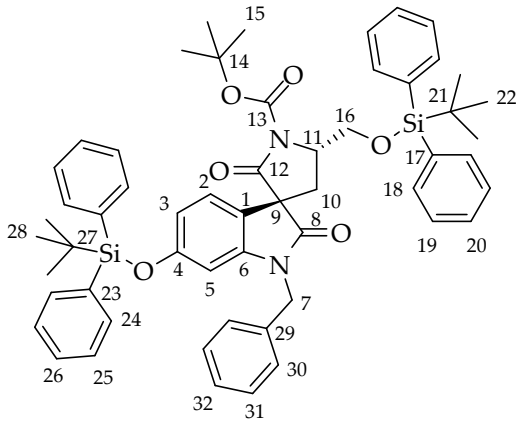
(5*S*)-*tert*-Butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-3-((3-(*tert*-butyldiphenylsilyloxy)phenyl)(methyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (336)



(5*S*)-1-(*tert*-Butoxycarbonyl)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (**331**, 864 mg), *N*-benzyl-3-(*tert*-butyldiphenylsilyloxy)aniline (835 mg, 1.91 mmol), 2-chloro-1-methylpyridinium iodide (664 mg, 2.60 mmol) and triethylamine (1.21 mL, 8.68 mmol) in CH_2Cl_2 (15 mL) were reacted according to general procedure E. Flash column chromatography [10–20% EtOAc/PE] afforded **336** (1.09 g, 68% over 2 steps, >20:1 dr; major diastereoisomer tentatively assigned based on a lack of NOE enhancement between H-2 and H-4) as an off-white sticky foam. R_f (1:4 EtOAc:PE) = 0.50; ν_{max}/cm^{-1} (thin film) 3071, 3051, 3031, 2959, 2932, 2891, 2858,

1785, 1747, 1716, 1657, 1594, 1486, 1473; $[\alpha]_D^{20}$ 32.0 (*c* 1.03, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.64–7.60 (4H, m), 7.54–7.46 (4H, m) (H-9, H-24), 7.45–7.30 (12H, m, H-10, H-11, H-25, H-26), 7.21–7.16 (3H, m, H-31, H-32), 7.09–7.05 (2H, m, H-30), 6.90 (1H, t, *J* = 8.0, H-19), 6.64 (1H, br s, H-18 or H-20), 4.91 (1H, br s, H-16a), 4.40 (1H, v br s, H-16b), 4.22 (1H, br d, *J* = 9.5, H-4), 3.88 (1H, dd, *J*= 10.0, 9.5, H-2), 3.79 (1H, dd, *J* = 10.5, 2.0, H-5a), 3.50 (1H, dd, *J* = 10.5, 2.0, H-5b), 2.73–2.64 (1H, m, H-3a), 1.97 (1H, v br s, H-3b), 1.42 (9H, s, H-14), 1.07 (9H, s), 0.78 (9H, s) (H-7, H-28), some aromatic peaks not visible due to broadening; δ_C (100 MHz, $CDCl_3$) 170.8, 169.4 (C-1, C-15), 156.3 (C-21), 149.4 (C-12), 142.0 (C-17), 136.6 (C-29), 135.5, 135.5, 135.4, 135.4 (C-9, C-24), 132.8, 132.4, 132.3, 132.3 (C-8, C-23), 130.0, 130.0, 129.8, 129.8 (C-11, C-26), 128.6 (C-30), 128.2 (C-31), 127.8, 127.7 (C-10, C-25), 127.2 (C-32), 120.0 (C-18, C-20 or C-22), 82.8 (C-13), 64.9 (C-5), 57.2 (C-4), 53.4 (C-16), 47.5 (C-2), 27.9 (C-14), 26.6, 26.5 (C-7, C-28), 26.2 (C-3), 19.4, 18.7 (C-6, C-27), some aromatic peaks not visible due to broadening; *m/z* (ESI) 939 $[MNa]^+$; [HRMS (ESI): calcd for $C_{56}H_{64}N_2NaO_6Si_2$, 939.4195. Found: $[MNa]^+$, 939.4155 (4.3 ppm error)].

(3*S*,5'*S*)-*tert*-Butyl 1-benzyl-6-(*tert*-butyldiphenylsilyloxy)-5'-((*tert*-butyldiphenylsilyloxy)methyl)-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (337$_p$'')



(5S)-*tert*-Butyl 5-((*tert*-butyldiphenylsilyloxy)methyl)-3-((3-(*tert*-butyldiphenylsilyloxy)phenyl)(methyl)carbamoyl)-2-oxopyrrolidine-1-carboxylate (**336**, 267 mg, 0.29 mmol) and copper(II) acetate monohydrate (6 mg, 0.03 mmol) in mesitylene (6 mL) were reacted for 30 min according to general procedure F. Flash column chromatography [1:9 EtOAc/PE] afforded **337$_p$''** (44 mg, 16%) as a yellow oil,

as well as an inseparable mixture of other isomers, whose identity could not be firmly established, R_f (1:9 EtOAc:PE) = 0.30; ν_{max}/cm^{-1} (thin film) 3071, 3050, 3027, 2958, 2931, 2893, 2858, 1785, 1751, 1721, 1618, 1500, 1472, 1458; $[\alpha]_D^{20}$ +3.7 (*c* 0.89, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.69–7.66 (4H, m), 7.63–7.60 (4H, m) (H-18, H-24), 7.45–7.31 (12H, m, H-19, H-20, H-25, H-26), 7.22–7.18 (3H, m, H-31, H-32), 7.10–7.06 (2H, m, H-30), 6.78 (1H, d, *J* = 8.0, H-2), 6.42 (1H, dd, *J* = 8.0, 2.0, H-3), 6.12 (1H, d, *J* = 2.0, H-5), 4.75 (1H, d, *J* = 15.5, H-7a), 4.51 (1H, d, *J* = 15.5, H-7b), 4.34 (1H, tdd, *J* = 8.5, 4.5, 3.5, H-11), 4.24 (1H, dd, *J* = 9.5, 8.5, H-16a), 4.06 (1H, dd, *J* = 9.5, 3.5, H-16b), 2.93 (1H, dd, *J* = 14.0, 8.5, H-10a), 2.91 (1H, dd, *J* = 14.0, 4.5, H-10b), 1.38 (9H, s, H-15), 1.06 (9H, s), 1.02 (9H, s) (H-22, H-28); δ_C (100 MHz, $CDCl_3$) 174.7 (C-8), 170.2 (C-12), 156.6 (C-4), 149.5 (C-13), 144.2 (C-6), 135.6, 135.5, 135.4, 135.4 (C-18, C-24), 135.0 (C-29), 133.5, 132.5, 132.5 (C-17, C-23), 130.0, 129.7 (C-20, C-26), 128.7 (C-31), 127.8, 127.7 (C-19, C-25), 127.4 (C-32), 127.1 (C-30), 123.2 (C-2), 122.2 (C-1), 113.8 (C-3), 102.2 (C-5), 83.6 (C-14), 64.2 (C-16), 58.4 (C-9), 56.5 (C-11), 44.0 (C-7), 30.7 (C-10), 27.8 (C-15), 26.8, 26.5 (C-22, C-28), 19.4, 19.3 (C-21, C-27); Stereochemistry assigned based on an NOE enhancement between H-2 and H-11; *m/z* (ESI) 937 $[MNa]^+$; [HRMS (ESI): calcd for $C_{56}H_{62}N_2NaO_6Si_2$, 937.4039. Found: $[MNa]^+$, 937.4013 (2.7 ppm error)].

