Dearomatising Cyclisations of Pyridine Derivatives

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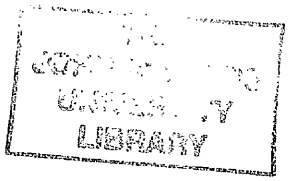

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Abbreviations

Å	Angstrom
Ar	Aryl
aq	Aqueous
BnBr	Benzyl bromide
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
t-BuLi	*tert*-Butyllithium
s-BuLi	*sec*-Butyllithium
n-BuLi	*n*-Butyllithium
DCC	N,N'-Dicyclohexylcarbodiimide
DIAD	Diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
ee	enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Ether	Diethyl ether
EtOAc	Ethyl acetate
g	Grams
h	Hour
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography

Hz	Hertz
LDA	Lithium diisopropylamide
Lit	Literature
LiHMDS	Lithium hexamethyldisilazide
max	Maximum
*m*CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeI	Iodomethane
MeOH	Methanol
min	Minute
ml	Millilitres
mmol	Millimole
mol	Mole
mp	Melting point
MS	Mass spectroscopy
$NaIO_4$	Sodium periodate
NH_4Cl	Saturated aqueous ammonium chloride solution
NMR	Nuclear magnetic resonance
nm	Nanometre
^{i}Pr	Isopropyl
py	Pyridine
Ph	Phenyl
RT	Room temperature
THF	Tetrahydrofuran

TFA	Trifluoroacetic acid
TMEDA	N,N,N',N'-Tetramethylethylenediamine

Abstract

This thesis describes investigations into the anionic dearomatising cyclisations of pyridine derivatives.

Chapter 1 is the introduction and details previous work carried out within the Clayden group on the dearomatising cyclisation. The rest of the chapter details other dearomating reactions of pyridine derivatives, specifically Birch reduction of pyridines and nucleophilic attack of activated pyridines.

Chapter 2 details attempts to apply the dearomatising cyclisation to isonicotinamides, nicotinamides and picolinamides. It was found that the isonicotinamides cyclise to form a novel 1,4-dihydropyridine/β-lactam ring system whilst the nicotinamides and picolinamides cyclise to form 6,5-fused ring systems.

Chapter 3 details the initial studies into the application of the dearomatising cyclisation onto pyridines to more general systems. Tethered anions generated from ketones, 1,3-dithianes and methylene nitriles were all found to cyclise onto pyridine rings.

Chapter 4 details the attempted synthesis of a pyridone regioisomer of acromelic acid C using the dearomatising cyclisation. A novel 6,6,6-fused ring system was discovered.

Finally, chapter 5 contains the experimental data pertaining to chapters two to four.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification at this or any other university or institute of learning.

Copyright Statement

Preface

The Author graduated from Imperial College (London) in July 2001 with a Class two division one degree of Master of Chemistry (Honours). Research in the final year of this course was carried out under the supervision of Dr. David Widdowson, and entitled "Chemistry for PET Science: Aromatic Fluorination by Hypervalent Iodine Compounds". Since October 2001 he has been engaged in research in the Department of Chemistry at the University of Manchester under the supervision of Prof. Jonathan Clayden. The results of the work carried out during this period are embodied in this thesis.

Acknowledgements

I would firstly like to thank my superviser Jonathan Clayden, not only for the opportunity to carry out research in his group, but also for the help and support he provided. I am also grateful to the EPSRC for funding and to Astrazeneca for both funding and the opportunity to work in a research environment. Thank you to my industrial supervisor Rukhsana Mohammed and everybody else I met at the Loughborough site, where I was made very welcome on my placement.

I would like to express my gratitude to the Technical and Administrative staff at Manchester University for the excellect services they provide, especially NMR, Mass Spectrometry, IR and the X-ray Crystallography department. A special thanks is given

to Pete and his team from the Workshop, who fixed everything that I took them, whether chemistry related or not.

The best part of working in the Clayden group has been all of the wonderful people I have had the good fortune to meet. All of whom have contributed in their own way to make working in the lab both fun and enjoyable. Thanks to Ann, Faye, Rachel, Vas, Mark P, Andy, Sav, Prem, Dave, Katherine, Martin, Christel, Ben R, Ben L, Chris, Loic, Lluis, Nuria, Hazel, Sean and Steve. Special thanks also go to Mark B, Tim and Stimpers for proof reading this thesis.

Thank you to all my friends from home, who proved to be very able in taking my mind off writing this thesis when I needed a break!

Finally I would like to thank my family, particularly my parents for their support and for putting up with me. I couldn't have done it without you

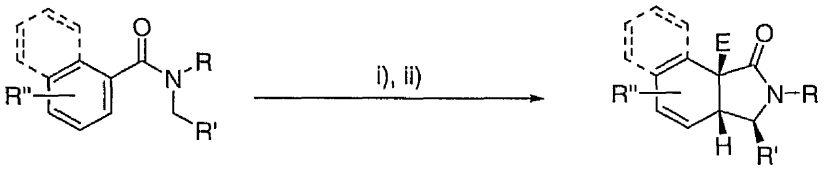
Thank you !

Chapter One

Introduction

1.1 Aim of the project

Since 1998, the Clayden group has been carrying out research on a dearomatising cyclisation reaction (scheme 1.1).[1]



1 **2**

i) organometallic base, THF; ii) E^+

Scheme 1.1

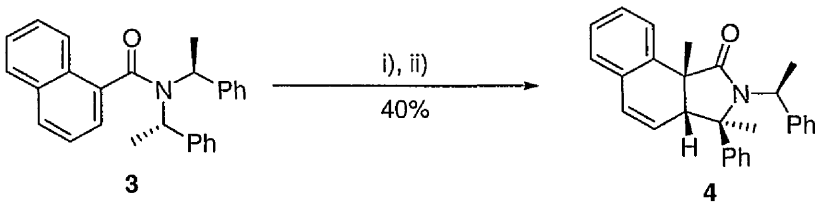
During this time, a great deal has been discovered about the reaction when the starting material **1** is either a benzamide or naphthamide. For example, the reaction has been carried out with a variety of substituents R, R', R'',[2] the origin of its stereochemistry has been elucidated[1,3] and the versatile products of the reaction **2** have even been used as intermediates in a number of elegant syntheses of members of the kainoid series of natural products.[4–7] These findings will be discussed more thoroughly as part of the introduction to this thesis.

The aim of this project is to extend this methodology to cyclisations onto pyridine and quinoline ring systems with a variety of substitution patterns.

1.2 Dearomatising Anionic Cyclisation of Tertiary Amides

1.2.1 Background

In 1995, attempted ortholithiation followed by alkylation of *N*,*N*-bis[(1*S*)-1-phenylethyl]-1-naphthamide **3** unexpectedly furnished the tricyclic isoindolone **4**. Remarkably, the product was isolated as a single diastereoisomer (scheme 1.2).[8]



3 **4**

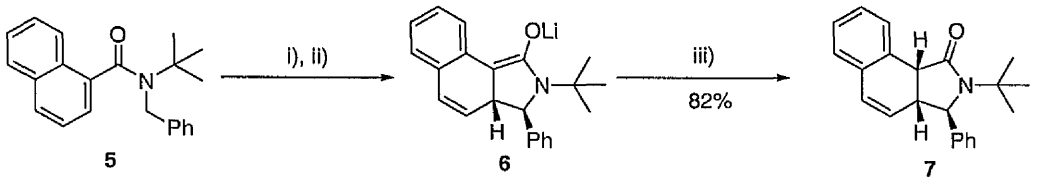
i) *t*-BuLi, THF, –78 °C; ii) MeI

Scheme 1.2

Anionic cyclisations onto alkenes and alkynes to form both carbocycles[9] and heterocycles[10] were already well precedented, but few examples of anionic cyclisations onto aromatic rings existed[11] and these tended to be low yielding, unwanted side reactions. As the above reaction creates a pharmacologically interesting 6,5-fused pyrrolidinone ring, bearing three contiguous stereogenic centres as a single diastereoisomer, a more thorough study was embarked upon.

1.2.2 Dearomatising Cyclisation of Tertiary Naphthamides

Initially, a simplified naphthamide **5** was used for the study in order to remove the complication of additional stereogenic centres. It was found that treatment of **5** with *t*-butyllithium, followed by addition of the lithium coordinating ligand HMPA then protic quench, furnished the benzo[*e*]isoindolone **7**, which could be isolated as a single diastereoisomer.[1] This remarkable reaction presumably occurs *via* the extended enolate **6** (scheme 1.3).



5 **6** **7**

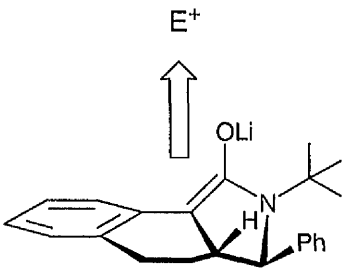
i) *t*-BuLi, THF, –78 °C, 2 h; ii) HMPA, –78 °C, 16 h, iii) NH_4Cl

Scheme 1.3

As well as the protic quench, enolate **6** could also be alkylated with a range of electrophiles to give products with the 6,5-*cis* ring junction analogous to **7** as the major diastereoisomer plus the 6,5-*trans* product as the minor diastereoisomer. The diastereoselectivity was found to be linked to the steric bulk of the electrophile, with larger electrophiles giving better diastereoselectivity.[1]

1.2.3 Stereochemistry of the Dearomatising Cyclisation

This stereochemistry is thought to arise from attack of the electrophile on the less hindered *exo*-face of the enolate **6** (figure 1.1).[1]



6

Figure 1.1

The 6,5-*cis* diastereoisomer of **7** was proved to be most stable of the two ring junction isomers as it remained unchanged after stirring overnight with *t*-BuOK in *t*-BuOH at 40 °C.[1]

The relative stereochemistry around the newly formed bond has been rationalised by considering the reaction to be a six electron thermal disrotatory electrocyclic reaction as shown in figure 1.2.[3]

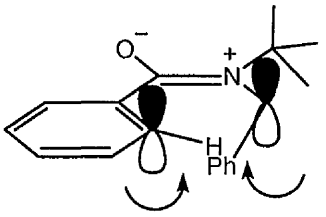
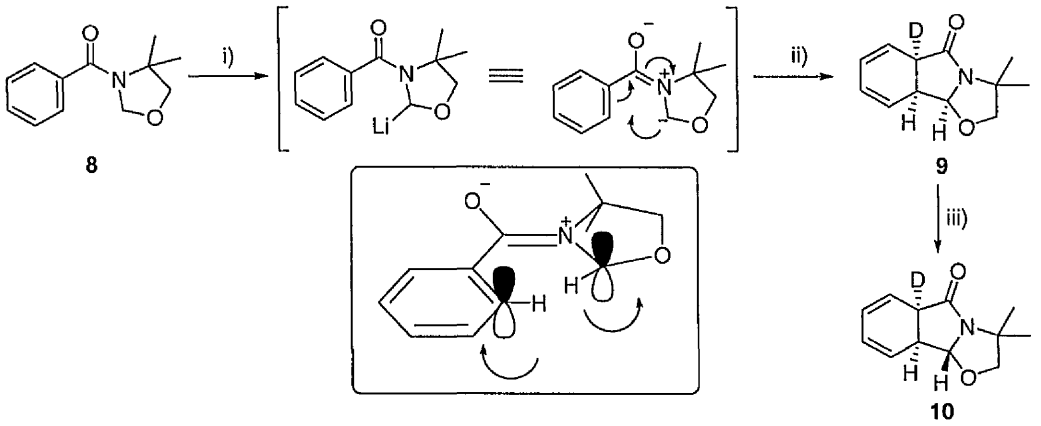


Figure 1.2

For this rationalisation to give the correct stereochemistry, the phenyl group has to be *trans* to the *t*-butyl group around the N-CH_2 bond prior to the cyclisation taking place and it has been found that it is necessary to have a bulky *N*-substituent such as *t*-butyl to give good stereochemical control around the newly formed bond.

The rationalisation has been backed up by Purewal, who used a cyclic moiety to lock the substituents of the N-CH_2 bond into a *cis* relationship (scheme 1.4). On cyclisation of **8**, the product **9** was formed bearing stereochemistry consistent with the reaction being a six-electron disrotatory electrocyclic process.[3] The *cis* fused epimer is the thermodynamically less stable epimer, as **9** epimerised to the more thermodynamically stable *trans* fused epimer **10** when treated with acid.[3]

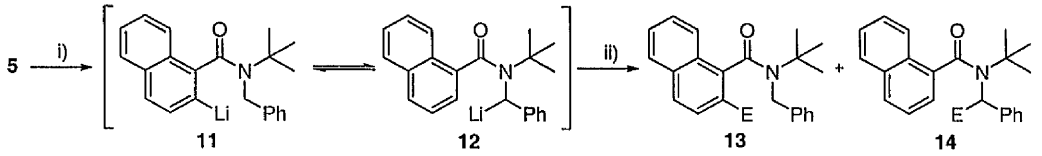


i) *t*-BuLi, DMPU, –78 °C; ii) D_2O; iii) 2 M HCl in Et_2O, 2 h, 20 °C

Scheme 1.4

1.2.4 The role of HMPA in the Dearomatising Cyclisation

The role of HMPA (and DMPU, which has been found to be a suitable, less toxic replacement) in the reaction was elucidated by Ahmed, who showed that addition of *t*-butyllithium to **5** resulted in a mixture of the ortho lithiated amide **11** and α-lithiated amide **12**. These were trapped with a series of electrophiles to give **13** and **14** (scheme 1.5). The results are represented in table 1.1.[12]



i) *t*-BuLi, THF, –78 °C, 2 h; ii) EX

Scheme 1.5

Entry	EX	Ratio 13:14
1	D_2O	1:2
2	MeI	1:2
3	EtI	2:1
4	TMSCl	>10:1
5	DMPU then MeI (after 2 min)	1:10

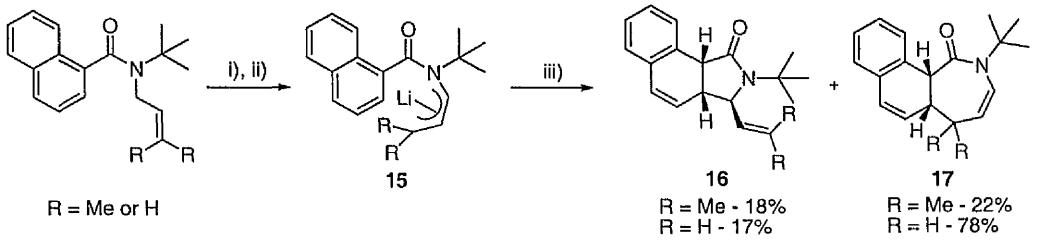
Table 1.1

The ratio of **13**:**14** was electrophile dependent (entries 1–4, table 1.1) which suggests that **11** and **12** are in equilibrium. The best estimate of the ratio of **11** and **12** in solution before the addition of the electrophile is given when the most reactive electrophiles are used (entries 1 and 2, table 1.1). One of the experiments partly reveals the role of the HMPA/DMPU in the reaction (entry 5, table 1.1). When it is added, 'anion translocation'[12] takes place and the equilibrium between **11** and **12** is shifted towards **12**, which is the only regioisomer of the two that can cyclise, however, this particular reaction was quenched before cyclisation could take place. The DMPU must also help in the cyclisation of **12** since no cyclisation is seen in the

entries without DMPU (entries 1-4, table 1.1) under these conditions. Presumably the DMPU helps by destabilising the anion by complexation with the lithium cation.

1.2.5 Cyclisation of *N*-Allyl-1-Naphthamides

In an effort to extend the utility of this novel reaction, anion stabilising groups other than benzyl were examined. It was found that cyclisation also took place with an allylic stabilising group to give not only the expected pyrrolidinone **16**, but also products featuring a seven membered tetrahydroazepinone ring **17** *via* cyclisation of the disubstituted end of the allyl anion **15** (scheme 1.6).[13]



i) *t*-BuLi, THF, –78 °C; ii) DMPU, –50 °C, 16 h; iii) NH_4Cl

Scheme 1.6

These were the first examples of seven membered rings formed by organolithium cyclisations onto C=C double bonds and the products, which are rare cyclic *N*-acyl enamines, posesses structures that resemble the pharmaceutically important benzazepin-2-ones (figure 1.3).[14]

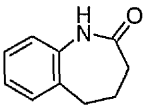
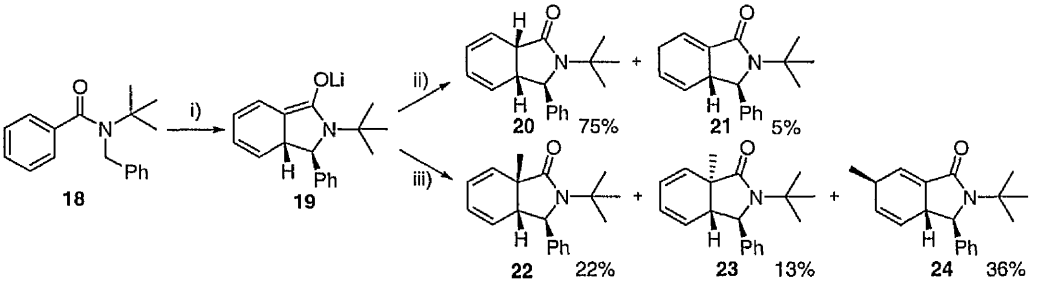


Figure 1.3

1.2.6 Cyclisation onto *N*-Benzyl Benzamides

Further elaboration of the dearomatising cyclisation methodology came about with the extension from naphthamides to benzamides.[15] Benzamides are more difficult to dearomatise than naphthamides as the benzamide loses all of its aromatic character during the reaction as opposed to a naphthamide, which is only partially dearomatised. Despite this, cyclisation of the simple benzamide **18** with *t*-butyllithium in the presence of HMPA or DMPU followed by a protic quench yielded tetrahydroisoindolones **20** and **21** as a mixture of C-C double bond regioisomers, and with methyl iodide as the electrophile **22**, **23** and **24** (scheme 1.7). The enolate **19** was also quenched with other electrophiles with varying stereoselectivity and regioselectivity.[15] Suprisingly, with the benzamide series it was found that direct α-lithiation occured rather than the combination of ortho and α-lithiation followed by anion translocation seen with the naphthamides.

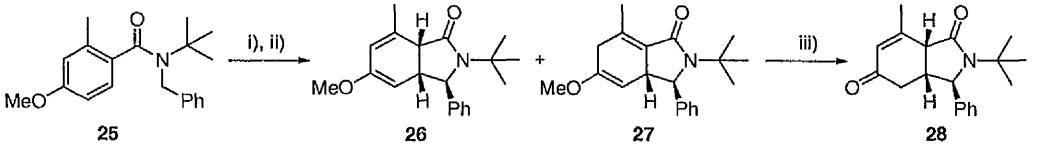


i) *t*-BuLi, HMPA, THF, −78 °C, 16 h; ii) H_2O, iii) MeI

Scheme 1.7

The problem of the reaction yielding a mixture of regioisomers (scheme 1.7) was largely overcome when it was found that methoxybenzamides in a variety of substitution patterns would undergo the dearomatising cyclisation reaction. A resulting mixture of regioisomers can then be hydrolysed to a single regioisomer of a synthetically versatile cyclohexenone. An example of this is shown in scheme 1.8

where methoxybenzamide **25** is cyclised to a regiochemical mixture of **26** and **27** that is smoothly hydrolysed to a single regioisomer of the cyclohexenone product **28**.[16]



25 26 27 28

i) *t*-BuLi, THF, HMPA, –40 °C; ii) NH_4Cl; iii) HCl, H_2O

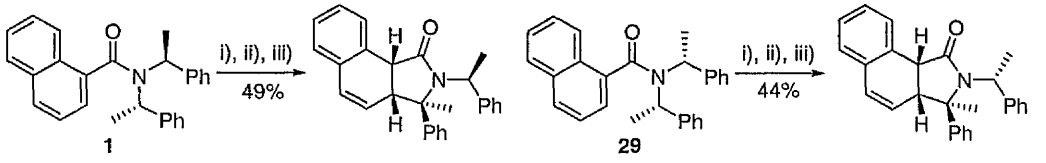
Scheme 1.8

The reaction conditions of the cyclisation were later improved for both the benzamides and the naphthamides when it was found that the non-nucleophilic bulky base LDA could lithiate the tertiary amides and that cyclisation took place in the absence of toxic HMPA or DMPU if the temperature of the reaction was raised to 0 °C. This greatly increased the scope of the reaction, as a wider range of substituents and substitution patterns could be tolerated – most notably functionality with reactivity towards *t*-BuLi such as cyano and bromo groups.[2]

1.2.7 Asymmetric Cyclisation

1.2.7.1 Stereospecific Cyclisations of Naphthamides Bearing Chiral *N*-Substituents

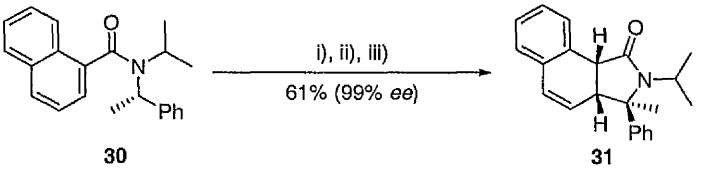
The very first naphthamide cyclisation of **1** posed an important stereochemical question – was the reaction stereospecific, with the stereochemistry controlled by the configuration of the α-lithiated cyclising centre, or stereoselective, with the stereochemistry controlled by the configuration of the exocyclic stereogenic centre? This question was answered by comparison of the cyclisation of **1** with the cyclisation of its diastereomer, the *meso* compound **29** (scheme 1.9).[17]



i) *t*-BuLi, THF, –78 °C, 2 h; ii) DMPU, –78 °C, 16 h; iii) MeOH

Scheme 1.9

Both **1** and **29** cyclised with retention at the cyclising centre, thus proving that the reaction is stereospecific and suggesting that the α-lithiated intermediate is configurationally stable. This observation was vindicated when it was shown that an enantiomerically pure naphthamide bearing chirality at the α-lithiated cyclising centre such as **30**, could be cyclised to furnish **31** in high enantiomeric excess (scheme 1.10).[17]

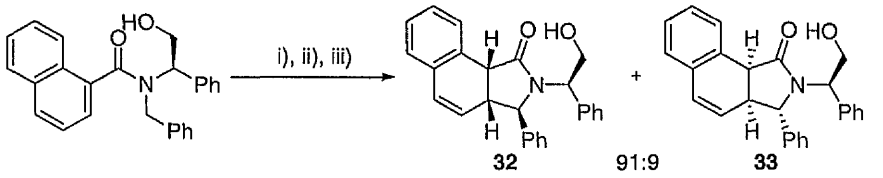


i) *t*-BuLi, THF, –78 °C, 2 h; ii) DMPU, –50 °C, 16 h; iii) MeOH

Scheme 1.10

1.2.7.2 Stereoselective Cyclisations of Tertiary Naphthamides Bearing a Chiral *N*-Substituent

In contrast to the previous stereospecific cyclisations shown in scheme 1.11 and 1.12 where the stereochemistry of the molecule is controlled by an *endo*-cyclic chiral centre in the ring being formed, it was found that stereoselective cyclisations could also be carried out when the naphthamide featured a chiral *N*-substituent *exo*-cyclic to the ring being formed. Using this methodology, a chiral auxiliary strategy can be employed. The best chiral auxiliary found was a phenylglycine group, which proved to be particularly versatile as both (*R*)- and (*S*)-phenylglycine are available and the auxiliary can be removed either by the mesylation-elimination protocol of Vernon,[18] or by the novel selenide oxidation-elimination protocol of Clayden and Bragg.[18] The addition of DMPU to the doubly lithiated naphthamide (scheme 1.12) effected a cyclisation to give a 10:1 mixture of diastereoisomers of **32** and **33** (scheme 1.11).[18]



32 **33**

i) *t*-BuLi, THF, –78 °C, 2 h; ii) DMPU, –35 °C, 16 h; iii) NH_4Cl

Scheme 1.11

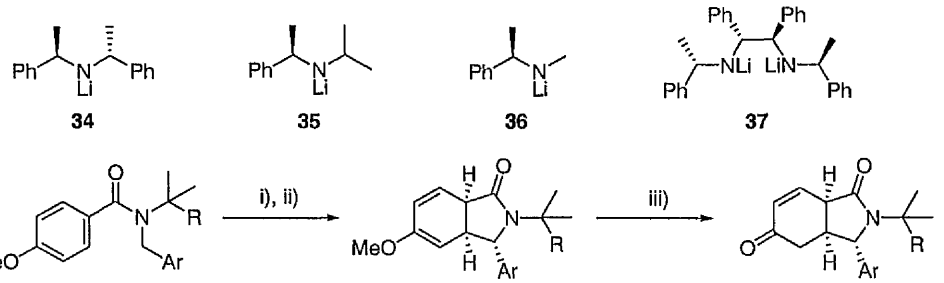
The stereoselectivity can be rationalised by the coordination of lithium by oxygen and by the prefered conformation of the doubly lithiated intermediate being as shown in scheme 1.12.[19]

Scheme 1.12

1.2.7.3 Asymmetric Deprotonation and Cyclisation using a Chiral Lithium Amide Base

With the knowledge that the reaction could now be carried out using LDA as the base,[2] the Clayden group turned towards chiral versions of LDA to determine if asymmetric cyclisations could be effected with their use. A chiral base strategy is a step forward from a chiral auxiliary strategy as extra steps to add and remove the chiral auxiliary are avoided.

A number of chiral lithium amides were screened, but the best results were found to be with **35** (table 1.2). This gave not only the highest enantiomeric excesses, but was also the easiest to remove from the product mixture by a simple acid wash. When amides **38-41** were treated with the chiral bases **34-37** under suitable conditions and subjected to a protic quench, cyclisation occurs to give enantiomerically enriched **42-45**. These were isolated as the hydrolysed products **46-49** (scheme 1.13).[20]



38 R = Me, Ar = Ph
39 R = Ph, Ar = Ph
40 R = Me, Ar = *m*-$MeOC_6H_4$
41 R = Ph, Ar = *m*-$MeOC_6H_4$

(–)-**42** R = Me, Ar = Ph
(–)-**43** R = Ph, Ar = Ph
(–)-**44** R = Me, Ar = *m*-$MeOC_6H_4$
(–)-**45** R = Ph, Ar = *m*-$MeOC_6H_4$

(–)-**46** R = Me, Ar = Ph
(–)-**47** R = Ph, Ar = Ph
(–)-**48** R = Me, Ar = *m*-$MeOC_6H_4$
(–)-**49** R = Ph, Ar = *m*-$MeOC_6H_4$

i) Chiral lithium amide, THF, –78-25 °C, 1.5 h; ii) NH_4Cl; iii) HCl, H_2O

Scheme 1.13

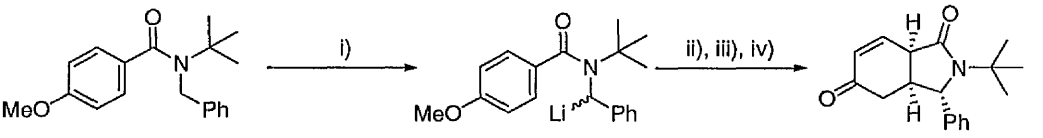
Starting Material	Base	Yield of 46-49 (%)	*ee* of 46-49 (%)	*ee* of 46-49 (after recrystallisation) (%)
38	**34**	73	80	>99
38	**34**	65	50	–
38	**35**	72	80	>99
38	**36**	72	17	–
38	**37**	38	–75	–
39	**34**	64	75	>99
39	**35**	72	81	>99
39	**37**	23	–30	–
40	**34**	59	73	–
40	**34**	67	60	–
41	**35**	87	84	–

Table 1.2

All of the bases gave products with laevorotatory stereochemistry except for **37** which gave dextrorotatory products. It should also be noted that a single recrystallisation was all that was needed to return the products of **46** and **47** in >99% *ee*.

This methodology does not work well for *ortho* substituted amides, giving either low yields or low enantioselectivities. This is thought to be because at the temperatures at which the reaction is conducted, these compounds are chiral themselves.[20]

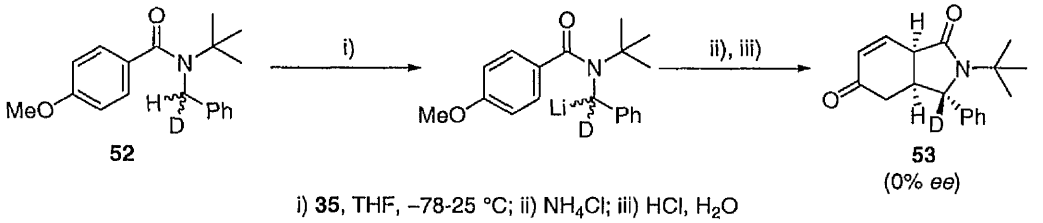
The origin of the enantioselectivity is thought to be due to an asymmetric deprotonation of the achiral starting material to yield an enantiomerically enriched organolithium which is configurationally stable on the timescale of the reaction; a *stereospecific* cyclisation ensues. A couple of experiments have been carried out that confirm this reasoning.



i) *t*-BuLi, THF, –78 °C; ii) chiral amine, –78-25 °C; iii) NH_4Cl; iv) HCl, H_2O

Scheme 1.14

In the first (scheme 1.14), an achiral organolithium **50** was generated from **38** using *t*-butyllithium. The free amine of the chiral base **35** was then added to the reaction mixture to mimic the conditions of the asymmetric cyclisation, but with the essentially racemic organolithium. After protic quench and acidic work-up, the enone **51** was returned in almost racemic form. This proves that the enantioselectivity of the reaction is determined before the cyclisation step i.e. during the intial deprotonation and is not due to the asymmetric influence of the amine after deprotonation.[20]



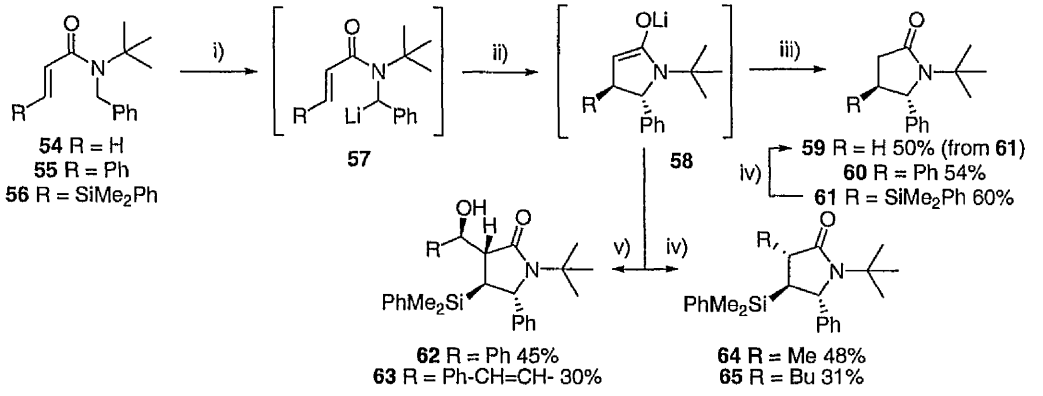
i) **35**, THF, –78-25 °C; ii) NH_4Cl; iii) HCl, H_2O

Scheme 1.15

In the second experiment (scheme 1.15), the racemic deuterium labelled compound **52** was used as the starting material for the cyclisation. Treatment of **52** with **35** followed by protic quench and hydrolysis gave the >99% deuterated compound **53** in racemic form. This result shows that the primary isotope effect ($k_H/k_D > 100$) has completely overturned the enantioselectivity of the chiral base. Thus, the enantioselective step must be subject to the primary kinetic isotope effect and is therefore the deprotonation.[20]

1.2.8 Cyclisation onto Alkenes[21]

Watson found that *N*-benzylamines of α,β-unsaturated carboxylic acids **55-56** can be lithiated at the benzylic position and cyclised to give moderate yields of 5-arylpyrrolidinones **59-65** or β-aryl-β-lactams depending on the substitution pattern - both of which are components of many biologically active compounds. Some representative results are shown in scheme 1.16.



i) LDA/LiTMP; ii) 2 h, 0 °C; iii) NH_4Cl; iv) KF, DMSO, Δ (only for **59**); (v) PhCHO or PhCH=CHCHO; vi) MeI or BuBr

Scheme 1.16

The reaction presumably proceeds *via* the lithiated intermediate **57** which cyclises to the enolate **58**. This can be trapped by a proton (**59-61**), alkylating agents (**64-65**) or it can take part in aldol reactions (**62-63**). All of the products are isolated as single diastereoisomers. β-Substitution of the alkene in the starting material is necessary for the reaction as attempted cyclisation of **54** resulted in polymerisation – no cyclised products were formed in the reaction. When the acrylamide is β-substituted with a phenyl ring (**55**) or silyl substituent (**56**) the reaction proceeds to give moderate yields of the pyrrolidinone **60** and **61-65** respectively. Pyrrolidinone **59** cannot be made directly due to the aforementioned polymerisation but can be made by the desilylation

of **61**. The reaction is also tolerant of a range of substituents in the α-position of the alkene.

The stereochemical outcome of the aldol reaction can be rationalised by a Zimmerman-Traxler transition state shown in figure 1.4. The R group in the approaching aldehyde occupies an equatorial position in the six membered transition state.

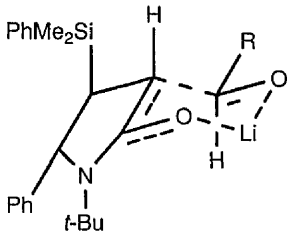
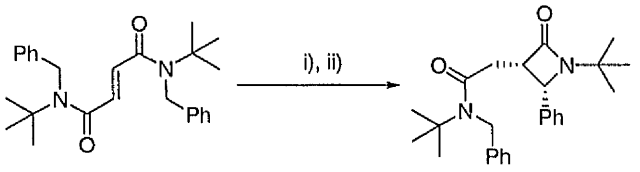


Figure 1.4

It is not known whether or not the mechanism of the reaction is a disrotatory electrocyclic ring closure similar to the cyclisations of benzamides and naphthamides or an intramolecular 5-*endo-trig* conjugate addition.

When the acrylamide is substituted in the β-position with an electron withdrawing group such as in **66**, the mode of cyclisation changes completely and the product of the cyclisation is the *syn*-diastereomer of the β-lactam **67**, which is the result of a 4-*exo-trig* cyclisation (scheme 1.17).



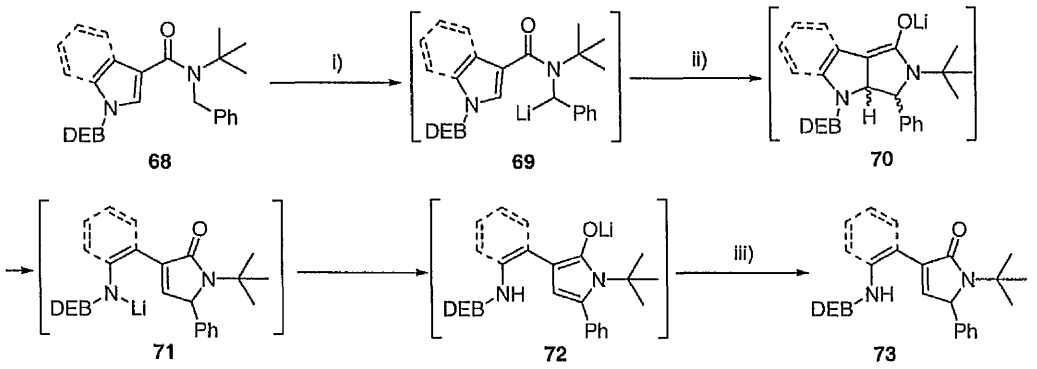
66 **67**

i) LDA, 0 °C, 2 h; ii) NH_4Cl

Scheme 1.17

1.2.9 Cyclisation onto pyrroles and indoles[22]

Turnbull found that DEB (2,2-diethylbutanoyl) protected pyrroles and indoles such as **68** could be used as the acceptor in the dearomatising cyclisation reaction. The products were not the expected 5,5-fused ring systems, as the cyclisation is followed by opening of the original ring to yield pyrrolidinones **73**. The mechanism for this transformation is shown in scheme 1.18.



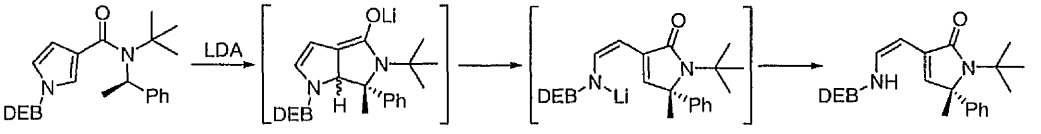
i) 3 equiv. LDA, THF, 0 °C; ii) 3 h, 0 °C; iii) NH_4Cl

Scheme 1.18

On lithiation, the starting material **68** lithiates in the benzylic position to give **69**, which then cyclises at the 2-position. The product is an extended enolate **70**, which is unstable due to extensive unsaturation in the 5,5-fused ring system. The ring strain is relieved *via* either a 5-*endo-trig* or an electrocyclic ring opening to furnish **71**. An intramolecular proton transfer yields a new extended enolate **72**, which is protonated to give **73**.

It should be noted that protecting groups other than DEB were tried, all the others (Boc, AdOC, Me) lead to deprotection of the pyrrole nitrogen rather than cyclisation. The only exception to this is the pivaloyl group, which gave much poorer yields.

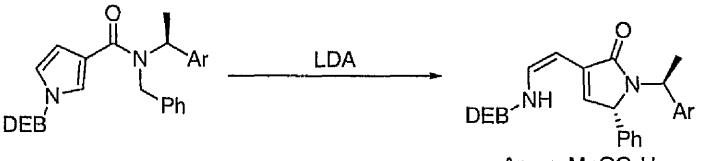
Unfortunately, the chiral base strategy which worked well for the benzamide series (section 1.2.6.3) failed to work in the pyrrole ring system, as all stereochemical information is lost on formation of the achiral enolate **72**. However, similar to the naphthamides, cyclisation of a chiral starting material **74** gives an enantiomerically pure product **76** *via* a stereospecific lithiation and cyclisation of a configurationally stable organolithium (scheme 1.19). The stereochemical information is not lost because **75** cannot re-form an enolate.



74 **75** **76** 87% (99% ee)

Scheme 1.19

Remarkably, it is also possible to carry out the cyclisation stereoselectively (scheme 1.20) similar to previous benzamide cyclisations. Cyclisation of amide **77** bearing an α-methyl-*p*-methoxybenzyl "auxiliary" furnishes **78** as a single diastereoisomer. It is thought that the auxiliary controls the facial selectivity of the final protonation step.

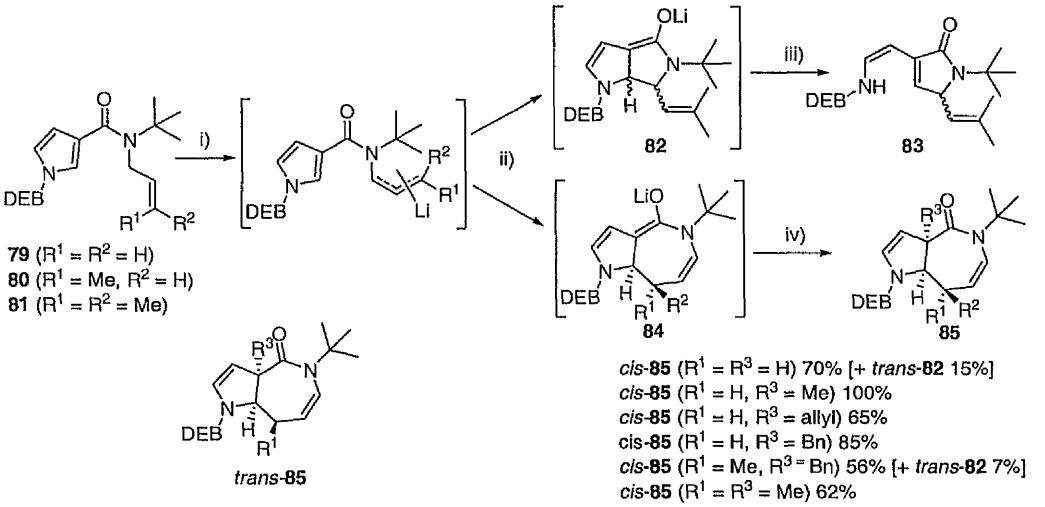


77

Ar = *p*-$MeOC_6H_4$
78 56%

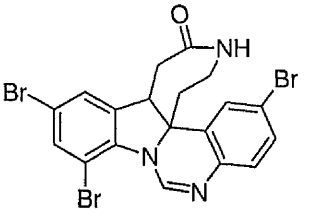
Scheme 1.20

It was found that the ring opening of the extended enolate could be avoided in the cyclisation of *N*-allyl pyrrolecarboxamides (scheme 1.21), whereby treatment of amides **79-81** with LDA furnished single diastereomers of the *cis*-fused 7,5-fused pyrroloazepinones of the type **85**.