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A one-pot oxidation/allylation/oxidation sequence for the preparation of β,γ-unsaturated ketones directly from primary alcohols

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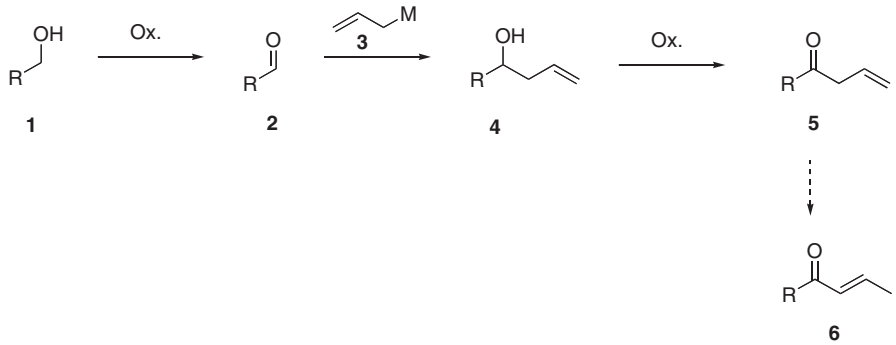
ABSTRACT

A one-pot oxidation/allylation/oxidation procedure has been developed for the conversion of primary alcohols into β,γ-unsaturated ketones. The methodology has been applied to a range of alcohols, and in some cases, isomerisation to produce the corresponding α,β-unsaturated ketones has been carried out.

α,β- and β,γ-Unsaturated ketones are important building blocks in organic synthesis.[1] As part of a natural product project, we required a straightforward method of preparing β,γ-unsaturated ketones **5** (R = aryl, hetaryl, alkyl, etc.). Most of the available procedures, such as the Barbier-type allylation of nitriles[2] and the Hosomi–Sakurai reaction of allyl silanes with acid chlorides,[3] proceed from carboxylic acid derivatives,[4] whereas we wished to use alcohols **1** as simple starting materials.[5,6] Given our interest in tandem oxidation processes,[7] the approach outlined in Scheme 1 appeared to present an attractive option. The idea was to oxidise alcohols **1** to aldehydes **2** in the presence of an allylating reagent **3**; by using the oxidant in excess we hoped to achieve the in situ oxidation of allylic alcohol **4** to produce the target β,γ-unsaturated ketones **5** in a one-pot process. In addition, we anticipated that it would be straightforward to extend this sequence to produce α,β-unsaturated ketones **6** given the numerous methods reported for effecting this type of isomerisation.[8]

Preliminary studies were carried out to assess the viability of a one-pot approach to β,γ-unsaturated ketones using *p*-chlorobenzyl alcohol (**7**), *p*-chlorobenzaldehyde (**8**) and secondary alcohol **9** as test substrates (Scheme 2). The initial oxidation of *p*-chlorobenzyl alcohol **7** was straightforward, as expected, with MnO_2 and Dess–Martin periodinane (DMP) giving the most reliable results.[9] Many methods are available for the allylation of aldehydes and



Scheme 1.

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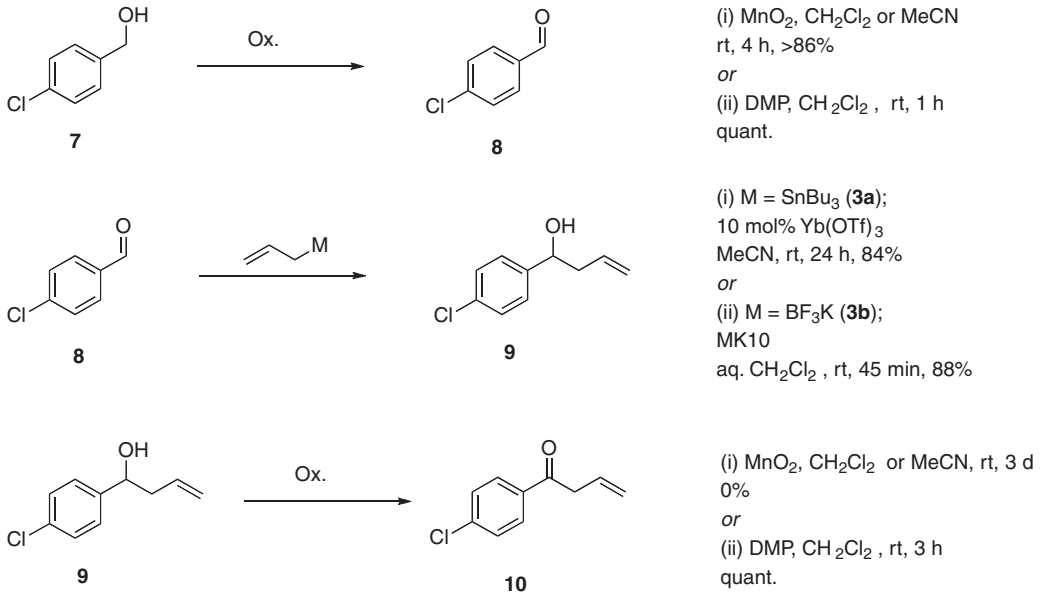
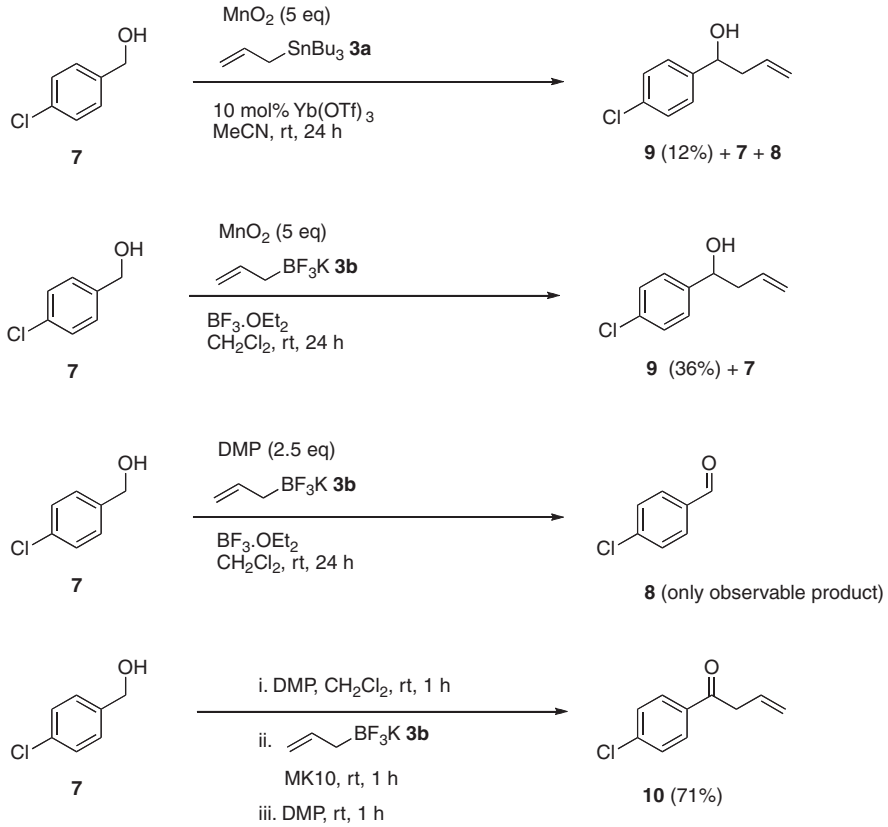
ketones,[10] but in our hands with *p*-chlorobenzaldehyde (**8**), the use of allyl stannane (**3a**) with catalytic $Yb(OTf)_3$,[11] or allyl trifluoroborate (**3b**) with boron trifluoride etherate[12,13] or Montmorillonite K10 (MK10)[13] proved the most straightforward giving the allyl alcohol **9** via a practically simple process at room temperature. The final step, the oxidation of the secondary benzylic alcohol **9**, proved more troublesome. No oxidation was observed using MnO_2 or TPAP/NMO, with DMP being most reliable for the formation of β,γ-unsaturated ketone **10**.[14]

Having studied the individual steps, we went on to examine one-pot processes for the three-step sequence (Scheme 3). As can be seen, with MnO_2 as oxidant, it was possible to carry out a tandem oxidation/allylation giving allylic alcohol **9** in low yield, but further oxidation did not occur (as was expected after the



Scheme 2.