Scheme 1.21

The *N*-prenyl pyrrolecarboxamide **81** furnished the 5-membered product **83** *via* the unstable enolate **82**, probably because of the steric hindrance at the far end of the allylic system. With a less bulky allyl (**79**) or crotyl *N*-substituent (**80**), cyclisation takes place to yield extended enolates of the type **84** bearing a 7,5-fused ring system. As this is much less strained than a heavily unsaturated 5,5-fused ring system, no ring opening takes place, and the enolate can be quenched with a variety of electrophiles to yield the *cis*-fused products of the type **85** in high yield. The 7,5-ring system formed in this reaction is novel but related to the pyrroloazepine present in the natural product hinckdentine A (figure 1.5).

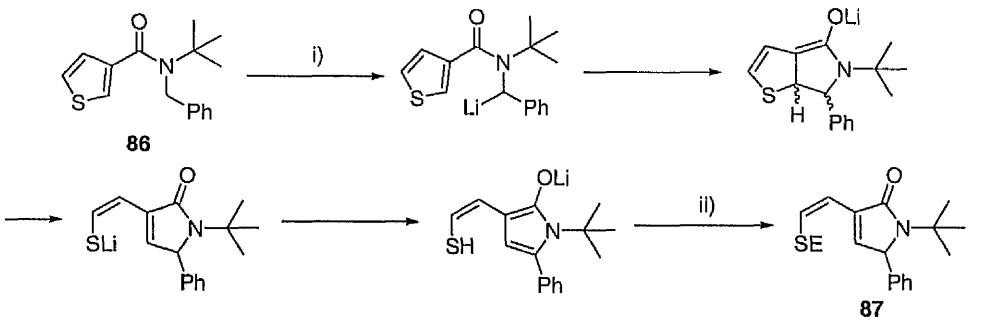


Hinckdentine **A**

Figure 1.5

1.2.10 Cyclisation onto Thiophenes[23]

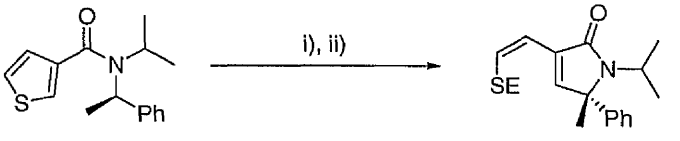
Turnbull also found that *N*-benzyl and *N*-allyl substituted thiophene-3-carboxamides undergo dearomatising cyclisations when treated with LDA (scheme 1.22).



i) LDA, THF, 0 °C; ii) EX

Scheme 1.22

Cyclisation of **86** furnished the pyrrolinones **87** in good yield *via* a mechanism identicle to the analogous pyrrole- and indole-3-carboxamides. The vinyl sulfide possesses *cis* stereochemistry, which has been retained from the thiophene. The reaction gave a complex mixture of products when quenched with a proton: this is thought to be due to the resulting unstable thioaldehyde. The reaction was tolerant to substitution in the 5-position of the thiophene to furnish vinyl sulfides substituted α to the sulfur atom. The reaction can also be carried out in a stereospecific manner analogous to the reaction carried out in scheme 1.19 (scheme 1.23).

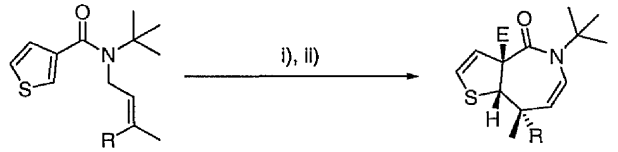


i) LDA, 0 °C; ii) EX

Scheme 1.23

In an attempt to isolate products with the thiophene ring intact, the reaction was carried out with *N*-allyl substituents. With prenyl (**88**) or crotyl (**89**) *N*-substituents,

the reaction furnished the expected 5,7-fused heterocycles **90** and **91** respectively in good yield (scheme 1.24).



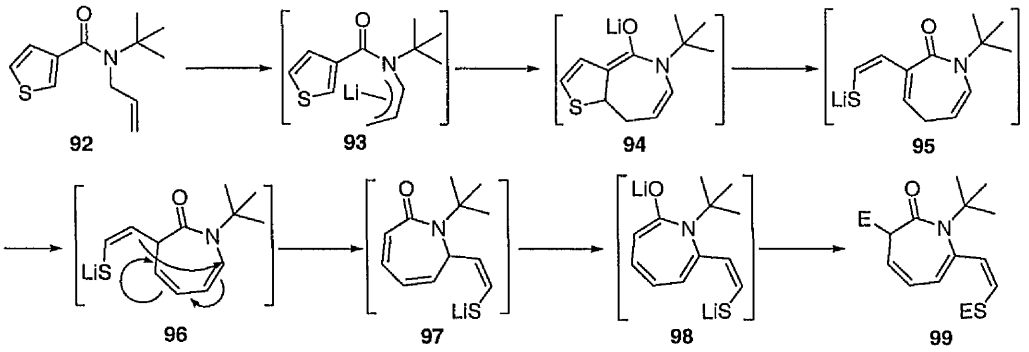
88 R = Me
89 R = H

90 R = Me 50-71%
91 R = H 50-65%

i) 3 equiv. LDA, THF, 0 °C, 3 h; ii) EX (E = H, Me, Et, Allyl, Bn, *p*-BrBn)

Scheme 1.24

However, when the *N*-allyl amide **92** was subjected to the same conditions, the product was a [3*H*]-azepinone **99** (scheme 1.25).



92 **93** **94** **95**

96 **97** **98** **99**

45-70%
(E = Me, Et,
Allyl, Bn, *p*-BrBn)

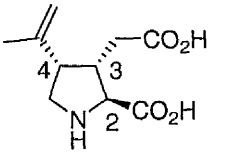
i) 3 equiv. LDA, THF, 0 °C, 3 h; ii) NH_4Cl

Scheme 1.25

The bicycle **94** is formed by the expected dearomatising cyclisation of the of the lithiated intermediate **93**. The thiophene ring then opens to give **95**, which undergoes a proton shift that sets up the π array necessary in **96** to allow a remarkable 1,5-shift of the thiovinyl group from C3 to C7 to give **97**. The proton shift is presumably LDA mediated and would be less favourable or impossible in the similar reactions depicted in scheme 1.22. Further deprotonation with excess LDA yields **98** which is alkylated to give **99**.

1.2.11 The Dearomatising Anionic Cyclisation used in Synthesis

The previously discussed dearomatising cyclisations of *N*-benzyl naphthamides and benzamides give products that share their relative stereochemistry and substitution pattern with the kainoids.[24] The parent of the kainoids, kainic acid (figure 1.6) exhibits a wide range of biological activity[25] and has been used as an anthelmintic,[26] an insecticide[27] and as a tool in neuropharmacology, where its potency as a neuroexcitor has been exploited.[28] Binding occurs specifically at the kainate receptor, which leads to specific neuronal death. The *cis* C-3–C-4 stereochemistry that is shared by all of the kainoids is vital for their biological activity.

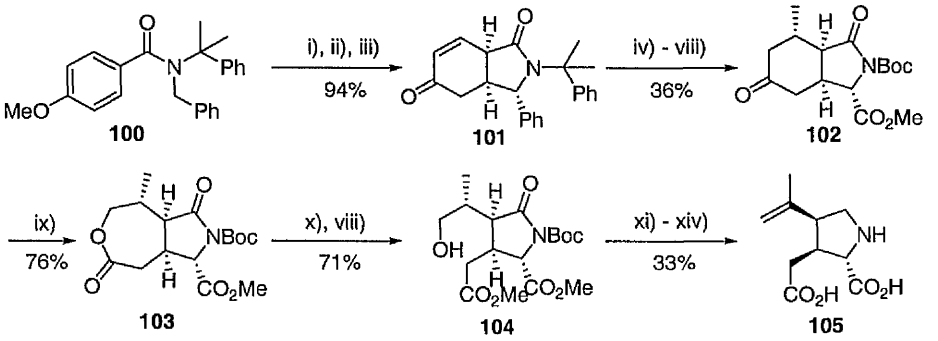


kainic acid

Figure 1.6

Members of the kainoid family differ only in their C-4 substituent, and as many of its natural and non-natural analogues posses even greater activity than kainic acid itself, a brief and versatile synthesis of kainoids is highly desirable.[7]

Syntheses of kainic acid in both its racemic and optially active forms are numerous, but the first synthesis making use of the anionic dearomatising cyclisation strategy was reported in 1999 (scheme 1.26).[4]



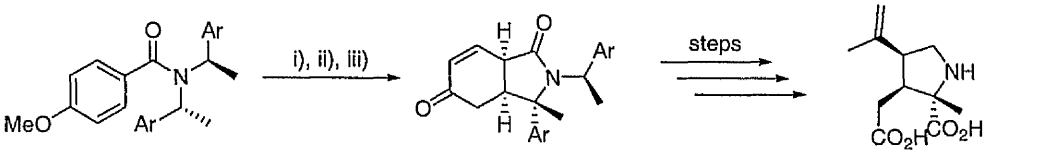
i) *t*-BuLi, HMPA, THF, –40 °C, 60 h; ii) NH_4Cl; iii) THF, 1 M HCl (aq); iv) Me_2CuLi, Me_3SiCl, THF, –78 °C, 1 h; v) CF_3CO_2H, reflux, 6 h; vi) Boc_2O, Et_3N, DMAP, CH_2Cl_2; vii) $NaIO_4$, cat. $RuCl_2$, 1:1 acetone-H_2O; viii) Me_3SiCHN_2, PhH, MeOH; ix) *m*CPBA, CH_2Cl_2; x) NaOH, MeOH, reflux, 2 h; xi) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, 20 °C; xii) H_2O_2, Py, THF, –40 °C; xiii) $NaBH(OMe)_3$, THF, reflux; xiv) 10:1 CF_3CO_2H-H_2O, reflux, 4 h.

Scheme 1.26

The cyclisation precursor chosen as the starting point for the synthesis has a cumyl *N*-substituent instead of the *t*-butyl group previously used. This was chosen after difficulty was experienced in the removal of the *t*-butyl group. The cumyl group is suitable because it is bulky, acid labile and resistant to organolithium reagents.[29] Benzamide **100** was cyclised using the original cyclisation conditions of *t*-BuLi and HMPA. After protonation, treatment with acid yielded the enone **101**. Conjugate 1,4-addition to the enone was effected with a cuprate reagent, which was quenched with trimethylsilyl chloride, resulting in the exclusive attack of the cuprate to the least hindered *exo* face of the molecule. Treatment with TFA both removed the cumyl group and hydrolysed the silyl enol ether. The lactam was protected as a Boc carbamate and the phenyl group was oxidised to a carboxylic acid using Sharpless conditions.[30] Esterification of the carboxylic acid with trimethylsilyldiazomethane[31] yielded **102**. Baeyer-Villiger oxidation was used to expand the ring, and remarkably, this produced the desired regioisomer with excellent selectivity, despite the carbonyl bearing almost identical substitution on each side. The lactone **103** was opened using methanol/NaOH, and a second esterification furnished the diester **104**. The isopropenyl group was installed by direct formation of the selenide,[32] which was

subsequently oxidised and eliminated under mild conditions, followed by a chemoselective reduction of the lactam in the presence of two esters, with sodium trimethoxyborohydride.[33] Boc deprotection furnished kainic acid **105**.

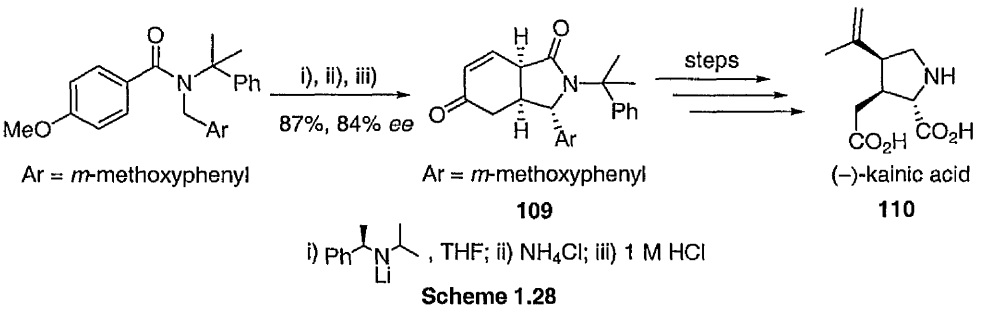
A synthesis of α-methyl kainic acid **108** was later carried out stereospecifically using a similar route (Scheme 1.27).[34] Starting from the chiral cyclisation precursor **106**, the dearomatising cyclisation followed by hydrolysis yielded **107** as a single diastereoisomer. This was transformed to α-methyl kainic acid *via* a similar route to the one depicted in scheme 1.26. The *p*-methoxyphenyl group was removed by oxidative cleavage with ceric ammonium nitrate.[35] The *p*-methoxyphenyl group was chosen over a phenyl group as it has been shown to be more easily removed.[34]



i) *t*-BuLi, THF, –78 °C to 20 °C; ii) NH_4Cl; iii) 0.5 M HCl

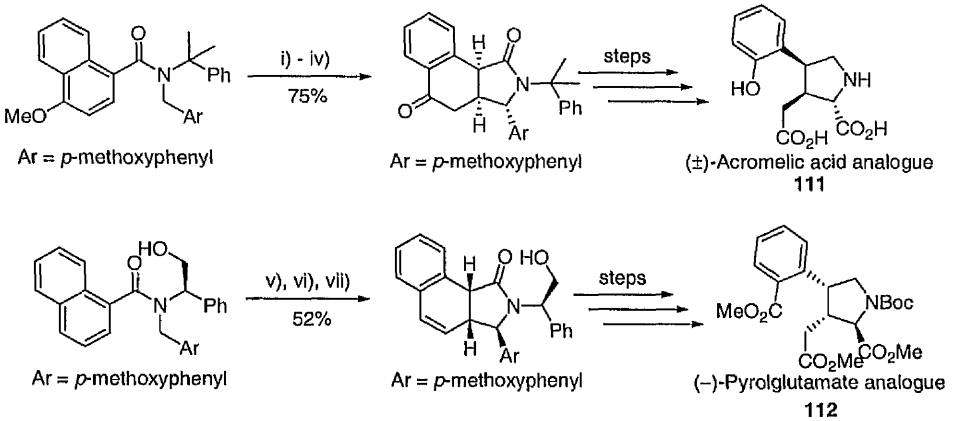
Scheme 1.27

The synthesis of kainic acid itself was further refined when the cyclisation was carried out stereoselectively using the chiral base methodology discussed in section 1.2.7.3.[5] The cyclisation product **109** was elaborated *via* a similar route using the same major steps as above to furnish (–)-kainic acid **110** in high enantiomeric excess. The initial dearomatising cyclisation gave an *ee* of 84%. Recrystallisation later in the synthesis increased the *ee* to 98% (Scheme 1.28).



Scheme 1.28

The naphthamide cyclisations have also been used in natural product syntheses to make kainoids bearing a substituted phenyl group in the C-4 position. The potent known non-natural (±)-4-(2-hydroxyphenyl) analogue of the acromelic acids **111**[36] and a kainoid like pyroglutamate **112**[18] have both been synthesised (scheme 1.29). The synthesis of **111** took advantage of a similar route to the ones developed for the syntheses exploiting products of benzamide cyclisations, whilst **112** differed in that it avoided the Baeyer-Villiger oxidation to open the ring and instead used modified Sharpless conditions.[37] Analogue **111** was synthesised racemically, but the synthesis of **112** used the phenylglycinol-derived chiral auxiliary methodology discussed in section 1.2.7.2 to form the target asymmetrically.



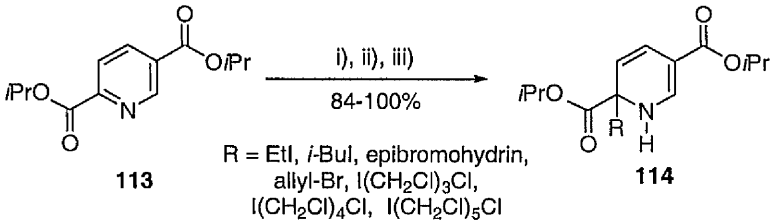
i) *t*-BuLi, THF, –78 °C, 2 h; ii) DMPU. –78 °C, 16 h; iii) NH_4Cl, H_2O; iv) 1 M HCl, THF, 2 h;
v) *t*-BuLi, THF, –78 °C, 2 h; vi) DMPU, –35 °C, 16 h; vii) NH_4Cl, H_2O

Scheme 1.29

1.3 Dearomatisation of Pyridines

1.3.1 Birch Reduction of Pyridines

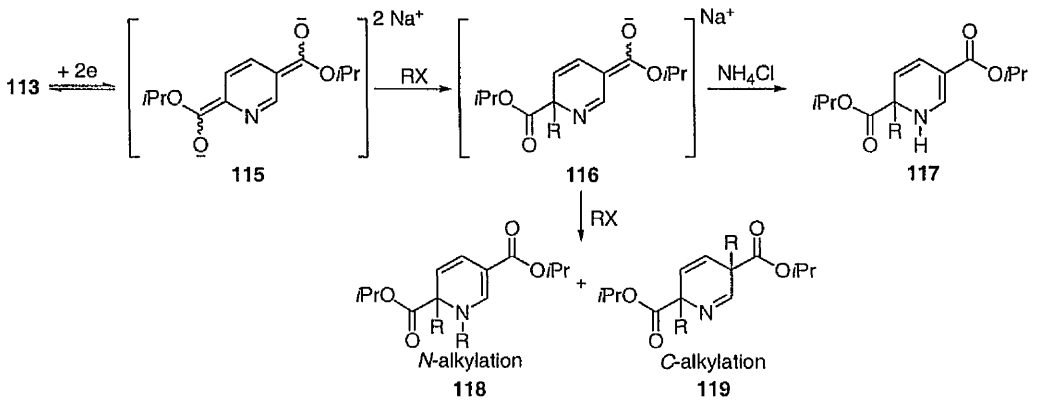
Donohoe *et al.* found that if the 2,5-diester **113** is treated under either Birch or sodium naphthalenide reducing conditions then alkylated and protonated, 2-alkyl-1,2-dihydropyridines of the type **114** can be isolated in excellent yield (Scheme 1.30).[38]



i) Na, NH_3 or Na, naphthalene, THF; ii) RX, iii) NH_4Cl

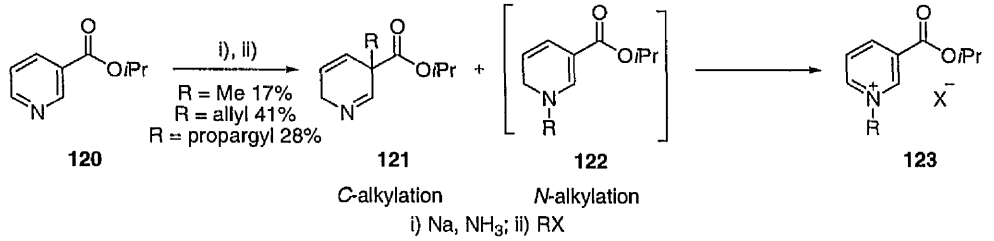
Scheme 1.30

The mechanism proposed for the reaction (Scheme 1.31) starts with the addition of two electrons from the metal to give the dianion **115**. On addition of an electrophile, the first alkylation takes place at the C-2 position forming **116**. If the reaction is left long enough, a second non-regioselective alkylation takes place to give mixtures of the *C*-alkylation product **119** and the *N*-alkylation product **118**. If the reaction is quenched with aqueous ammonium chloride at the correct time after the addition of the initial electrophile, the regioselectivity of the quench is unimportant as the products tautomerise to the more thermodynamically stable *N*-alkylated product **117**. The time lag between the addition of the electrophile and the aqueous ammonium chloride is crucial and differs depending on the electrophile.[38]



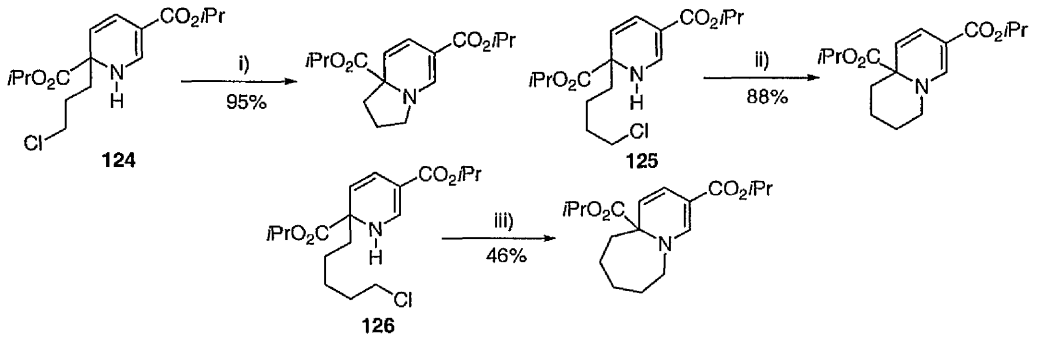
Scheme 1.31

It is interesting to note that pyridine rings bearing only one electron-withdrawing group were poor substrates for this reaction.[38] Pyridines substituted in the 2- and 4-positions resulted in multi component mixtures and those substituted in the 3-position gave poor yields. This was again traced to the regiochemistry of the quench. When **120** was treated under Birch conditions then alkylated, a mixture of *C*-alkylation and *N*-alkylation products resulted yielding **121** and **122** respectively (scheme 1.32). Dihydropyridine **121** can be isolated in the usual manner, but **122** spontaneously auto-oxidises to **123**, which is washed into the aqueous layer.



Scheme 1.32

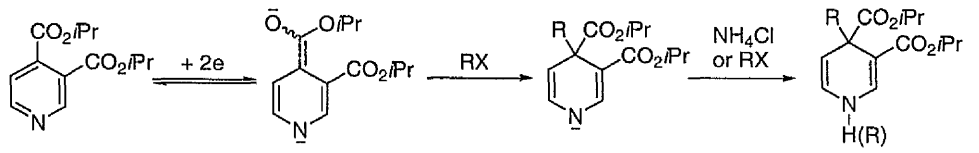
This methodology has been used to synthesise various nitrogen containing bicyclic ring systems with the ring junction between C-2 and the ring nitrogen (scheme 1.33).[38] It was found that if the enolate **115** was quenched with chloroiodoalkanes with different chain lengths, the resulting 2-chloroalkyl-1,2-dihydropyridines **124-126** could be made to undergo cyclisation reactions using basic conditions.



I) DBU, CH_2Cl_2, Δ; ii) DBU, acetone, Δ; iii) KHMDS, 18-c-6, THF, Δ

Scheme 1.33

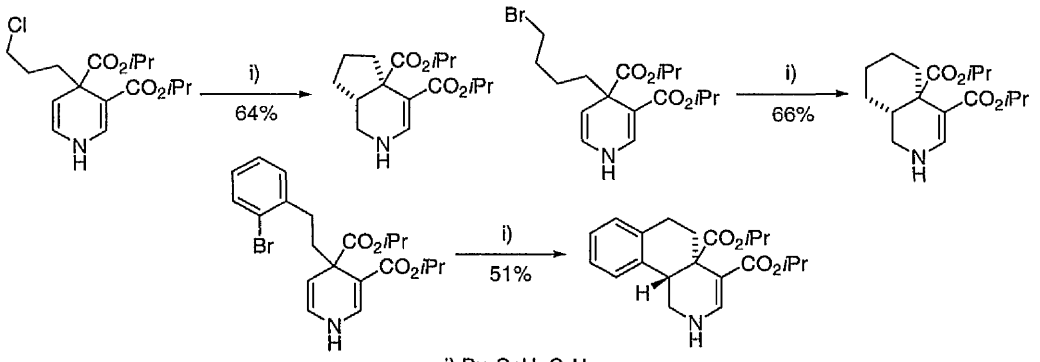
It was later found that the reductive alkylation methodology could be transferred to 3,4-diesters of the type **127** (scheme 1.34).[39] Other substitution patterns were tried, but only the 2,5- and 3,4- gave satisfactory results. Unlike the 2,5-diesters, there are no regiochemical problems with the electrophilic quench, and as such, both double alkylation and alkylation followed by protonation results in only single products **128**.



Yield - 56–99% RX = MeI, EtI, epibromohydrin, $I(CH_2)_3Cl$, $Br(CH_2)_3Br$, $Br(CH_2)_4Br$, $PhCH_2Br$, 2-$BrC_6H_4(CH_2)_2Br$

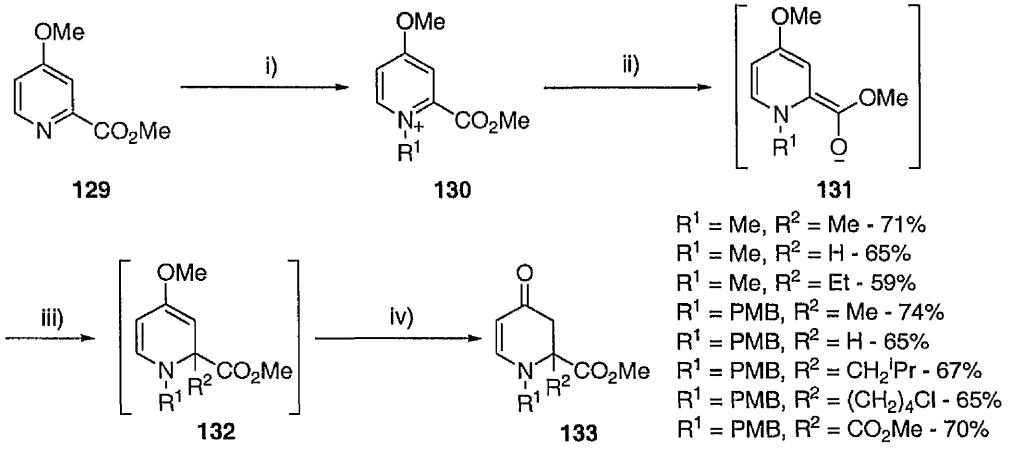
Scheme 1.34

Unfortunately, the cyclisation protocol used for the 2,5-diesters (scheme 1.33) failed in the case of the 3,4-diesters, probably because the C-5 carbon cannot be alkylated without losing much of the conjugation between the nitrogen and the vinylogous carbamate. To circumvent this problem radical cyclisations were used to generate the *cis*-fused ring systems seen in scheme 1.35. These systems possess functionality ripe for further elaboration and may provide useful synthetic intermediates towards the synthesis of azasteroids and alkaloids.[39]



Scheme 1.35

Unfortunately, it was found that the restrictions on substitution pattern imposed by the reaction limited its utility. As such, other methods of pyridine activation were sought. It was found that the activation of one of the esters could be replaced by converting the pyridine **129** into a pyridinium salt **130** (Scheme 1.36).[40] Addition of two electrons to the pyridinium salts resulted in the formation of enolates **131**, which were quenched with a variety of electrophiles then hydrolysed to dihydropyridones **133**. The methoxy substituent at C-4 was designed into the substrate when it was found that the 1,2-dihydropyridines **132** were too unstable to be isolated. After hydrolysis to dihydropyridones **133**, they are relatively stable.



129 **130** **131** **132** **133**

i) MeI, Δ, 16 h or PMBI, Et_2O, 20 °C, 48 h; ii) Li, DBB, THF, –78 °C; iii) RX, –78 °C, 3 h; iv) H_3O^+, –78 °C to 20 °C

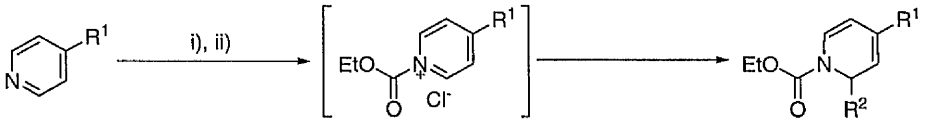
Scheme 1.36

The template produced by this methodology has proved to be extremely versatile; functionality can be introduced at any position around the dihydropyridone ring using precedented transformations.[40]

1.3.2 Dearomatising Nucleophilic Attack of Activated Pyridines

1.3.2.1 Regiochemistry of the Reaction

In 1970 Fraenkel *et al.* found that pyridine derivatives **134** react with Grignard reagents in the presence of ethyl chloroformate to give 1,2-dihydropyridines **136** *via* the pyridinium chloride **135** (scheme 1.37).[41]



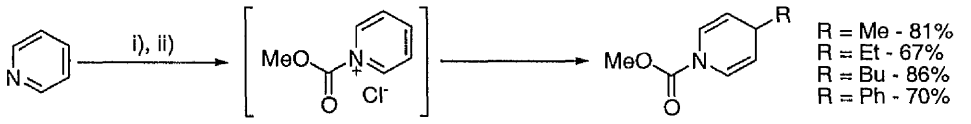
134 **135** **136**

i) R^2MgCl, THF, 0 °C; ii) EtOCOCl

Scheme 1.37

It is interesting to note that the ethyl chloroformate can be added to a solution of the pyridine derivative and the Grignard reagent. The reaction of the ethyl chloroformate with the pyridine derivative is so fast that the competing reaction with the Grignard reagent is not a factor. Without the activation of the pyridine ring offered by the chloroformate, reaction with Grignard reagents requires harsh and forcing conditions and is generally low yielding.[42]

This methodology was extended to the synthesis of the corresponding 1,4-dihydropyridines **137** in 1974 by Piers and Soucy.[43] They discovered that if dialkyl- or diarylcuprates are utilised instead of Grignard reagents, attack at the 4-position of the pyridine ring is predominant (scheme 1.38). Previous to this work, substituted 1,4-dihydropyridines (which have been shown to posess a variety of useful physiological properties) had been extremely difficult to prepare.[43]



137

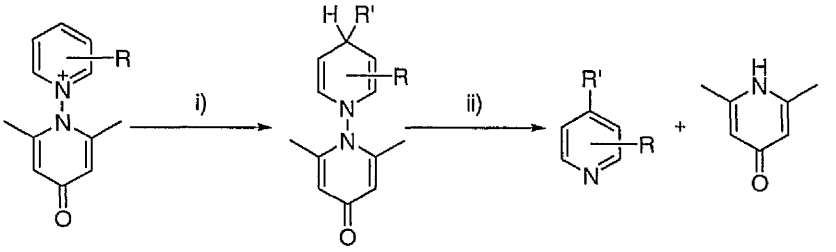
i) R_2CuLi, Et_2O, –78 °C; ii) MeOCOCl, –78 °C to 0 °C

Scheme 1.38

Trace amounts of the corresponding 1,2-dihydropyridine compounds were also isolated, but the regioselectivity of the reaction was generally found to be very high, with the ratio of 1,4- to 1,2-dihydropyridines never falling below 9:1.

Dihydropyridines of the type **136** and **137** are only air stable when substituted with electron withdrawing groups. Pure *N*-methyl- and *N*-phenyl-dihydro-derivatives have been isolated but this requires stringent oxygen free conditions.[44]

Katritzky *et al.* explored an alternative method of controlling the regiochemistry of this type of reaction. Instead of modifying the reactivity of the nucleophile to force addition to the γ-position, they designed an activating *N*-substituent that would block both of the α-positions on the ring. They also designed the *N*-substituent to be a good leaving group so that rearomatisation of the 1,4-dihydropyridine to the corresponding substituted pyridine would be facile.[45]



138 **139** **140** **141**

R' = cyano, alkyl, aryl, alkyl/aryl ketones, nitroalkyl, alkyl/arylthio, benzimidazolyl, benzotriazolyl, phosphonate

i) R'^-, THF, 20 °C, 70 h; ii) Heat or acid-base w/u

Scheme 1.39

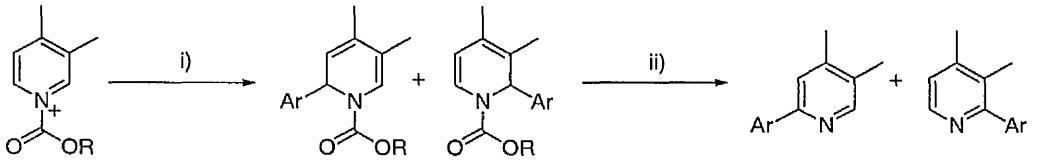
The *N*-substituent that they designed was the 2,6-dimethyl-4-oxopyridin-1-yl moiety, this can be attached to the pyridine nitrogen in two high yielding stages.[46] Pyridinium salt **138** can be reacted with a wide range of nucleophiles to yield intermediates **139**, this was too unstable to be isolated in most cases so was usually converted to a mixture of the pyridine **140** and dihydropyridone **141** either by heating or using an acid base work-up (scheme 1.39). The results of their findings of the reaction of **138** with Grignard reagents are shown in table 1.3.

R	Nu	Yield (%)
H	Et	74
H	^{i}Pr	78
H	^{n}Bu	85
H	Ph	68
H	2-MeC_6H_4	41
H	4-MeOC_6H_4	73
2-Me	^{i}Pr	27
2-Me	Ph	47
3-Me	^{i}Pr	61
3-Me	Ph	36

Table 1.3

More about the regiochemistry of the reaction was discovered by Lyle and Comins.[47] A synthetic problem required a series of 2-aryl-4,5-lutidines and *N*-activation followed by attack of Grignard reagents looked like a convenient pathway to these compounds. However, organometallic reagents usually attack 3-substituted pyridine systems in the sterically demanding 2-position in both activated and unactivated pyridines,[47] whereas for their required compounds attack at the 6-position would be needed. This unexpected regiochemistry is thought to be due to the "ortho" effect of the 3-alkyl group, and is probably related to London forces.[48] They reasoned that if a sterically demanding group was to be introduced on the nitrogen atom, attack would be forced to take place at the less hindered 6-position (scheme 1.40).[47] to yield **142**

enriched mixtures of 1,2-dihydropyridines **142** and **143** which could be easily rearomatised to the corresponding pyridines **144** and **145**.



142 **143** **144** **145**

i) ArMgBr, THF/Et_2O, 0 °C; ii) sulfur, heat

Scheme 1.40

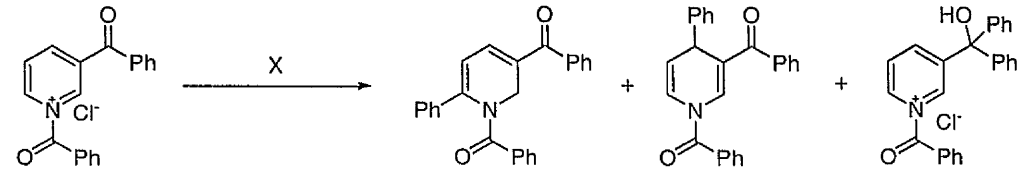
R	Ar	144:145	Overall Yield (%)
Et	Ph	78:22	31
i-Bu	Ph	75:72	27
i-Pr	Ph	90:10	32
Ph	Ph	92:8	35
Et	*p*-ClPh	62:38	40
Ph	*p*-ClCy	95:5	55
Et	*o*-CH_3Ph	95:5	46
Ph	*o*-CH_3Ph	>95	56

Table 1.4

This proved to be the case, and the series of results shows that attack at the 6-position becomes more favourable and therefore the ratio of **144:145** increases as both the R group on the chloroformate and the aryl group being introduced from the Grignard reagent increase in size (table 1.4). The best results were obtained with a phenyl group on the chloroformate and *o*-tolyl Grignard as the group being introduced, when only a trace of 2-substituted product could be detected in the crude ^1H NMR. As pyridines rather than dihydropyridines were required for the study, rearomatisation was carried out by heating with sulphur.

The reactions we have seen so far have featured attack of Grignard reagents on 1-alkoxycarbonylpyridinium salts. Lyle *et al.* used acyl chlorides to activate the pyridine derivatives to give 1-acylpyridinium salts as intermediates in the reaction. They reasoned that since 1-acylpyridinium salts are intermediates in acylations where pyridines are used as catalysts, attack would be most likely to take place on the carbonyl carbon instead of on the heterocyclic ring. This proved not to be the case – both Grignard and organocadmium reagents attacked 1-acylpyridinium salts to give 1,2-dihydropyridines as major products.[49] Their results back up those of Lyle and Comins in that 2-substitution is favoured but 6-substitution can be accomplished if forced by sterically demanding groups on the *N*-substituent and/or the attacking group.

They found that the organocadmium and Grignard reagents gave similar results, except that the organocadmium reagent was advantageous when the pyridine ring was substituted with a carbonyl group as is the case with 1,3-dibenzoylpyridinium chloride **146**. The Grignard reagent results in addition at the carbonyl carbon at the 3-position to give **149,** as well as the expected ring addition at the 6 and 4 positions to yield **147** and **148** respectively. The cadmium reagent does not attack the carbonyl carbon at the 3 position and gives good yields of ring addition only (scheme 1.41).[49]

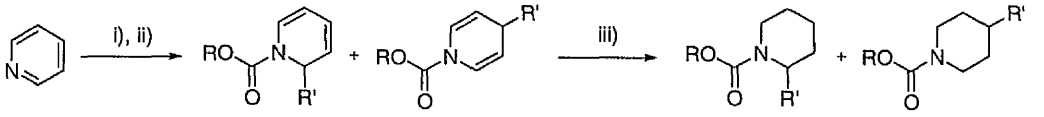


	146	**147**	**148**	**149**
X=PhMgBr		49%	13%	15%
X=PhCd[PhMgBr]		61%	19%	0%

Scheme 1.41

Comins and Abdullah noticed that most of the previous investigations into the addition of nucleophiles to activated pyridines employed 4-substituted pyridines, so the genuine regiochemistry of the reaction was not known. They investigated the regiochemistry of the reaction between pyridine, and a variety of Grignard reagents and acyl chlorides.[50]

Their findings showed that the reaction was limited in scope with regard to the synthesis of 2-alkylpyridines. This is because unless the 4-position of the original pyridine is blocked, significant attack at the 4-position occurs yielding mixtures of 1,2-dihydropyridine **150** and 1,4-dihydropyridine **151**, which for this study were hydrogenated to the corresponding piperidines **152** and **153** using catalytic palladium on charcoal and hydrogen (scheme 1.42 and table 1.5). Substituted piperidines are another group of pharmacologically interesting products available using this methodology.[50]



150 **151** **152** **153**

i) RMgX, THF, –20 °C; ii) R'COCl; iii) H_2, Pd/C

Scheme 1.42

The method is more successful with aryl pyridines, since aryl Grignards attack almost exclusively at the 2-position giving a high ratio of **150:151**. They also investigated the viability of this reaction with respect to the synthesis of 4-substituted pyridines. Previous work by Piers and Soucy showed that addition to the 4-position predominates when lithium dialkylcuprates are used as the nucleophilic component,[43] so Comins and Abdullah examined the effect of a catalytic amount of CuI on the regioselectivity of the reaction.[50] The CuI had a dramatic effect on the reaction,

causing nearly exclusive attack at the 4-position in all cases and thus forming predominantly **153** – a finding that is consistent with that of other results published just prior to the Comins and Abdullah study that utilised stoichiometric organocopper reagents (e.g., RCu, $RCu{\cdot}BF_3$).[51]

R'MgX	Acyl chloride (R)	Overall Yield (%)	Ratio 152:153
C_2H_5MgBr	CH_3	76	70:30
C_2H_5MgBr	C_2H_5O	73	64:36
C_2H_5MgBr	$(CH_3)_3C$	73	52:48
C_6H_5MgCl	CH_3	70	93:7
C_6H_5MgCl	C_2H_5O	80	93:7
C_6H_5MgCl	C_6H_5	77	73:27
C_6H_5MgCl	$(CH_3)_3C$	66	82:48
$(CH_3)_2CHMgCl$	CH_3	56	51:49
$(CH_3)_2CHMgCl$	C_2H_5O	82	41:59
$(CH_3)_2CHMgCl$	$(CH_3)_3C$	80	13:87
C_6H_5MgCl + 5% CuI	CH_3	65	0:100
C_2H_5MgBr + 5% CuI	C_2H_5O	79	5.3:94.7
C_2H_5MgBr + 5% CuI	C_6H_5	30	0:100
$(CH_3)_2CHMgCl$ + 5% CuI	C_2H_5O	62	1.6:98.4

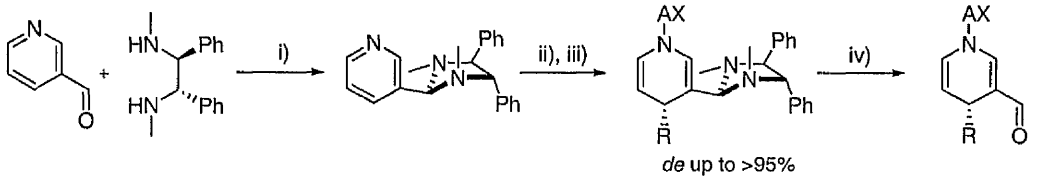
Table 1.5

It should be noted that this method overcomes the main shortcoming of the procedure devised by Piers and Soucy. In their procedure only one of the R groups of the lithium diarylcuprate is transferred to the pyridine ring, whereas with the above procedure the single R group of the nucleophile is transferred.[50]

1.3.2.2 Asymmetric Attack of Activated Pyridines

In 1994 Mangeney *et al.* reported an asymmetric synthesis of 3-formyl-1,4-dihydropyridines using a chiral diamine **155** as a chiral inductor (scheme 1.43 and table 1.6), which can be reacted with the aldehyde **154** cleanly and in high yield.[52]

The resulting aminal **156** can then undergo a wide range of additions to furnish 1,4-dihydropyridines of the type **157** in high yield with high diastereomeric excess aided by the addition of various acid chlorides. When Grignards were employed instead of cuprates, the result was the same poor regioselectivity noted in the previous study by Commins and Abdullah.[50] The chiral diamine **155** can be recovered and the product converted to the corresponding aldehyde **158** *via* a simple acid hydrolysis.



154 **155** **156** **157** **158**

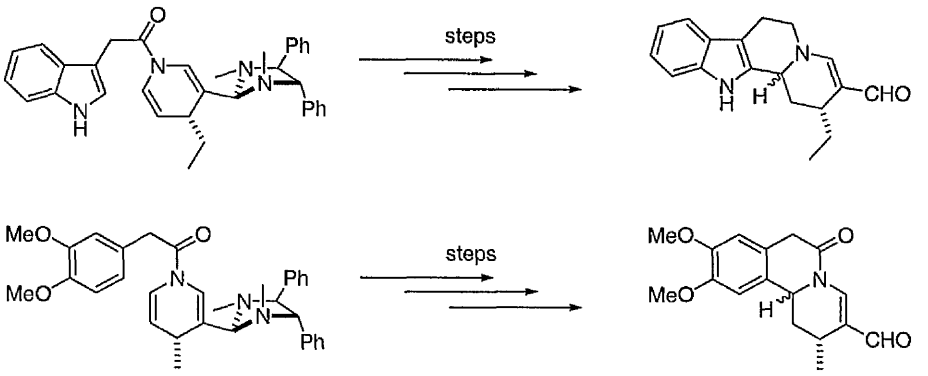
i) Et_2O, 20 °C; ii) RM, THF/Et_2O, –70 °C; iii) AX; iv) 5% HCl

Scheme 1.43

AX	RM	C-4/C-6	Overall Yield (%)	*de* of C-4 adduct (%)
CH_3OCOCl	MeMgBr	14/86	71	93
CH_3OCOCl	$Me_2CuMgBr$	100/0	90	95
CH_3OCOCl	$Et_2CuMgBr$	100/0	90	82
CH_3OCOCl	Bu_2CuLi	100/0	90	95
CH_3OCOCl	$(CH_2{=}CH)_2CuMgCl$	100/0	90	95
CH_3COCl	PhCu	100/0	90	>95
CH_3COCl	*i*-$Pr_2CuMgCl$	100/0	90	85
CH_3OCOCl	$CH_3O_2C(CH_2)_3Cu$	100/0	80	95
CH_3OCOCl	$(Indolyl)_2CuLi$	100/0	50	95

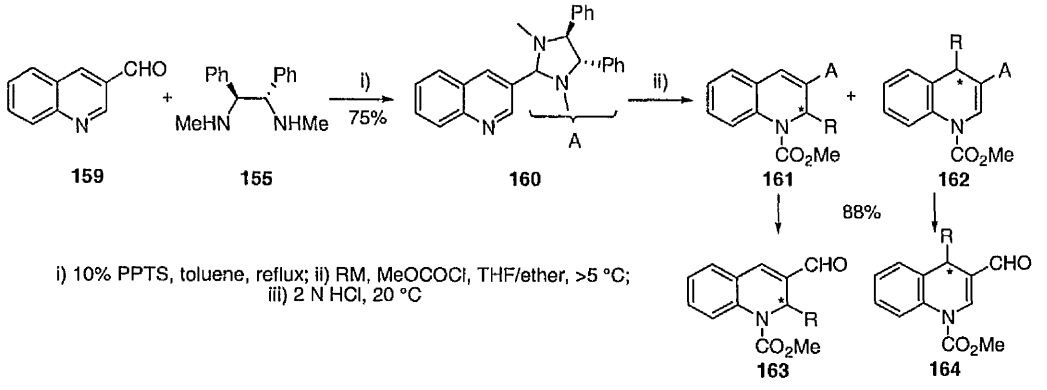
Table 1.6

The utility of this methodology has been demonstrated by its use in enantioselective syntheses of indoloquinolizine and benzoquinolizine frameworks and thus giving a very short and efficient access to various natural products (scheme 1.44).[52]



Scheme 1.44

Mangeney *et al.* carried out a similar study based around quinolines instead of pyridines.[53] They attached the same chiral diamine **155** to aldehyde **159** then attacked the resulting aminal **160** with a range of nucleophiles following activation with methyl chloroformate to yield regioisomeric mixtures of **161** and **162** (scheme 1.45, table 1.7). Following hydrolysis, **155** could be recovered and **161** and **162** could be isolated as the corresponding aldehydes **163** and **164**.



Scheme 1.45

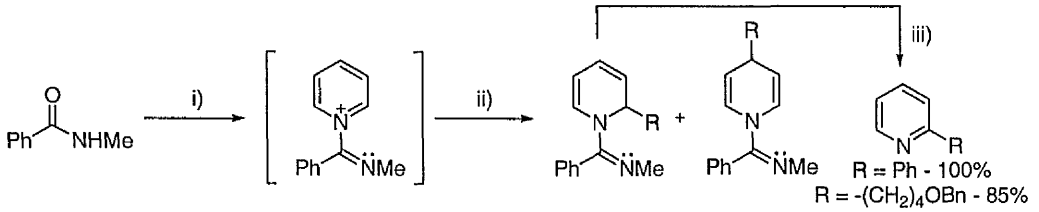
They noticed a couple of important ways in which quinolines differ to pyridines in this type of reaction. Firstly, there is a marked difference in their reactivity: whereas activated pyridines are attacked by organometallic nucleophiles at –78 °C, the

activated quinolines require temperatures of over 5 °C. The second major difference was in the regioselectivity of the reaction; they found that Grignard reagents regioselectively offered 1,2-adducts. Suprisingly, in the presence of 10% of a copper salt, only a slight 1,4-selectivity was seen. Also, with stoichiometric organocopper reagents there was no increase in the selectivity (table 1.7).

RM	Overall Yield (%)	Ratio 161:162	161 *de* (%)	162 *de* (%)
MeMgBr	83	95/5	33	-
BuMgBr	73	67/33	20	-
PhMgBr	70	90/10	100	-
NaphthMgBr	68	95/5	100	-
TMSC≡CMgBr	67	98/2	80	-
BuZnBr	78	60/40	86	-
MeMgBr (10% CuI)	85	30/70	53	4
BuMgBr (10% CuI)	87	40/60	33	54
PhMgBr (10% CuI)	94	43/57	53	28
NaphthMgBr (10% CuI)	78	35/65	50	20
MeCu	89	40/60	56	20
PhCu	92	40/60	60	22

Table 1.7

Such novel methodology whereby nucleophiles regioselectively attack the 4-position of unsubstituted pyridines is complemented by work published by Charette.[54] In this work he developed a regioselective approach to 2-substituted dihydropyridines that relies on the powerful directing ability of the imidate group (scheme 1.46).



165 **166** **167** **168** **169**

i) Tf_2O, pyr; ii) RMgX, –78 °C; iii) DDQ, THF, 25 °C

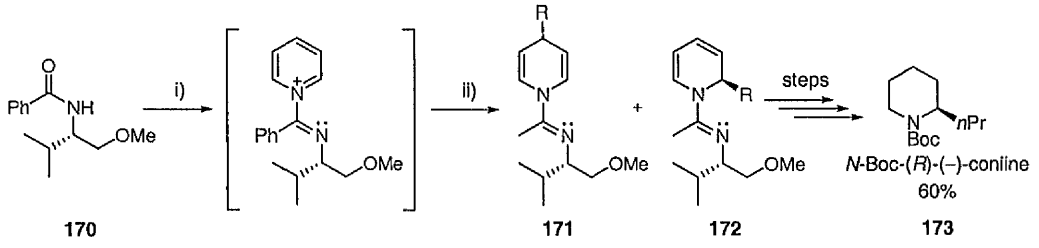
Scheme 1.46

The success of this approach relies on the stereoselective formation of the (*E*)-isomer of *N*-pyridinium imidate **166** from the corresponding amide **165**, where the imidate lone pair is orientated in such a way that it directs the addition of the nucleophile to the 2-position of the ring. It is interesting to note that the directing power of the imidate group even reverses the selectivity for the 4-position of a cuprate reagent! This method gives excellent yields and selectivity for the 2-position (table 1.8) and the 1,2-dihydropyridine products **167** are easily oxidized to the corresponding pyridines **169** by treatment with DDQ in excellent yield.[54]

RMgX	167:168	Yield (%)
MeMgBr	>95:5	83
PhMgBr	>95:5	84
VinylMgBr	>95:5	86
EtMgBr	90:10	82
EtCuCNMgBr	92:8	65
2-FurylMgBr	>95:5	96
$BnO(CH_2)_4MgBr$	90:10	70
$BnO(CH_2)_4CuCNMgBr$	94:6	76

Table 1.8

They later found that a bidentate chiral auxiliary **170** derived from valinol gave excellent regio- and diastereoselectivities (scheme 1.47, table 1.9).[54] To demonstrate the synthetic potential of this latter methodology, they conducted a short synthesis of the piperidine alkaloid (*R*)-(–)-coniine which was isolated as its Boc derivative **173** with an overall yield of 60%.



i) Tf_2O, pyridine; ii) RMgX, –78 °C

Scheme 1.47

RM	172:171	d.r	Yield (%)
MeMgBr	>95:5	>95:5	77
EtMgBr	75:25	>95:5	79
Et_2Zn	>95:5	>95:5	73
PhMgBr	90:10	>95:5	74
PhMgBr (from PhLi)	>95:5	>95:5	89
2-FurylMgBr	>95:5	>95:5	68
1-HexynylMgBr	>95:5	>95:5	65

Table 1.9

1.3.2.3 Pyridones from Nucleophilic Attack on 4-Methoxypyridinium Salts

One of the most versatile classes of synthetic building blocks that can be made using this methodology are the 2,3-dihydro-4-pyridones (figure 1.7). The utility of these building blocks has been demonstrated many times in short, stereocontrolled syntheses of piperidine,[55] indolizine,[56] quinolizine[57] and *cis*-decahydroquinoline[58] alkaloids. Their use is so widespread because they are easily prepared, possess functionality suitable for further elaboration in a regio- and stereocontrolled manner and they possess good air stability.[59]

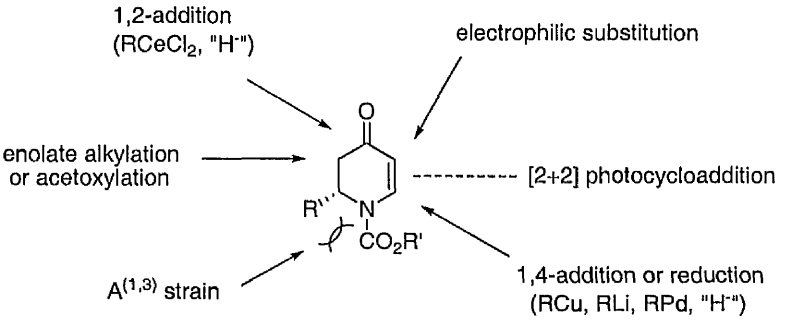
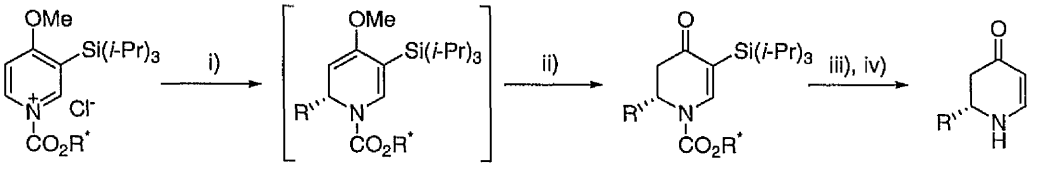


Figure 1.7[59]

A method for the synthesis of enantiomerically pure 2,3-dihydro-4-pyridones is that described by Comins *et al.* and involves a chiral pyridinium salt **174** formed *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine and an optically pure chloroformate.[60] The choice of chiral auxiliary on the chloroformate was found to be crucial to the

diastereoselectivity of the reaction and the most suitable proved to be (–)-8-phenylmenthol and (–)- or (+)-*trans*-(α-cumyl)cyclohexanol (TCC). Also crucial to the success of the reaction is a bulky C-3 substituent in order to direct the nucleophile away from C-4, to C-6. This halves the number of reactive positions and thus increases the diastereoselectivity. Studies so far have found the triisopropylsilyl group to be most suitable as it gives good diastereomeric excesses and is easily introduced and removed.[60]



174 **175** **176** **177**

R* = 8-phenylmenthol or TCC

i) RMgX, –78 °C, toluene/THF; ii) H_3O^+; iii) NaOMe/MeOH; iv) H_3O^+

Scheme 1.48

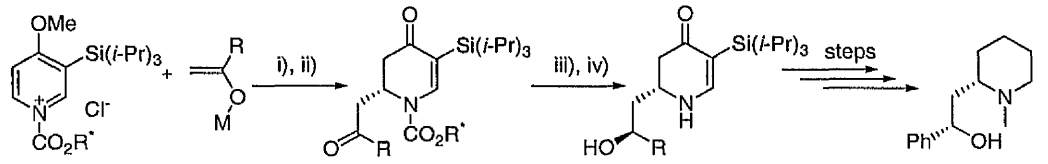
Attack of **174** at the 2-position by a wide range of Grignard reagents yielded an intermediate 1,2-dihydropyridine **175** that was easily hydrolysed on work-up to the pyridone **176**, furnished in high yield with diastereoselectivities ranging from 85–95% (scheme 1.48, table 1.10). At this point the pyridone can be purified either by recrystallisation or chromatography to give the major diastereoisomer as an air stable white solid. Usually the chiral auxiliary is recovered and the triisopropyl group cleaved in one pot to furnish **177**.[60]

RMgX	Chiral Auxiliary	Yield (%)	*de* (%)
PhMgCl	(–)-8-phenylmenthol	80	94
p-MePhMgBr	(–)-8-phenylmenthol	75	82
o-MePhMgBr	(–)-8-phenylmenthol	66	60
p-MeOPhMgBr	(–)-8-phenylmenthol	68	73
p-ClPhMgBr	(–)-8-phenylmenthol	67	81
MeMgCl	(–)-8-phenylmenthol	85	91
i-BuMgBr	(–)-8-phenylmenthol	86	92
c-HexMgBr	(–)-8-phenylmenthol	83	81
n-PrMgCl	(–)-8-phenylmenthol	88	91
1-HexynylMgCl	(–)-8-phenylmenthol	74	83
VinylMgCl	(–)-8-phenylmenthol	75	85
n-PrMgCl	(–)-*trans*-2-(α-cumyl)cyclohexanol	98	90
PhMgCl	(+)-*trans*-2-(α-cumyl)cyclohexanol	90	92

Table 1.10

1.3.2.4 Addition of Metallo-enolates to 4-Methoxypyridinium Salts

The utility of the above methodology prompted Comins *et al.* to investigate the preparation of 2,3-dihydro-4-pyridones bearing various functionality and stereocentres in the C-2 side chain.[61] They accomplished this with the addition of metallo-enolates of the type **178** to pyridinium salts (scheme 1.49). Initially, this was carried out with achiral 1-acylpyridinium salts to yield racemic 1,2- and 1,4-dihydropyridines, but the methodology developed for addition of Grignard reagents to asymmetric 1-acylpyridinium salts was eventually applied to the addition of metallo-enolate addition so that synthetically useful 2-(2-oxoalkyl)-2,3-dihydro-4-pyridones **179** could be prepared in high yield with high diastereomeric excess (table 1.11).



178 179 180 181

R* = (–)-8-phenylmenthyl or TCC

(–)-sedamine

i) toluene/Et_2O/THF; ii) H_3O^+; iii) K-Selectride, THF, –78 °C; iv) Na_2CO_3/MeOH

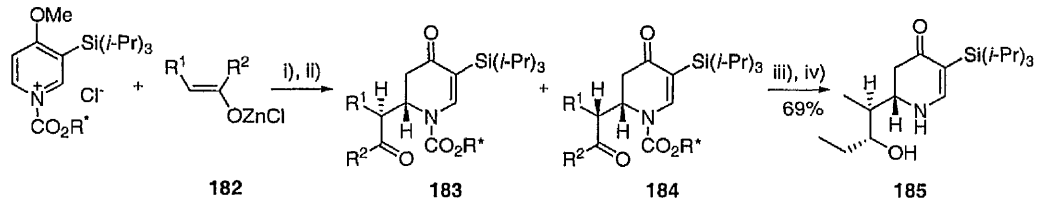
Scheme 1.49

R	R*	MX	Solvent (tol:Et_2O:THF)	Yield (%)	*de* (%)
n-propyl	(–)-TCC	Ti(*i*-PrO)$_3$	1:0:1	38	90
n-propyl	(–)-TCC	$TiCl_3$	1:0:1	42	65
n-propyl	(–)-TCC	$SnCl_3$	2:0:1	49	68
n-propyl	(–)-TCC	Li	1:0:1	73	82
n-propyl	(–)-TCC	ZnCl	1:1:0	74	90
n-propyl	(–)-TCC	ZnCl	3:1:1	86	89
n-propyl	(–)-8-phenyl menthyl	ZnCl	3:1:1	89	92
n-propyl	(–)-TCC	MgBr	1:0:1	82	94
Phenyl	(–)-TCC	ZnCl	3:1:1	82	90
Methyl	(–)-TCC	ZnCl	3:1:1	83	93
n-butenyl	(–)-TCC	ZnCl	3:1:1	80	94

Table 1.11

Usefully, the carbonyl of the C-2 side chain of **179** can be reduced with K-Selectride to furnish the alcohol **180** in 84% yield and >98% *de*. To demonstrate the potential of this sequence, alcohol **180** was converted to the piperidine alkaloid (–)-sedamine (**181**) in five steps (scheme 1.49).[61]

When a prochiral metallo-enolate of the general type **182** is used as the nucleophile, two new chiral centres are formed with a high degree of diastereoselectivity (scheme 1.50). In all cases the major isomer is **183** – the *anti* isomer, which is easily separated from **184** by chromatography or recrystallisation (table 1.12).[59,62]



R* = (-)-TCC

i) THF/toluene, –78 °C; ii) H_3O^+; iii) K-Selectride, THF, –78 °C; iv) Na_2CO_3/MeOH

Scheme 1.50

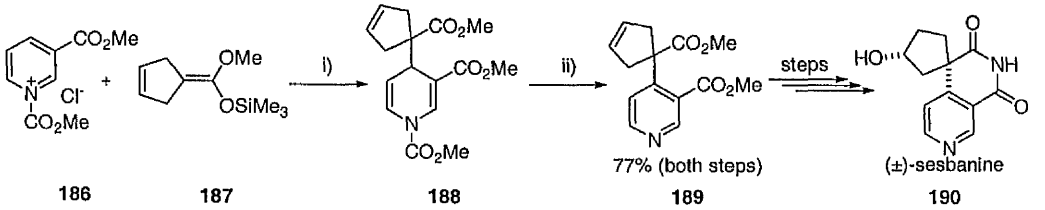
It should be noted that the product can be stereoselectively reduced with K-Selectride in high diastereoselectivity (>96%) to yield an enantiopure dihydropyridone **185** containing three contiguous stereocentres (scheme 1.50).

R^1	R^2	Ratio 183:184	Yield of major diastereoisomer (%)
$-CH_2CH_2CH_2-$		88:12	82
$-CH_2CH_2CH_2CH_2-$		86:14	79
Me	Et	92:8	83

Table 1.12

1.3.2.5 Addition of Silyl Enol Ethers to Pyridinium Salts

Another highly regioselective method for the introduction of substituents into the 4-position was described by Akiba *et al.* (scheme 1.51).[63] They found that when a silyl enol ether **187** is added to activated pyridine **186**, reaction occurs spontaneously to yield the γ-addition product **188** in good yield as a single regioisomer. The product was isolated as the rearomatised pyridine derivative **189** in good yield. This methodology was successfully applied to the synthesis of (±)-sesbanine **190**.[63]

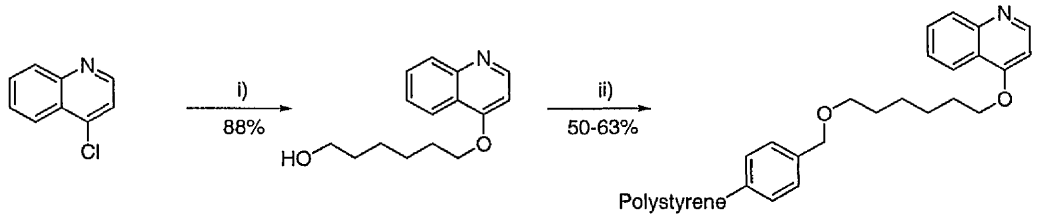


i) CH_2Cl_2, 20 °C, 30 min; ii) DDQ, C_6H_6, reflux, 6 h

Scheme 1.51

1.3.2.6 Nucleophilic Attack on Solid Supported Quinolines

The strategy of activation, followed by nucleophilic attack, has been utilised by Wendeborn to synthesise 2,3-dihydroquinolin-4-ones on the solid phase.[64] An ether linkage was attached to 4-chloroquinoline **191** to furnish **192**, this was then attached to Merrifield resin to give **193** which is both acid and base stable (scheme 1.52).

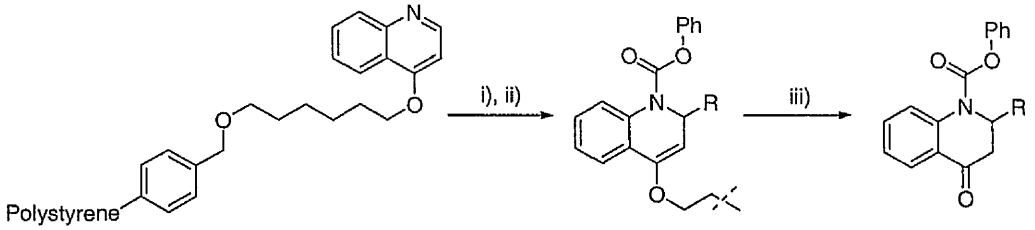


191 **192** **193**

i) 7 equiv. 1,6-hexanediol, 1.2 equiv. NaH, THF:DMF (7:3), 60 °C, 20 h;
ii) Merrifield resin (1.7 mmol/g), 4 equiv. **192**, 4 equiv. NaH, THF:DMA (1:1), 80 °C, 16 h.

Scheme 1.52

In solid supported **193** the 4-position is blocked by the ether linkage, and as such, with only one available α position, there are no problems with regioselectivity. Wendeborn activated the quinoline with phenyl chloroformate and attacked the resulting quinoline with a range of Grignard reagents to furnish **194** (scheme 1.53). After acid catalysed cleavage of the enol ether and thus cleavage from the solid support, the products **195** were isolated in both high purity and yield without the need for further purification (table 1.13).



193 **194** **195**

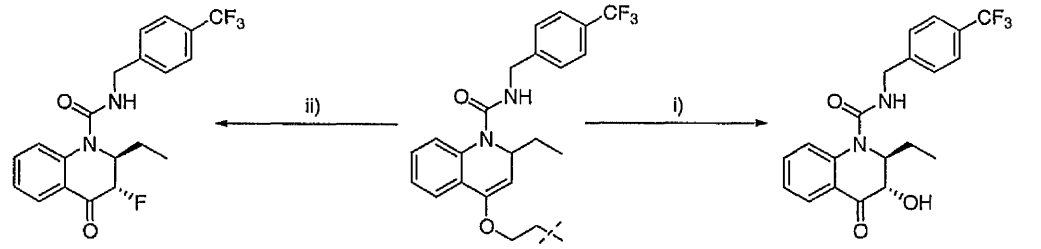
i) 5 equiv. RMgHal, THF; ii) PhOCOCl, –40 °C to 10 °C; iii) 5% TFA, 0.1% H_2O, CH_2Cl_2, 20 °C, 1.5 h

Scheme 1.53

RMgX	Weight Recovery (%)	Purity (%)
MeMgCl	quant.	>95
EtMgBr	quant.	95
i-PrMgBr	57	90
(Pentyl)MgBr	quant.	95
(Cyclopenyl)MgBr	quant.	90
(Vinyl)MgBr	quant.	95
CH≡CMgBr	95	90
PhC≡CMgBr	80	>95
PhMgBr	quant.	95
BnMgBr	quant.	>70
(Allyl)MgBr	quant.	90

Table 1.13

Wendeborn also made attempts to combine the cleavage step with additional functionalisation to produce α-substituted ketones.[64] The solid phase bound enol ether **197** can be oxidised with dimethyl dioxirane, which after concomitant cleavage of the support, gave the α-hydroxy ketone **198** in good yield and purity as a single diastereoisomer. Similarly, reaction with Selectfluor™ in a mixture of acetonitrile and water gave the expected fluorinated product **196** in low yield but high purity (scheme 1.54).[64]



35% (89% pure by ^{1}H NMR) — **196**; **197**; 80% (95% pure by ^{1}H NMR) — **198**

i) 3 equiv. 0.1M dimethyl dioxirane/acetone, 0 °C, 3 h; ii) 4 equiv. Selectfluor™, CH_3CN:H_2O (4:1), 20 °C, 24 h

Scheme 1.54

Chapter 2

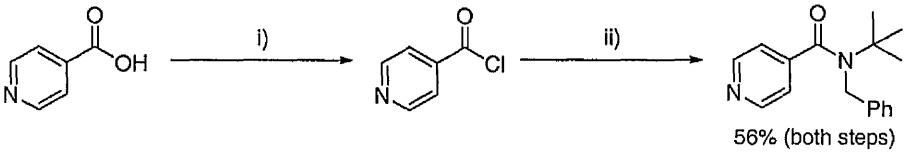
Amide cyclisations

2.1 Introduction

The dearomatising cyclisation onto benzamides and naphthamides has already been comprehensively investigated (see section 1.2), but previous to this study, only a few preliminary cyclisations onto aromatic heterocycles had been attempted. As these had shown promising results, we wanted to extend the utility of the dearomatising cyclisation reaction by replacing the benzene and naphthalene rings with pyridine and quinoline rings in a variety of substitution patterns. At the same time another study was taking place within the group on similar cyclisations onto furans, thiophenes and pyrroles.[22, 23, 65]

2.2.1 Cyclisations of Isonicotinamides

The starting material **201** was prepared by refluxing the commercially available isonicotinic acid **199** in thionyl chloride overnight at 85 °C to give the corresponding acid chloride **200**. This was further transformed to the isonicotinamide **201** by reaction with *t*-butylbenzylamine and triethylamine in dichloromethane overnight. After purification, this gave the desired amide in moderate yield (scheme 2.1).



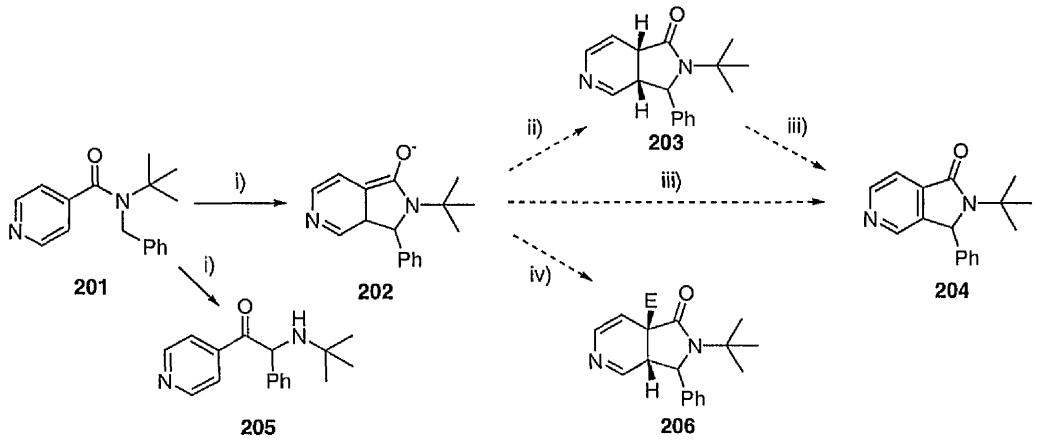
56% (both steps)

199 **200** **201**

i) $SOCl_2$, 85 °C, 16 h; ii) *t*-$BuNCH_2Ph$, Et_3N, CH_2Cl_2, 20 °C, 16 h

Scheme 2.1

It was expected that **201** would cyclise to yield the dearomatised compound **203** analogous to products of the cyclisation of the benzamides and naphthamides. However, the initial attempts were not promising. Conditions similar to those used for benzamides and naphthamides (2 equiv. LDA, 16 h, –40 °C) yielded a 1:1 mixture of starting material and **205**, which results from attack of the benzylically stabilised organolithium on the carbonyl.



i) LDA, 16 h, various temperatures (see table 2.1); ii) NH_4Cl; iii) [O]; iv) EX

Scheme 2.2

As it appeared that very little cyclisation was taking place at all using these conditions, the temperature of the cyclisation was raised to 0 °C overnight. This gave a single product in the crude ^1H NMR spectrum - the rearomatised cyclisation product **204**, presumably *via* the extended enolate **202**. **204** was isolated in moderate yield. Raising the temperature to room temperature for the duration of the reaction gives a different result, 10% of **204** and strangely 28% of **205** (scheme 2.2, table 2.1).

There are two possible explanations for the formation of **204** and the absence of **203**. Firstly there is the possibility that the enolate **202** is formed, which then rearomatises directly to the isolated product **204**. The other possibility is that of the enolate being stable until the reaction is quenched with aqueous ammonium chloride. The resulting

dearomatised product **203** then rearomatises to **204**. The transformation of both **203** and **202** to **204** formally correspond to an oxidation, but the mechanism for this is not obvious.

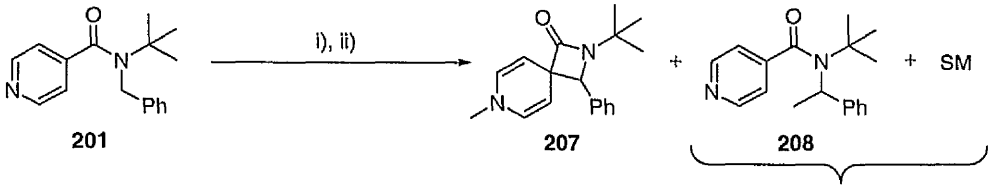
Entry	Temerature (°C)	Electrophile	Result
1	–40	NH_4Cl	1:1 mixture of SM and product **205** in crude ^1H NMR
2	0	NH_4Cl	All SM converted to **204** in crude ^1H NMR. 46% isolated yield of **204**.
3	20	NH_4Cl	28% of **205** and 10% of **204** isolated
4	–40	MeI	^1H NMR spectrum appeared identical to entry 1
5	0	MeI	^1H NMR spectrum appeared identical to entry 2
6	20	MeI	^1H NMR spectrum appeared identical to entry 3

Table 2.1

With the above in mind, attempts were made to trap the enolate **202** with an alkylating agent rather than a proton. This would hopefully yield **206**, which should be more stable with respect to rearomatisation, as for this to occur, a C-C bond would have to be broken rather than a C-H bond. The alkylating agent chosen for this was methyl iodide, but unfortunately, under all of the conditions tried, the crude ^1H NMR spectra appeared identical to the spectra when aqueous ammonium chloride was used as the electrophile. This suggests that the enolate **202** is unstable under the reaction conditions and that **204** is formed directly from **202**.

Attempted cyclisations on other amides carried out within the group had shown that shorter reaction times were often successful at yielding dearomatised products. This is thought to be because the extended enolate of the type **202** can be trapped before it has had chance to rearomatise. Therefore shorter reaction times were used on this

substrate. In order to speed up the deprotonation, more equivalents of base were used. Carrying out the same reaction with 5 equivalents of base for 10 minutes at 0 °C and using methyl iodide as the electrophile gave a complicated mixture of products, but it was obvious from the crude ^{1}H NMR spectrum that dearomatised products had been formed in the reaction. Unfortunately, these were in such small yield that no products were isolated from the column. Lowering the temperature of the reaction to –40 °C for 30 minutes (entry 1, table 2.2,) gave the unexpected dearomatised product **207**, which by comparison of the ^{1}H NMR spectrum was the same as the major dearomatised product in the previous reaction, plus an inseparable mixture of starting material and the methylated starting material **208**. **207** is interesting as it contains a novel spiro β-lactam/1,4-dihydropyridine ring system (scheme 2.3.



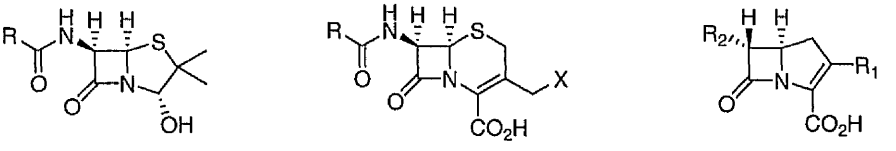
201 **207** **208**

45% 30% 2:1 mixture

i) 5 eqiuv. LDA, THF, –40 °C, 30 min; ii) MeI

Scheme 2.3

The β-lactam is a common signature in several widely used families of antibiotics such as penicillins, cephalosporins and thienamycins (figure 2.1) and is largely responsible for their biological activity.[66] 1,4-Dihydropyridines are versatile synthetic intermediates and have been shown to possess interesting physiological properties.[43] It was therefore decided that this type of compound required further research.

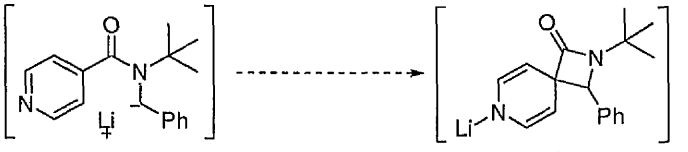


Penicillins Cephalosporins Thienamycins

Figure 2.1

2.2.2 Optimisation of Spirocycle formation

As it appeared that the reaction had not gone to completion, the cyclisation was repeated, but with a reaction time of 100 minutes instead of 30 minutes (entry 2, table 2.2). However, the increased reaction time made no difference whatsoever to the product ratio. More attempts were made to improve the cyclisation with the use of additives, as these have been shown to influence this type of cyclisation by complexing with the lithium cation in analogues of **209** and therefore generating an ion-pair. This has the effect of destabilising the anion and making nucleophilic attack of the aromatic system to yield a spirocyclic organolithium **210** more likely (scheme 2.4). Unfortunately the addition of DMPU (10 equiv.), TMEDA (10 equiv.) or LiCl (15 equiv.) made no difference to the product ratio (entries 3-5, table 2.2).



209 **210**

Scheme 2.4

As extra equivalents of LDA improved the reaction earlier on, even more equivalents were employed in an attempt to force the reaction to completion. However, under the same conditions with 10 equivalents of LDA instead of 5 equivalents, there was no difference to the outcome of the reaction (entry 6, table 2.2). Two reactions were tried at a higher temperature to see if this would push the reaction towards completion, but essentially this had no effect on the product ratio (entries 7-8, table 2.2).

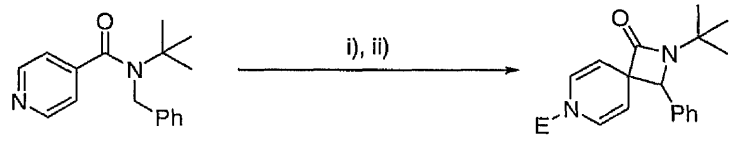
Dimethyl sulfate was tried as an alternative electrophile to methyl iodide (entries 9-10, table 2.2). The crude ^{1}H NMR spectrum obtained when dimethyl sulfate was used as the electrophile contained only the desired spiro compound **207** and dimethyl

sulfate. Unfortunately, attempted purification of the reaction mixture yielded no material whatsoever. It appears that **207** is incompatible with dimethyl sulfate. Accordingly, another attempt was made where at the end of the reaction the excess dimethyl sulfate was removed from the crude reaction mixture by the addition of aqueous ammonia. This reacts with dimethyl sulfate to give trimethylamine, which is simply removed under reduced pressure. The crude ^{1}H NMR spectrum resulting from this reaction looked like a pure sample of **207**, but attempted purification by chromatography gave only a 15% yield.

Entry	Equiv. LDA	Time (min)	Temp. (°C)	Additives	Electrophile	Result
1	5	30	–40	–	MeI	45% yield of **207**. See scheme 2.3
2	5	100	–40	–	MeI	Identicle crude ^{1}H NMR to entry 1
3	5	30	–40	DMPU 10 equiv.	MeI	Identicle crude ^{1}H NMR to entry 1
4	5	30	–40	TMEDA 10 equiv.	MeI	Identicle crude ^{1}H NMR to entry 1
5	5	30	–40	LiCl 15 equiv.	MeI	Identicle crude ^{1}H NMR to entry 1
6	10	30	–40	–	MeI	Identicle crude ^{1}H NMR to entry 1
7	5	30	0	–	MeI	Complicated mixture
8	5	30	–20	–	MeI	Identicle crude ^{1}H NMR to entry 1
9	5	30	–40	–	Me_2SO_4	Only **207** in crude ^{1}H NMR. 0% yield
10	5	30	–40	–	Me_2SO_4	Only **207** in crude ^{1}H NMR. 15% yield

Table 2.2

Although the reactions using dimethyl sulfate as the electrophile were not a complete success, they suggested that the reason for the unfavourable product ratio (scheme 2.3) was linked to the electrophile. A range of other electrophiles were tried (scheme 2.5, table 2.3).