Scheme 3.

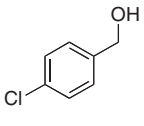
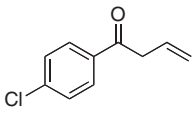
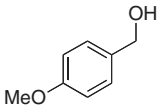
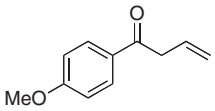
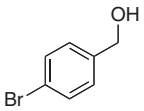
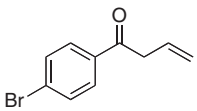
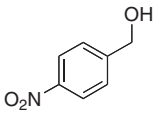
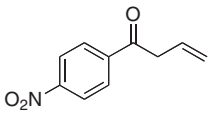
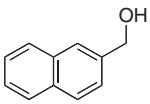
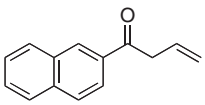
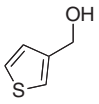
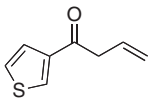
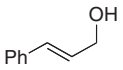
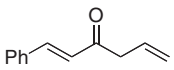
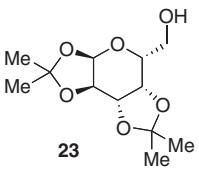
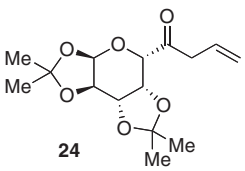
preliminary studies shown in Scheme 2). Concentrating on the use of DMP as oxidant, the tandem process gave mainly aldehyde **8** with trace amounts of allylated adducts **9** and **10**, at best. We, therefore, developed a sequential process in which DMP oxidation was followed by the addition of allyl trifluoroborate (**3b**) and MK10, and finally additional DMP was added to ensure complete oxidation. In this manner, the required α,β-unsaturated ketone **10** was obtained in a 71% yield by a one-pot procedure.

Having established a reliable one-pot procedure for the oxidation/allylation/oxidation route to β,γ-unsaturated ketone **10**, we went on to explore its scope (Table 1). As can be seen, the sequence was successful with a range of electron-rich and electron-poor benzylic alcohols (entries i–iv), with 2-naphthyl-methanol (entry v) and with thiophene-2-methanol (entry vi). In addition to benzylic and related systems, an allylic example proved successful (entry vii), as did an unactivated alcohol (1,2:3,4-di-*O*-isopropylidene-D-galactopyranose, entry viii). In all cases the yields were good to excellent and the β,γ-unsaturated ketones were usually stable for a day or so, although isomerisation to give the corresponding α,β-unsaturated ketones was observed on prolonged storage.

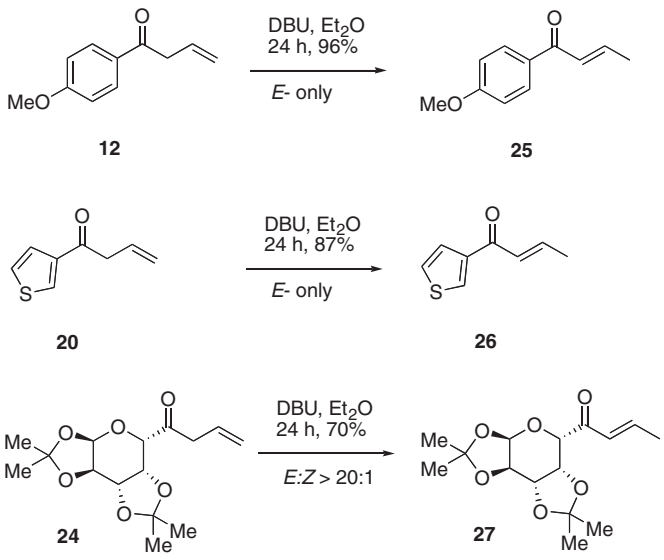
As mentioned earlier, if conjugated ketones are required, these are easily obtained from the corresponding β,γ-unsaturated ketones. In our hands, DBU in diethyl ether[16] gave the cleanest isomerisation, with α,β-unsaturated ketones **25**–**27** being isolated in almost quantitative yields, exclusively or predominantly as the *E*-isomers (Scheme 4).

In summary, we have developed a one-pot oxidation/allylation/oxidation procedure for the conversion of primary alcohols into β,γ-unsaturated ketones which involves DMP oxidation followed by the addition of allyl trifluoroborate (**3b**) and Montmorillonite K10 and finally additional DMP. The methodology has been applied to a range of benzylic alcohols, as well as to an allylic and an

Table 1
One-pot oxidation/allylation/oxidation sequence[a]

Entry	Substrate	Product	Isolated Yield[b] (%)
i	 **7**	 **10**	71[4a]
ii	 **11**	 **12**	92[4b]
iii	 **13**	 **14**	85[4a,c]
iv	 **15**	 **16**	96[4a]
v	 **17**	 **18**	75[4d]
vi	 **19**	 **20**	76[4e]
vii	 **21**	 **22**	67[4f]
viii	 **23**	 **24**	75[15]

[a] On a 0.25 mmol scale; (i) DMP (1.5–2.0 equiv), CH_2Cl_2, rt, 1 h; (ii) MK10, **3** (1.5–2.0 equiv), rt, 1 h; (iii) DMP (2.0–2.5 equiv), rt, 1 h.
[b] Quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$; purified by flash column chromatography.



Scheme 4.

unactivated carbohydrate example. In three examples, base-mediated isomerisation to produce the corresponding α,β-unsaturated ketones has been carried out. We are currently applying this sequence to more complex systems as part of a natural product programme.