201 211

i) 3 equiv. LDA, THF, –40 °C, 30 min; ii) EX

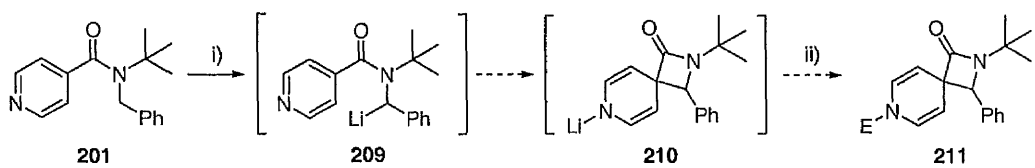
Scheme 2.5

Entry	Electrophile	Product	Isolated yield of 211 (%)
1	BnOCOCl	**211a**	81
2	MeOCOCl	**211b**	91
3	AdOCOCl	**211c**	76
4	BzCl	**211d**	86
5	MeOTf	**207**	82
6	MeI	**207**	45 (+ some **208**)
7	NH_4Cl	-	0

Table 2.3

2.2.3 Possible Mechanism of Spirocycle Formation

The above results point towards the mechanism of the reaction being completely different to the one first envisaged. Originally, it was thought that after lithiation, **209** cyclised to give the spirocyclic organolithium **210**, which was then quenched with an electrophile to give the final product of the type **211**, as is the case with the cyclisations of benzamides and naphthamides (scheme 2.6).

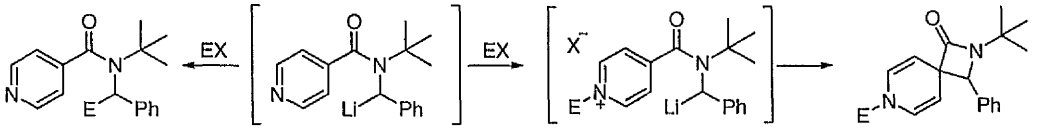


201 209 210 211

i) LDA; ii) EX

Scheme 2.6

The fact that the nature of the electrophile has such an effect of the product ratio of the reaction makes this mechanism unlikely. A more plausible mechanism is shown in scheme 2.7.

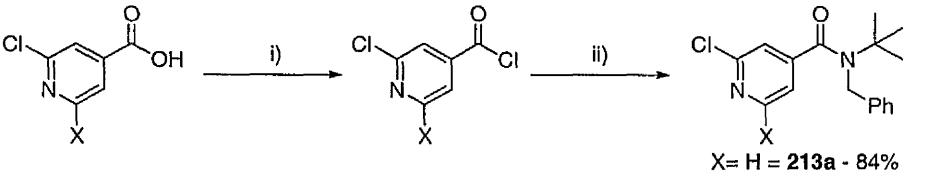


Scheme 2.7

Here, cyclisation occurs after the electrophile has been added. The reason that the electrophile has such an effect on the ratio of the cyclised to uncyclised product is that when the electrophile is added to the reaction, the intermediate in solution is **209**. At this point there are two positions at which the electrophile can react. Either directly at the organolithium to yield benzylically quenched starting material of the type **213**, as has happened in scheme 2.4 with the formation of **208,** or on the pyridine nitrogen. When the electrophile attacks the pyridine nitrogen to form **212**, the ring is activated towards nucleophilc attack in the 2 and 4-position (section 1.4). In this case, the ring is then rapidly attacked in the 4-position by the organolithium to yield spirocyclic products **211**. Chloroformate (entries 1-3, table 2.3), acid chloride (entry 4, table 2.3) and triflate (entry 5, table 2.3) electrophiles quickly react exclusively at the nitrogen to give the spirocyclic products 211, whilst when methyl iodide was used (entry 6, table 2.3), there was competition between the two reactive centres, to give both **211** and **208**. Further evidence for this mechanism comes from the protic quench (entry 7, table 2.3), which offers no activation of the ring and effectively gives a snapshot of what is in solution at the time (intermediate **209**) – only starting material is returned.

2.2.4 Spirocycle Formation with Differently Substituted Pyridine Rings

We then wanted to see if this reaction would tolerate different ring substituents. Accordingly, two starting materials bearing electron-withdrawing groups in the 2-position **213a** and **213b** were synthesised by the methods used previously to make **201** (scheme 2.8).

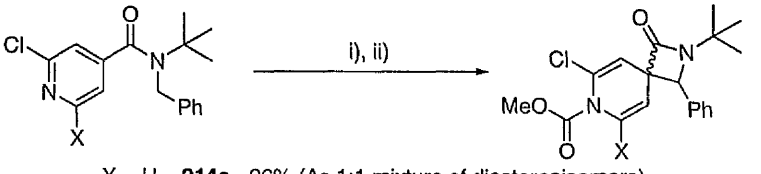


X= H = **213a** - 84%
X = Cl = **213b** - 65%
(both steps)

i) $SOCl_2$, 85 °C, 16 h; ii) *t*-$BuNCH_2Ph$, Et_3N, CH_2Cl_2, 20 °C, 16 h

Scheme 2.8

The reaction was tolerant of electron-withdrawing groups in the 2-position of the pyridine ring. When the pyridine ring bears only one substituent (as with **213a**), the product was formed as an inseparable 1:1 mixture of diastereoisomers (scheme 2.9).



X = H = **214a** - 96% (As 1:1 mixture of diastereoisomers)
X = Cl = **214b** - 83%

i) 3 equiv. LDA, THF, –40 °C, 30 min; ii) MeOCOCl

Scheme 2.9

The cyclisation product of **214b** was crystalline and X-ray crystallography of the sample confirmed the suspected structure of this family of compounds (figure 2.2). Note that in the figure, the *t*-butyl group is not shown for clarity.

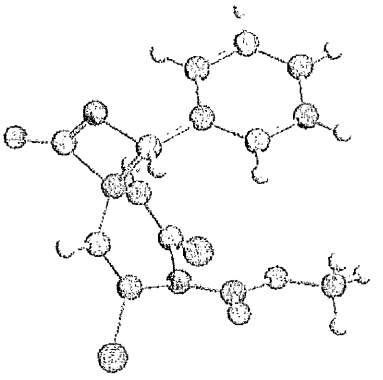
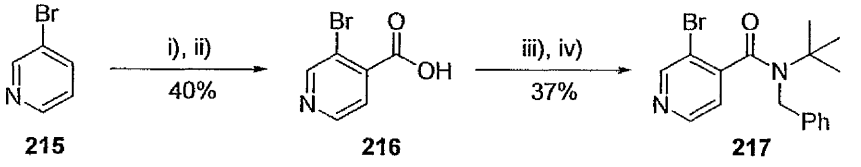


Figure 2.2

The cyclisation precursor bearing an electron-withdrawing group in the 3-position was synthesised from 3-bromopyridine **215**, which was ortho lithiated and then quenched with carbon dioxide.[67] The resulting acid **216** was converted to the amide **217** *via* the acid chloride using methods discussed previously (scheme 2.10).

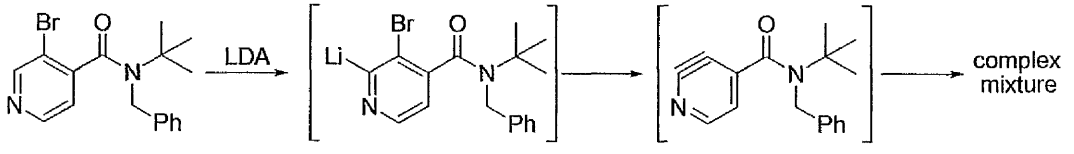


215 **216** **217**

i) LDA, THF; ii) CO_2; iii) $SOCl_2$; iv) *t*-$BuNCH_2Ph$, Et_3N, CH_2Cl_2

Scheme 2.10

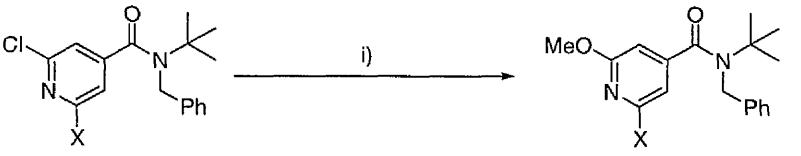
Unfortunately, cyclisation of **217** resulted in a complex mixture of products. A rationalisation of this is that the proton in the 2-position of the ring has been acidified by the electron-withdrawing group, and this proton is removed in preference to one of the benzylic protons. **218** then collapses to give a reactive benzyne type intermediate **219**, which rapidly decomposes (scheme 2.11).



217 **218** **219**

Scheme 2.11

The cyclisation precursors to test the tolerance of the reaction to electron donating groups in the 2-position were made by displacing the aromatic halides of compounds **213a** and **213b** with methoxy groups by reaction with sodium methoxide in methanol to furnish **220** and **221** respectively (scheme 2.12).



X = H = **213a**
X = Cl = **213b**

X = H = **220** - 86%
X = MeO = **221** - 82%%

i) NaOMe, MeOH, Sealed Tube, 125 °C

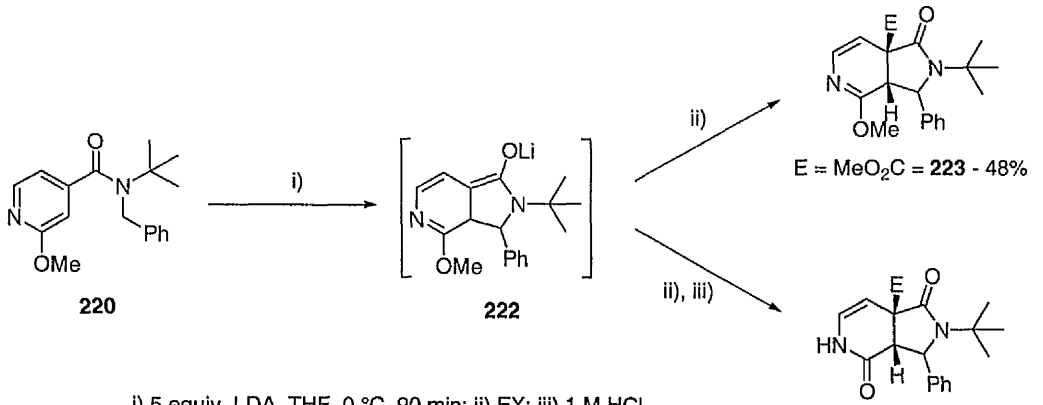
Scheme 2.12

Early attempts at cyclisation of **220** using the conditions used previously to obtain good yields of β-lactam products (entry 1, table 2.4) returned only starting material. This could be expected, as the methoxy group makes the ring more electron-rich and therefore less susceptible to nucleophilic attack. Accordingly, the temperature of the reaction was raised to 0 °C. The deprotonation should work well at this temperature and also this should help the cyclisation after the electrophile is added. With these new conditions (entry 2, table 2.4) a tiny amount of dearomatised material could be seen in the ^{1}H NMR spectrum. The product did not appear to be the expected β-lactam.

This suspicion was proved to be correct as when the length of time before the reaction was quenched was increased, the crude ^{1}H NMR spectrum of the reaction showed that all of the starting material had been converted to **223** (scheme 2.13), a product analogous to those made by cyclisation of benzamides and naphthamides (section 1.2) – presumabily *via* the extended enolate **222**, therefore cyclisation occurs before the electrophile is added. Attempted purification of **223** by flash column chromatography

on silica proved difficult due to decomposition and hydrolysis, but **223** could be isolated in good yield with care (entry 3, table 2.4). Strangely, when the reaction was repeated with 3 equivalents of base, the reaction was markedly messier (entry 4, table 2.4). This is unusual as when the analogous reaction was carried out on benzamides and naphthamides, stoichiometric amounts of base typically gave a clean reaction. The reaction was repeated with 5 equivalents of base and it was found that **222** could be hydrolysed to **224** on workup by washing with 1 M, which could be isolated in good yield (entry 5, table 2.4).

As the cyclisation happens before the electrophile is added, the activating action of the chloroformate/acid chloride is not needed. The reaction was repeated with an alkylating agent and a protonating agent as electrophiles, and these worked well (entries 6-7, table 2.4). The fact that they did work well reinforces the argument for the cyclisation occurring before addition of the electrophile. The stereochemistry has been tentatively assigned based on findings with the benzamides and naphthamides.



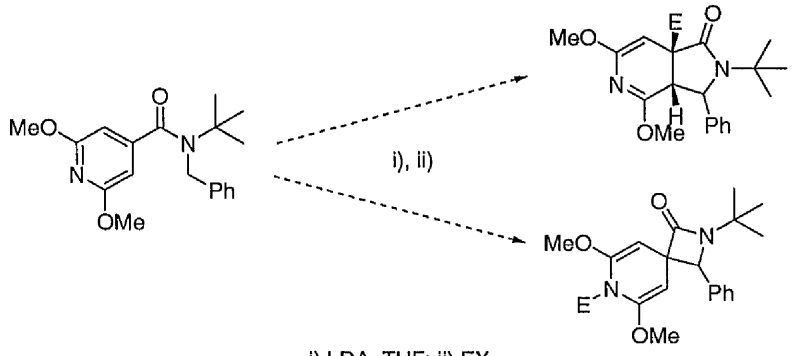
i) 5 equiv. LDA, THF, 0 °C, 90 min; ii) EX; iii) 1 M HCl

Scheme 2.13

Entry	Eqivalents of Base	Temperature (°C)	Time (min)	EX	Result
1	3	–40	30	MeOCOCl	Returned SM
2	3	0	10	MeOCOCl	Trace of **223**
3	5	0	90	MeOCOCl	48% yield of **223**
4	3	0	90	MeOCOCl	Messy reaction
5	5	0	90	MeOCOCl (+ hydrolysis)	62% yield of **224**
6	5	0	90	MeI (+ hydrolysis)	75% yield of **225**
7	5	0	90	H (+ hydrolysis)	77% yield of **226**

Table 2.4

Unfortunately, all attempts to cyclise the dimethoxy derivative **221** to either a β-lactam or a compound analogous to **223** or **224-226** failed – even though a wide range of conditions was tried (scheme 2.14). This is likely to be due to the ring being too electron rich to allow attack of a nucleophile. This result correlates well with work carried out on the benzamides, where a similarly substituted benzamide with methoxy substituents *para* to the possible points of attack failed to cyclise.[2]

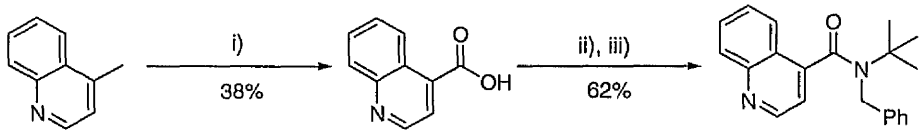


i) LDA, THF; ii) EX

Scheme 2.14

2.2.5 Cyclisation of Quinoline-4-amides

As well as differently substituted pyridine rings, attempts were made to transfer this methodology to the quinoline ring system. The carboxylic acid **228** required to make the starting material for this reaction is prohibitively expensive, therefore **228** was made from lepidine **227** by oxidation with selenium dioxide (scheme 2.15).[68] A simple amide coupling furnished the required amide **229** in good yield.



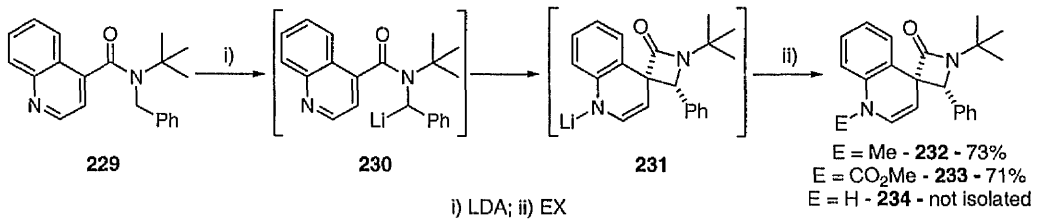
227 **228** **229**

i) SeO_2, Xylene, 135 °C, 16 h; ii) $SOCl_2$, 85 °C, 16 h; iii) *t*-$BuNCH_2Cl_2$, Et_3N, CH_2Cl_2, 20 °C, 16 h

Scheme 2.15

Preliminary investigations into the cyclisation of **229** were carried out at the same time as the unsubstituted pyridine starting material **201** and early experiments were carried out with a low number of equivalents of base (1.5 - 2.0 equiv.) with long reaction times. These reactions generally gave complex mixtures of products with very little in the way of dearomatised material, with one notable exception (entry 1, table 2.5). However, this result proved to be impossible to reproduce and the reaction is clearly capricious under these conditions. More equivalents of base and shorter reaction times led to a much more reliable reaction (entries 2-4, table 2.5). It should be noted however, that the results suggest that the mechanism of the reaction is significantly different to the analogous pyridines (scheme 2.7). When aqueous ammonium chloride was used to quench the reaction, the result was almost total transformation into the unstable product **234**, which rapidly decomposed on silica. As this electrophile would offer no activation of the quinoline system, the mechanism shown in scheme 2.16 seems more plausible, with spontaneous cyclisation of the

lithiated intermediate **230** occurring prior to the addition of the electrophile to form **231**. Electrophilic quench furnishes the cyclised products **232**, **233** and **234**, whose stereochemistry was assigned tentatively to avoid a steric clash between the phenyl and naphthyl rings.



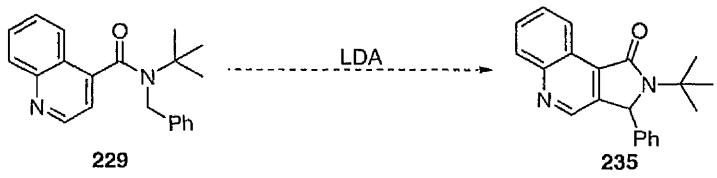
Scheme 2.16

Entry	Temperature (°C)	Equivalents of base	Time (h)	Electrophile	Result
1	20	1.5	3.5	MeI	59% of **232**
2	0	5	1	MeI	73% of **232**
3	0	5	1	MeOCOCl	71% of **233**
4	0	5	1	H	**234** (Not isolated)

Table 2.5

A possible reason for the difference in mechanism for the pyridines and quinoline systems is that on cyclisation, the quinoline system loses less of its total aromaticity and is thus more easily dearomatised. It should be noted that the spiro compounds were formed as single diastereoisomers and the stereochemistry was assigned tentatively to position the phenyl group away from the naphthyl group.

Attempts were made to isolate the rearomatised compound **235** analogous to **204** (scheme 2.2) seen in the pyridine series by using long reaction times and a low number of equivalents of base (scheme 2.17).



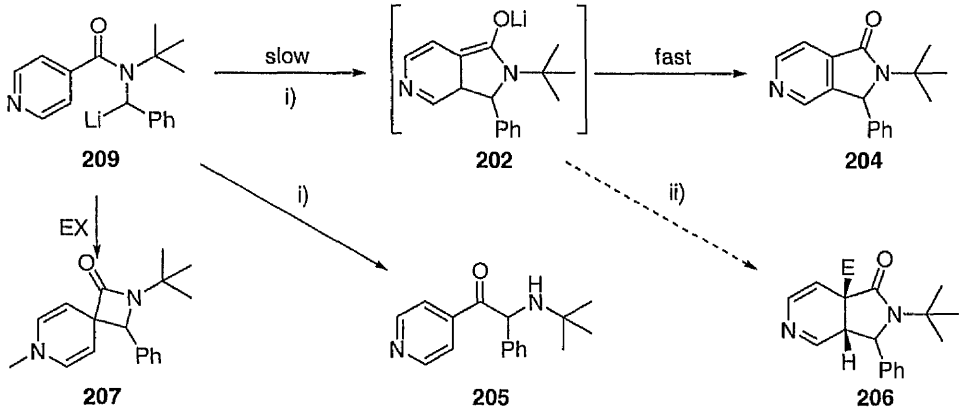
229 235

Scheme 2.17

Compound **235** was never seen in crude ^{1}H NMR spectra or isolated. This seems counter-intuitive after what was said previously about the quinoline system being more easily cyclised due to easier dearomatisation and thus cyclisation, but this is probably a consequence of the main component of the reaction mixture being **231** after lithiation in the quinoline series and **209** in the pyridine series. When **231** is quenched early enough we obtain spirocyclic products; if it is left for a long time we see decomposition. When **209** was quenched with an activating agent under a large excess of base spirocyclic products were obained, when it was left for a long time without an excess of base, cyclisation to **204** was the result (scheme 2.2).

2.2.6 Further Attempts to form Dearomatised Products Analogous to those of the Benzamides and Naphthamides

As mentioned previously, **223-226** (scheme 2.13) are analogous to the products of cyclisation of the benzamides and naphthamides and are the type of products that were first expected. We wondered whether this reaction was more general, or if an electron-donating group on the ring was necessary. Further attempts were made to cyclise organolithium **209** to **206** (scheme 2.18).



i) LDA; ii) EX (Conditions in table 2.6)

Scheme 2.18

We had seen previously that with a low number of equivalents of base, the cyclisation would take place, but no dearomatised products were ever isolated, only the rearomatised analogue.

Using 5 equivalents of LDA at –40 °C and allowing cyclisation to occur overnight before quench with methyl iodide (entry 1, table 2.6), we obtained a crude ^{1}H NMR spectrum that was exactly the same as if the reaction was left for only 30 minutes before the electrophile was added – a mixture of the spiro product **207**, methylated starting material **208** and starting material (scheme 2.3). No rearomatised **204** was seen. This is an interesting result, as when a similar experiment was carried out but

with 2 equivalents of base, the result was a 1:1 mixture of the rearomatised **204** and rearrangement product **205** (scheme 2.2). The result suggests that with 5 equivalents of LDA in solution, the intermediate **209** (scheme 2.18) is stable at –40 °C and the reaction mixture contains only this intermediate until the electrophile is added, but with only 2 equivalents, it is unstable and cyclisation occurs to **204**, presumably *via* **202**.

When the same reaction was carried out at 0 °C with 5 equivalents of base, **209** was unstable, and cyclised to give a 1:1 mixture of **204** and **205**. No dearomatised compound was isolated. The time the reaction was allowed to run was further shortened (entries 3-4, table 2.6) until mixtures of starting material, **204** and **205** were seen. This shows that **202** must be very short lived with respect to its own formation and therefore will not be possible to trap. The methoxy group in **220** must stabilise the enolate **223** (scheme 2.13), so that it can be trapped with electrophiles to yield isolatable dearomatised products.

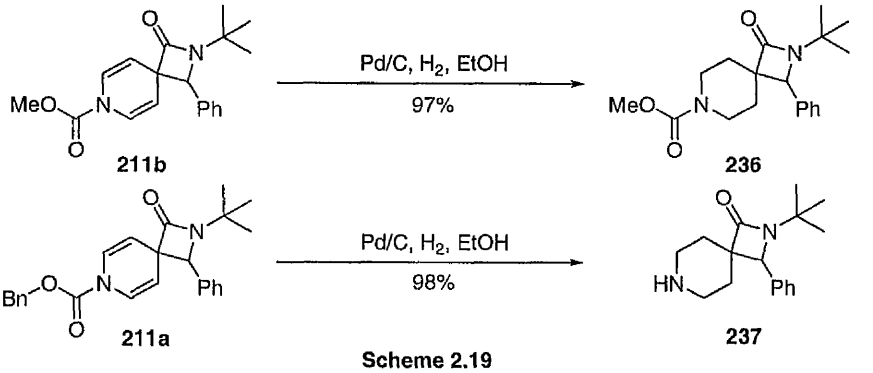
Entry	Temperature (°C)	Time of cycliation (h)	Result
1	–40	16	Mixture of **207**, **208** and SM, shows only **209** was in solution when electrophile was added.
2	0	16	Mixture of **204** and **205**. Shows that all had rearomatised before electrophile was added.
3	0	4	Same as above.
4	0	1	Mixture of **204**, **205** and starting material.

Table 2.6

2.2.7 Transformations of the β-lactam Products

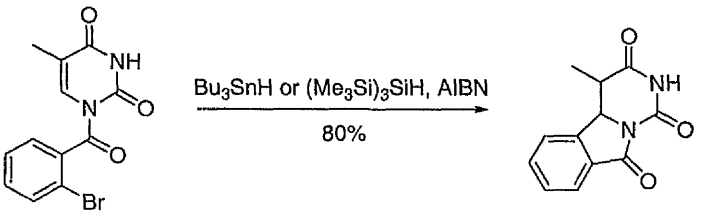
The β-lactam/1,4-dihydropyridine products are an interesting and previously unknown ring system. It was therefore decided that a couple of simple chemical transformations would be carried out on this ring system in order to explore its reactivity and maybe extend its utility.

Two of the β-lactam/1,4-dihydropyridine products were subjected to hydrogenation conditions using palladium on carbon and hydrogen gas (scheme 2.19). Both substrates were found to hydrogenate cleanly to the analogous piperidines **236** and **237**. Also note that concurrent removal of the Cbz group has occurred in the case of **237**.



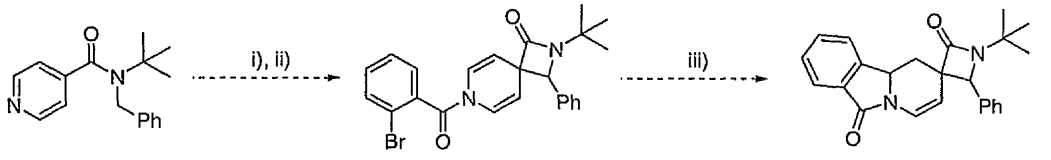
Scheme 2.19

Zhang and Pugh reported a thermally initiated radical cyclisation onto various unsaturated *N*-heterocycles, an example of which is shown in scheme 2.20. The isoindolone products this reaction creates are a class of alkaloids that possess interesting biological activities.[69]



Scheme 2.20

Attempts were made to apply this methodology to the dihydropyridine compounds made in this project. If **238** could be made, it may be possible to the effect a similar cyclisation to yield **239** (scheme 2.21).



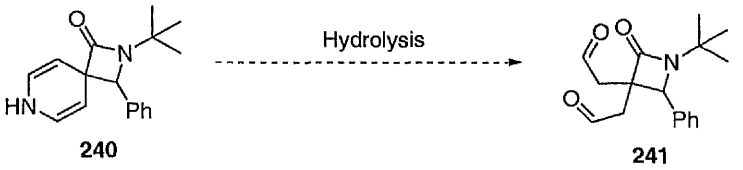
238 **239**

i) 3 equiv. LDA; –40 °C, 30 min; ii) *o*-BrPhCOCl; iii) Bn_3SnH or $(Me_3Si)_3SiH$, AIBN

Scheme 2.21

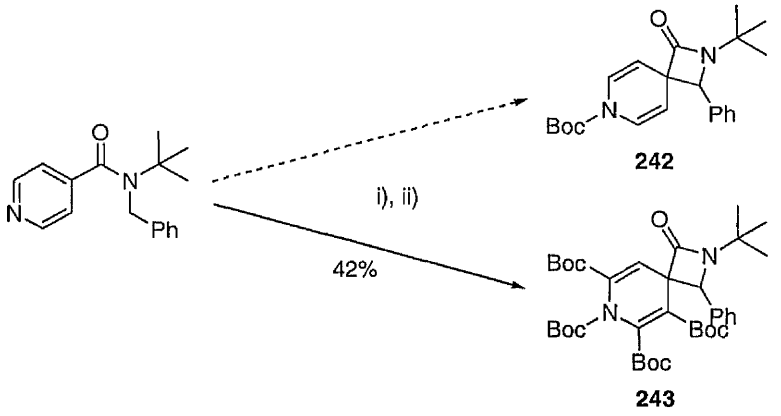
It proved to be impossible to synthesise **238** as the electrophile appears to be incompatible with this reaction. On addition of the electrophile, the reaction mixture turns black and a complicated mixture is generated. Lowering the temperature of the reaction mixture to –78 °C prior to the addition of the electrophile failed to improve matters.

Attempts were also made to open the dihydropyridine ring. Danishefsky *et al.* found that 1,4-dihydropyridine rings bearing a proton on the ring nitrogen were susceptible to hydrolysis to a dialdehyde.[70] Therefore if **240** could be synthesised it would maybe be possible to hydrolyse the ring open to **241** (scheme 2.22). As the aldehydes are useful groups for further chemical elaboration **241** could be a useful synthetic intermediate.



Scheme 2.22

240 cannot be made directly due to reasons discussed previously (section 2.2.3), but a possible route to it would be to make the acid labile Boc derivative **242** followed by removal of the Boc group (scheme 2.23). Unfortunately, polyacylation defeated all attempts to synthesise **242**. The initial attempt using 1.5 equivalents of Boc anhydride as the electrophile yielded **243** as the major product. This turned out to be unavoidable as the spirocyclisation does not work with less than 3 equivalents of base and polyacylation occurs even when only 1 equivalent of the electrophile is used.



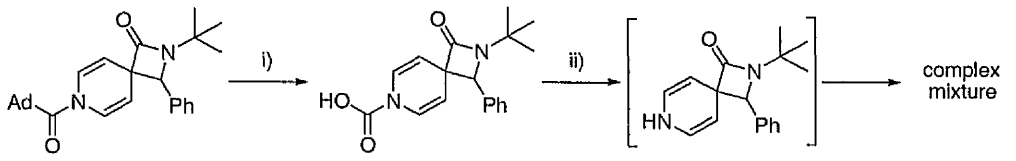
i) 3 equiv. LDA, THF, –40 °C, 30 min; ii) 1.5 equiv. Boc anhydride

Scheme 2.23

Instead of a Boc group, the similarly acid labile AdOC group was employed. Using adamantyl fluoroformate as the electrophile, the reaction proceeded smoothly furnishing **211c** in 76% yield (scheme 2.24).

Attempts to remove the AdOC group with TFA proved to be problematic – the reaction just giving a complex mixture of products (scheme 2.24). By simply removing the TFA and solvent from the reaction under reduced pressure (without

workup), a crude ^{1}H NMR showed that **211c** was being converted to a compound tentatively assigned as **240** by the action of the TFA, presumably *via* **245**. On contact with water a complex mixture is formed. As such, this way of opening the 1,4-dihydropyridine ring was not pursued further.

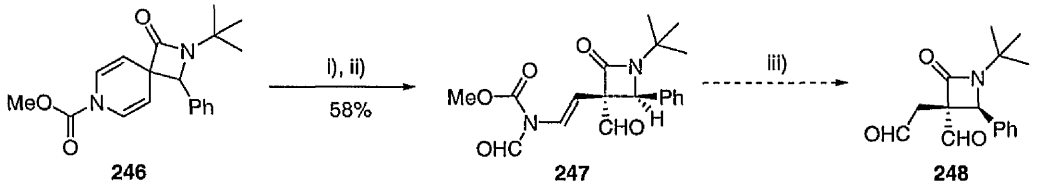


211c **245** **240**

i) 10% TFA/CH_2Cl_2, 20 °C, 30 min; ii) H_2O

Scheme 2.24

A more successful way of opening the 1,4-dihydropyridine ring was with the use of ozonolysis (scheme 2.25). It was found that by treating a solution of **246** in dichloromethane with ozone, one of the alkenes was selectively opened to yield **247** in good yield as a single diastereoisomer. The relative configuration of **247** was confirmed by NOE studies, where irradiation of the benzyl proton returned an enhancement of 5.8% for the signal for the aldehyde proton. No enhancement of either signal for the alkene protons was detected. The alkene geometry was assigned as *trans* due to a large coupling constant between the two alkene protons.



246 **247** **248**

i) O_3, CH_2Cl_2, –78 °C; ii) Me_2S; Hydrolysis

Scheme 2.25

The yield of **247** could probably be much higher as the reaction itself appeared to be fairly clean. Unfortunately **247** is very difficult to purify by flash column chromatography. **247** looks like it could possibly be a useful synthetic intermediate. It would be expected that the hydrolysis of **247** to **248** would be facile under acidic conditions. This would be desirable, as **248** would also look to be a useful synthetic

intermediate bearing two aldehyde 'handles' for further synthetic elaboration. The two aldehyde groups would most likely possess different reactivities so that they could be selectively reacted. Unfortunately **247** proved to be more stable than initially thought, and a few preliminary attempts to hydrolyse off the side chain failed. It is certainly stable to 2 M and 6 M HCl and TFA in small concentrations (up to 50%) at 0 °C. Reflux in 100% TFA leads to decomposition.

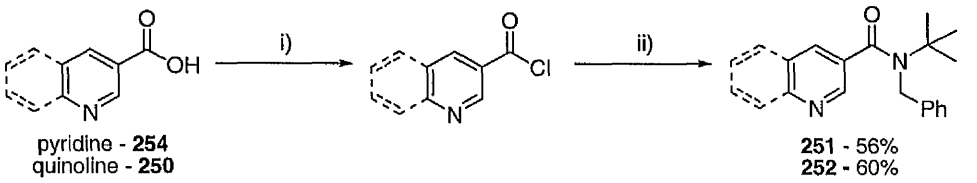
2.2.8 Future Work

There are many methods already developed within the group for the benzamides and naphthamides that should transfer straight over to the cyclisations of isonicotinamides. Replacement of the *t*-butyl group with a cumyl group should still allow the cyclisation to take place, but allow the group to be easily removed, leaving the resulting secondary amide available for further transformation. The chiral base methodology may allow the products to be formed in high enantiomeric excess. The ring opening using ozonolysis methodology discussed above is potentially very interesting and should be developed further, but was carried out at the end of the project when time was strictly limited.

2.3 Cyclisation of Nicotinamides

2.3.1 Pyridine Derivative

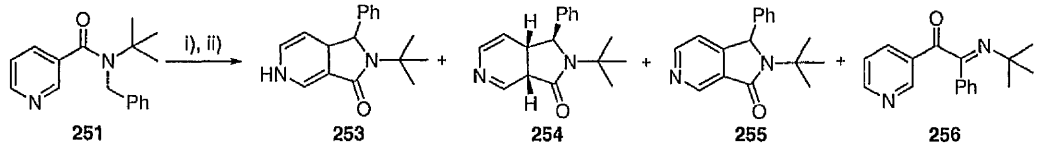
The starting materials **251** and **252** for these cyclisations were prepared *via* a simple amide coupling from the corresponding acids **249** and **250** by the procedure used previously to prepare the cyclisation precursors in section 2.2.1. (scheme 2.26).



i) $SOCl_2$, 85 °C, 16 h; ii) *t*-$BuNCH_2Ph$, Et_3N, CH_2Cl_2, 20 °C, 16 h

Scheme 2.26

Preliminary attempts to cyclise **251** employed conditions similar to those used for the cyclisation of benzamides. Many attempts were made at this cyclisation using two equivalents of LDA using long reaction times (3-16 h) with temperatures ranging from –40-20 °C. It proved difficult to draw any conclusions from these initial attempts as the product ratios were so inconsistent. The range of products formed by the reactions is shown in scheme 2.27.



i) 2 equiv. LDA, THF, –40 to 20 °C; ii) MeI or NH_4Cl

Scheme 2.27

The dearomatised products **253** and **254** were not often seen, but once at low temperature, these were the only products from the reaction except for a trace of **255** (entry 1, table 2.7). However, it proved impossible to repeat this result – even with exactly the same conditions. Higher temperatures tended to yield 1:1 mixtures of **255**

and the rearranged compound **256**, but sometimes the same product distribution would be seen with low temperatures. **256** was not isolated but assigned tentatively by comparison with work with the 2- and 4- substituted pyridines. **253** and **254** are both unstable and rapidly rearomatise to **255**, very quickly on silica and rather more slowly in air. The rearomatised product **255** and the rearranged product **256** are inseparable by chromatography. The above results are for when aqueous ammonium chloride was used as the electrophile (entries 1, 3 and 5, table 2.7). When the reaction was quenched with methyl iodide (entries 2 and 4, table 2.7), the results were identical except that products **253** and **254** tended to be replaced by a complicated mixture of dearomatised products.

Entry	Temperature (°C)	Time (h)	EX	Result
1	–40	16	NH_4Cl	Varying mixtures of **253**, **254**, **255** and SM. Sometimes traces of **256**
2	–40	16	MeI	Varying mixtures of **255** and SM. Sometimes evidence many dearomatised compounds. Messy.
3	0	3	NH_4Cl	Mostly **255** with traces of **253** and **254**.
4	0	4	MeI	Mostly **255** with messy dearomatised products.
5	20	16	NH_4Cl	1:1 **255** and **256**

Table 2.7

As it was noticed that high numbers of equivalents of base and short reaction times favoured dearomatised products with the 4-substituted pyridines and quinolines (section 2.2.1), these conditions were also tried in this case. Starting with 5 equivalents of base at 0 °C for 10 minutes followed by electrophilic quench with methyl iodide (entry 1, table 2.8) gave a result where in the crude ^1H NMR spectrum all of the starting material had been used up, to give a complicated mixture of dearomatised products plus the rearomatised compound **255**. This appears to indicate that the cyclisation occurs very rapidly to yield an extended enolate, which rapidly

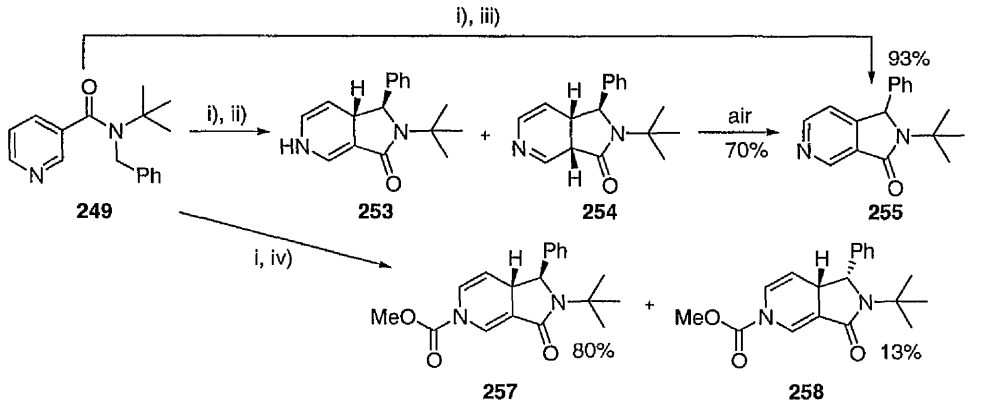
starts to rearomatise to give **255** and also decompose to other products. From previous experience within the group, it was expected that once this type of enolate is quenched with an alkylating agent, no rearomatisation could occur. Therefore the time of reaction was shortened to reduce the amount of rearomatisation, first to 2 minutes (entry 2, table 2.8), then to 20 seconds (entry 3, table 2.8). Both of these reactions resulted in crude spectra identical to the reaction that was left over 10 minutes (entry 1, table 2.8). This shows that the cyclisation is very fast, as is the rearomatisation at this temperature. Another possibility is that the rearomatisation occurs after the electrophile is added. As such the reaction was tried at lower temperature and quenched with aqueous NH_4Cl (entry 4, table 2.8), this resulted in a 5:1 mixture of the regioisomers **253** and **254** in the crude ^1H NMR spectrum with only a very small trace of the rearomatised product **255**. **253** and **254** could not be isolated due to their instability. However, if the crude mixture is left overnight, **253** and **254** rearomatise cleanly to **255**, which can be isolated in good yield (scheme 2.28).

Entry	Temperature (°C)	Time (min)	EX	Result
1	0	10	MeI	Messy mixture of many dearomatised products and some **255**.
2	0	2	MeI	Crude ^1H spectrum identical to Entry 1.
3	0	0.33	MeI	Crude ^1H spectrum identical to Entry 1.
4	–40	10	NH_4Cl	5:1 mixture of **253** and **254**. Trace amount of **255**. In air rearomatised to 70% **255**.
5	–40	10	MeI	Similar to Entry 1. When columned most of the mixture rearomatised to yield **255** in 93% yield.
6	–40	10	MeOCOCl	Formed mixture of diastereomers **257** and **258** in 80% and 13% yield respectively.

Table 2.8

This result shows that the cyclisation itself occurs cleanly under these conditions, so other electrophiles were tried with the hope that isolatable dearomatised products could be isolated.