Acknowledgements

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15. *Representative experimental procedure*: Galactopyranose derivative **24**: To 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**23**) (64 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL) at rt under argon was added DMP (209 mg, 0.49 mmol) and the mixture stirred for 1 h. Montmorillonite K10 (50 mg) was then added followed by potassium allyl trifluoroborate (73 mg, 0.49 mmol) and the mixture stirred for 1 h before adding a further portion of DMP (261 mg, 0.62 mmol). After stirring for a further 1 h, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and sat. aq $Na_2S_2O_3$ (5 mL) and allowed to stir for 1 h before diluting with brine (10 mL) and CH_2Cl_2 (10 mL). The mixture was filtered and then the layers separated. The aqueous portion was further extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (0–5% acetone in CH_2Cl_2) to give the compound **24** (55 mg, 75%) as a colourless micro-crystalline solid, mp 47–49 °C; R_f (CH_2Cl_2) = 0.15; ν_{max}/cm^{-1} (thin film) 2988, 2936, 1723 (C=O), 1383; $[\alpha]_D$ −144 (*c* 0.4, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 5.97 (1H, ddt, *J* = 17.0, 10.5, 7.0, H-8), 5.64 (1H, d, *J* = 5.0, H-1), 5.20–5.08 (2H, m, H-9), 4.63 (1H, dd, *J* = 8.0, 2.5, H-3), 4.56 (1H, dd, *J* = 8.0, 2.0, H-4), 4.35 (1H, dd, *J* = 5.0, 2.5, H-2), 4.22 (1H, d, *J* = 2.0, H-5), 3.50 (1H, ddt, *J* = 18.5, 7.0, 1.5, H-7a), 3.33 (1H, ddt, *J* = 18.5, 7.0, 1.5, H-7b), 1.49 (3H, s), 1.44 (3H, s), 1.33 (3H, s), 1.30 (3H, s); δ_C (100 MHz, $CDCl_3$) 207.2 (C-6), 130.0 (C-8), 118.7 (C-9), 109.6, 109.0, 96.4 (C-1), 73.5 (C-5), 72.3 (C-4), 70.6 (C-3), 70.4 (C-2), 44.6 (C-7), 25.9, 25.8, 24.8, 24.2; *m*/*z* (ESI) 321 $[M+Na]^+$; [HRMS (ESI): Calcd for $C_{15}H_{22}NaO_6$, 321.1309. Found: $[M+Na]^+$, 321.1317 (−2.7 ppm error)]; [$C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43. Found C, 60.35; H, 7.35].
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Copper-catalysed approach to spirocyclic oxindoles via a direct C–H, Ar-H functionalisation

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ABSTRACT

A practical and efficient entry to spirocyclic oxindoles from readily accessible anilide precursors, using only catalytic amounts of an inexpensive copper salt together with air as the sole re-oxidant, is described. In addition to providing access to a broad range of spiro-oxindole products, the utility of this method is demonstrated in a formal synthesis of the natural product, horsfiline.

The oxindole structure has long fascinated synthetic chemists, partly due to the synthetic challenges that many oxindole-containing targets present, and partly owing to the exciting biological profiles they exhibit and their potential as pharmaceuticals.[1]

In terms of their structure, naturally-occurring oxindoles tend to be appended with two substituents at the benzylic position (i.e., 3,3-disubstituted), with a large proportion of these having the side-chains tied together, thus giving rise to a spirocyclic junction.[2] They can range from small members, such as horsfiline (**1**),[3] to the more imposing representatives, such as the polycyclic alkaloid gelsemine (**2**),[4] which has stimulated a number of total synthesis programmes across the globe simply as a result of the attraction of its formidable and striking structure (Fig. 1).[5] More importantly, many spiro-oxindole natural products display remarkable biological properties: for example, strychnofoline (**3**) displays useful antimitotic activity against cultures of mouse melanoma,[6] and has already succumbed to a creative total synthesis by the Carreira laboratories.[7] Most notably, the prominence of the oxindole motif in naturally-occurring compounds of medicinal value has spurred the development of a valuable collection of fully synthetic clinical drugs and candidates thereof. This is well exemplified by satavaptan (**4**, SR-121463),[8] an orally-active and selective vasopressin V_2 receptor antagonist, which belongs to a new class of drugs developed for the treatment of hyponatraemia and is currently in Phase III trials.

From the synthetic viewpoint, the transition metal catalysed cyclisation of linear anilide precursors is a particularly efficient

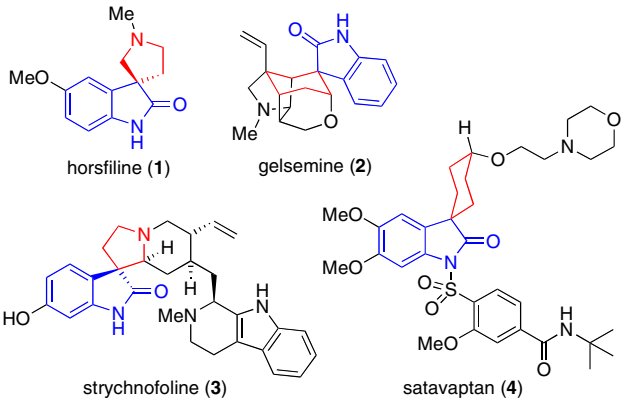
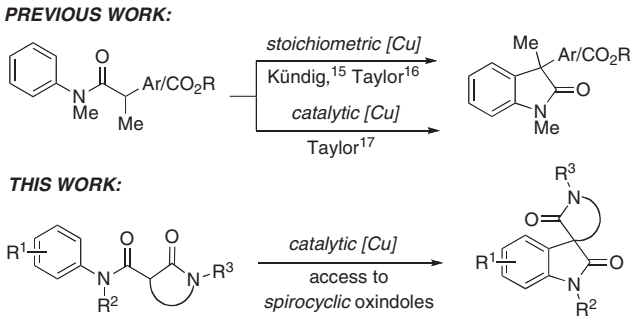


Figure 1. Examples of spirocyclic oxindoles.



Scheme 1. Copper-mediated oxindole cyclisation.

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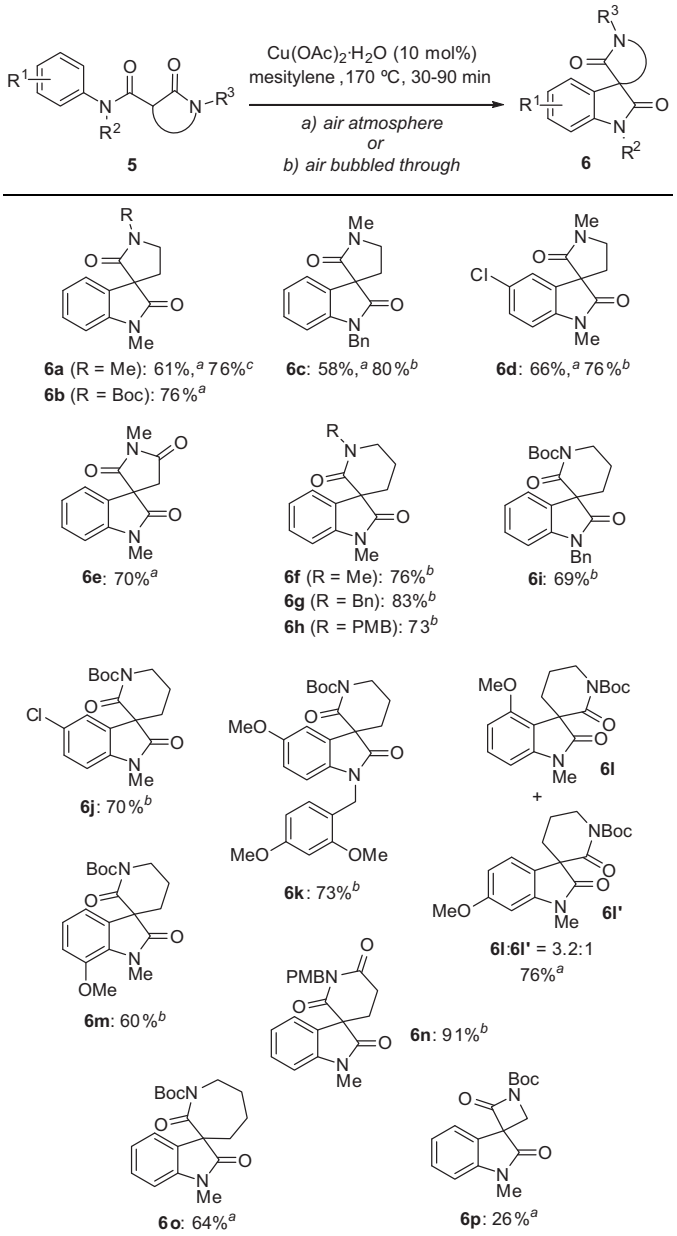
strategy for the synthesis of 3,3-disubstituted oxindoles.[9] Most of these methods make use of palladium catalysis, namely in Heck cyclisations,[10] C–H activation processes,[11] and enolate arylations,[12] as well as others.[13] Copper salts have also found utility as reagents for cyclisations leading to oxindoles,[14] however, it was in 2009 that Kündig and Jia,[15] as well as ourselves,[16] reported a copper-mediated cyclisation of *unfunctionalised* anilides to the 3,3-disubstituted oxindole core via a formal double C–H activation approach (Scheme 1). We subsequently disclosed an improved variant of this reaction process,[17] which utilised sub-stoichiometric amounts (5 mol %) of a copper catalyst with no loss in reaction efficiency. Herein we communicate a practical extension of this methodology for the straightforward synthesis of *spirocyclic* oxindoles, which enables the installation of a quaternary all-carbon centre via a direct C–H, Ar-H functionalisation by means of copper catalysis without the need for additional base.

Table 1
Reaction scope investigation (yields are isolated)



[a] Reaction was carried out with the reflux condenser open to air.
[b] Reaction was carried out by vigorously bubbling compressed air through the refluxing reaction mixture.
[c] Reaction was carried out in toluene at 120 °C for 15 h with the reflux condenser open to air.

In the current study, the use of just 10 mol % of the environmentally benign and inexpensive copper(II) acetate monohydrate as the catalyst and air as the stoichiometric re-oxidant enabled us to rapidly establish the broad scope of this spirocyclisation reaction (Table 1). The cyclisation precursors **5** were easily prepared in just three straightforward synthetic steps from protected lactams (see Supporting Information). All cyclisations were carried out with mesitylene as the solvent at 170 °C, thus cutting down on reaction time (30–90 min). Comparable results could also be achieved by running the reactions in refluxing toluene (120 °C), although a longer reaction time was needed in order to achieve full conversion (typically overnight). Oxygen in air was all that was required to re-oxidise the copper catalyst. In certain cases a small amount of substrate **5** was found to undergo cleavage to the corresponding aniline and lactam/imide under the reaction conditions, resulting in lower yields of the oxindole products **6**. This obstacle was eventually overcome by simply bubbling air through the refluxing reaction mixture, thus accelerating the rate of copper re-oxidation and, ultimately, oxindole cyclisation. In this way, the undesired cleavage of the starting anilides **5** was minimised and the efficiency of the cyclisation step improved.

In terms of substrate scope, anilides containing butyrolactam unit **5a–d**, appended with a range of substituents on the nitrogen atoms and the benzene ring, as well as that incorporating the succinimide motif (**5e**), all provided the cyclic products **6a–e** in good to excellent yields (Table 1). The desired oxindoles **6f–i** were also successfully obtained with six-membered valerolactam-containing anilides **5f–i** as substrates. We were able to obtain a suitable crystal of spirocyclic product **6i** for X-ray crystallographic analysis and conclusively established its identity (Fig. 2).[18]

Substitution on the benzene ring was next explored and products **6j–m** were furnished in good yields. It is noteworthy that access to aryl chlorides of type **6j** allows for further palladium-mediated manipulation to structurally more elaborate, and potentially medicinally relevant, oxindoles. The result obtained with the *meta*-methoxy-substituted example **5l** was also intriguing: a mixture of regioisomers **6l** and **6l′** was isolated,[13f] with the major isomer **6l** arising from radical addition to the position more encumbered sterically, but potentially preferred electronically, presumably due to the higher degree of stabilisation of the intermediate cyclohexadienyl radical. Glutaramide- and caprolactam-based anilides **5n** and **5o** also furnished spirocyclic oxindoles **6n** and **6o**, respectively, in good yields. Of potential medicinal interest are ß-lactam-containing oxindoles of type **6p**,[19] albeit the efficiency of the cyclisation of **5p** was found to be somewhat lower. Postulating that, mechanistically, this reaction proceeds via an intermediate enol, the lower yield of cyclic product **6p** could be attributed to the high strain associated with the enol (or the resultant radical species following oxidation of the enol), which contains three adjacent sp^2 centres within a four-membered ring. It should be noted that, to the best of our knowledge, all the oxindole products described here and accessed via the copper-catalysed cyclisation method are novel compounds.

Having established the broad scope of this cyclisation methodology we sought to demonstrate its utility in the synthesis of the natural product horsfiline (**1**, Scheme 2).[3] In this context, benzylcarboxylation of commercially available *N*-methylpyrrolidone (**7**) afforded intermediate **8** which, upon hydrogenolysis and amide coupling, swiftly furnished the linear cyclisation precursor **9** on gram scale in excellent overall yield. Ready access to anilide **9** paved the way for the application of our copper(II)-mediated cyclisation, which successfully provided the desired oxindole **10** in a

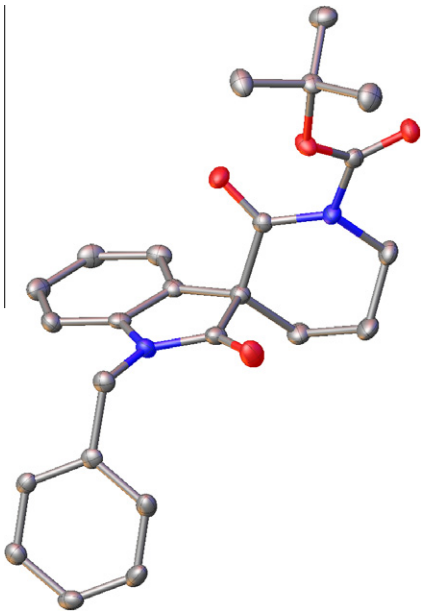
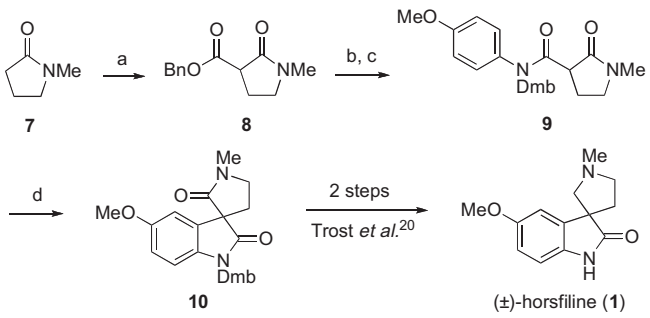


Figure 2. Crystal structure of **6i**.



Scheme 2. Formal total synthesis of horsfiline (**1**). Reagents and conditions: (a) LDA, CbzCl, THF, −78 °C, 1 h (48%); (b) H_2, Pd/C, EtOAc, rt, 1 h (97%); (c) *N*-Dmb-4-methoxyaniline, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h (97%); (d) $Cu(OAc)_2{\cdot}H_2O$ (10 mol %), mesitylene, air bubbled through, 170 °C, 90 min (71%). LDA = lithium di-iso-propylamide; Cbz = carboxybenzyl; THF = tetrahydrofuran; Dmb = 2,4-dimethoxybenzyl.