Using the same cyclisation conditions followed by quenching with methyl iodide gave a complex mixture of dearomatised product plus rearomatised product **255** in the crude ^{1}H NMR. Chromatography on silica resulted in complete rearomatisation of the mixture to furnish **255** in good yield. Quench with methyl chloroformate yielded a mixture of diastereoisomers **257** and **258,** which were isolated in good yield (scheme 2.28). From this result one could make the assumption that the opposite regioisomer to products **253** and **254** would be present in small concentrations in all the other examples containing **253** and **254**. This is probably the case, but it is difficult to be certain as **253** and **254** cannot be separated from each other due to their instability, and as such, this would make it difficult to detect the other diastereoisomer in the crude ^{1}H NMR spectrum. Unfortunately, it proved to be impossible to assign the relative stereochemistry of **257** and **258** using ^{1}H NMR. **257** and **258** are both fairly shortlived, and as such, no other techniques were tried. The stereochemistry was thus tentatively assigned on the basis of previous results from the benzamides and naphthamides, where the major products almost always had the same relative stereochemistry as **257**.

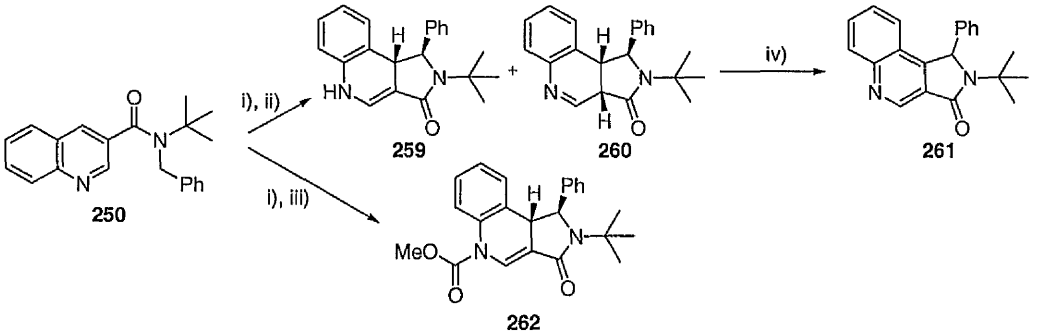


i) 3 equiv. LDA, THF, –40 °C, 10 min; ii) NH_4Cl; iii) MeI; iv) MeOCOCl

Scheme 2.28

2.3.2 Quinoline Derivative

The conditions used for the cyclisation of **249** were applied to **250** with very similar results (scheme 2.29). On lithiation, **250** rapidly cyclises and protic quench yields a mixture of diastereoisomers **259** and **260** (analogous to **253** and **254**) in a 5:1 ratio. On attempted purification the mixture rearomatised to **261**. With methyl chloroformate as the electrophile, **262** was isolated as a single diastereoisomer. The diastereoisomer analogous to **258** was neither isolated nor seen in the crude ^{1}H NMR spectrum.



i) 3 equiv. LDA, THF, –40 °C, 10 min; ii) NH_4Cl; iii) MeOCOCl; iv) SiO_2

Scheme 2.29

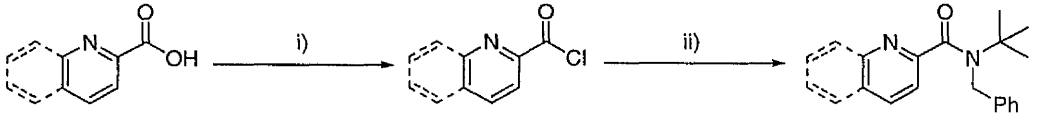
2.3.3 Future Work

As with the isonicotinamides, it would be interesting to see if some of the methodology known to work with the benzamides and naphthamides would transfer over, i.e. removal of cumyl group, the chiral base strategy etc. Also, some of the transformations attempted on the nicotinamides e.g. ozonolysis, the radical cyclisation etc. would be worthy of further research.

Of particular interest would be studies into attempts to force a change of regiochemistry so that the organolithium attacks the 2-position of the pyridine, as this could yield some interesting products. Possible ways of doing this would include modification of the metal to something other than lithium to change the properties of the anion, adoption of the imidate strategy used by Charette[54] (section 1.3.2.2), or even adoption of the methoxy blocking group strategy used by Comins *et al.*[59] (section 1.3.2.3) to furnish stable pyridones.

2.4 Cyclisation of Picolinamides

The starting material for these cyclisations was prepared from the commercially available picolinic acid **263** and quinaldic acid **264** (scheme 2.30). These were converted to the amides **265** and **266** *via* the methods used previously (section 2.2.1).



pyridine - **263**
quinoline - **264**

265 - 63%
266 - 66%

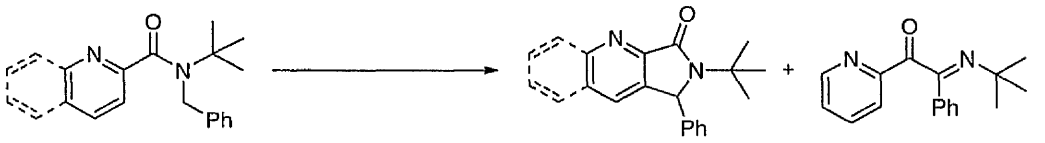
i) $SOCl_2$, 85 °C, 16 h; ii) *t*-$BuNCH_2Ph$, Et_3N, CH_2Cl_2, 20 °C, 16 h

Scheme 2.30

As with the 3- and 4-substituted pyridines and quinolines, initial attempts at cyclisation of these substrates employed similar conditions to those used for cyclisation of benzamides and naphthamides, that is low numbers of equivalents of base (1.5-2.0 equivalents) and long reaction times (2-16 h).

It was found that at –40 °C, no cyclisation took place for both the pyridine **265** and quinoline **266** derivatives. The reactions returned almost exclusively starting material with small traces of other aromatic products.

Raising the temperature to 0 °C started to give cyclised products. With **265**, mixtures of **267** and **268** were formed (scheme 2.31), where **267** is the rearomatised cyclised material and **268** is analogous to the previously seen rearrangement compounds. The product ratios of these two products were again unpredictable. The highest isolated yield of **267** was 29%. This pattern was repeated with the quinoline derivative **266**, and the highest yield of the rearomatised **269** was 31%. No compound analogous to **268** was seen.



pyridine - **265**
quinoline - **266**

267
269

268

pyridine - 2 equiv. LDA, 0 °C, 4 h - 29%
quinioline - 3 equiv. LDA, 0 °C, 16 h - 31%

Scheme 2.31

When it was found that high equivalences of base and short reaction times coupled with an acyl quench were successful with the other amides, these conditions were tried on **265** and **266**. The result was that a plethora of dearomatised and rearomatised compounds were formed in the reaction and that all of the starting material had been used in the reaction. As the wide range of dearomatised products was possibly due to poor regioselectivity of the quench, the reaction was repeated but quenched at –78 °C. This made no difference whatsoever to the crude ^{1}H NMR. An attempt to isolate some of the compounds from the crude mixture *via* flash column chromatography proved futile, as most of the fractions were mixtures of aromatic compounds. It appeared that whatever dearomatised compounds were, they were unstable. As such, work on these amides was suspended, as other avenues looked more fruitful.

Chapter Three

Cyclisation of Other Tethered Anions onto Pyridine Rings

3.1 Introduction

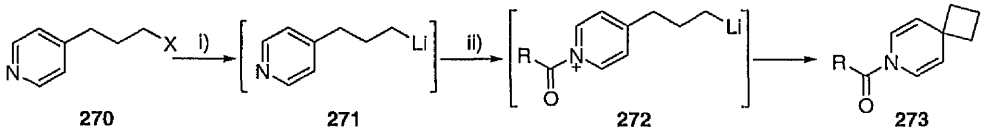
As some of the cyclisations onto pyridines and quinolines that we saw in the previous chapter were successful, we wanted to test the scope and generality of this methodology – particularly the activation followed by cyclisation strategy seen with the 4-substituted pyridines and quinolines, by seeing if it could be transferred to simpler systems.

3.2 Attempted Cyclisation of Tethered Organolithiums Generated from Halides onto Pyridine Rings

On the face of it, the simplest system of all would be to have a halogen tethered to a pyridine ring. It should then be possible to carry out a halogen-metal exchange reaction followed by activation of the ring. This would hopefully force a cyclisation to take place (scheme 3.1).

One potential problem with this design of reaction is that compared to the previous amide cyclisations, the intermediate organolithium **271** would be more reactive than the previous benzylically stabilised organolithiums. This raises the possibility of reaction directly at the organolithium instead of activation of the pyridine ring.

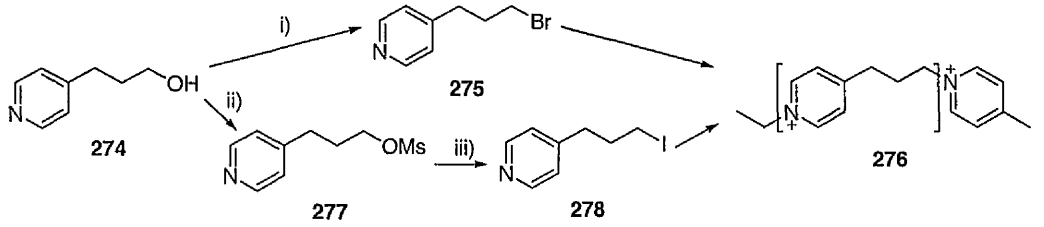
The first target starting material was **270** – which on cyclisation should form a spirocyclic four membered ring product **273** similar to the ones formed with the isonicotinamides (section 2.2.1) *via* the activated organolithium **272**.



i) *t*-BuLi, THF, ii) Activating agent

Scheme 3.1

An attempt was made to synthesise the bromide **275** from the commercially available alcohol **274**[71] but the product of the reaction was a completely insoluble white powder (scheme 3.2). Another attempt was made to synthesise the iodide **278** *via* the mesylate **277**,[72,73] but again, the product of this reaction quickly became an insoluble solid on concentration. The most likely explanation for the insoluble products is that both **275** and **278** polymerise to give a structure of the type **276**.

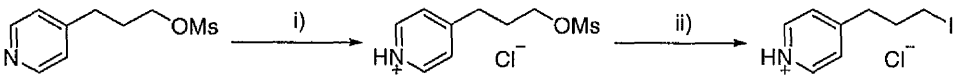


i) PBr_3, Et_2O, ii) MsCl, Et_3N, CH_2Cl_2, iii) NaI, Acetone

Scheme 3.2

In order to prevent the polymerisation, it was decided to protect the pyridine nitrogen as the hydrochloride salt (scheme 3.3). The mesylate was resynthesised, and in the crude ^1H NMR and mass spectrum, dimers and trimers could be seen. This reinforces the previous suggestion that the iodide **278** and the bromide **275** polymerise. The mesylate was then converted to the hydrochloride salt **279** by the action of acetyl chloride in methanol.[74] Finally **279** was converted to the iodide **280** using the methods

discussed previously. The result of this was a brown semi solid that proved impossible to purify, and as such, a yield has not been quoted.

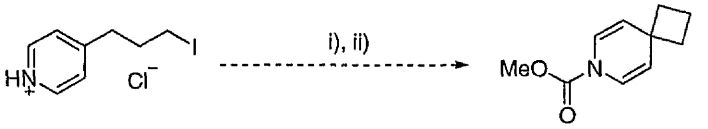


277 **279** **280**

i) AcCl, MeOH, ii) NaI, Acetone

Scheme 3.3

Even though the iodide was not pure, a few preliminary cyclisations were carried out on **280** to see if the reaction was at all viable (scheme 3.4). The reactions were characterised by very low crude yields of complex mixtures. In the crude ^{1}H NMR spectra of these reactions, all of the starting pyridine had disappeared to give complex mixtures of dearomatised products. No recognisable products were ever isolated. A likely explanation for these observations is that formation of a 4-membered ring is difficult, it would probably be easier for the very reactive primary organolithium to attack the 2-position of a pyridine of another molecule – we should remember that activation of the pyridine activates both the 2 and 4 position of the ring towards nucleophilic attack. Other possible pitfalls with this reaction are that the hydrochloride also activates the ring towards attack. *t*-Butyllithium has already been shown to attack unactivated pyridines,[75] so there is definitely the possibility that it would attack this activated pyridine – admittedly though, this reaction would be in competition with the halogen-lithium exchange reaction, which is known to be very fast. Another problem, is that the hydrochloride salt **280** proved to be extremely hydroscopic.



280 **273**

i) 3equiv. *t*-BuLi, THF, –78 °C, 5 min, ii) MeOCOCl warm to 20 °C

Scheme 3.4

With so many potential problems connected with the reaction, work in this area was discontinued.

On reflection, the decision to try and form a 4-membered spirocyclic ring was perhaps not so shrewd, as experience has shown these are difficult to form. A better approach would have been to aim for a fused ring, preferably 5 or 6 membered. If a fused ring could be formed, the lessons learned could then be put to good use in attempts to form **273**.

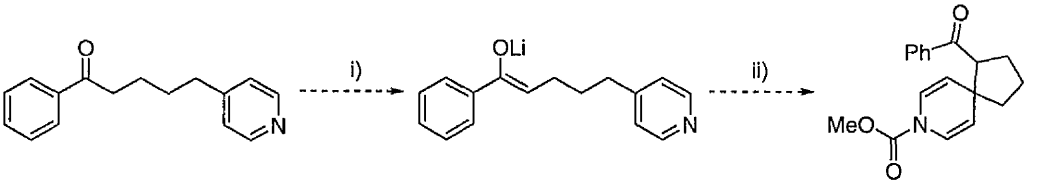
3.3 Cyclisation of Tethered Enolates onto Pyridine Rings

3.3.1 Introduction

In the previous section, it was learned that in order to cyclise a tethered anion onto an activated pyridine ring. A group on the end of the tether that will stabilise an anion to the correct degree whilst not reacting with the ring nitrogen is required, as this leads to polymerisation of the starting material. A possible candidate as a stabilising group is an enolate. These look particularly promising as attack of enolates on activated pyridines in an intermolecular sense is already well documented (section 1.3.2.4).

3.2.2 Formation of a Spiro Fused 5-membered Ring

The cyclisation precursor **281** was designed as a good way of probing whether or not this type of reaction could be made to work. On application of suitable conditions, **281** should form a 5-membered ring product **283** *via* the enolate **282** (Scheme 3.5).



281 **282** **283**

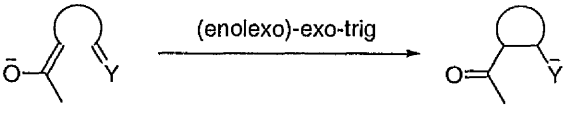
i) LDA; ii) MeOCOCl

Scheme 3.5

A 5-membered ring was chosen, as these tend to be easy to form. A 4-substituted pyridine was used as in theory only the spiro product should be formed by attack at the 4-position. Attack at the 2-position is unlikely as it is difficult for the tether to reach and attack at the 3-position in unfavourable for electronic reasons. The

substituent on the opposite side of the ketone to the tether, a phenyl ring, was chosen so that only one side of the ketone is enolizable.

It should be noted at this point, that depending on how the starting materials are drawn, this type of cyclisation can be considered to be an (enolexo)-exo-trig type cyclisation as rationalised under Baldwins rules (scheme 3.6).[76] The only difference being that the rules are written for cyclisations onto alkenes, and in this case the cyclisastion is onto a pyridine. Essentially though, this is still an sp^2 centre. Under these rules (enolexo)-exo-trig cyclisation for ring sizes from three to seven are all favoured, and thus the cyclisations of **281**, **292**, **300** and **305** attempted in this section can all be considered to be favoured.



Scheme 3.6

Attempts at synthesising the cyclisation precursor started with the alkylation of acetophenone **284** with the unstable mesylate **277** as used in section 3.2 (scheme 3.7).

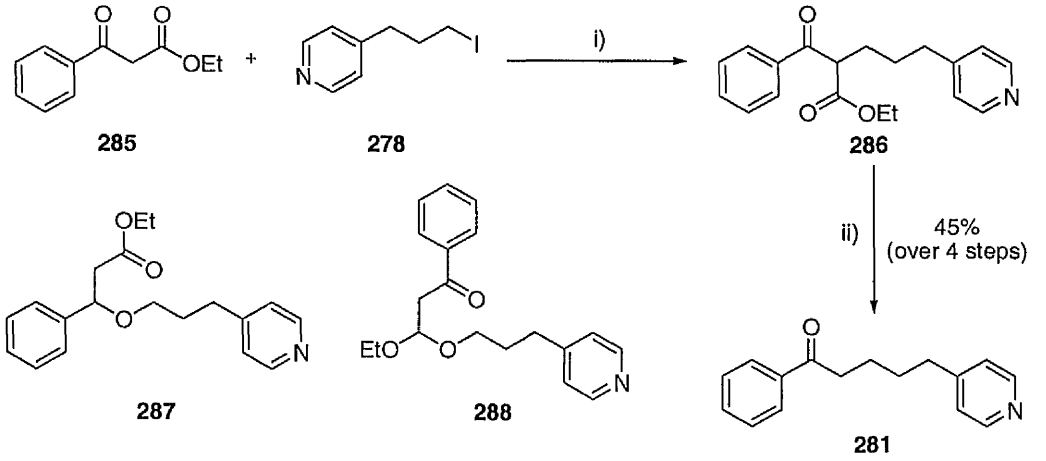
284 **281**

i) LDA, THF, –78 °C, 1h; ii) **277**

Scheme 3.7

As the reaction gave only a trace of **281**, a test reaction was conducted by attempting to alkylate acetophenone with methyl iodide. This also worked very poorly, giving just a trace of the expected product in the crude ^1H NMR spectrum. Accordingly this route to the cyclisation precursor was not pursued.

Instead, traditional 1,3-dicarbonyl chemistry was used. 1,3-dicarbonyl compound **285** was deprotonated with potassium carbonate[77] (scheme 3.8) and alkylated with the unstable iodide **278** used in section 3.2 to furnish **286**. Decarboxylation of **286**[77] furnished the required cyclisation precursor **281**. The iodide **278** was used instead of the mesylate **277** after the latter was found to alkylate the malonate not only on carbon, but also on oxygen to give inseparable mixtures of **287** and **288**.



i) K_2CO_3, Acetone, Δ, 16 h; ii) NaOH/EtOH, Δ, 4 h

Scheme 3.8

For the cyclisation of **281**, the initial conditions (entry 1, table 3.1) were to deprotonate at 0 °C for 30 minutes with 1.1 equivalents of LDA, then after addition of the electrophile (1.1 equiv. methyl chloroformate), the reaction was left for a further 30 minutes at the same temperature before being worked up. The deprotonation conditions for this reaction were unlikely to be problematic, as it is known that enolates are easily and rapidly formed with LDA at a range of temperatures. The resulting enolate should be relatively stable and remain intact until the electrophile is added. After the addition of the electrophile, the reaction was left for a certain amount of time before being worked up. This differs from the amide cyclisations in chapter 2 (which cyclised almost instantaneously on addition of the electrophile) because the enolates should be quite stable and therefore the cyclisation could be slow.

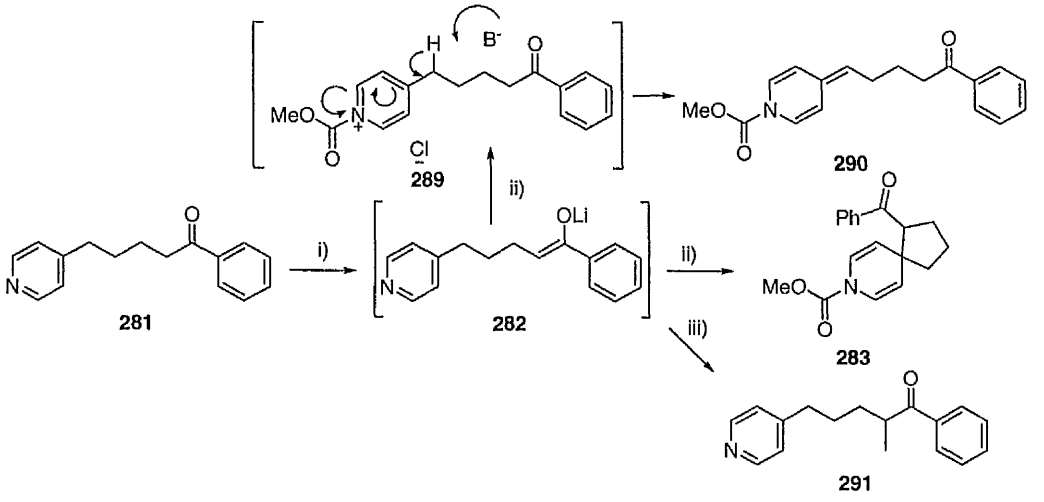
The result of this preliminary cyclisation was promising – all of the starting material was used up to yield a complex mixture of dearomatised products. To try and clean up the reaction the temperature was lowered to –40 °C (entry 2, table 3.1). The result of this was that the reaction returned mostly starting material, what had reacted had given a complex mixture of products. This indicates that the reaction is very slow at –40 °C. Next, the enolate was formed at –78 °C, but after the electrophile was added, the reaction was allowed to warm to room temperature over about 30 minutes. The result was again a complex mixture (entry 3, table 3.1).

In order to check that the enolate itself was stable, the starting material was deprotonated at 0 °C then quenched after 30 minutes with ammonium chloride (entry 4, table 3.1). This indicated that the enolate was stable by returning starting material. Next, it was checked that the deprotonation was occurring in the correct place in the molecule – after deprotonation, the reaction was quenched with iodomethane. This resulted in a 1:1 mixture of **291** and starting material (scheme 3.9), so the molecule is being deprotonated in the correct place. The last two results indicate that the problems in the reaction are occurring after the electrophile is added.

As such, the reaction was left for a longer time at lower temperature after the electrophile was added (entries 6-7, table 3.1). In both cases the only product formed was tentatively assigned as **290**. This product could not be isolated as it appears to rapidly convert back into starting material on silica. A proposed mechanism for its formation is shown in scheme 3.9. This reaction occurs when the electrophile has been added and activation of the molecule occurs to yield **289**, but the temperature is

too low for cyclisation to happen. Instead, excess base or another molecule of the enolate removed the proton α to the pyridine ring.

The final attempt (entry 8, table 3.1) was carried out to check whether or not the messy dearomatised products were due to polymerisation. This was done by doubling the dilution of the reaction, which appeared to have little effect. To conclude, with this cyclisation the deprotonation is facile and it yields a stable enolate. When the electrophile is added, no cyclisation occurs until the temperature is somewhere between –40 °C and 0 °C. If the reaction is left at low temperature with the electrophile in solution a side reaction yields **290**.



i) LDA, THF; ii) MeOCOCl; iii) MeI

Scheme 3.9

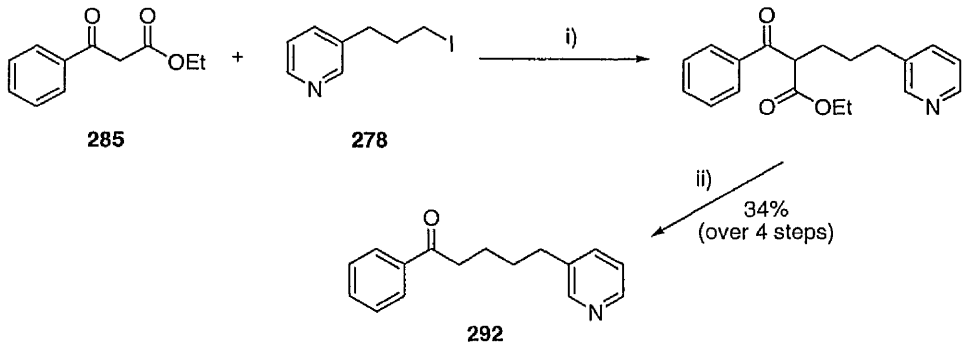
Entry	Temperature of Deprotonation (°C)	Electrophile (1 equiv.)	After Addition of E^+	Result
1	0	MeOCOCl	Quenched at 0 °C after 30 min	All SM used. Complex mixture
2	–40	MeOCOCl	Quenched at –40 °C after 30 min	Mostly SM, what had reacted had given a complex mixture
3	–78	MeOCOCl	Quenched at –78 °C. Allowed to warm to 20 °C over 30 min	All SM used to give a complex mixture of products. 19% isolated yield of **283**
4	0	NH_4Cl	-	Returned SM
5	–78	MeI	Allowed to warm to 20 °C over 30 min	1:1 mixture of **291** and SM
6	–78	MeOCOCl	Warmed to 20 °C very slowly	6:1 mixture of **290** and SM
7	–40	MeOCOCl	Left for 16 h at –40 °C	1:1 mixture of **290** and SM
8	–78	MeOCOCl	Quenched at –78 °C then allowed to warm to 20 °C	^1H NMR spectrum identical to entry 3 – complex mixture

Table 3.1

3.3.3 Formation of a Fused 6-membered Ring

3.3.3.1 Organolithium Cyclisations

The 3-substituted cyclisation precursor **292** analogous to **281** was prepared *via* the same route in moderate yield (scheme 3.10).

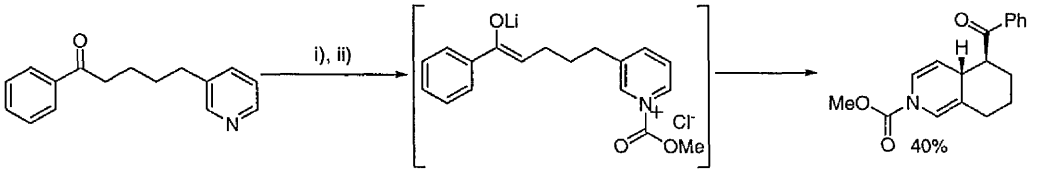


i) K_2CO_3, Acetone, Δ, 16 h; ii) NaOH/EtOH, Δ, 16 h

Scheme 3.10

Preliminary attempts to cyclise **292** showed that it behaved in a similar way to **281**. It did not give products analogous to **290** as this reaction pathway is not plausible, as an anion α to the pyridine ring will not gain extra stabilisation through delocalisation on the nitrogen. When cyclisation did occur though, a similar complex mixtures of products were formed as with **281**. Here there is not only the possibility of attack on the pyridine ring through oxygen, but also possibility of attack in both the 4 and 2-position of the pyridine ring. Only the expected product is stable enough to isolate. A large range of temperatures and reaction times were tried, though all using 1.1 equivalents of base, and the best result obtained was an isolated yield of 40% of the expected product **293** (scheme 3.11). Due to coincident signals obscuring crucial coupling constants in the ^{1}H NMR and the instability of the compound, the relative

stereochemistry of **293** was tentatively assigned to place the phenyl ketone away from the 1,4-dihydropyridine ring.



292 **293**

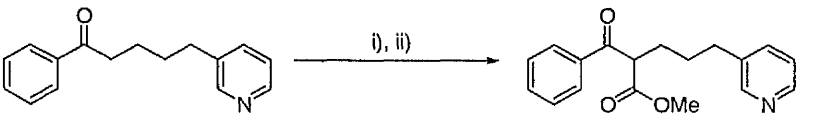
i) LDA, THF, –78 °C, 30 min, ii) MeOCOCl, –78 to 20 °C

Scheme 3.11

Another approach that was tried was to add the electrophile before the base. This had failed previously with amide cyclisations due to nucleophilic attack of the base on the activating group at the expense of deprotonation. This was tried again because the enolate should form much more easily than the benzylic anion, and therefore may occur before the base has chance to attack the activating group. However, this proved not to be the case and the starting material was returned.

3.3.3.2 Use of Other Metals

The metal of the enolate was changed to see if the reaction improved (scheme 3.12). Changing the metal would have consequences for the reactivity of the enolate and could also cause potentially interesting changes to the regiochemistry of the reaction. The only two metals that were tried were potassium and sodium. Unfortunately, both of these metals produced an enolate that was too unstable, and at the point in the reaction where there are two centres at which the electrophile can react, instead of activating the ring to force a cyclisation the electrophile reacted directly at the now much more reactive enolate to give **294**.



292 294

KHMDS - 84%
NHMDS - 80%

i) KHMDS/NHMDS, THF, –78 °C, 1 h, ii) MeOCOCl, –78 to 20 °C

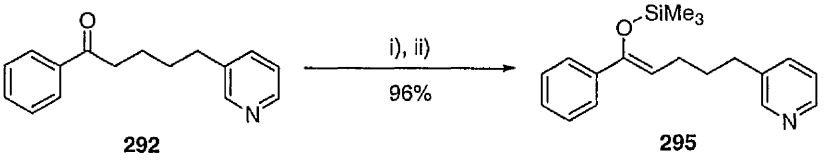
Scheme 3.12

There are other metals that could be used which would produce a more stable enolate than a lithium enolate – particularly magnesium or zinc. However, investigations in this area were brought to a natural close when the problems with the reaction were overcome by forming the product *via* the silyl enol ether.

3.3.3.3 Silyl Enol Ether Cyclisations

It is known in the literature that if a silyl enol ether is added to an activated pyridine, an intermolecular reaction occurs spontaneously (section 1.3.2.5).[63] If this could be made to work in an intramolecular sense it would be useful for this cyclisation.

The silyl enol ether precursor **295** was made simply by lithiation of **292** with LDA followed by electrophilic quench with trimethylsilyl chloride (scheme 3.13).



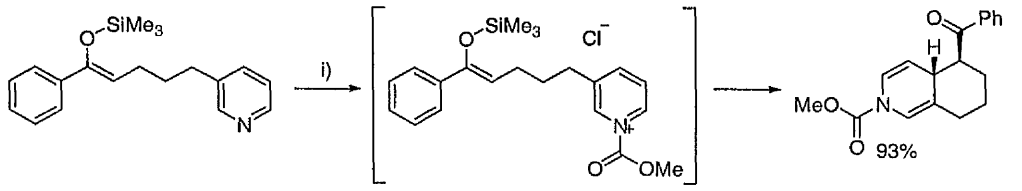
292 295

i) LDA, THF, –78 °C, 30 min, ii) TMSCl, –78-20 °C

Scheme 3.13

When **295** was activated by addition of methyl chloroformate, it did indeed cyclise to give the expected product **293**, but as a 1:1 mixture with **292**, the product of the hydrolysis of the silyl enol ether. This problem was solved by adding triethylamine to

the reaction mixture to remove any excess acid, the reaction was then rapidly worked-up to yield the product in 93% yield and as a single diastereoisomer (scheme 3.14).

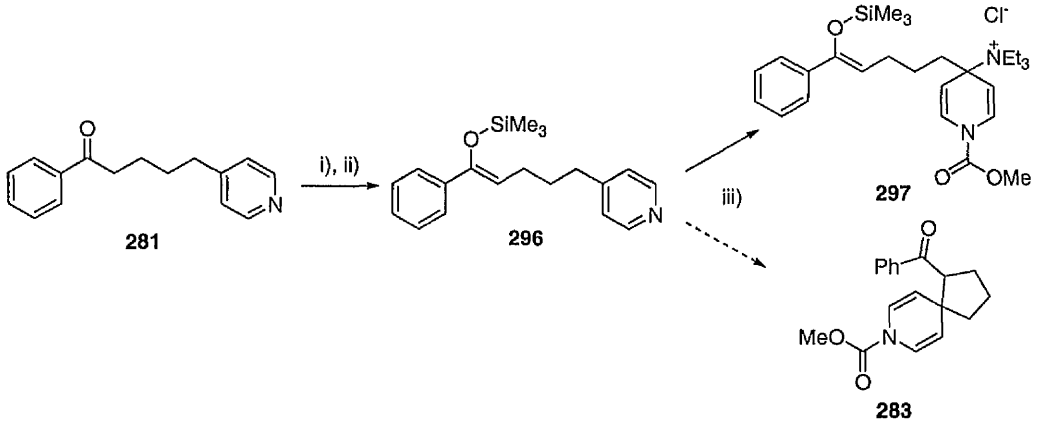


295 293

i) 5 equiv. MeOCOCl, 1 equiv. Et_3N, CH_2Cl_2, –78 to 20 °C

Scheme 3.14

With the success of the previous reaction, we wanted to see if we could extend its scope and apply this methodology to the 4-substituted pyridine **281**. **281** was converted into the silyl enol ether **296** by the same method used previously, but on attempted cyclisation of the silyl enol ether by application of the conditions used for the cyclisation of **295**, the reaction just returned the starting materials. Only when a ^1H NMR spectrum was recorded of the crude reaction mixture (prior to work up) could we see what was actually happening in the reaction. The activated pyridine was being attacked by the triethylamine to give an unstable dearomatised product tentatively identified as **297** by ^1H NMR that decomposed on aqueous work-up (scheme 3.15).



281 296 297 283

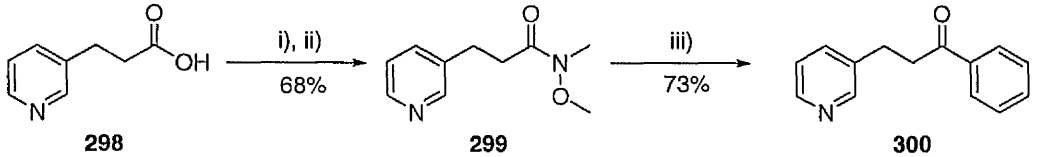
i) LDA, THF, –78 °C; ii) Me_3SiCl; iii) 5 equiv. MeOCOCl, 1 equiv. Et_3N, –78-20 °C

Scheme 3.15

This problem was circumvented by using a more bulky base – Hünig's base was chosen. This appeared to stop the attack of the base on the activated pyridine, a ^1H NMR spectrum of the crude reaction mixture showed no presence of any product analogous to **297**, only starting materials. It was of course possible that a product analogous to **297** was being formed, but due to the extra steric bulk of the base, was even more unstable than **297** and had decomposed before the ^1H NMR spectrum had been recorded. To prove that this was not the reason the reaction for the failure of the reaction, it was run without base, the result was just partial desilylation of the starting material – there was no trace of the desired cyclisation product **283**.

3.3.4 Attempted Formation of a Fused 4-membered Ring

Although the previous reaction did not work, it may have been due to a peculiarity of spirocycle formation – the formation of fused rings may still work with this methodology. Accordingly the cyclisation precursor for a 4-membered fused ring **300** was synthesised from the commercially available acid **298** *via* its Weinreb's amide **299** (scheme 3.16).[78] Although the cyclisation itself looks unlikely, it can corresponds to a 4-(enolexo)-exo-trig cyclisation, which is favoured under Baldwin's rules.[76]



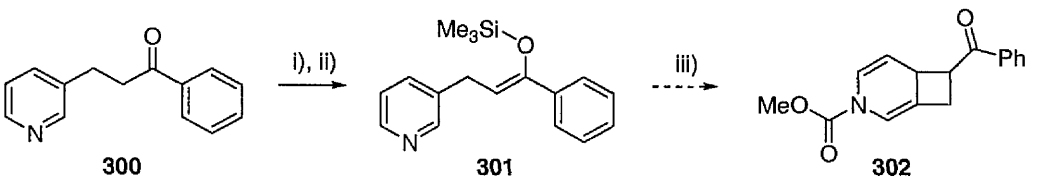
298 **299** **300**

i) $SOCl_2$, 20 °C; ii) MeNHOMe, Et_3N, CH_2Cl_2; iii) PhLi, THF

Scheme 3.16

Ketone **300** was converted to the silyl enol ether **301** by the same method used previously, but on attempted cyclisation of **301** by application of the conditions used

for the cyclisation of **295**, the reaction just returned the starting materials – no trace of the expected **302** was seen (scheme 3.17).



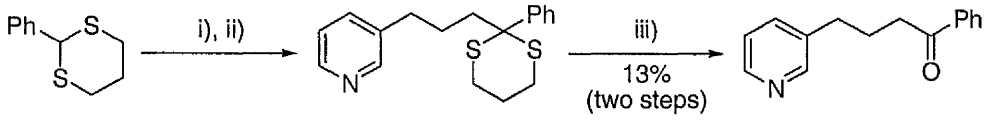
300 **301** **302**

i) LDA, THF, –78 °C; ii) Me_3SiCl; iii) MeOCOCl, Et_3N, CH_2Cl_2, –78-20 °C

Scheme 3.17

3.3.5 Attempted Formation of a Fused 5-membered Ring

As one would expect this cyclisation to be difficult anyway, work on the cyclisation of **300** was suspended and the cyclisation precursor **305** that would form a 5-membered fused ring product **307** was synthesised (scheme 3.18). This was accomplished *via* lithiation of the commercially available 2-phenyl-1,3-dithiane[79] (**303**) followed by electrophilic quench with the unstable iodide **278**. This resulted in an inseperable mixture of **304** and the electrophile. The mixture was subjected to hydrolysis conditions[80] that converted the dithiane ring into a carbonyl group. **305** was then isolated in moderate yield for both steps.



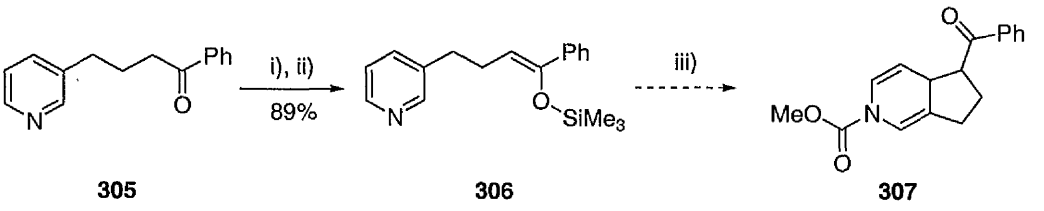
303 **304** **305**

inseperable mixture with SMs

i) *n*-BuLi, THF; ii) **278**; iii) MeCN, H_2O, HgO, HgCl

Scheme 3.18

Ketone **305** was converted to the silyl enol ether **306** *via* the methods used previously, but unfortunately when **306** was subjected to the cyclisation conditions, no reaction was seen. Increasing both the reaction times and temperatures failed to have any effect, neither did running the reaction without any base (scheme 3.19).



305 **306** **307**

i) LDA, THF; ii) Me_3SiCl; iii) MeOCOCl, CH_2Cl_2

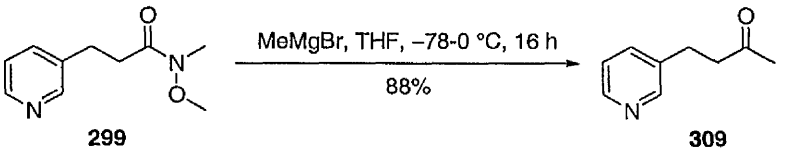
Scheme 3.19

As a last resort, **305** was subjected to the original cyclisation conditions whereby the lithium enolate is generated followed by the activation of the ring. This again just returned the starting materials. The cyclisation precursor for a 4-membered fused ring **300** was subjected to the same conditions and this too just returned the starting material. This is not too surprising, as 4-membered rings are often difficult to form, but the failure of the 5-membered ring precursor to cyclise is quite surprising as these tend to form much more easily. A probable reason is that the tethered enolate/silyl enol ether cannot reach around to the activated pyridine.

3.3.6 Formation of a Fused 6-membered Ring *via* an '*endo*' cyclisation

So far, all of the cyclisation reactions attempted were to form products with the carbonyl group *exo* to the ring being formed. Next it was decided to try form a ring with the carbonyl group *endo* to the ring being formed. As the only reaction that has worked satisfactorily so far formed a 6-membered fused ring, this is what we wanted to try again.