71% yield and intercepted Trost's intermediate for the formal synthesis of horsfiline (**1**).[20]

In summary, the copper(II)-mediated cyclisation methodology enables entry to a large class of spirocyclic oxindoles via a direct C–H, Ar-H functionalisation with high efficiency from easily accessible starting materials with cheap reagents. This method allows the installation of a quaternary carbon centre at the spirocycle junction and constitutes an attractive approach for the preparation of oxindole-based natural products and their analogues. The development of a stereoselective variant of this process is currently underway in our laboratories: preliminary studies have been carried out using enantiopure additives but, to date, no significant enantioselectivity has been obtained.

Acknowledgments

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Supplementary data

Supplementary data (full experimental procedures, characterisation data, ^1H NMR traces and crystallographic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.120.

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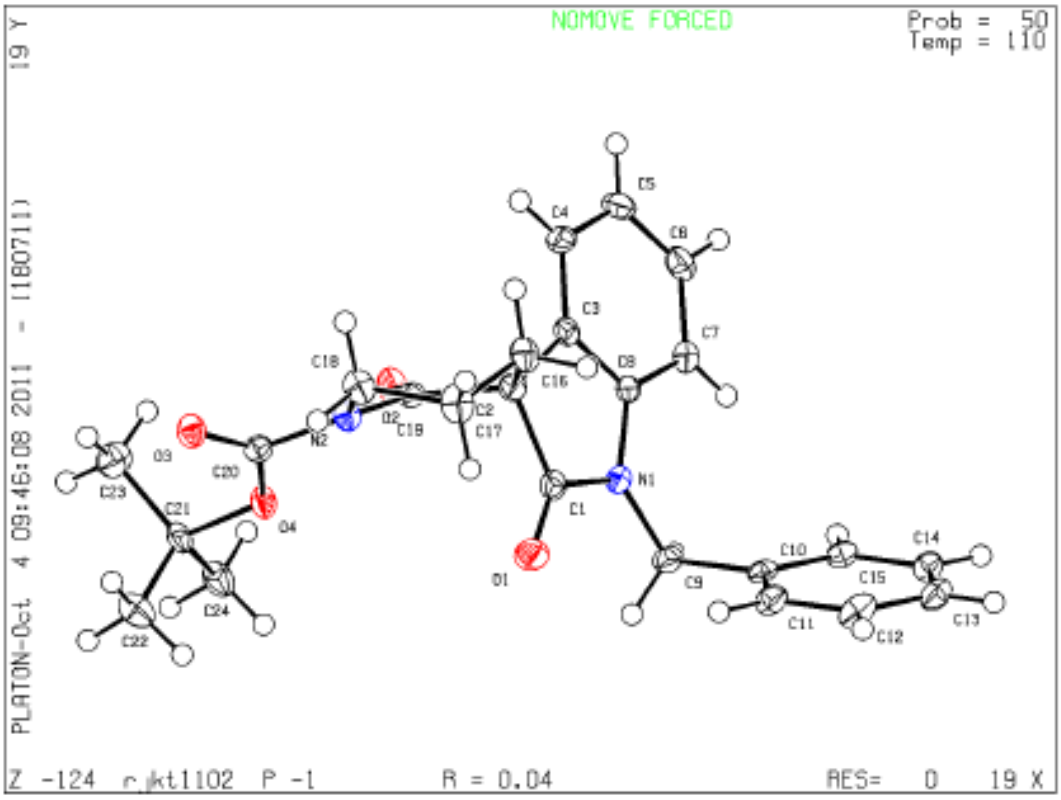
Appendix III

X-ray data for *tert*-butyl 3-(benzyl(phenyl)carbamoyl)-2-oxopiperidine-1-carboxylate (20u)



CCDC deposition number 857976

Table 1 Crystal data and structure refinement for rjkt1102

Identification code	rjkt1102
Empirical formula	$C_{24}H_{26}N_2O_4$

Formula weight	406.47
Temperature/K	110.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.1023(6)
b/Å	10.7446(8)
c/Å	11.3413(6)
α/°	74.878(6)
β/°	75.082(5)
γ/°	81.943(6)
Volume/Å^3	1031.52(12)
Z	2
ρ_{calc}mg/mm^3	1.309
m/mm^{-1}	0.089
F(000)	432
Crystal size/mm^3	0.199 × 0.1057 × 0.0813
2Θ range for data collection	5.8 to 55.82°
Index ranges	-11 ≤ h ≤ 7, -14 ≤ k ≤ 13, -14 ≤ l ≤ 13
Reflections collected	6258
Independent reflections	4045[R(int) = 0.0179]
Data/restraints/parameters	4045/0/274
Goodness-of-fit on F^2	1.093
Final R indexes [I>=2σ (I)]	R_1 = 0.0423, wR_2 = 0.0988
Final R indexes [all data]	R_1 = 0.0503, wR_2 = 0.1045
Largest diff. peak/hole / e Å^{-3}	0.236/-0.218
Flack Parameter	N/A

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for rjkt1102. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
C1	214.1(18)	-1063.5(15)	7767.2(15)	17.8(3)
C2	1992.1(18)	-1153.0(15)	7408.1(15)	16.5(3)
C3	2334.0(18)	-1519.1(14)	6164.0(15)	16.3(3)
C4	3704.8(18)	-1705.6(15)	5333.4(16)	20.0(4)
C5	3689(2)	-2013.3(16)	4218.0(16)	23.4(4)
C6	2321(2)	-2122.2(16)	3938.9(16)	23.1(4)
C7	922.1(19)	-1921.8(15)	4760.8(15)	19.3(3)
C8	964.8(18)	-1619.7(14)	5864.1(15)	16.0(3)
C9	-1884.0(18)	-1275.6(16)	6799.8(16)	18.7(3)
C10	-2534.9(17)	-2581.2(15)	7249.5(15)	16.5(3)
C11	-2786.2(18)	-3204.9(17)	8518.8(15)	21.1(4)
C12	-3375.3(19)	-4404.9(17)	8948.0(16)	23.7(4)
C13	-3738.4(19)	-4995.2(17)	8118.9(16)	22.2(4)
C14	-3497.2(18)	-4381.7(16)	6854.6(16)	20.1(4)
C15	-2891.0(17)	-3187.6(16)	6422.8(15)	17.5(3)
C16	2668(2)	-2151.3(16)	8421.6(16)	21.8(4)
C17	2502(2)	-1634.1(16)	9581.1(16)	24.5(4)
C18	3276(2)	-386.5(16)	9233.9(16)	21.1(4)
C19	2410.2(17)	239.4(15)	7217.7(15)	15.5(3)
C20	2634.9(18)	1889.8(15)	8270.2(14)	16.3(3)
C21	1455.2(19)	4032.9(15)	7456.0(15)	17.8(3)
C22	766(2)	4411.6(18)	8691.1(17)	27.5(4)
C23	2981(2)	4579.4(17)	6802.6(17)	27.0(4)
C24	364(2)	4405.5(17)	6597.1(17)	25.1(4)
N1	-271.5(15)	-1343.3(13)	6825.1(12)	16.4(3)
N2	2651.7(15)	576.4(12)	8245.9(12)	16.1(3)