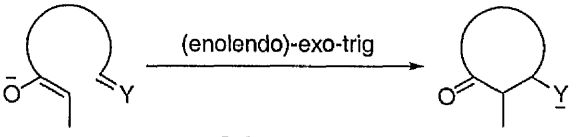
The necessary ketone **309** was formed in excellent yield from the reaction of the previously synthesised Weinreb amide **299** with methyl Grignard (scheme 3.20).[78]



299 **309**

Scheme 3.20

Depending on how the starting material is drawn, the cyclisation of **309** can correspond closely to an (enolendo)-exo-trig reaction (scheme 3.21). With this type of cyclisation, ring sizes of three to five are disfavoured and ring sizes of six to seven are favoured. Therefore under Baldwin's rules, this cyclisation can be favoured.[76]

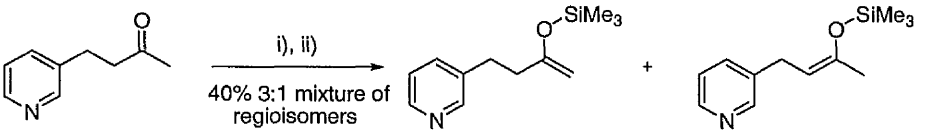


Scheme 3.21

A preliminary reaction was carried out where **309** was lithiated then quenched with methyl chloroformate, as if this reaction failed, there would be little point in trying to cyclise a silyl enol ether. The reaction worked in a similar way to its *exo* analogue, the cyclisation of **292** (scheme 3.11) - the reaction yielded a complex mixture of dearomatised products, which was a good sign, but it was clear from past experiences that there would be little point in trying to improve this reaction.

Formation of the silyl enol ether **310** of **309** proved much more difficult than before. When the silylation was carried out in the same way as the previous silylations, a 3:1:1 mixture of the expected product **310**, its unwanted regioisomer **311** and starting mixture was the result in the crude ^{1}H NMR spectrum. **310** and **311** were inseparable by chromatography and gave a combined yield in a 3:1 ratio of 40% (scheme 3.22). The isolated yield of **310** and **311** was much less than would be expected from the

crude spectrum and this would appear to be due to the instability of **310** and **311**, both of which are easily hydrolysed back to **309**.



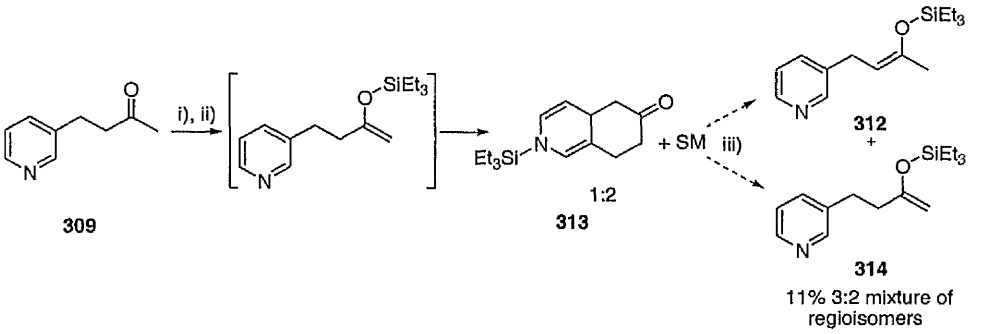
309 **310** **311**

i) LDA, THF, –78 °C, 10 min; ii) Me_3SiCl

Scheme 3.22

The methods of House[81] and the inverse addition strategy of Corey[82] were also tried. They also resulted in a 3:1 mixture of **310** and **311** with varying amounts of unreacted starting material – although this is again more likely due to slight differences in the handling of the unstable **310** and **311**.

A possible reason for the unexpected poor yields delivered by this reaction was given when an attempt was made to synthesise the triethyl silyl ether **314** (scheme 3.23). In the crude ^1H NMR spectrum of one of the attempts was a 2:1 mixture of starting material and a compound tentatively assigned as **313** – a cyclised product formed when the expected silyl enol ether is activated by another molecule of triethylsilyl chloride, activation by silylation is known in the literature.[83] It was not possible to isolate **313**, as on silica the mixture was converted to a 3:2 mixture of **314** and **312** (scheme 3.23) *via* an unknown mechanism, although it is most likely that **313** decomposes and the excess SM is converted to **312** and **314**.

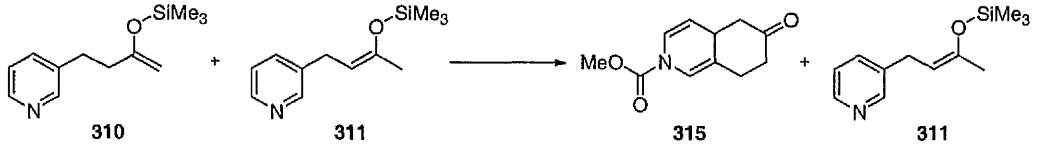


i) LDA, THF; ii) Et_3SiCl; iii) silica

Scheme 3.23

It seems probable that a reaction analogous to the one depicted in scheme 3.23 also occurs when trimethylsilyl chloride is used as the electrophile, and this is a possible reason why the reaction depicted in scheme 3.22 gives an unexpected mixture of regioisomers. However, no products analogous to **313** have been seen, but this could be due to instability, so that it has already turned to a mixture of regioisomers before any spectroscopy is carried out.

Although no pure samples of **310** were obtained, an attempt was still made to cyclise the 3:1 mixture of **310** and **311**. The result was that in the crude ^1H NMR spectrum we see mostly a 1:1 mixture of **315** and **311** (scheme 3.24). After purification by flash column chromatography, there was an isolated yield of 36% of the expected product **315**, which turns out to be very unstable. Unfortunately this could not be isolated without a small amount of an impurity containing the 3-substituted pyridine ring, probably a rearomatised compound.



i) 5 equiv. MeOCOCl, Et_3N, CH_2Cl_2, –78 to 20 °C

Scheme 3.24

3.37 Future Work

The cyclisation of the silyl enol ether **295** worked excellently and is potentially a very powerful reaction, particularly due to its diastereoselectivity. The scope of this reaction could be widened by the use of different activating groups. Particularly interesting would be chiral activating groups as discussed in section 1.3.2.2 to see if enantiomerically enriched products could be formed. Also, the phenyl group could be changed to something more suitable for further chemical transformation. An alkoxy group would leave a more versatile ester at the end of the reaction. Incorporation of a heteroatom into the ring being formed would also be very interesting.

Out of the other two fused rings attempted, it is suprising that **306** did not cyclise to give the 5 membered ring product **307**. This reaction could possibly be persuaded to work by substituting the chain to favour cyclisation.

The spirocyclisation suffers from many problems and is probably not worth pursuing unless valuble lessons are learned whilst attempting the other cyclisations.

The final endo cyclisation of **310** itself appears to be very encouraging, but only if the problems with the synthesis of the starting material can be ironed out.

3.4 Cyclisation of Tethered 2-lithio-1,3-dithianes onto Pyridine Rings

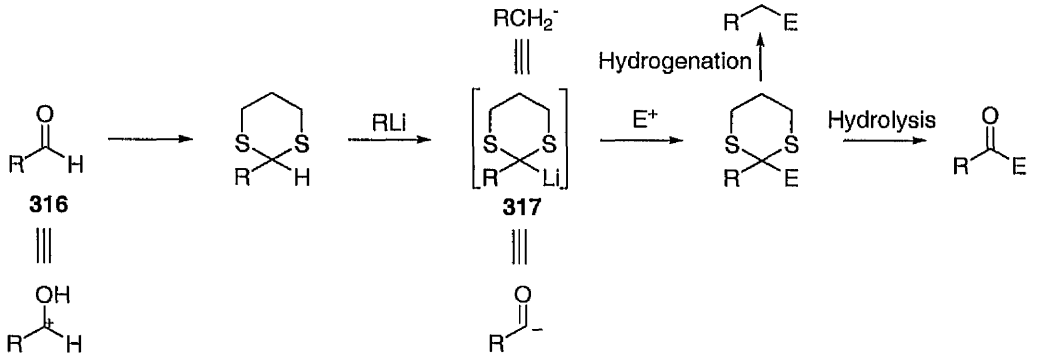
3.4.1 Introduction

As discussed in section 3.3.1 the main criteria for a stabilising group to be tethered to a pyridine are that it should stabilise an anion to the correct degree, not be susceptible to polymerisation from reaction with the ring nitrogen and also give a useful 'handle' on which other synthetic transformations can be carried out after the cyclisation is over. Another possibility which should fit these criteria is the 1,3-dithiane group.

1,3-Dithianes have found favour in chemical synthesis for their ability to temporarily reverse the reactivity of a carbonyl group – so called umpolung behaviour.[84] The reactivity changes from electrophilic as an unmasked carbonyl group **316** to nucleophilic as the 2-lithio-1,3-dithiane derivative **317**.

The 1,3-dithiane moiety is easily introduced into a molecule, either by nucleophilic attack of a 1,3-dithiane anion,[79] with or without substitution in the 2-position, or by conversion of a carbonyl group to a 1,3-dithiane by reaction with 1,3-propanedithiol and acid (scheme 3.25).[74]

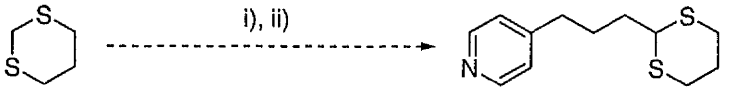
Once the dithiane has served its purpose, it can either by hydrolysed back to a carbonyl group[80] or reduced to a methylene group (scheme 3.25).[85] This useful reactivity has seen 1,3-dithiane chemistry used in many total syntheses.[85]



Scheme 3.25

3.4.2 Formation of a Spiro Fused 5-Membered Ring

Initial attempts at making a suitable cyclisation precursor **319** involved attempting to alkylate the commercially available 1,3-dithiane **318** by lithiation followed by quenching with the unstable mesylate **277** as an electrophile, which was previously used in section 3.2 (scheme 3.26).

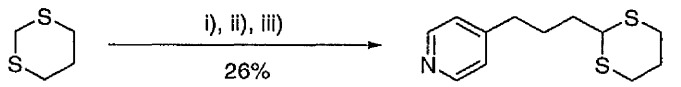


318 **319**

i) 1.1 equiv. *n*-BuLi, –30 °C, 1.5 h; ii) 1.2 equiv. **277**, –78 °C, 4h

Scheme 3.26

The reaction failed, most probably for the same reason that the reactions using mesylates as electophiles in section 3.3 failed – the mesylate is too hard an electrophile to react well with an organolithium – on the timescale of the reaction, the mesylate polymerises and leaves the dithiane unreacted. Once it was found in section 3.3 that the problem could be solved by using the corresponding iodide electrophile **278**, the same methodology was transferred to this reaction (scheme 3.27). The yield was poor, this was attributed to the electrophile's propensity to polymerise, which it seems to do very rapidly in THF.



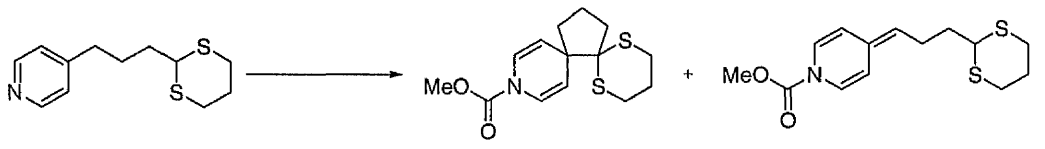
318 **319**

i) 1.2 equiv. *n*-BuLi, –25 °C, 2 h; ii) 1.2 equiv. **278**, –78 °C, 1 h; iii) –25 °C, 2 h

Scheme 3.27

For the cyclisation of this precursor, it soon became apparent that the choice of base could be a problem. A search through the literature revealed that the only examples of lithiation of 1,3-dithianes use butyllithium as the base. It is already known that all isomers of butyllithium act as an effective nucleophile in the presence of pyridines, so they have to be ruled out.[89] LDA was chosen as the base for these cyclisations due to its success for previous cyclisations in this project, even though there is no literature precedent for its deprotonation of 1,3-dithianes.

Initially, low temperatures and short reaction times were used with 1.1 equivalents of base (entries 1 and 2, table 3.2) to see what happened during the reaction under relatively mild conditions. These initial results were encouraging, with the ratio of products to starting materials increasing with increasing the time (entry 1-2, table 3.2). In the crude ^{1}H NMR spectrum of both of these attempts, two main dearomatised products could be seen, the expected product **320**, which could be isolated, and another product, which could not be isolated. It is now assumed that this product is **321** (scheme 3.28).

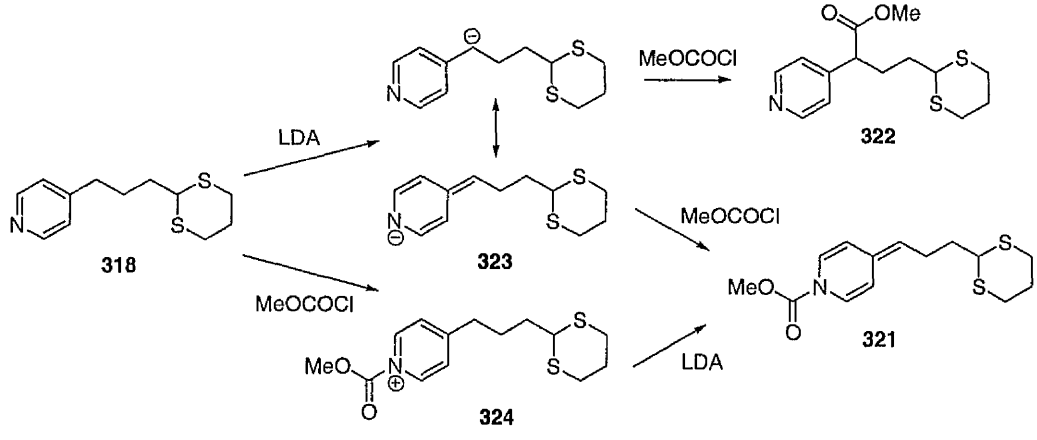


318 **320** **321**

Results and conditions: See table 3.2

Scheme 3.28

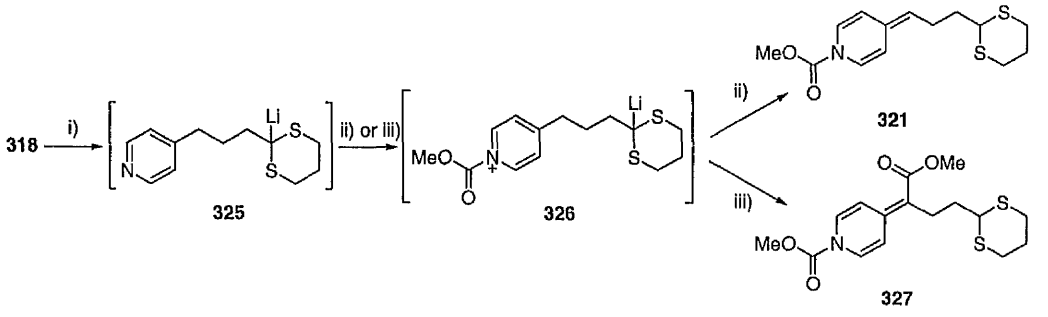
There are two ways in which **321** could be formed. Instead of removing the required proton on the dithiane ring, the base could remove the proton α to the pyridine ring to give **323** (scheme 3.29). Indeed, this proton is quite acidic and there is less steric hinderance here than around the required proton on the dithiane ring. This anion would be stabilised by charge delocalisation on the pyridine nitrogen. On addition of the electrophile, there are two positions where the electrophile can react – either α to the pyridine ring to give **322**, or on the pyridine nitrogen to give **321**. **321** is much more prevalent than **322**, but was never isolated as it seems to revert rapidly to starting material on attempts at isolation by column chromatography. Another way in which **321** can be formed is if any unlithiated starting material is in solution when the electrophile is added, this would rapidly attack the pyridine nitrogen to give **324**. This would acidify the proton α to the pyridine nitrogen, which would then rapidly be removed by any unreacted base. **322** proved to be inseparable from the starting material and was seen in most of the crude ^{1}H NMR spectra of the attempts, but never in any great quantities.



Scheme 3.29

For the next attempts, the number of equivalents of base was raised to three to see the effect (entries 3 and 4, table 3.2), both of these attempts only returned starting

material. The reason for this is not completely clear, but a likely explanation is that the cyclisation is slow, so when the electrophile is added to the reaction mixture, which is probably composed mostly of **325**, this is activated to give **326**. The excess base in solution then removes the proton α to the pyridine ring in a manner analogous to that in scheme 5.5 and the major product is **321** (scheme 3.30). The reason **321** is not seen in the crude ^{1}H NMR spectrum is because it rapidly reverts to starting material at some point, maybe slightly acidic conditions during workup caused by the hydrolysis of the methyl chloroformate speed up this process.



i) 3 equiv. LDA, THF, –78 or –40 °C, 30 min; ii) 1 equiv. MeOCOCl; iii) 3 equiv. MeOCOCl

Scheme 3.30

An attempt was made where the electrophile was added before the base (entry 5, table 3.2), this resulted in a crude ^{1}H NMR spectrum showing mainly **321**, presumably made *via* **324** (scheme 3.29). This result backs up the assumption made earlier that **321** can be formed *via* this route.

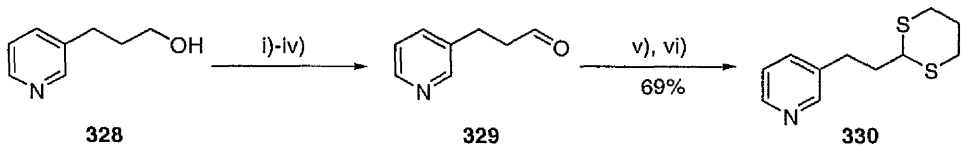
When an excess of base and electrophile was used (entry 6, table 3.2) the major product was the unstable **327** (scheme 3.30). This was more stable than **321** and did not revert to starting material on the column, but it still proved impossible to obtain a pure sample. The best result employed a short reaction time combined with a quite high temperature gave a 2:1 product to starting material ratio in the crude ^{1}H NMR spectrum and an isolated yield of 35% (entry 7, table 3.2).

Entry	Equivalents of base	Time (min)	Temperature (°C)	Equivalents of electrophile	Result
1	1.1	5	–78	1	1:1:2 of **320**:**321**:SM
2	1.1	30	–78	1	2:2:1 of **320**:**321**:SM 20% isolated yield of **320**
3	3	30	–78	1	SM
4	3	30	–40	1	SM
5	1.1	30	0	1	All SM converted to **321**. Not isolated
6	3	180	–40	3	Mainly **327** in crude ^{1}H NMR.
7	1.1	30	0	1	2:1 **320**:SM in crude ^{1}H NMR spectrum. 35% isolated yield

Table 3.2

3.4.3 Formation of a Fused 5-Membered Ring

We wanted to see if this methodology could be transferred to 3-substituted pyridines, but as the route to the previous cyclisation precursor **318** was troublesome and low yielding, a different route was tried. Instead of adding the 1,3-dithiane ring to the molecule by nucleophilic substitution, it was decided to synthesise the ring from an aldehyde. As such, the commercially available alcohol **328** was oxidised *via* a conventional Swern oxidation[86] to furnish the aldehyde **329**. This was not isolated due to instability. The aldehyde functionality was then transformed to a 1,3-dithiane ring by reaction with 1,3-propanedithiol in an acidic medium[74] to give the required cyclisation precursor **330** in 69% yield over 2 steps (scheme 3.31).



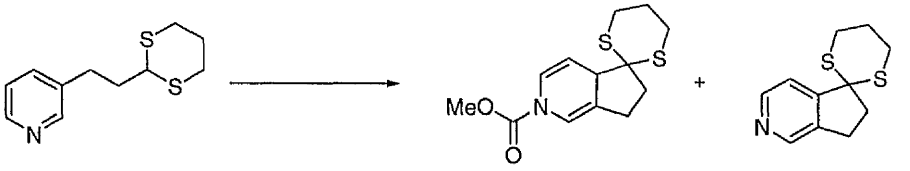
328 **329** **330**

i) $(COCl)_2$, DMSO, CH_2Cl_2, –60 °C,15 min; ii) **328**, 20 min; iii) Et_3N, 5 min; iv) 20 °C; v) AcCl, MeOH, 0 °C, 5 min, vi) 1,3-propanedithiol, 10 min

Scheme 3.31

The transformation of the aldehyde to the 1,3-dithiane functionality was also attempted using the method of Samajdar *et al.*,[87] whereby molecular iodine is used to catalyse the reaction. Unfortunately, this method just returned starting material.

Some representative results for the attempts at cyclisation of **330** are shown in table 3.3. Initial attempts at cyclisation of **330** (entries 1 and 2, table 3.3) were done using 1.1 equivalents of base as for the 4-substituted pyridine, and these attempts were quite successful, with the initial attempt giving a product ratio of 1:1 of **331**:SM (entry 1, table 3.3). Raising the temperature from –40 °C to 0 °C (entry 2, table 3.3) improved the product ratio to 3:1 **331**:SM, but by now the reaction had become quite messy with extra peaks in the aromatic region – some of which appear to be a rearomatised product, tentatively assigned as **332**. It was noticed that the change of substitution pattern from 4-substituted to 3-substituted meant that the side reactions that blighted the cyclisation of **318** could no longer take place – this opened up the door to using an excess of base, which would possibly speed up the reaction.



330 **331** **332**

Results and Conditions: See table 3.3

Scheme 3.32

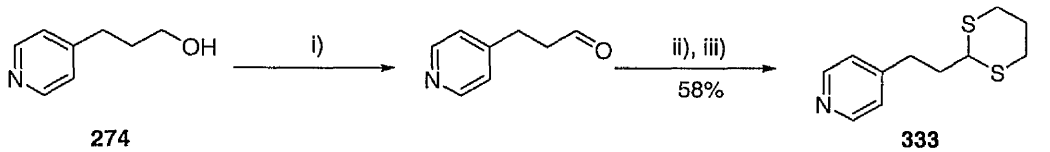
Therefore the number of equivalents of base was raised to 3 for the next reaction and the temperature was lowered to –78 °C (entry 3, table 3.3), a temperature at which the cyclisation of **318** had worked with some success, unfortunately this resulted in no product formation, which is quite surprising as it means that the dithane ring cannot be deprotonated at –78 °C in **330** but it can in **318**. Even though the reaction was kept cold for a time after addition of the electrophile, if any deprotonation had occurred, we would expect some cyclisation to occur when the reaction was allowed to warm up after this time. As such, the temperature was raised to 0 °C (entry 4, table 3.3), and the time of the deprotonation reduced to 10 minutes. This was a big improvement and the crude ^{1}H NMR showed that all of the starting material had been converted to **331**. However, the isolated yield was poor – only 47%. In a bid to improve this, the reaction was carried out again at lower temperature and for longer (entry 5, table 3.3). This again showed that all of the starting material had been turned to **331** in the crude ^{1}H NMR spectrum and this time the isolated yield was 61%. It seems likely that the relatively low isolated yields for the most successful attempts are due to problems during purification rather than problems during the reaction (entries 4-5, table 3.3). **331** is rather unstable and slowly rearomatises to **332** in air. This probably occurs rather more rapidly on silica, and this is likely to be the source of the loss of yield.

Entry	Equivalents of base	Temperature (°C)	Time	Temperature (°C)	Time (min)	Result
1	1.1	–40	30 m	–40	30	1:1 **331**:SM
2	1.1	0	30 m	0	30	3:1 **311**:SM
3	3	–78	30 m	–78	30	Trace of product
4	3	0	10 m	0	30	Only **331** in crude. 47%
5	3	–40	3 h	–78-20	-	Only **331** in crude. 61%

Table 3.3

3.4.4 Attempted Formation of a Fused 4-membered Ring

The 4-substituted starting material analogous to **330**, **333** was also made by the same method in moderate yield (scheme 3.33).

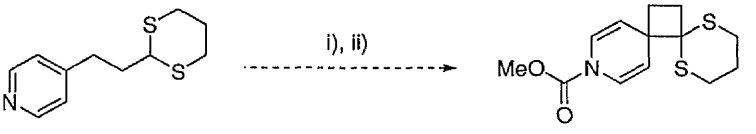


274 **333**

i) Swern Oxidation; ii) AcCl, MeOH, 0°C, 5 min.; iii) 1,3-propanedithiol, 10 min.

Scheme 3.33

Unfortunately, preliminary reactions on this substrate offered little hope, with none of the expected **334** being either isolated or seen in the crude ^{1}H NMR (scheme 3.34). The conditions for this reaction were easy to choose after lessons learned from the cyclisation of **318**. Obviously, it was necessary to use one equivalent of both the base and the electrophile, but using these conditions, the reaction returned mostly starting material even with long reaction times (both before and after quench) at high temperatures.



333 **334**

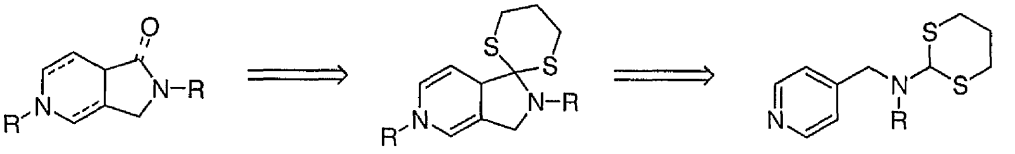
i) LDA, THF, various conditions; ii) MeOCOCl

Scheme 3.34

It seems for this type of reaction a 4-membered spirocyclic ring is too difficult to form – especially when we consider that the 5-membered ring was quite difficult and the reaction low yielding.

3.4.5 Attempt to Apply the Methodology to Natural Product Synthesis

The most successful of these dithiane stabilised cyclisations so far has been the cyclisation of **330** (scheme 3.32). We wanted to see if this cyclisation could be used in the synthesis of any small natural products. A literature search revealed that no natural products contain the cyclopentane fused dihydropyridine/piperidine ring system contained in **330**, but there were many containing the analogous ring system containing a nitrogen atom in the cyclopentane ring **355** (scheme 3.35).

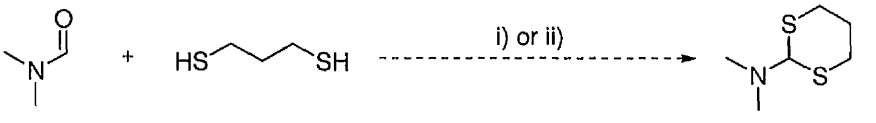


355 **356** **357**

Scheme 3.35

Synthesis of the ring system would require a cyclisation product of the type **356** from a cyclisation precursor of the type **357**.

As there were no examples in the literature of molecules of this type a model reaction was carried out on dimethylformamide **358** (scheme 3.36). Reaction with 1,3-dithiopropane **359** under the conditions which had previously been successful[74] or Dean Stark conditions failed to form the model compound **360**.



358 **359** **360**

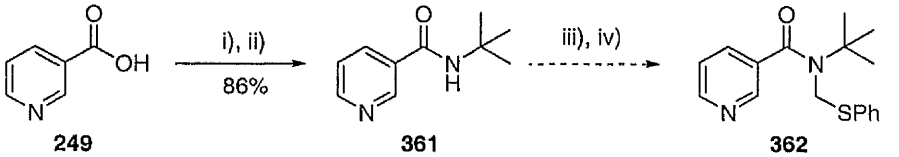
i) AcCl/MeOH; ii) Dean Stark

Scheme 3.36

We can see from **355** in scheme 3.35 that this type of target molecule is similar to the products formed by the cyclisations of nicotinamides as seen in section 2.3 except

there is no phenyl group. If a cyclisation could be carried out similar to those but with a group that could be removed completely, it would provide an easy entry to some of the products of the type **355**.

Another sulfur based stabilising group that should both stabilise an anion to the correct degree yet be removable is a phenyl sulfide group. An attempt was made to synthesise the cyclisation precursor **362** by first making the secondary amide **361** *via* the acid chloride of nicotinic acid **249**. Unfortunately, all attempts to alkylate **361** by deprotonation with sodium hydride followed by quench with chloromethylphenylsulfide failed (scheme 3.37). On addition of the electrophile, the solution instantly turns black and the crude ^{1}H NMR of the reaction mixture showed that the pyridine ring had been destroyed, probably *via* a mechanism involving activation of the pyridine with the electrophile.



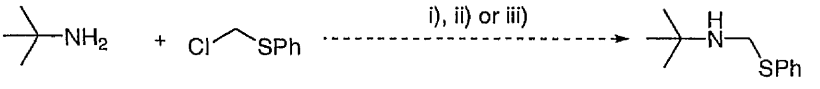
249 **361** **362**

i) $SOCl_2$, 20 °C, 16 h; ii) *t*-$BuNH_2$, Et_3N, CH_2Cl_2, 20 °C, 16 h; iii) NaH, DMF, 0 °C, 30 min.; iv) $PhSCH_2Cl$

i) $SOCl_2$, 20 °C, 16 h; ii) *t*-$BuNH_2$, Et_3N, CH_2Cl_2, 20 °C, 16 h; iii) NaH, DMF, 0 °C, 30 min.; iv) $PhSCH_2Cl$

Scheme 3.37

As the electrophile appears to be incompatible with this substrate, next an attempt was made to synthesise amine **363** (scheme 3.38) with the aim of coupling this to nicotinic acid **249**.



363

i) NaH/DMF, Δ; ii) Et_3N/THF, Δ; iii) *t*-$BuNH_2$, neat, Δ

Scheme 3.38

Unfortunately, this reaction failed under a variety of condition. Different bases, sodium hydride, triethylamine and an excess of *t*-butylamine itself were all tried

combined with high reaction temperatures, but the reaction only ever returned starting material.

3.4.6 Future Work

The cyclisation to form the 5-membered fused ring **330** worked particularly well, but it is unfortunate that this methodology has not yet been transferable to products that resemble natural products. Perhaps the reaction could be made to work with other heteroatoms other than nitrogen in the ring being formed. From work in section 3.3.3, it seems likely that the product analogous to **293** containing a fused six membered ring would be easy to make *via* this method.

3.5 Nitrile as a Stabilising Group for Amide Cyclisation

3.5.1 Introduction

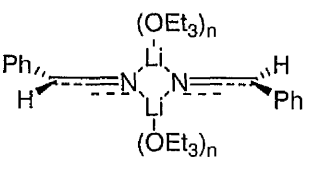
Most of the anionic dearomatising cyclisations carried out previously in the Clayden group have employed a benzyl group as the anion stabilising group (section 1.2). So far, this has proved to be perfectly satisfactory for the cyclisations themselves, as it stabilises the anion to the correct degree – stable enough so that deprotonation is facile with LDA, but unstable enough that it will attack the aromatic system and force a cyclisation to take place. Once the cyclisation has taken place however, synthetic transformations on the resulting phenyl group have proved to be very difficult indeed. A more versatile stabilising group on which further transformations could be carried out more easily could prove to be very useful.

Results from the previous chapters have shown that both activated and unactivated pyridines and quinolines are much more susceptible to anionic dearomatising cyclisation than the benzenoid systems used previously. As a result of this, they can be dearomatised by anions more stable than benzylic anions, such as enolates (section 3.3) and anions stabilised by 1,3-dithianes (section 3.4). This gives the possibility of expanding the scope of the reactions explored in chapter 2 by using a different anion stabilising group more conducive to further synthetic transformations than a benzyl stabilising group.

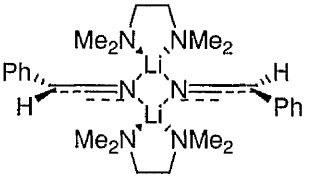
The cyano group was chosen as a potential candidate for further research as it is easily deprotonated to provide an anion that is less stable than an enolate and is therefore

more likely to cyclise. At the end of the cyclisation, the nitrile group is an excellent synthetic precursor to the carbonyl and amino groups.[88]

Deprotonated nitriles have proved to be valuable tools in organic synthesis,[89] but there is little information about the stuructures of these anions in solution. Carlier *et al.* showed using NMR experiments with [^{6}Li, ^{15}N] lithiophenylacetonitrile that in a 0.1 M 2:1 toluene:diethyl ether solution the lithiophenylacetonitrile exists as a cyclic oligomer, characteristic of related *N*-lithiated species, whilst ether and TMEDA solvated lithiophenylacetonitrile have the similar cyclic dimmer structures **364** and **365** respectively. The evidence suggests that lithiophenylacetonitrile is monomeric in THF (figure 3.1).[90]



364



365

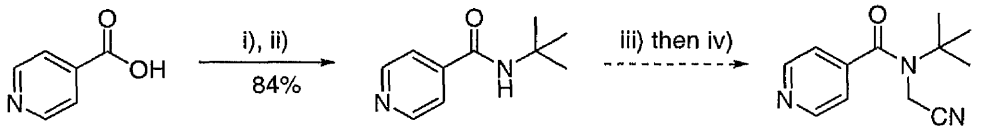
Figure 3.1

3.5.2 Cyclisation of Isonicotinamides

First, we wanted to see whether spirocyclisations analogous to those in section 2.2 could be carried out with a cyano anion stabilising group.

The first attempt at preparing a suitable starting material **367** was by alkylation of the secondary amide **366**, formed from an amide coupling from isonicotinic acid **199** (scheme 3.39). The amide coupling, as expected, gave the required product in high

yield, but the alkylation just resulted in a complicated mixture of products. From the crude ^1H spectrum, it appeared as though the pyridine ring had lost its aromaticity.

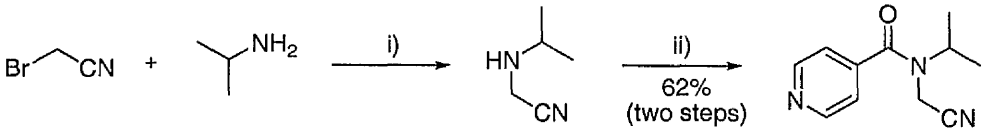


199 **366** **367**

i) $SOCl_2$, 20 °C, 16 h; ii) *t*-$BuNH_2$, Et_3N, CH_2Cl_2, 20 °C, 16 h; iii) NaH, DMF, 30 min, 0 °C; iv) $BrCH_2CN$, 0 °C, 3 h.

Scheme 3.39

The next attempt to form **369** involved first forming the required secondary amine **368** by reaction of bromoacetonitrile with excess isopropylamine (scheme 3.40). The amine was not isolated due to its volatility. This amine was then coupled with the necessary acid chloride.

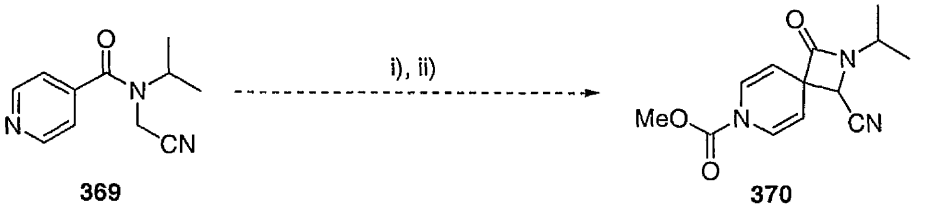


368 **369**

i) MeCN, 20 °C, 16 h; ii) **200**, CH_2Cl_2, Et_3N, 20 °C, 16 h

Scheme 3.40

Attempts to cyclise this starting material to yield the expected **370** proved futile and no dearomatised products at all were formed (scheme 3.41). The results are presented in table 3.4.



369 **370**

i) LDA, THF; ii) MeOCOCl

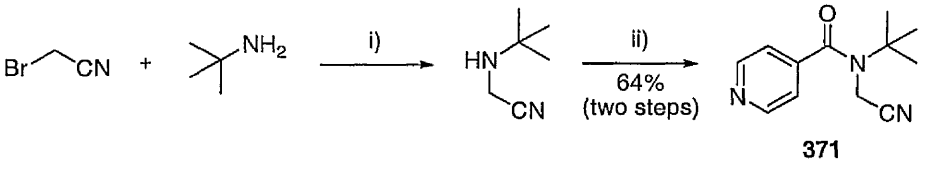
Scheme 3.41

Entry	Equivalents of LDA	Temp (°C)	Time of deprotonation	EX	Time of cyclisation	Result
1	3	–40	30 min	1.1 equiv. MeOCOCl	10 min	Very Messy
2	1	–78	30 min	1.1 equiv. MeOCOCl	10 min	Mostly SM
3	5	–78	30 min	1.1 equiv. MeOCOCl	10 min	Mostly SM
4	5	–78	30 min	1.1 equiv. MeOCOCl	16 h	Mostly SM
5	5	–78	30 min	5 equiv. MeOCOCl	16 h	Mostly SM

Table 3.4

Initially, the reaction was carried out in accordance with the conditions used with a benzylic stabilising group (entry 1, table 3.4). This gave a complicated mixture of products, so less harsh conditions were used, with both a lower temperature of deprotonation and only 1 equivalent of base (entry 2, table 3.4). This was changed because the cyano group should be much more easily deprotonated than the benzyl group, unfortunately, the result was that starting material was returned. As such, 5 equivalents of base were used (entry 3, table 3.4), as with a benzylic stabilising group, it was shown that the reaction only worked well with at least 3 equivalents of base. Again, only starting material was returned. It was then thought that the cyclisation after the pyridine ring is activated could potentially be very slow as the cyano stabilised anion should be more stable than the benzylically stabilised anion, therefore after the addition of the electrophile, the reaction was left overnight at 20 °C (entry 4, table 3.4). This was later repeated (entry 5, table 3.4) except that 5 equivalents of electrophile was used to rule out the possibility that the first equivalent was being used for something other than activating the pyridine ring. Again, both of these entries only returned starting material.

The reaction was initially carried out with an isopropyl group instead of a *t*-butyl group as it was thought that it would make the preparation of the starting material easier and have little effect on the cyclisation. We needed to prove that this was the case so starting material **371** was prepared with a *t*-butyl group replacing the isopropyl group. The same reaction protocol was used (scheme 3.42).

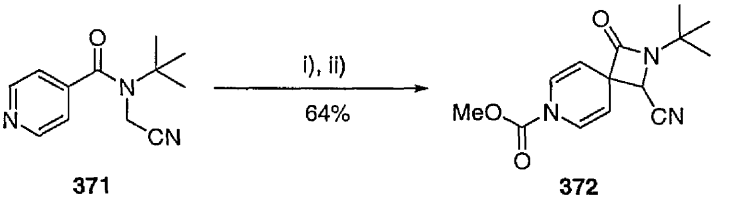


371

i) MeCN, 20 °C, 16 h; ii) **200**, CH_2Cl_2, Et_3N, 20 °C, 16 h

Scheme 3.42

Attempts to cyclise this starting material to yield the expected **372** proved much more successful (scheme 3.43), eventually giving the expected product in good yield. The results are presented in table 3.5.



371 **372**

i) 1 equiv. LDA, THF, –78 °C, 1 min; ii) MeOCOCl, 20 °C, 4 h

Scheme 3.43

Entry	Equiv. of LDA	Temp (°C)	Time of deprotonation (min)	EX	Time of Cyclisation (min)	Result
1	5	–78	30	1.1eq MeOCOCl	–78 °C - 30 20 °C - 30	Very Messy
2	1	–78	1	1.1eq MeOCOCl	–78 °C - 10 20 °C - 30	~1:1 Product :SM
3	1	–78	10	1.1eq MeOCOCl	20 °C - 30	~1:1 Product :SM
4	1	–78	1	1.1eq MeOCOCl	20 °C - 240	64% Product

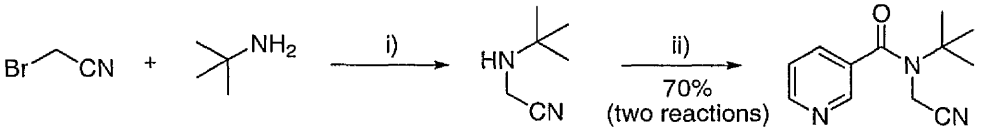
Table 3.5

The cyclisation was initially tried with a large excess of base at low temperature (entry 1, table 3.5), but this gave a complicated mixture of products. No dearomatised products could be seen in the crude ^{1}H NMR spectrum, but all of the starting material had disappeared, which was shown by the absence of the methylene peak. It was clear that less harsh conditions were required, and as it was suspected that the deprotonation should be facile, for the next attempt only 1 equivalent of base was used and the time allowed for deprotonation was reduced to 1 minute (entry 2, table 3.5). In the crude ^{1}H NMR spectrum, this gave a mixture of 1:1 product to starting material. It was suspected that 1 minute was not long enough for the deprotonation to take place, therefore the time for deprotonation was increased to 10 minutes (entry 3, table 3.5). This gave no change in the product ratio, but it was noted that the crude yield had dropped between the second and third attempt.

As the change in deprotonation time made no difference to the product ratio, it was fixed at 1 minute for further reactions and our attention turned to the time left to the reaction after the electrophile had been added. As was previously mentioned, the cyclisation will potentially be slower as the cyano-stabilised anion is more stable than the benzylically stabilised one. Therefore for the next attempt (entry 4, table 3.5,) after activation, the reaction was left at 20 °C for 4 h. This allowed the isolation of **372** in 64% yield.

3.5.3 Cyclisation of Nicotinamides

With the success of the reaction on the above 4-substituted pyridine, attempts were made to apply the methodology to the corresponding 3-substituted pyridine. The starting material **373** for this was made in a reaction analogous to that used to for the 4-substituted pyridine (scheme 3.44).



373

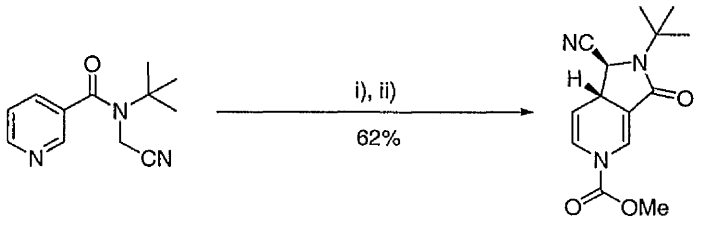
i) MeCN, 20 °C, 16 h; ii) nicotinoyl chloride, CH_2Cl_2, Et_3N, 20 °C, 16 h

Scheme 3.44

The initial conditions for the cyclisation were arrived at by comparison with the conditions used with a benzylic stabilising group. To recap, activation of the pyridine ring was not necessary for cyclisation to take place, and after lithiation, cyclisation was complete (prior to addition of the electrophile) and all of the starting material had disappeared within 10 minutes. We knew from the previous experiments that cyclisation employing the cyano stabilising group happened much more slowly, so it was decided to add the electrophile soon after lithiation to force the cyclisation to occur by activating the ring.

For the first attempt, starting material was lithiated, then quenched after 1 minute (entry 1, table 3.6). The crude ^1H NMR spectrum showed roughly a 1:1 mixture of product and starting material. It was also quite messy. For the next attempt (entry 2, table 3.6), the electrophile was added prior to lithiation. This had been tried previously with starting materials with benzylic stabilising groups, but had failed, as attack at the carbonyl on the activating group was faster than the removal of a

benzylic proton. However, as the proton α to the cyano group is so much more acidic in this case, it was attempted again. The result was that starting material was returned, probably for the same reason. The next attempt (entry 3, table 3.6) was to lithiate, then leave the cyclisation to take place in absence of any activation of the pyridine ring. This resulted in the crude ^{1}H NMR spectrum showing almost exclusively the expected product **374** quite cleanly: after purification it was isolated in 62% yield (scheme 3.45).



373 **374**

i) 1.1 equiv. LDA, THF, –78 °C, 4 h; ii) MeOCOCl

Scheme 3.45

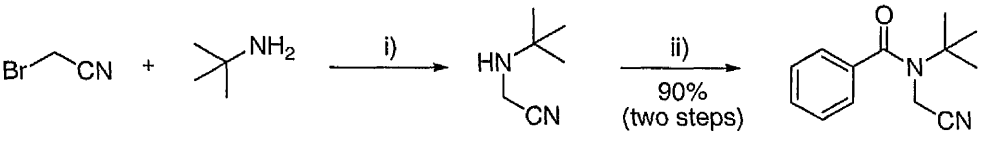
Entry	Time between steps i) and ii) (min)	Notes and Result
1	1	~1:1 mixture of SM and expected product. Very Messy.
2	1	Inverse Addition. Returned SM
3	240	Crude ^{1}H spectrum predominantly **374**. 62% yield after purification

Table 3.6

3.5.4 Cyclisation of Benzamides

As this methodology had worked with some success with pyridine acceptor rings, it was decided to apply it to reactions where there is a benzenoid acceptor ring. If the methodology could be carried across, it could prove to be very useful. The early anionic dearomatising cyclisations carried out within the Clayden group where a benzenoid acceptor ring and a benzylic stabilising group have been employed have been used as the basis for a few natural product syntheses. As discussed previously, one of the most problematic parts of the syntheses was the transformation of the phenyl group into CO_2H. Therefore if these cyclisations could be carried out with a cyano stabilising group, the resulting cyano group left after cyclisation should be synthetically more versatile. This would avoid some of the more difficult parts of the syntheses.

The cyclisation precursor **375** was made in the same way as described previously in excellent yield (scheme 3.46).



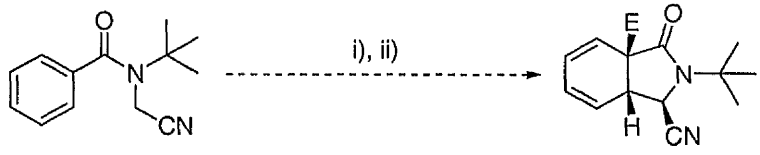
375

i) MeCN, 20 °C, 16 h; ii) PhCOCl, CH_2Cl_2, Et_3N, 20 °C, 16 h

Scheme 3.46

Unfortunately, although this reaction was tried under a large variety of conditions, it has so far proved impossible to isolate any of the cyclised product **376** (scheme 3.47). As well as being tried over a broad range of reaction times, temperatures and number of equivalents of base, the reaction was also tried with DMPU and also with both a protic quench and MeI. It appears that the cyano stabilising group stabilises the anion

to such an extent that it is unable to disrupt the aromaticity of the ring. It also appears that when more than one equivalent of base is used, the CH_2CN part of the molecule becomes unstable and is changed in some way so that the methylene peak disappears from the ^1H NMR spectrum. Later results point to this being due to attack of the base on the CN group. One possible symptom of this is that when more than one equivalent of base was used, on addition of the base, the solution rapidly underwent a colour change from colourless to orange, then red, then back to colourless – possibly indicating that none of the required anion remained in solution.

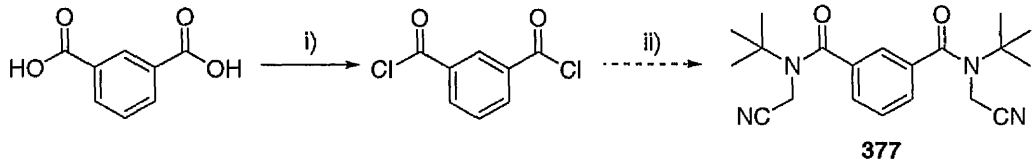


375 **376**

i) LDA, THF, various conditions; ii) EX

Scheme 3.47

As it appeared that the cyano stabilised anion is not nucleophilic enough to attack an unsubstituted benzene ring, the next attempt involved trying to cyclise onto a more activated ring. As such, attempts were made to synthesise a similar starting material **377**, this time bearing an extra amide group *meta* to the first one. This should activate the ring towards nucleophilic attack due to the electron withdrawing effect of the amide. Unfortunately, it proved impossible to make using normal methods (scheme 3.48).



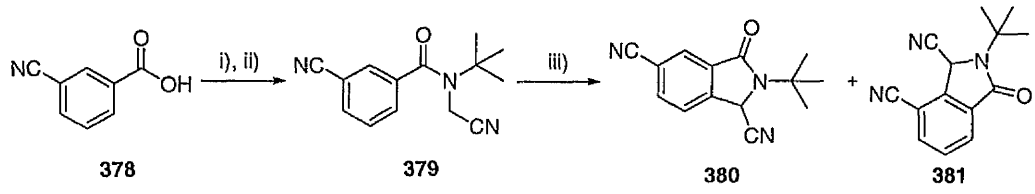
377

i) $SOCl_2$, Δ, 16 h; ii) *t*-$BuNCH_2CN$, Et_3N, CH_2Cl, 20 °C, 16 h

Scheme 3.48

Instead, a starting material bearing a cyano group *meta* to the amide **379** was synthesised from the commercially available acid **378**. The cyano group activates the ring towards nucleophilic addition in the *para* and *ortho* positions.

Attempts to cyclise **379** were initially encouraging, as cyclised products were isolated. Unfortunately though, they were isolated as an inseparable mixture of the rearomatised regioisomers **380** and **381** (scheme 3.49).



378 **379** **380** **381**

50% inseparable 1:1 mixture

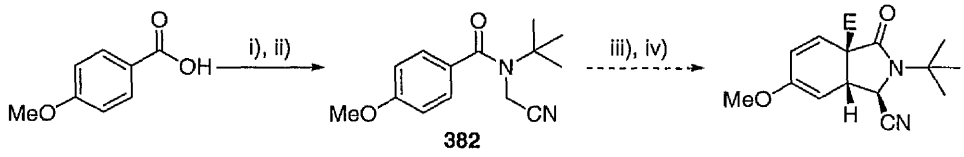
i) $SOCl_2$, 20 °C, 16 h; ii) *t*-$BuNHCH_2CN$, Et_3N, CH_2Cl_2; iii) 1.1 equiv. LDA, THF, –40 °C, 4 h; ii) NH_4Cl

Scheme 3.49

Other conditions were tried in order to try to suppress rearomatisation such as lower temperatures and shorter reaction times, but no attempts were successful. Rearomatisation was also a problem when cyano substituted rings were employed in this reaction when a benzylic stabilising group was used.[2] This coupled to the fact that the regioselectivity is so poor curtailed research in this area, it is interesting though as this is the first cyclisation that has taken place onto a benzamide with a cyano stabilised anion.

An electron-donating substituent on the ring was also tried. Although it seems counterintuitive, as an electron-donating group would deactivate the ring towards nucelphilic attack, this was tried as it was found that yields were often higher in the early dearomatising cyclisations with a benzylic stabilising group when there was a methoxy substituent on the ring.[2] Therefore **382** was synthesised in excellent yield *via*

the usual method, but unfortunately after subjecting the starting material to a variety of cyclisation conditions, no cyclisation products were seen or isolated (scheme 3.50).



i) $SOCl_2$, 20 °C, 16 h; ii) *t*-BuNHCH$_2$CN, Et_3N, CH_2Cl; iii) 1.1 equiv. LDA, THF, various conditions; iv) EX

Scheme 3.50

3.5.5 Cyclisation of Naphthamides

The final modification to the 'acceptor ring' to be tried was to replace the benzene ring with a naphthalene ring. The reason for this change is that a naphthalene ring is supposedly more easily dearomatised than a benzene ring as it loses less of its aromaticity during the cyclisation – indeed a benzene ring loses all of its aromaticity.

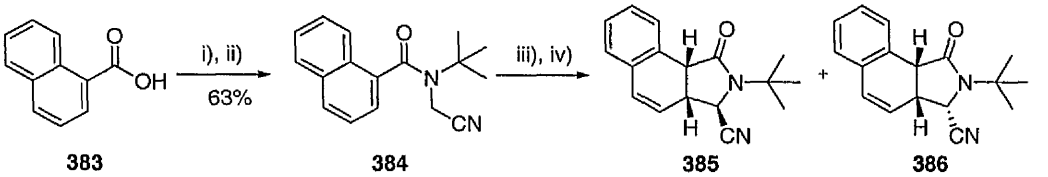
The starting material **384** was made from the commercially available acid **383** *via* the usual method in excellent yield (scheme 3.51). The initial attempts at this cyclisation used 1.1 equivalents of LDA after previous results have shown that when a large excess of base is used the cyano group is nucleophilically attacked by the base. A high reaction temperature, 0 °C, was used for the first attempt (entry 1, table 3.7) as the cyclisation, (if it was going to occur at all) was expected to be slow. The result was that a trace amount of dearomatised product could be seen in the crude ^{1}H NMR. This was very encouraging, but the aromatic region in the crude spectrum was messy. For this reason, for the second attempt (entry 2, table 3.7) there seemed little point in raising the reaction temperature or time, as this would most likely make the reaction even more messy. Therefore DMPU was added for the second attempt (entry 2, table

3.7). This seemingly had no effect on the outcome of the reaction. For the final attempt, the reaction temperature was lowered to –40 °C and the reaction was left overnight in the hope the cyclisation would still go ahead, but with less mess. The result was that no reaction took place at all (entry 3, table 3.7). It had now become clear that no amount of changing the reaction condition was going to help this reaction.

Entry	Temperature (°C)	Reaction time (h)	DMPU	Notes and appearance of crude ^{1}H NMR spectrum
1	0	1	-	Messy aromatic region, trace of dearomatised product, mostly SM.
2	0	1	6 equiv.	As above
3	–40	16	6 equiv.	Returned SM

Table 3.7

As it appeared that the cyano stabilised lithium anion was too stable and not nuclephilic enough to disrupt the aromaticity of this ring, another approach was needed. It was decided that instead of modifying the ring to make it more activated towards nucleophilic addition, the anion should be destabilised. This was done by preparing the potassium ion by using KHMDS as the base instead of LDA.



383 **384** **385** **386**

i) $SOCl_2$, 20 °C, 16 h; ii) *t*-$BuNHCH_2CN$, Et_3N, CH_2Cl_2; iii) LDA/KHMDS, THF; iv) NH_4Cl

Scheme 3.51

The first attempt using this approach used 1 equivalent of KHMDS at 0 °C for 1 hour (entry 1, table 3.8), this clearly gave 2 dearomatised products in the crude ^{1}H NMR spectrum, but these were accompanied by rearomatised products and starting material. As there was still some starting material left over, the reaction was repeated, but this time was left longer and quenched after 2.5 h (entry 2, table 3.8). Suprisingly, not

much more of the starting material appeared to have been used up, but there was a higher proportion of rearomatised products to dearomatised products than there was in the first attempt (entry 1, table 3.8). This indicates that the intermediate enolate is unstable in these conditions and leaving the cyclisation for longer does not appear to be helping.

The next attempts were conducted at a lower temperature (entries 3 and 4, table 3.8), but no cyclisation took place at this temperature. Back at 0 °C, the amount of base used was increased to 2 equivalents (entry 5, table 3.8). This lead to a dramatic improvement, all of the starting material had been used up and the major products were two diastereoisomers **385** and **386** of the expected product. The reaction was quite messy though, and there appeared to be quite a lot of different rearomatised products. In case the improvement was linked to the fact that 2 equivalents of base were used, the reaction was repeated with 2 equivalents of base at –40 °C and left overnight (entry 6, table 3.8) – no dearomatised products were seen.

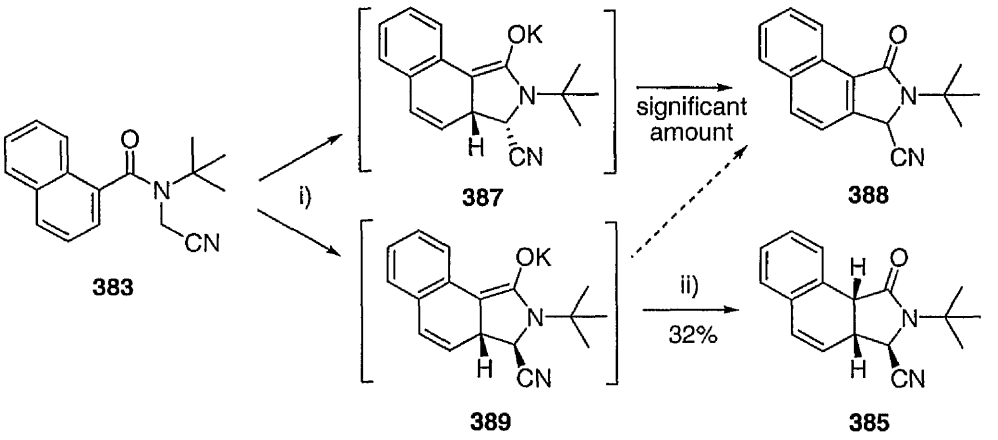
As all of the starting material had been used up in one of the attempts (entry 5, table 3.8), the time of the reaction was shortened, with the hope that less rearomatised products and a less messy reaction in general would be seen. This turned out to be the case – there was an improvement, but the reaction was still messy. As all of the starting material had been used up, the reaction time should be shortened further, unfortunately, at this point time ran out and no further refinements of the conditions were made.

The reaction was also tried using NaHMDS as the base. Theoretically, this should provide an anion intermediate in stability between a lithium anion and a potassium anion, but in practice the reaction yielded a complicated mixture of products.

Entry	Temperature (°C)	Reaction time (h)	Equiv. of base	Notes and appearance of crude ^{1}H NMR spectrum
1	0	1	1	~1:1 dearomatised products:SM.Also rearomatised products.
2	0	2.5	1	Slightly less starting material, much higher proportion of dearomatised products.
3	-40	16	1	Mostly SM, some evidence of attack at CN. No dearomatised products.
4	-40	16	3	~2:1 attack at CN product:SM. No dearomatised products.
5	0	2.5	2	36% **385** and 23% **386**. No SM, but plenty of rearomatised products.
6	-40	16	2	~1:1 attack at CN product:SM. No dearomatised products.
7	0	1	2	Appears to be some improvement on entry 5 in crude. All SM used up.
8	0	1	2 (NaHMDS)	No dearomatised products or SM. Complicated mixture.

Table 3.8

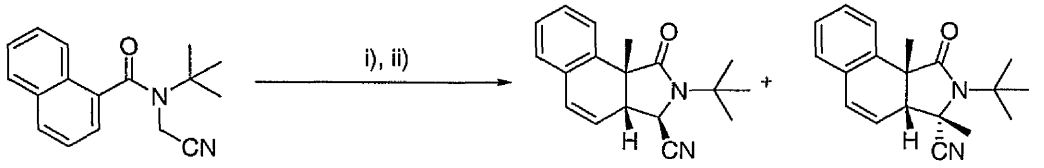
Time ran out at this point, but this work was continued by Lujan.[91] Lujan found that when the reaction was carried out at room temperature, the result was a mixture of **385** and the rearomatised product **388** (scheme 3.52). No **386** was seen. This suggests that the enolate **387** is unstable under these conditions, but enolate **389** is stable. This is almost certainly the origin of the rearomatised product seen at lower temperatures. It is of course possible for **389** to rearomatise to **388** and this may contribute to its formation. However, from this experiment it is not possible to know the extent to which this is occurring – if at all.



i) 1.5 equiv. KHMDS, THF, 20 °C, 30 min; ii) aq. NH_4Cl

Scheme 3.52

Lujan also tried the reaction with different electrophiles and had some success using methyl iodide as the electrophile. As well as the expected product **390**, the doubly quenched product **391** was also seen. It appears that the diastereoisomer analogous to **386** is more susceptible to further deprotonation than **389**. It is also worth noting that this reaction was quenched after 5 minutes and no starting material was seen in the reaction mixture. This shows that the reaction is fast and some improvement could probably be made to the earlier protic quench reaction that employed longer reaction times (scheme 3.53).



i) 1.5 equiv. KHMDS, THF, 20 °C, 5 min; ii) MeI

Scheme 3.53

3.5.6 Future Work

The cyclisations onto isonicotinamides and nicotinamides are promising and potentially powerful reactions. It would be interesting to see if picolinamides would cyclise with this stabilising group. The next logical step would be to see if esters could be used as a stabilising group for this reaction.

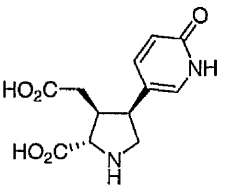
The cyclisations onto the benzamides and naphthamide were less successful. In the case of the naphthamide, the fact that the reaction yields a mixture of diastereoisomers limits its utility. The reason for the poor diastereoselectivity is most likely to be because the cyano group is not sterically demanding enough. Therefore even a *t*-butyl group cannot force the CN group into the *trans* conformation around the N–CH_2 bond necessary for good stereoselectivity (section 1.2.3).

Chapter Four

Attempted Synthesis of Pyridone Regioisomer of Acromelic Acid C

4.1 Introduction

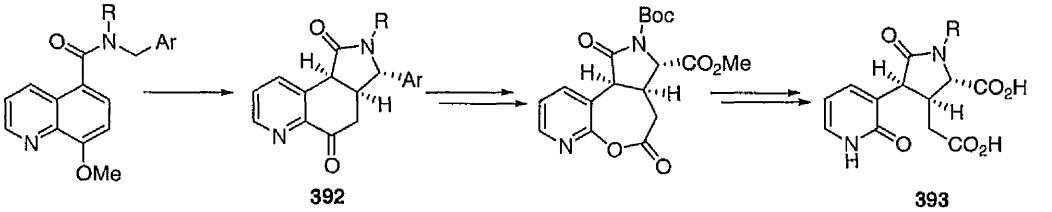
The acromelic acids are very potent neuroexcitory amino acids that are members of the kainoid family of natural products. They were isolated from the poisonous Japanese mushroom *Clitocybe acromelalga* in 1983, and since then, both their natural and unnatural analogues have been in high demand by pharmacologists and physiologists due to their interesting neurophysiological functions.[92]



Acromelic acid C

Figure 4.1

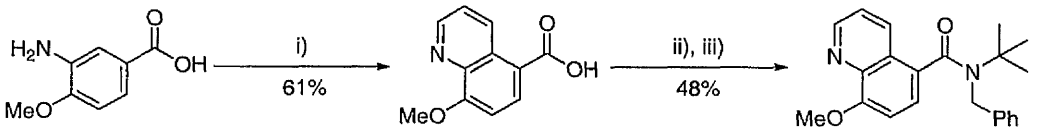
This regioisomer of a natural product features the same stereochemistry around its 5-membered ring as that given by the novel dearomatising cyclisation researched within the group. As such, it should be possible to convert the product of the cyclisation **392** into the target molecule **393** in relatively few steps (scheme 4.1), also see section 1.2.11.



Scheme 4.1

4.2 Cyclisation to Yield a 6,6,6-Fused Ring System

The precursor for the cyclisation was synthesised in two steps from the commercially available acid **394** *via* a Skraup reaction[93] which provided the acid **395**, followed by an amide coupling which furnished amide **396** in 48% yield (scheme 4.2).



394 **395** **396**

i) glycerol, I_2, H_2SO_4, 180 °C, 2 h; ii) $SOCl_2$, CH_2Cl_2, 20 °C, 16 h; iii) *t*-BuNHCH$_2$Ph, Et_3N, CH_2Cl_2

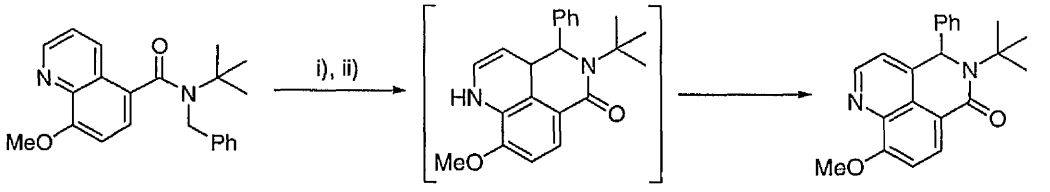
Scheme 4.2

Although the cyclisation needed for the synthesis is actually a cyclisation onto a heterocyclic quinoline system, it has most in common with cyclisations onto simple benzenoid and naphthalene systems (section 1.2), as the 'acceptor ring' in this case does not contain a heteroatom. Therefore initial attempts at this cyclisation were carried out under conditions suitable for cyclisations onto simple benzenoid and naphthalene rings (entries 1 and 2, table 4.1).

In both cases it was thought that the product was the expected product analogous to **392**, but rearomatised. This was difficult to explain at the time because similar substrates from the benzenoid and naphthalene series produced the desired dearomatised products in good yield. An attempt was made to suppress this rearomatisation by carrying out the cyclisation at a lower temperature with a longer reaction time (entry 3, table 4.1), but this reaction only returned starting material.

The real reason for the rearomatisation only became clear when it was noticed from other examples (e.g. the isonicotinamides and the nicotinamides) that the cyclisation

reaction preferentially occurs at the 4-position in nitrogen containing heterocyclic systems. The previous results from these reactions were misassignments and it was eventually proven by ^{1}H NMR in benzene (to spread out the aromatic region) that the cyclisation had occurred at the 4 position of the quinoline system, presumably initially giving the dearomatised compound **397** which rearomatises to the observed compound **398** (scheme 4.3).



396 **397** **398**

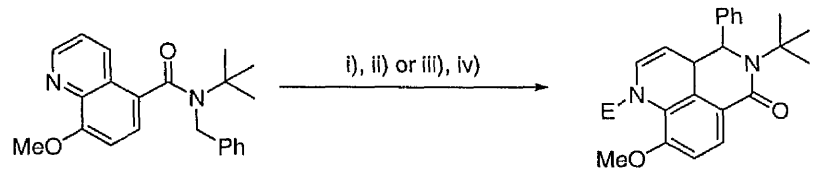
i) 2 equiv. LDA, 20 °C, 16 h; ii) NH_4Cl

Scheme 4.3

The highest yield of **398** obtained was 48% (entry 5, table 4.1), but it is likely that this figure could be increased significantly using conditions that have been used subsequently for other cyclisations i.e. more equivalents of LDA, lower temperatures and shorter reaction times.

Results in previous sections have shown that the dearomatised proton quenched products such as **397** have proven to be difficult to isolate. As such, attempts were next made to see if dearomatised compounds analogous to **398** could be isolated by quenching with MeI. The first attempt at 0 °C for 4 hours (entry 6, table 4.1) yielded only the rearomatised compound **398**, so the enolate is obviously fairly unstable under these conditions. Therefore the reaction time was reduced significantly to 10 minutes and the equivalents of LDA were increased to 5 to speed up the reaction (entry 7, table 4.1). In the crude ^{1}H NMR of this reaction the only major product was the dearomatised compound **399**. Unfortunately, attempts to isolate **399** using flash

column chromatography failed, and it appears from this observation and from previous experience that the *N*-methylated compound may be unstable. Accordingly, the reaction was carried out using methyl chloroformate as the electrophile and the conditions were changed slightly. Using these conditions **400** appeared to be the only product in the crude ^{1}H NMR – although markedly more messy than the previous reaction. **400** was more stable than **399** but proved to be too unstable to isolate in a pure form (scheme 4.4).



396

399 E = Me - not isolated
400 E = CO_2Me - not isolated

i) 5 equiv. LDA, 0 °C, 10 min; ii) MeI; iii) 5 equiv. LDA, –78 °C, 10 min; iv) MeOCOCl, –78 °C to 20 °C

Scheme 4.4

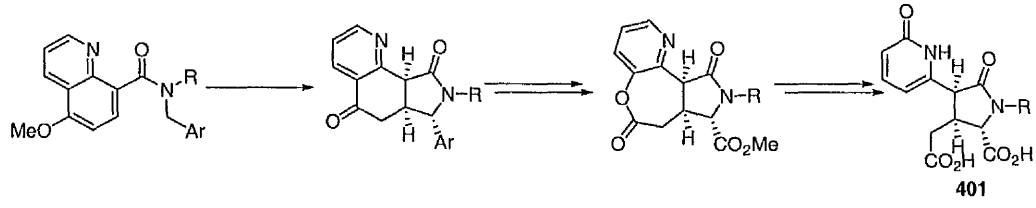
Entry	Temperature (°C)	Time	Equivalents of LDA	Quench	Notes and appearance of ^{1}H NMR spectrum
1	0-20	1 h	2	NH_4Cl	1:1 mixture of SM and **398**
2	0	4 h	2	NH_4Cl	1:1 mixture of SM and **398**
3	–40	16 h	2	NH_4Cl	Only SM
4	20	16 h	2	NH_4Cl	Almost all **398**
5	20	16 h	2	NH_4Cl	Almost all **398** – 48% yield of **398** isolated from column
6	0	4 h	2	MeI	Only rearomatised products isolated
7	0	10 min	5	MeI	Major product is **399**. Not isolated
8	–78	10 min	5	MeOCOCl (the allowed to warm to 20 °C	Major product is **400**. Not isolated

Table 4.1

Although the above reactions that create the 6,6,6-fused ring system are interesting and create a novel ring system, it was realised that there was no obvious way in which the regiochemistry of the reaction could be changed to give the expected 6,6,5-ring system. Thus it was not possible to synthesise the target molecule using this route.

4.3 Cyclisation to Yield a 6,6,5-Fused Ring System

Accordingly, the target molecule was changed to a different regioisomer, **401** – in which at the cyclisation step of the synthesis, the position at which cyclisation occurs in the above reactions is blocked by the quinoline nitrogen (scheme 4.5).



401

Scheme 4.5

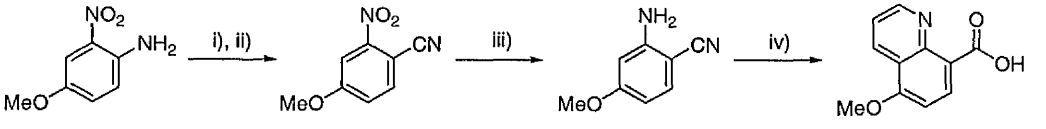
The synthesis of the required cyclisation precursor was initially attempted following the route of Bradford, Elliott and Rowe,[94] who had previously synthesised the required acid from the commercially available amine **402**, which was diazotised followed by displacement with cyanide to give **403**. Reduction of the nitro group furnished **404**, which was converted *via* a Skraup reaction to give the required acid **405** (scheme 4.6).

As the actual procedures used in this route were very old, more modern replacements were used. The variation of the Sandmeyer reaction used for the diazotization was the procedure of Clive *et al.*,[95] the reduction of the nitro group with $SnCl_2$ used the

procedure of Bellamy *et al.*[96] and Larock *et al.*,[97] and for the Skraup reaction the procedure employed previously in this section was used.[93]

Unfortunately, the Sandmeyer reaction proved to be troublesome – it was both very time consuming and low yielding when carried out on a large enough scale. The problem appeared to be in the neutralisation stage of the reaction which liberated a lot of gas and possibly enough heat to destroy the diazonium salt when carried out on a large scale. The best yield obtained using this procedure was 44%.

The reduction of the nitro group with $SnCl_2$ also proved to be troublesome as removal of the $SnCl_2$ from the product was not possible as the whole mixture tended to emulsify during workup using both procedures. Due to these problems this route was discontinued.



402 **403** **404** **405**

i) $NaNO_2$, H_2SO_4, 0 °C; ii) CuCN, NaCN, H_2O; iii) $SnCl_2$, AcOH, DME, 60 °C; iv) glycerol, I_2, H_2SO_4, 180 °C

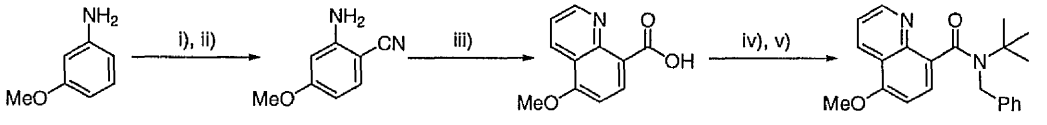
Scheme 4.6

Sugasawa and Adachi had published a one step synthesis of 2-cyano and 2-alkylthiocarbonyl anilines and phenols,[98] and this could be used to synthesise **404** in one step from *m*-anisidine **406**. **404** was conveniently synthesised in only a 37% yield, but the reaction could be carried out more easily on a large enough scale (scheme 4.7).

Amine **404** was converted to the quinoline **405** *via* the Skraup reaction as seen previously, early attempts were plagued with extremely poor yields as **405** appears to be more water soluble than **395** and failed to crystallise out of the solution easily.

Extraction with dichloromethane solved this problem and **405** could be isolated in 55% yield (scheme 4.7).

The amide coupling was initially problematic. Previously, the acid chlorides had been made dissolving the acid in neat thionyl chloride and stirring at room temperature or heating under reflux. Addition of neat thionyl chloride to **405** caused apparent decomposition as the solution instantly turned black, but it was found that by adding 1.1 equivalents of thionyl chloride to a solution of the acid in dichloromethane, the acid chloride could be made and the following amide coupling furnished the required cyclisation precursor **407** in 51% yield (scheme 4.7).



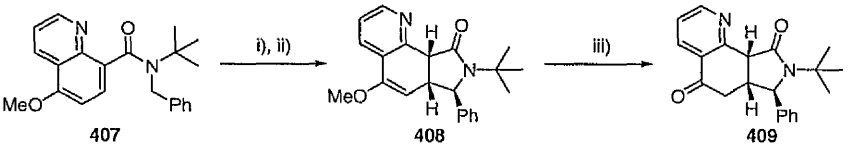
406 **404** **405** **407**

i) CCl_3CN, BCl_3, $AlCl_3$, 20 °C; ii) K_2CO_3, MeOH, reflux; iii) glycerol, I_2, H_2SO_4, 180 °C; iv) 1.1 equiv. $SOCl_2$, 20 °C; v) *t*-$BuNCH_2Ph$, Et_3N, CH_2Cl_2, 20 °C.

Scheme 4.7

Initial attempts to cyclise **407** at –40 °C using 3 equivalents of LDA showed that no reaction takes place at this temperature and only starting materials are returned (entry 1, table 4.2). Raising the temperature to 0 °C and allowing the cyclisation to take place for 1.5 h resulted in products that appeared to be dearomatised cyclisation products in the the crude ^{1}H NMR spectrum (entry 2, table 4.2). However, the reaction was messy, and attempts to separate the various products failed. As all of the starting materials had been used up in the second attempt, the time the reaction was allowed to run for was reduced to 10 minutes (entry 3, table 4.2). This resulted in a crude ^{1}H NMR spectrum that was almost a pure sample of **408**. After purification, the compound was isolated in an 88% isolated yield. **408** appears to be relatively unstable and rapidly starts to decompose to other products. Accordingly, **409** was made in the

same way except that the enol ether **408** was not isolated - at the end of the reaction, 2 M HCl was added to hydrolyse **408** to the more stable ketone **409**. This was then isolated after purification in 63% yield (scheme 4.8).



407 408 409

i) 3 equiv. LDA, 0 °C, 10 min; ii) aq. NH_4Cl; iii) 2 M HCl, 20 °C, 16 h

Scheme 4.8

Entry	Temperature (°C)	Time of Cyclisation	Result
1	–40	16 h	Returned starting material.
2	0	1.5 h	Some dearomatised material, but very messy.
3	0	10 min	88% isolated yield of **408**. Unstable.
4	0	10 min	2M HCl added at end of reaction. 63% isolated yield of **409**.

Table 4.2

The stereochemistry of **408** and **409** has been tentatively assigned based on previous results, however, the ^1H NMR spectra of both of the compounds were unusual in that the phenyl group was represented by five separate signals, indicating slow rotation of the phenyl ring on the NMR timescale.

The reason for the slow rotation is unclear, but it possibly indicates that the phenyl could be on the more hindered *endo* face of the molecule and thus possess the opposite stereochemistry to that shown in scheme 4.8. Why this would be the case is not apparent. Another possibility is that the conformation of the molecule is somehow twisted by the interaction between the pyridine nitrogen and the carbonyl oxygen and this is somehow forcing the phenyl into a more congested position.

4.4 Future work

Unfortunately, time ran out at this point, but now it has been proved that the key cyclisation step works, it should be possible to finish the synthesis using chemistry used before within the Clayden group (section 1.2.11). The novel 6,6,6-ring system is interesting and warrants further investigations into both the generality of the reaction and the reactivity of its products.

Chapter Five

Experimental

5.1 General Experimental

All non-aqueous reactions were performed under an atmosphere of dry nitrogen at temperatures that were those of an external bath.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini 200 (200 MHz), Varian XL 300 (300 MHz) or a Bruker Ultrashield 500 (500 MHz) spectrometer with residual non-deuterated solvent as the internal standard. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian XL 300 (75 MHz) spectrometer or a Bruker Ultrashield 500 (125 MHz). Chemical shifts are quoted in parts per million (ppm) down-field from tetramethylsilane. *J* values are quoted in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), septet (sept), multiplet (m), broad (br) or a combination of these. The solvent used was deuterated chloroform, benzene or dimethylsulfoxide.

The infrared spectra were recorded on a Perkin Elmer Spectrum RX1 FTIR spectrometer. All samples were run as evaporated films on a sodium chloride plate. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass spectra were recorded on Kratos MS25, Kratos Concept and Fisons VG Trio 2000 spectrometers using electron impact (EI), chemical ionisation (CI) and electrospray (ES).

Thin layer chromatography (TLC) was carried out on aluminium-backed Kieselgel 60 F_{254} silica plates. Visualisation was achieved using ultraviolet light, permanganate in water adsorbed on silica gel, or 10% dodecamolybdophosphoric acid in ethanol followed by heating.

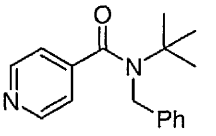
Tetrahydrofuran (THF) and diethyl ether were dried over sodium using benzophenone as a radical indicator and distilled under an atmosphere of nitrogen. Water refers to distilled water. Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4 Å molecular sieves. Dichloromethane and toluene were distilled over calcium hydride under at atmosphere of nitrogen. Petrol refers to the fraction of petroleum ether that boils between 40 and 60 °C and was distilled before use.

Flash chromatography[99] was carried out using Merck silica gel 60H (40-60 μm, 230-400 mesh).

Melting points were determined on a Kofler microscope melting point machine and are uncorrected.

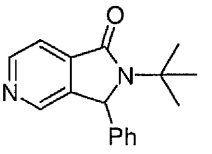
5.2 Experimental for Chapter Two

N-Benzyl-N-tert-butyl-isonicotinamide **201**



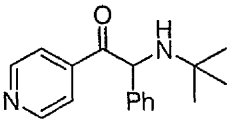
A solution of isonicotinic acid (1.85 g, 15 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (100 ml), then triethylamine (3.14 ml, 22.5 mmol) and *N-tert*-butylbenzylamine was added and stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml) and brine (40 ml), dried ($MgSO_4$) filtered and concentrated under reduced presssure. Purification by flash column chromatography (SiO_2; ether) afforded the title compound an off white crystalline solid (2.40 g, 8.4 mmol, 56%); silica gel TLC R_f 0.23 (ether); ν_{max}/cm^{-1} (thin film) 1639 (C=O); δ_H (300 MHz; $CDCl_3$) 8.58 (2H, d, *J* 6, py-H_2 and py-H_6), 7.4–7.2 (7H, m, py-H_3, py-H_5 and Ph-H), 4.56 (2H, s, CH_2), 1.55 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 171.0, 150.0, 146.3, 139.0, 128.6, 127.2, 125.9 and 120.2 (aromatic), 58.5 (^{t}Bu-C), 51.1 (CH_2), 28.5 (^{t}Bu-CH_3); *m/z* (CI) 269 (45%, M+H$^+$), 268 (100%, M$^+$). [Found: M$^+$, 268.1572. $C_{17}H_{20}N_2O$ requires 268.1576].

2-tert-Butyl-3-phenyl-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one **204**



A solution of *N*-benzyl-*N-tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (1 mmol) in THF (15 ml) at 0 °C *via* cannula. This solution was allowed to warm up overnight before it was quenched with aq. NH_4Cl. Water was added (20 ml) and this was extracted with ether (2 × 20ml), the combined ether layers were washed with water (2 × 20ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. This was purified by flash column chromatography (SiO_2; 1:1 petrol:EtOAc) to give a brown oil (62 mg, 0.23 mmol, 46%) silica gel TLC R_f 0.05 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1686 (C=O); δ_H (300 MHz; $CDCl_3$) 8.61 (1H, d, *J* 4, py-H_2), 8.35 (1H, s, py-H_3), 7.62 (1H, d, *J* 4, py-H_6) 7.3–7.1 (5H, m, Ph-H) 5.77 (1H, s, Bn-H), 1.40 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 167.9, 149.0, 145.1, 139.4, 139.2, 129.2, 128.3, 126.0 and 116.9 (aromatic), 63.9 (^{t}Bu-C), 56.5 (Bn-C), 28.3 (^{t}Bu-CH_3); *m/z* (CI) 267 (100%, M+H^+). [Found: M^+, 266.1420. $C_{17}H_{18}N_2O$ requires 266.342].