O1	-608.6(13)	-798.2(12)	8711.7(11)	26.3(3)
O2	2457.8(14)	992.7(11)	6206.5(10)	21.1(3)
O3	3430.0(13)	2243.0(11)	8801.9(11)	20.7(3)
O4	1604.0(13)	2600(1)	7689.7(11)	20.2(3)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for rjkt1102. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	19.3(8)	14.9(8)	18.4(8)	-3.0(6)	-2.5(7)	-4.1(7)
C2	16.5(8)	15.1(8)	17.8(8)	-3.2(6)	-4.6(6)	-0.9(6)
C3	18.2(8)	10.8(7)	19.5(8)	-2.6(6)	-5.3(6)	-0.2(6)
C4	15.0(8)	16.3(8)	27.5(9)	-4.3(7)	-4.4(7)	0.8(6)
C5	20.7(8)	20.6(8)	25.1(9)	-8.1(7)	2.4(7)	1.4(7)
C6	30.7(9)	19.3(8)	19.6(8)	-8.0(7)	-2.2(7)	-2.6(7)
C7	21.2(8)	17.3(8)	21.3(8)	-5.3(7)	-6.4(7)	-3.6(7)
C8	16.6(8)	10.0(7)	19.4(8)	-2.0(6)	-1.8(6)	-2.1(6)
C9	14.5(8)	20.1(8)	21.1(8)	-4.5(7)	-4.5(6)	-0.5(7)
C10	9.8(7)	18.7(8)	19.6(8)	-3.0(7)	-3.1(6)	0.4(6)
C11	17.2(8)	28.3(9)	18.7(8)	-6.4(7)	-3.8(7)	-4.4(7)
C12	19.6(8)	30.7(10)	17.8(8)	3.7(7)	-6.3(7)	-6.4(7)
C13	17.2(8)	20.2(8)	26.5(9)	1.3(7)	-5.4(7)	-4.9(7)
C14	16.9(8)	21.7(8)	23.0(9)	-5.6(7)	-6.1(7)	-2.2(7)
C15	13.7(7)	21.2(8)	16.2(8)	-2.0(6)	-3.8(6)	-0.7(7)
C16	27.4(9)	14.4(8)	23.8(9)	-1.0(7)	-10.1(7)	-0.9(7)
C17	33.6(10)	19.2(9)	20.4(9)	2.0(7)	-12.3(7)	-2.0(8)
C18	26.2(9)	19.0(8)	19.6(8)	-2.8(7)	-11.8(7)	2.0(7)
C19	12.5(7)	16.1(8)	17.6(8)	-3.7(6)	-3.9(6)	0.1(6)
C20	16.0(8)	18.0(8)	14.2(7)	-3.1(6)	-2.4(6)	-2.0(6)
C21	21.3(8)	11.3(7)	21.8(8)	-5.0(6)	-7.0(7)	1.3(6)

C22	32.2(10)	26.3(9)	25.4(9)	-11.4(8)	-6.9(8)	4.1(8)
C23	26.1(9)	21.3(9)	30.3(10)	0.3(8)	-6.4(8)	-2.8(8)
C24	28.3(9)	19.0(8)	32.5(10)	-9.6(8)	-16.0(8)	6.3(7)
N1	15.1(7)	16.9(7)	18.0(7)	-4.9(5)	-3.3(5)	-3.3(5)
N2	19.1(7)	13.3(6)	16.1(7)	-1.7(5)	-7.2(5)	0.1(5)
O1	22.5(6)	35.3(7)	22.7(6)	-13.6(6)	0.2(5)	-5.1(6)
O2	29.9(7)	16.5(6)	17.2(6)	-1.3(5)	-8.5(5)	-2.0(5)
O3	23.3(6)	20.8(6)	21.4(6)	-6.5(5)	-9.8(5)	-1.7(5)
O4	21.8(6)	13.3(5)	29.2(6)	-5.8(5)	-12.8(5)	0.7(5)

Table 4 Bond Lengths for rjkt1102.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
C1	C2	1.559(2)	C11	C12	1.385(2)
C1	N1	1.369(2)	C12	C13	1.388(2)
C1	O1	1.2149(19)	C13	C14	1.387(2)
C2	C3	1.507(2)	C14	C15	1.386(2)
C2	C16	1.545(2)	C16	C17	1.522(2)
C2	C19	1.542(2)	C17	C18	1.515(2)
C3	C4	1.381(2)	C18	N2	1.485(2)
C3	C8	1.398(2)	C19	N2	1.383(2)
C4	C5	1.392(2)	C19	O2	1.2133(19)
C5	C6	1.389(3)	C20	N2	1.416(2)
C6	C7	1.398(2)	C20	O3	1.2052(19)
C7	C8	1.383(2)	C20	O4	1.3234(19)
C8	N1	1.409(2)	C21	C22	1.515(2)
C9	C10	1.511(2)	C21	C23	1.515(2)
C9	N1	1.467(2)	C21	C24	1.510(2)
C10	C11	1.394(2)	C21	O4	1.4853(18)
C10	C15	1.394(2)			

Table 5 Bond Angles for rjkt1102.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
N1	C1	C2	107.82(13)	C14	C13	C12	119.64(15)
O1	C1	C2	126.74(15)	C15	C14	C13	120.09(16)
O1	C1	N1	125.44(15)	C14	C15	C10	120.72(15)
C3	C2	C1	101.77(12)	C17	C16	C2	111.33(13)
C3	C2	C16	113.91(13)	C18	C17	C16	110.40(14)
C3	C2	C19	110.27(12)	N2	C18	C17	110.27(13)
C16	C2	C1	111.39(13)	N2	C19	C2	117.21(13)
C19	C2	C1	104.71(12)	O2	C19	C2	119.43(14)
C19	C2	C16	113.75(13)	O2	C19	N2	123.30(14)
C4	C3	C2	130.81(15)	O3	C20	N2	122.25(15)
C4	C3	C8	119.79(15)	O3	C20	O4	127.56(15)
C8	C3	C2	109.36(13)	O4	C20	N2	110.13(13)
C3	C4	C5	118.84(15)	C22	C21	C23	112.73(15)
C6	C5	C4	120.71(15)	C24	C21	C22	111.23(14)
C5	C6	C7	121.28(16)	C24	C21	C23	110.80(14)
C8	C7	C6	117.02(15)	O4	C21	C22	108.81(13)
C3	C8	N1	109.46(14)	O4	C21	C23	110.65(13)
C7	C8	C3	122.36(15)	O4	C21	C24	102.09(12)
C7	C8	N1	128.17(15)	C1	N1	C8	111.59(13)
N1	C9	C10	113.04(13)	C1	N1	C9	123.34(13)
C11	C10	C9	119.73(14)	C8	N1	C9	124.96(13)
C15	C10	C9	121.57(14)	C19	N2	C18	121.67(13)
C15	C10	C11	118.70(15)	C19	N2	C20	121.07(13)
C12	C11	C10	120.57(15)	C20	N2	C18	115.88(13)
C11	C12	C13	120.27(16)	C20	O4	C21	121.58(12)

Table 6 Torsion Angles for rjkt1102.

A	B	C	D	Angle/°
C1	C2	C3	C4	177.59(16)
C1	C2	C3	C8	0.07(16)
C1	C2	C16	C17	-74.53(17)
C1	C2	C19	N2	92.15(16)
C1	C2	C19	O2	-85.20(17)
C2	C1	N1	C8	0.25(17)
C2	C1	N1	C9	-176.09(13)
C2	C3	C4	C5	-178.38(15)
C2	C3	C8	C7	178.83(14)
C2	C3	C8	N1	0.07(17)
C2	C16	C17	C18	-57.89(19)
C2	C19	N2	C18	31.0(2)
C2	C19	N2	C20	-162.94(13)
C3	C2	C16	C17	171.06(13)
C3	C2	C19	N2	-159.08(13)
C3	C2	C19	O2	23.6(2)
C3	C4	C5	C6	0.5(2)
C3	C8	N1	C1	-0.21(18)
C3	C8	N1	C9	176.05(14)
C4	C3	C8	C7	1.0(2)
C4	C3	C8	N1	-177.76(14)
C4	C5	C6	C7	0.3(3)
C5	C6	C7	C8	-0.4(2)
C6	C7	C8	C3	-0.2(2)
C6	C7	C8	N1	178.28(15)
C7	C8	N1	C1	-178.87(15)
C7	C8	N1	C9	-2.6(2)
C8	C3	C4	C5	-1.1(2)

C9	C10	C11	C12	-179.69(15)
C9	C10	C15	C14	-179.56(14)
C10	C9	N1	C1	-99.46(17)
C10	C9	N1	C8	84.70(18)
C10	C11	C12	C13	-0.7(3)
C11	C10	C15	C14	0.6(2)
C11	C12	C13	C14	0.5(3)
C12	C13	C14	C15	0.3(2)
C13	C14	C15	C10	-0.8(2)
C15	C10	C11	C12	0.1(2)
C16	C2	C3	C4	-62.4(2)
C16	C2	C3	C8	120.07(15)
C16	C2	C19	N2	-29.69(19)
C16	C2	C19	O2	152.96(15)
C16	C17	C18	N2	56.13(19)
C17	C18	N2	C19	-44.2(2)
C17	C18	N2	C20	149.06(14)
C19	C2	C3	C4	66.9(2)
C19	C2	C3	C8	-110.63(14)
C19	C2	C16	C17	43.53(19)
C22	C21	O4	C20	-71.80(18)
C23	C21	O4	C20	52.58(19)
C24	C21	O4	C20	170.54(14)
N1	C1	C2	C3	-0.19(16)
N1	C1	C2	C16	-121.95(14)
N1	C1	C2	C19	114.68(14)
N1	C9	C10	C11	71.24(19)
N1	C9	C10	C15	-108.58(17)
N2	C20	O4	C21	-173.42(13)
O1	C1	C2	C3	179.60(16)

O1	C1	C2	C16	57.8(2)
O1	C1	C2	C19	-65.5(2)
O1	C1	N1	C8	-179.54(15)
O1	C1	N1	C9	4.1(2)
O2	C19	N2	C18	-151.73(15)
O2	C19	N2	C20	14.3(2)
O3	C20	N2	C18	19.8(2)
O3	C20	N2	C19	-146.99(15)
O3	C20	O4	C21	9.4(2)
O4	C20	N2	C18	-157.50(13)
O4	C20	N2	C19	35.70(19)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for rjkt1102.

Atom	***x***	***y***	***z***	**U(eq)**
H4	4622	-1627	5516	24
H5	4605	-2147	3654	28
H6	2336	-2333	3191	28
H7	4	-1989	4574	23
H9A	-1993	-897	5948	22
H9B	-2468	-711	7325	22
H11	-2556	-2812	9082	25
H12	-3528	-4817	9795	28
H13	-4141	-5798	8409	27
H14	-3743	-4772	6296	24
H15	-2720	-2787	5572	21
H16A	2150	-2940	8657	26
H16B	3739	-2360	8079	26
H17A	1429	-1480	9958	29

H17B	2956	-2271	10193	29
H18A	3114	-42	9971	25
H18B	4365	-556	8931	25
H22A	-144	3974	9106	41
H22B	519	5329	8536	41
H22C	1486	4171	9215	41
H23A	3636	4377	7380	41
H23B	2833	5501	6516	41
H23C	3442	4207	6098	41
H24A	819	4136	5831	38
H24B	142	5327	6412	38
H24C	-564	3990	7002	38

Crystal Data. $C_{24}H_{26}N_2O_4$, M =406.47, triclinic, a = 9.1023(6) Å, b = 10.7446(8) Å, c = 11.3413(6) Å, a = 74.878(6)°, β = 75.082(5)°, γ = 81.943(6)°, U = 1031.52(12) Å^3, T = 110.00(10), space group P-1 (no. 2), Z = 2, μ(Mo Kα) = 0.089, 6258 reflections measured, 4045 unique (R_{int} = 0.0179) which were used in all calculations. The final $wR(F_2)$ was 0.1045 (all data).

Abbreviations

Å	Angstrom
ABH	Aza-Baylis–Hillman
Ac	Acetyl
approx.	Approximately
aq.	Aqueous
Ar	Aryl/Aromatic
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Cbz	Carboxybenzyl
CbzCl	Carboxybenzyl chloride
calcd	Calculated
conc.	Concentrated
cat.	Catalyst/catalytic
COSY	Correlation spectroscopy
CuTC	Copper(I) thiophene-2-carboxylate
δ	Chemical shift
Δ	Heat/reflux
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	*o*-Dichlorobenzene
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DEPT	Distortionless enhancement by polarisation transfer
DIBAL-H	Di*iso*butylaluminium hydride
DMAP	Dimethylaminopyridine
Dmb	2,4-Dimethoxybenzyl
DMF	Dimethylformamide

DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
dppb	Diphenylphosphinobutane
dr	Diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	Enantiomeric excess
ESI	Electrospray ionisation
eq or eq.	Equivalents
Et	Ethyl
Ether	Diethyl ether
FCC	Flash column chromatography
g	Gram(s)
h	Hour(s)
HFIP	Hexafluoro-*iso*propanol
HMDS	Hexamethyldisilazane
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i	*iso*
IBX	2-Iodoxybenzoic acid
IPA	*iso*-Propylalcohol
IR	Infrared
J	Coupling constant in Hz
KF-SiO_2	10% w/w of finely ground KF and 90% w/w silica
KHMDS	Potassium hexamethyldisilazide
L	Litres
LDA	Lithium di*iso*propylamide
LG	Leaving group
lit.	Literature
LHMDS	Lithium hexamethyldisilazane
m	Multiplet
m	*meta*
M	Molar
M^+	Molecular ion

m-CPBA	*meta*-Chloroperbenzoic acid
μν	Microwave irradiation
Me	Methyl
MeCN	Acetonitrile
min	Minute(s)
MK10	Montmorillonite K10
mL	Millilitre
mmol	Millimole
mol. sieves	Molecular sieves
mp	Melting Point
MS	Mass spectrometry
μL	Microlitre
m/z	Mass to charge ratio
n-BuLi	*normal*-Butyllithium
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
o	*ortho*
[O]	Oxidant
OAc	Acetate
O/A/O/I	Oxidation/allylation/oxidation/isomerisation
OTf	Triflate/trifluoromethanesulfonate
P	Undefined protecting group
p	*para*
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PE	Petroleum Ether (that fraction which boils at 40-60 ^{o}C)
Ph	Phenyl
phen	1,10-phenanthroline
PhMe	Toluene
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine

q	Quartet
R	Undefined group
R_f	Retention factor
rt	Room temperature
s	Singlet
sat.	Saturated
SM	Starting material
t	Triplet
t- or *tert*-	Tertiary
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
UV	Ultraviolet
w/w	Weight to weight ratio
X	Undefined halogen
Z	Undefined electron withdrawing group

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