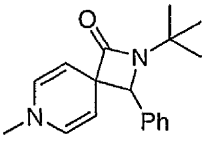
2-(tert-butylamino)-2-phenyl-1-(pyridin-4-yl)ethanone **205**



A solution of *N*-benzyl-*N-tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (1 mmol) in THF (15 ml) at 20 °C *via* cannula. This solution was stirred overnight before it was quenched with aq. NH_4Cl. Water was added (20 ml) and this was extracted with ether (2 ×

20ml), the combined ether layers were washed with water (2 × 20ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. This was purified by flash column chromatography (SiO_2; 9:1 toluene:acetone) to give a colourless oil (38 mg, 0.14 mmol, 28%) silica gel TLC R_f 0.16 (4:1 toluene:acetone); ν_{max}/cm^{-1} (thin film) 3311 (N-H), 1667 (C=O); δ_H (300 MHz; $CDCl_3$) 8.82 (1H, d, *J* 5, py-H_2 or py-H_6), 8.71 (1H, s, py-H_2 or py-H_6), 7.84–7.78 (2H, m, py-H_3 or py-H_5), 7.67–7.46 (5H, m, Ph-H), 5.99 (1H, s, Bn-H), 1.95 (1H, br, N-H), 1.40 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 195.4 (C=O), 164.9, 151.7, 149.2, 144.0, 136.4, 133.9, 129.7, 128.7, 121.3 (aromatic), 52.3 (Bn-C), 28.1 (^{t}Bu-CH_3); *m/z* (EI) 267 (10%, M^+), 210 (100%, M–^{t}Bu).

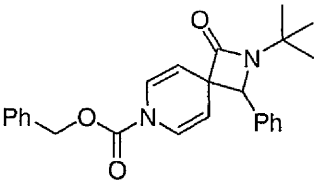
***2-tert-Butyl-7-methyl-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-dien-1-one* 207**



Lithium diisopropylamide solution (2.5 mmol) was added to solution of *N*-benzyl-*N*-*tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (20 ml) at –40 °C. After 30 min the reaction was quenched with methyl triflate (0.082 ml, 0.5 mmol). Ether was added (60 ml) and the organic layer was washed with water (3 × 20 ml) then brine (20 ml). The combined aqueous layers were re-extracted with ether (20 ml), the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The resulting brown oil was purified by column chromatography (SiO_2; 7:3 petrol:EtOAc) to give a light brown oil (134 mg, 0.41 mmol, 82%); silica gel TLC R_f 0.45 (SiO_2; 7:3 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1741 (C=O); δ_H (300 MHz; $CDCl_3$) 7.5–7.2 (5H, m, Ph-H), 6.04 (1H, dd, *J* 2 and 8, py-H_2 or py-H_6), 5.77 (1H, dd, *J* 2 and 8, py-H_2 or py-H_6), 4.56 (1H, dd, *J* 3 and 8, py-H_3 or py-H_5), 4.22 (1H, s, Bn-H), 4.08 (1H, dd, *J* 3

and 8, py-H_3 or py-H_5), 2.84 (3H, s, N-CH_3), 1.33 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 174.1 (C=O), 137.1, 132.9, 132.3, 128.1, 127.3 and 127.2 (aromatic, py-C_2 and py-C_6), 97.8 and 93.6 (py-C_3 and py-C_5), 76.3 (Bn-C), 59.7 (^{t}Bu-C), 53.7 (C), 40.2 (CH_3), 28.2 (^{t}Bu-CH_3); *m/z* (CI) 283 (30%, M+H$^+$). [Found: M$^+$, 327.1706. $C_{19}H_{23}N_2O_3$ requires 327.1709].

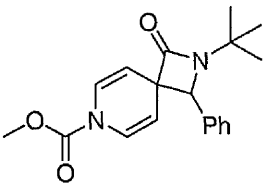
2-tert-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid benzyl ester **211a**



n-Butyllithium (1.5 mmol) was added to a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of *N*-benzyl-*N*-*tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added *via* cannula. After 30 min, the orange solution was quenched by addition of benzyl chloroformate (0.071 ml, 0.5 mmol). Diethyl ether (60 ml) was added and the organic fraction was washed with water (4 × 20 ml), brine (20 ml) and the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 10:1 petrol:EtOAc) to afford the title compound as a colourless oil (164 mg, 0.41 mmol, 81%); silica gel TLC R_f 0.32 (20:1 toluene:acetone); ν_{max}/cm^{-1} (thin film) 1747 (lactam C=O), 1686 (C=O); δ_H (300 MHz; $CDCl_3$) 7.44–7.23 (10H, m, Ph-H), 7.08 (1H, br, py-H_2 or py-H_6), 6.80 (1H, br, py-H_2 or py-H_6), 5.26–5.15 (2H, m, CH_2), 5.06 (1H, br, py-H_3 or py-H_5), 4.58 (1H, br, py-H_3 or py-H_5), 4.43 (1H, s, CH), 1.36 (9H, s,

^{t}Bu); δ_C (75 MHz; $CDCl_3$) 171.5 and 151.0 (C=O), 136.7, 129.3, 128.9, 128.8, 128.8, 128.6, 128.3 and 127.4 (aromatic), 125.8, 125.8, 125.7 and 125.6 (py-C_2 or py-C_6), 125.5, 125.2, 125.1 and 125.0 (py-C_2 or py-C_6), 106.5 and 106.0 (py-C_3 or py-C_5), 102.9 and 102.3 (py-C_3 or py-C_5), 72.2 (Bn-C), 68.8 (CH_2), 58.7 (^{t}Bu-C), 54.5 (C), 28.5 (^{t}Bu-CH_3); *m/z* (CI) 403 (50%, M+H$^+$), 269 (40%, M-$PhCH_2OCO$), 267 (50%, M-$PhCH_2OCO$), 161 (100%, PhCH(N)^{t}Bu), *m/z* (EI) (91%, $PhCH_2$). [Found: M+H$^+$, 403.2021. $C_{25}H_{27}N_2O_3$ requires 403.2022].

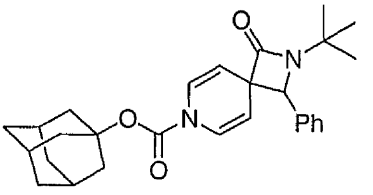
2-tert-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid methyl ester **211b**



n-Butyllithium (1.5 mmol) was added to a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of *N*-benzyl-*N*-*tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added *via* cannula. After 30 min, the orange solution was quenched by addition of methyl chloroformate (0.039 ml, 0.5 mmol). Diethyl ether (60 ml) was added and the organic fraction was washed with water (3 × 20 ml) and brine (20 ml) and the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the title compound as a white crystalline solid (146 mg, 0.44 mmol, 91%); mp 104–106 °C; silica gel TLC R_f 0.39 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1747 (lactam C=O), 1682 (C=O); δ_H (300 MHz; $CDCl_3$) 7.43–7.15 (5H, m,

Ph-H), 7.03 (1H, br, py-H_2 or py-H_6), 6.75 (1H, br, py-H_2 or py-H_6), 5.03 (1H, br, py-H_3 or py-H_5), 4.55 (1H, br, py-H_3 or py-H_5), 4.41 (1H, s, CH), 3.76 (3H, br-s, OCH_3), 1.34 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 171.5 and 151.7 (C=O), 136.7, 128.8, 128.3 and 127.4 (aromatic), 126.0–124.9 (py-C_2 and py-C_6), 106.5–105.7 (py-C_3 or py-C_5), 102.9–102.1 (py-C_3 or py-C_5), 72.3 (Bn-C), 58.6 (^{t}Bu-C), 54.5 (C), 54.0 (OCH_3), 28.5 (^{t}Bu-CH_3); *m/z* (CI) 327 (100%, M^+), 227 (20%, M-(CO)N^{t}Bu); *m/z* (EI) 228 (70%, M-(CO)N^{t}Bu), 137 (100%, M-N(CO)(^{t}Bu)(CHPh)). [Found: M^+, 327.1706. $C_{19}H_{23}N_2O_3$ requires 327.1709].

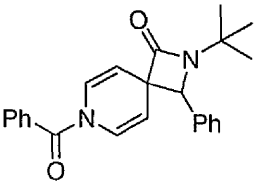
2-tert-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid adamantan-1-yl ester **211c**



n-Butyllithium (1.5 mmol) was added to a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of *N*-benzyl-*N*-*tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added *via* cannula. After 30 min, the orange solution was quenched by addition of adamantyl fluoroformate (0.1 g, 0.5 mmol). Diethyl ether (60 ml) was added and the organic fraction was washed with water (3 × 20 ml) and brine (20 ml), and the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 2% acetone:toluene) to afford the title compound as a white crystalline solid (169 mg, 0.38 mmol, 76%); mp175–178 °C; silica gel TLC R_f 0.43 (8:2 petrol:EtOAc); ν_{max}/cm$^-$

^{t} (thin film) 1748 (lactam C=O), 1684 (C=O); δ_H (300 MHz; $CDCl_3$) 7.41-7.13 (5H, m, Ph-H), 7.10-6.91 (1H, br, py-H_2 or py-H_6), 6.83-6.65 (1H, br, py-H_2 or py-H_6), 5.06-4.85 (1H, br, py-H_3 or py-H_5), 4.58-4.40 (1H, br, py-H_3 or py-H_5), 4.40 (1H, s, Bn-H), 2.23-1.96 (10H, m, Ad-H), 1.63 (6H, s, Ad-H), 1.32 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 171.9 (lactam C=O), 149.2 (amide C=O), 136.9, 128.7, 128.5, 128.2 and 127.4 (Ph-C), 126.2, 125.8, 125.5 and 125.1 (py-C_2 and py-C_6), 105.5, 105.0, 101.6 and 101.0 (py-C_3 and py-C_5), 82.8 (Ad-C), 72.5 (Bn-C), 58.8 (^{t}Bu-C), 54.4 (C), 41.5, 41.3, 41.2, 36.3, 36.2 and 31.1 (Ad-CH_2 and CH), 28.4 (^{t}Bu-CH_3); *m/z* (EI) 447 (<1%, $M+H^+$), 135 (100%, Ad). [Found: $M+H^+$, 447.2638. $C_{28}H_{35}N_2O_3$ requires 447.2642].

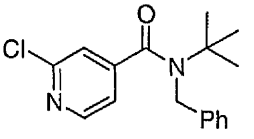
7-Benzoyl-2-tert-butyl-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-dien-1-one **211d**



n-Butyllithium (1.5 mmol) was added to a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of *N*-benzyl-*N*-*tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added *via* cannula. After 30 min, the orange solution was quenched by addition of benzoyl chloride (0.17 ml, 1.5 mmol). Diethyl ether (60 ml) was added and the organic fraction was washed with water (3 × 20 ml), brine (20 ml) and the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 10:1 petrol:EtOAc) to afford the title compound as a colourless oil (163 mg, 0.44 mmol, 86%); silica gel

TLC R_f 0.35 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1747 (lactam C=O), 1667 (C=O); δ_H (300 MHz; $CDCl_3$) 7.59–7.12 (8H, m, Ph-H), 6.79 (2H, br, py-H_2 and py-H_6), 5.16 (1H, br, py-H_3 or py-H_5), 4.62 (1H, br, py-H_3 or py-H_5), 4.49 (1H, s, CH), 1.35 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 171.1 and 167.4 (C=O), 136.6, 133.3, 131.4, 128.8, 128.8, 128.6, 128.5 and 127.4 (aromatic), 128–124 (br, py-C_2 and py-C_6), 109–107 and 104–102 (br, py-C_3 and py-C_5), 71.8 (C), 59.1 (^{t}Bu), 54.6 (CH), 28.4 (^{t}Bu); *m/z* (CI) 373 (100%, $M+H^+$), 162 (50%, PhCH(N)tBu), 105 (90%, PhCO). *m/z* (EI) 105 (100%, PhCO) [Found: M^+, 372.1841. $C_{24}H_{24}N_2O_2$ requires 372.1838].

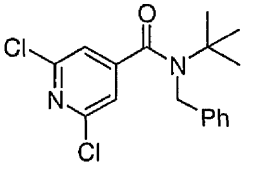
***N-tert-Butyl-N-benzyl-2-chloropyridine-4-carboxamide* 213a**



A solution of 2-chloropyridine-4-carboxylic acid (1.22 g, 7.72 mmol) in thionyl chloride (50 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (50 ml), triethylamine (1.61 ml, 11.58 mmol) and *N-tert*-butylbenzylamine (2.15 ml, 11.58 mmol) was added and stirred overnight at room temperature. The resulting solution was diluted with dichloromethane (50 ml), washed with water (3 × 30 ml) and brine (30 ml), and the combined aqueous layers were re-extracted with dichloromethane (30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a dark brown oil. This was purified by flash column chromatography (SiO_2; 4:1 petrol/EtOAc) to yield the title compound as a colourless oil (1.97 g, 6.51 mmol, 84%); silica gel TLC R_f 0.35 (7:3 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1644 (C=O); δ_H (300 MHz; $CDCl_3$) 8.31 (1H, d, *J* 5, py-H_6), 7.41–7.45

(4H, m, Ph-H and py-H), 7.21–7.12 (3H, m, Ph-H and py-H), 4.52 (2H, s, CH_2), 1.53 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 169.8 (C=O), 152.1, 150.3, 149.5, 138.9, 129.1, 127.7, 126.1, 121.4 and 119.2 (aromatic), 59.1 (^{t}Bu), 51.3 (CH_2), 28.7 (^{t}Bu); *m/z* (CI) 303 (100%, $M+H^+$). [Found: $M+H^+$, 303.1269. $C_{17}H_{20}N_2OCl$ requires 303.1265].

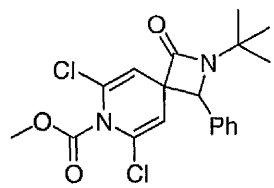
N-tert-Butyl-N-benzyl-2,6-dichloropyridine-4-carboxamide **213b**



A solution of 2,6-dichloropyridine-4-carboxylic acid (1.21 g, 7.16 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (100 ml), triethylamine (1.49 ml, 10.74 mmol) and *N-tert*-butylbenzylamine (1.99 ml, 10.74 mmol) were added and the solution was stirred overnight at room temperature. The resulting solution was diluted with dichloromethane (100 ml), washed with water (3 × 40 ml) and brine (40 ml), and the combined aqueous layers were re-extracted with dichloromethane (40 ml). The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure to yield a dark brown oil. This was purified by flash column chromatography (SiO_2; ether) to afford the title compound as a white crystalline solid (1.58 g, 4.68 mmol, 65%); mp 126–129 °C; silica gel TLC R_f 0.22 (9:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1645 (C=O); δ_H (300 MHz; $CDCl_3$) 7.43–7.28 (3H, m, Ph-H), 7.19–7.15 (3H, Ph-H and py-H), 4.53 (2H, s, CH_2), 1.54 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 168.4 (C=O), 151.6, 151.1, 138.6, 129.2, 127.9, 126.1 and

119.9 (aromatic), 59.3 (^{t}Bu), 51.3 (CH_2), 28.7 (^{t}Bu); *m/z* (CI) 337 (35%, M+H$^+$), 58 (100%, ^{t}Bu). [Found: M+H$^+$, 337.0876. $C_{17}H_{18}N_2OCl_2$ requires 337.0874].

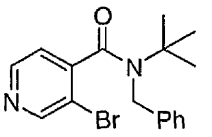
2-tert-Butyl-6,8-dichloro-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid methyl ester **214b**



n-butyllithium (0.75 mmol) was added to a stirred solution of diisopropylamine (0.11 ml, 0.75 mmol) in THF (7.5 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of *N-tert*-butyl-*N*-benzyl-2,6-dichloropyridine-4-carboxamide (**213b**) (84 mg, 0.25 mmol) in THF (2.5 ml) was added *via* cannula. After 30 min, the reaction mixture was quenched by addition of methyl chloroformate (0.03 ml, 0.375 mmol). Diethyl ether (30 ml) was added and the organic fraction was washed with water (3 × 10 ml) and brine (10 ml), and the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 4:1 petrol:EtOAc) to afford the title compound as a colourless oil (82 mg, 0.21 mmol, 83%); mp 142–146 °C; silica gel TLC R_f 0.20 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1749 (lactam C=O), 1650 (C=O); δ_H (300 MHz; $CDCl_3$) 7.46–7.22 (5H, m, Ph-H), 5.95 (1H, s, py-H_3 or py-H_5), 5.38 (1H, s, py-H_3 or py-H_5), 4.64 (1H, s, CH), 3.81 (3H, s, OCH_3), 1.33 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 167.0 and 152.7 (C=O), 136.7 (aromatic), 132.2 and 131.9 (py-C_2 and py-C_6), 129.1 and 127.0 (aromatic), 118.7 and 116.2 (py-C_3 and py-C_5), 67.0 (CH), 61.5 (^{t}Bu-C), 55.2 (OCH_3), 54.3 (C), 28.4 (^{t}Bu-CH_3); *m/z* (CI) 412 (100%, M+NH_4^+), 395 (35%,

M+H$^+$) 162 (15%, $PhCH_2N^tBu$), *m/z* (EI) 205 (75%, M-N(C=O)(^{t}Bu)(CHPh)), 146 (65%, M-N(C=O)(^{t}Bu)(CHPh)-CO_2Me), 57 (95%, ^{t}Bu). [Found: M+H$^+$, 395.0930. $C_{19}H_{21}N_2O_3Cl_2$ requires 395.0929].

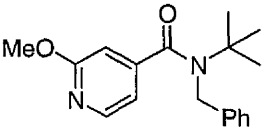
***N-tert-Butyl-N-benzyl-3-bromopyridine-4-carboxamide* 217**



n-butyllithium (18 mmol) was added to a stirred solution of diisopropylamine (2.54 ml, 18 mmol) in THF (15 ml) at 0 °C. After 10 min, the resulting solution was cooled to –78 °C and 3-bromopyridine (1.47 ml, 15 mmol) was added slowly over 5 min. Once the 3-bromopyridine had been added, the solution was immediately cooled to –90 °C and maintained at this temperature for 20 min. Dry CO_2 gas was bubbled through the solution whilst it was allowed to warm to room temperature. Dichloromethane was added (60 ml) and the solution was washed with water (3 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with dichloromethane (20 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield 3-bromopyridine-4-carboxylic acid as a brown solid. Thionyl chloride (50 ml) was added to the solid and allowed to stir overnight at room temperature. The thionyl chloride was removed under reduced pressure and the resulting brown oil was dissolved in dichloromethane (50 ml) and cooled to 0 °C. Triethylamine was added (0.989 ml, 7.11 mmol) followed by *t*-butylbenzylamine (1.316 ml, 7.106 mmol). The solution was allowed to warm up overnight before being diluted with dichloromethane (50 ml), washed with water (3 × 30 ml) and brine (30 ml), and the combined aqueous layers were re-extracted with dichloromethane (30 ml). The combined organics were dried ($MgSO_4$), filtered and

concentrated under reduced pressure to yield a dark brown oil. This was purified by flash column chromatography (SiO_2; 7:3 petrol/EtOAc) to yield the title compound as large pale yellow platelets (732 mg, 2.11 mmol, 14%); mp 96–99 °C; silica gel TLC R_f 0.21 (7:3 petrol/EtOAc); ν_{max}/cm^{-1} (thin film) 1642 (C=O); δ_H (300 MHz; $CDCl_3$) 8.71 (1H, s, py-H_2), 8.40 (1H, d, *J* 5, py-H_6), 7.39–7.24 (3H, m, Ph-H), 7.21–7.13 (3H, m, Ph-H and py-H_4), 4.47 (2H, dd, *J* 93 and 18, CH_2), 1.59 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 168.4 (C=O), 152.2, 148.7, 147.3, 138.9, 129.0, 127.6, 126.0, 121.8 and 117.4 (aromatic), 59.5 (^tBu), 50.7 (CH_2), 28.7 (^tBu); *m/z* (CI) 349 (20%, $M+H^+$ (^{81}Br)), 347 (30%, $M+H^+$ (^{79}Br)), 91 (75%, $PhCH_2$). [Found: M^+ (^{79}Br), 346.0682. $C_{17}H_{19}N_2OBr$ requires 346.0681].

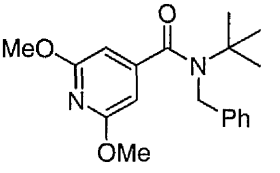
***N-tert-Butyl-N-benzyl-2-methoxypyridine-4-carboxamide* 220**



Sodium methoxide (702 mg, 13 mmol) was added to a solution of *N*-tert-butyl-*N*-benzyl-2-chloropyridine-4-carboxamide (**213a**) (400 mg, 1.32 mmol) in methanol (50 ml). The resulting solution was heated under sealed tube conditions with stirring at 125 °C for 48 h. The methanol was removed under reduced pressure and the residue was dissolved in dichloromethane (100 ml) and washed with water (3 × 40 ml) and brine (40 ml). The combined aqueous layers were re-extracted with dichloromethane (40 ml) and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to furnish the title compound as a white crystalline solid (337 mg, 1.13 mmol, 86%); mp 98–100 °C; silica gel TLC R_f 0.66 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1640 (C=O); δ_H (300 MHz; $CDCl_3$) 8.13 (1H, dd, *J* 5 and 1, py-H_6), 7.41–7.16 (5H, m, Ph-H), 6.86 (1H, dd, *J* 5 and 1, py-H_5), 6.73

(1H, dd, *J* 1 and 1, py-H_3), 4.58 (2H, s, CH_2), 3.90 (3H, s, OCH_3), 1.53 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 171.2 (C=O), 164.5, 149.5, 147.6, 139.5, 128.9, 127.5, 126.3, 113.9 and 107.9 (aromatic), 58.7 (^tBu-C), 53.9 (OCH_3), 51.4 (CH_2), 28.2 (^tBu); *m/z* (CI) 299 (100%, $M+H^+$), 91 (25%, $PhCH_2$) *m/z* (EI) 298 (15%, M^+), 240 (30%, M-^tBu), 135 (55%, M-$PhCH_2N^tBu$), 90 (100%, $PhCH_2$). [Found: M^+, 298.1685. $C_{18}H_{22}N_2O_2$ requires 298.1681].

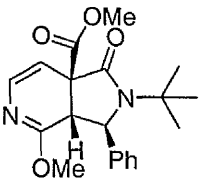
***N-tert-Butyl-N-benzyl-2,6-dimethoxypyridine-4-carboxamide* 221**



sodium methoxide (486 mg, 9 mmol) was added to a solution of N-*tert*-butyl-N-benzyl-2,6-dichloropyridine-4-carboxamide (**214**) (300 mg, 0.89 mmol) in methanol (50 ml). The resulting solution was heated under sealed tube conditions with stirring at 125 °C for 48 h. The methanol was then removed under reduced pressure and the residue was dissolved in dichloromethane (100 ml) and washed with water (3 × 40 ml) and brine (40 ml). The combined aqueous layers were re-extracted with dichloromethane (40 ml) and the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to furnish the title compound as a colourless oil (238 mg, 0.72 mmol, 82%); silica gel TLC R_f 0.30 (1:1 petrol: EtOAc); ν_{max}/cm^{-1} (thin film) 1643.7 (C=O); δ_H (300 MHz; $CDCl_3$) 7.41-7.19 (5H, m, Ph-H), 6.31 (2H, s, py-H_3 and py-H_5), 4.60 (2H, s, CH_2), 3.83 (6H, s, OCH_3), 1.54 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 171.5 (C=O), 163.6 (py-H_2 and py-H_6), 152.1 (py-H_4), 139.7, 128.9, 127.4 and 126.3 (Ph-C), 98.4 (py-C_3 and py-C_5), 58.6 (^tBu-C),

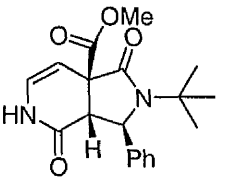
53.9 (OCH_3), 51.5 (CH_2), 28.8 (^tBu-CH_3); *m/z* (CI) 329 (100%, $M+H^+$). [Found: $M+H^+$, 329.1856. $C_{19}H_{25}N_2O_3$ requires 329.1860].

***(3R/S*,3aR/S*,7aR/S*)-Methyl-2-tert-butyl-2,3,3a,7a-tetrahydro-4-methoxy-1-oxo-3-phenyl-1H-pyrrolo[3,4-c]pyridine-7a-carboxylate* 223**



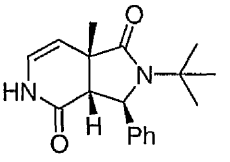
Lithium diisopropylamide solution (2.5 mmol) was added to a stirred solution of *N*-tert-butyl-*N*-benzyl-2-methoxypyridine-4-carboxamide (**220**) (150 mg, 0.5 mmol) in THF (20 ml) at 0 °C. After 60 min, the reaction was cooled to –78 °C, quenched with methyl chloroformate (0.19 ml, 2.5 mmol) and allowed to warm to room temperature. The reaction mixture was diluted with ether (60 ml) and washed with water (3 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with ether (20 ml) and the combined organics were dried (Na_2SO_4), filtered and concentrated. The resulting light yellow oil was purified using flash column chromatography (SiO_2; 7:3 petrol:EtOAc) to yield the title product as a colourless oil (84 mg, 0.24 mmol, 48%); silica gel TLC R_f 0.66 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1735 (C=O), 1696 (lactam C=O); δ_H (500 MHz; $CDCl_3$) 7.18–7.03 (5H, m, Ph-H), 6.40 (1H, d, *J* 7, py-H_6), 5.28 (1H, d, *J* 7, py-H_5), 4.45 (1H, d, *J* 6, Bn-H), 3.55 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 3.29 (1H, d, *J* 6, CH), 1.01 (9H, s, ^tBu-H) ; δ_C (125 MHz; $CDCl_3$) 171.4 and 170.9 (C=O), 165.0 (py-C_2), 144.5 (aromatic), 133.7 (py-C_6), 129.3, 128.4 and 126.7 (aromatic), 107.4 (py-C_5), 66.1 (py-C_4), 57.6 (^tBu-C), 57.4 (Bn-C), 54.2 (OCH_3), 53.7 (OCH_3), 45.9 (py-C_3), 28.5 (^tBu-CH_3); *m/z* (CI) 357 (100%, $M+H^+$). [Found: $M+H^+$, 357.1805. $C_{20}H_{25}N_2O_3$ requires 357.1809].

***(3R/S,3aR/S,7aR/S)-methyl 2-tert-Butyl-2,3,3a,4,5,7a-hexahydro-1,4-dioxo-3-phenyl-1H-pyrrolo[3,4-c]pyridine-7a-carboxylate* 224**



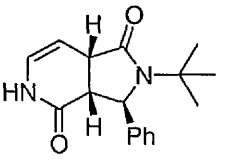
Lithium diisopropylamide solution (2.5 mmol) was added to a stirred solution of *N*-tert-butyl-*N*-benzyl-2-methoxypyridine-4-carboxamide (**220**) (150 mg, 0.5 mmol) in THF (20 ml) at 0 °C. After 60 min, the reaction was cooled to –78 °C, quenched with methyl chloroformate (0.19 ml, 2.5 mmol) and allowed to warm to room temperature. The reaction mixture was diluted with ether (60 ml) and hydrolysed by shaking with 2 M HCl (20 ml). The aqueous layer was neutralised with saturated Na_2SO_4 solution and removed. The organic layer was washed with water (3 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with ether (20 ml) and the combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting light yellow oil was purified using flash column chromatography (SiO_2; 1:1 petrol:EtOAc) to yield the title product as a colourless oil (106 mg, 0.31 mmol, 62%); silica gel TLC R_f 0.26 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1738 (C=O), 1692 (lactam C=O); δ_H (500 MHz; $CDCl_3$) 7.91 (1H, br-d, *J* 4, NH), 7.33–7.18 (5H, m, Ph-H), 6.13 (1H, dd, *J* 8 and 5, py-H_6), 5.20 (1H, d, *J* 8, py-H_5), 5.10 (1H, d, *J* 4, Bn-H), 3.64 (3H, s, OCH_3), 3.52 (1H, d, *J* 4, py-H_3), 1.25 (9H, s, ^{t}Bu-H); δ_C (125 MHz; $CDCl_3$) 170.9, 170.5 and 168.2 (C=O), 143.4, 129.2, 128.4, 126.4, 124.8 and 101.9 (aromatic and C=C), 64.4 (py-C_4), 57.2 (Bn-C), 57.0 (^{t}Bu-C), 53.8 (OCH_3), 50.7 (py-C_3), 28.4 (^{t}Bu-C); *m/z* (CI) 343 (100%, M+H^+). [Found: M+H^+, 343.1655. $C_{19}H_{23}N_2O_4$ requires 343.1652].

***(3R/S,3aR/S,7aS/R)-2-tert-Butyl-3,3a-dihydro-7a-methyl-3-phenyl-2H-pyrrolo[3,4-c]pyridine-1,4(5H,7aH)-dione* 225**



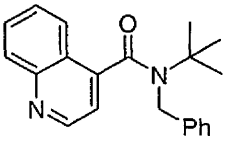
Lithium diisopropylamide solution (1.25 mmol) was added to a stirred solution of *N*-tert-butyl-*N*-benzyl-2-methoxypyridine-4-carboxamide (**220**) (75 mg, 0.25 mmol) in THF (10 ml) at 0 °C. After 60 min, the reaction was quenched with methyl iodide (0.017 ml, 0.275 mmol). After 30 min, aqueous NH_4Cl (1 ml) was added, the reaction mixture was diluted with ether (30 ml) and hydrolysed by shaking with 1 M HCl (10 ml). The aqueous layer was neutralised with saturated Na_2CO_3 solution and removed. The organic layer was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with ether (10 ml) and the combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting light yellow oil was purified using flash column chromatography (SiO_2; 3:2 petrol:EtOAc) to yield the title product as a colourless oil (56 mg, 0.187 mmol, 75%); silica gel TLC R_f 0.32 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1681 (C=O); δ_H (500 MHz; $CDCl_3$) 7.31–7.19 (6H, m, Ph-H and NH), 5.97 (1H, dd, *J* 8 and 5, py-H_6), 4.96 (1H, d, *J* 5, Bn-H), 4.90 (1H, d, *J* 8, py-H_5), 2.66 (1H, d, *J* 5, py-H_3), 1.27 (3H, s, CH_3), 1.24 (9H, s, ^{t}Bu-H); δ_C (125 MHz; $CDCl_3$) 177.5 and 169.2 (C=O), 145.0, 129.3, 128.2 and 126.3 (aromatic), 122.3 (py-C_6), 108.4 (py-C_5), 64.5 (Bn-C), 56.7 (^{t}Bu-C), 55.4 (py-C_4), 46.7 (py-C_3), 28.5 (^{t}Bu-CH_3), 25.8 (CH_3); *m/z* (CI) 299 (100%, M+H$^+$). [Found: M+H$^+$, 299.1752. $C_{18}H_{23}N_2O_2$ requires 299.1754].

***(3R/S,3aR/S,7aS/R)-2-tert-Butyl-3,3a-dihydro-3-phenyl-2H-pyrrolo[3,4-c]pyridine-1,4(5H,7aH)-dione* 226**



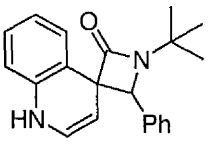
Lithium diisopropylamide solution (1.25 mmol) was added to a stirred solution of *N*-tert-butyl-*N*-benzyl-2-methoxypyridine-4-carboxamide (**220**) (75 mg, 0.25 mmol) in THF (10 ml) at 0 °C. After 60 min, the reaction was quenched with aqueous NH_4Cl (1 ml). The reaction mixture was diluted with ether (30 ml) and hydrolysed by shaking with 2 M HCl (10 ml). The aqueous layer was neutralised with saturated Na_2CO_3 solution and removed. The organic layer was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with ether (10 ml) and the combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting light yellow oil was purified using flash column chromatography (SiO_2; 1:1 petrol:EtOAc) to yield the title product as a colourless oil (55 mg, 0.193 mmol, 77%); silica gel TLC R_f 0.2 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1667 (C=O); δ_H (500 MHz; $CDCl_3$) 7.63 (1H, d, *J* 3, NH), 7.29–7.17 (5H, m, Ph-H), 6.04 (1H, dd, *J* 8 and 5, py-H_6), 5.45 (1H, s, Bn-H), 5.16 (1H, t, *J* 7, py-H_5), 3.52 (1H, dd, *J* 10 and 6, py-H_4), 2.75 (1H, d, *J* 10, py-H_3), 1.24 (9H, s, ^{t}Bu-H); δ_C (125 MHz; $CDCl_3$) 174.2 and 168.9 (C=O), 142.4, 129.4, 128.2 and 126.0 (aromatic), 125.1 (py-C_6), 101.6 (py-C_5), 63.4 (Bn-CH), 56.0 (^{t}Bu-C), 47.7 (py-C_4), 39.7 (py-C_3), 28.4 (^{t}Bu-CH_3); *m/z* (CI) 285 (100%, $M+H^+$). [Found: $M+H^+$, 285.1602. $C_{17}H_{21}N_2O_2$ requires 285.1598].

***Quinoline-4-carboxylic acid benzyl-tert-butyl-amide* 229**



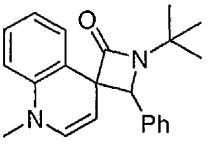
A solution of quinoline-4-carboxylic acid (1.50 g, 8.66 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed *in-vacuo* to give the acid chloride as an off white solid. This was dissolved in dichloromethane (100 ml), then triethylamine (1.81 ml, 13 mmol) and *N*-tert-butyl benzylamine (1.57 ml, 8.66 mmol) were added and stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml), brine (40 ml), dried ($MgSO_4$) and concentrated *in-vacuo*. Purification by flash column chromatography (SiO_2; 3:7 petrol/EtOAc) afforded the title compound as an off white crystalline solid (1.70 g, 5.37 mmol, 62%); silica gel TLC R_f 0.39 (1:4 petrol/EtOAc); ν_{max}/cm^{-1} (thin film) 1634 (C=O); δ_H (300 MHz; $CDCl_3$) 8.78 (1H, d, *J* 4.5, nap-H_2), 8.13 (1H, d, *J* 8.5, nap-H_5 or nap-H_8), 7.94 (1H, d, *J* 8, nap-H_5 or nap-H_8), 7.76 (1H, td, *J* 1.5 and 7, nap-H_6 or nap-H_7), 7.64 (1H, t, *J* 8, nap-H_6 or nap-H_7), 7.4–7.1 (6H, m, Ph-H and nap-H_3), 4.44 (2H, wide-d (slow rotation), Bn-H), 1.67 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 169.9, 150.0, 148.2, 144.2, 138.9, 130.0, 129.8, 128.6, 127.5, 127.1, 125.7, 124.3, 124.0, 116.8, 59.0, 51.0, 28.7; *m/z* (CI, NH_4^+) [Found: M^+, 318.1729. $C_{21}H_{22}N_2O$ requires 318.1732].

***2-tert-Butyl-3-phenyl-2,7-diaza-5,6-benzo-spiro[3.5]nona-5,8-dien-1-one* 234**



A solution of quinoline-4-carboxylic acid benzyl-*tert*-butyl-amide (**229**) (159 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (0.75 mmol) in THF (15 ml) at 0 °C *via* cannula. After 3.5 h this was quenched with saturated ammonium chloride solution (1 ml). Water was added (20 ml) and this was extracted with ether (2 × 20ml), the combined ether layers were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated. The resulting brown oil was too unstable to undergo further purification δ_H (200 MHz; $CDCl_3$) 7.47–7.19 (6H, m, Ph-H and qu-H_5 or qu-H_8), 7.08 (1H, td, *J* 7 and 1, qu-H_6 or qu-H_7), 6.95 (1H, td, *J* 7 and 1, qu-H_6 or qu-H_7), 6.54 (1H, d, *J* 7, qu-H_5 or qu-H_8), 6.11 (1H, br, NH), 5.97 (1H, dd, *J* 7 and 5, qu-H_2), 4.64 (1H, s, Bn-H), 4.21 (1H, d, *J* 7, qu-H_3), 1.45 (9H, s, ^{t}Bu-H).

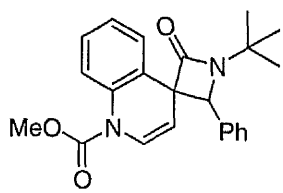
***2-tert-Butyl-7-methyl-3-phenyl-2,7-diaza-5,6-benzo-spiro[3.5]nona-5,8-dien-1-one* 232**



A solution of quinoline-4-carboxylic acid benzyl-*tert*-butyl-amide (**229**) (159 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (0.75 mmol) in THF (15 ml) at 0 °C *via* cannula. After 3.5 h this was quenched with MeI (0.75 mmol, 0.047 ml). Water was added (20 ml) and this was extracted with ether (2 × 20ml), the combined ether layers were washed with water (2 × 20 ml) and brine

(20 ml), then dried ($MgSO_4$), filtered and concentrated. The resulting brown oil was purified by column chromatography (SiO_2; 6:1 petrol/EtOAc) to give a colourless oil (98 mg, 0.33 mmol, 65%); silica gel TLC R_f 0.24 (3:1 petrol/EtOAc); ν_{max}/cm^{-1} (thin film) 1744 (C=O); δ_H (300 MHz; $CDCl_3$) 7.4–7.2 (7H, m, Ph-H and qu-H_5 or qu-H_8 and qu-H_6 or qu-H_7), 7.05 (1H, dt, *J* 1 and 7, qu-H_6 or qu-H_7), 6.76 (1H, dd, *J* 1 and 8, qu-H_5 or qu-H_8), 5.99 (1H, d, *J* 8, qu-H_2), 4.62 (1H, s, Bn-H), 4.32 (1H, d, *J* 8, qu-H_3), 3.05 (3H, s, N-CH_3), 1.47 (9H, s, ^{t}Bu-H); δ_C (125 MHz; $CDCl_3$) 173.1 (C=O), 140.5, 138.0, 134.8, 128.5, 128.1, 128.1, 128.0, 126.4, 121.9, 121.0, 112.3 and 92.4 (aromatic), 77.7 (Bn-C), 61.9 (^{t}Bu-C), 55.1 (C), 38.7 (N-CH_3), 29.1 (^{t}Bu-CH_3). *m/z* (CI) 333 (100%, $M+H^+$), *m/z* (EI) 233 (20%, M-N(^{t}Bu)(C=O)), 171 (50%, M-N(^{t}Bu)(CHPh)), 143 (M-N(^{t}Bu)(CHPh)(C=O)). [Found: $M+H^+$, 333.1962. $C_{22}H_{25}N_2O$ requires 333.1961].

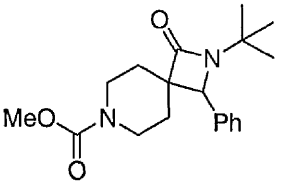
***2-tert-Butyl-1-oxo-3-phenyl-2,7-diaza-5,6-benzo-spiro[3.5]nona-5,8-diene-7-carboxylic acid methyl ester* 233**



Lithium diisopropylamide solution (0.275 mmol) was added to a stirred solution of quinoline-4-carboxylic acid benzyl-*tert*-butyl-amide (**229**) (80 mg, 0.25 mmol) in THF (10 ml) at –40 °C was added. After 10 min, the reaction was quenched with methyl chloroformate (0.021 ml, 0.275 mmol). Diethyl ether (30 ml) was added and the organics were washed with water (3 × 10 ml) and brine (10 ml), and the combined aqueous layers were re-extracted with ether (10 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a dark

brown oil. This was purified by flash column chromatography (SiO_2, 9:1 petrol:EtOAc) to afford the title compound as a white crystalline solid (35 mg, 0.093 mmol, 37%); mp 56–58 °C; silica gel TLC R_f 0.64 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1748 (lactam C=O), 1676 (amide C=O); δ_H (300 MHz; $CDCl_3$) 8.16 (1H, dd, *J* 8 and 1, qu-H), 7.42–7.19 (8H, m, Ph-H and qu-H), 6.87 (1H, d, *J* 8, qu-H_3), 5.06 (1H, d, *J* 9 qu-H_2), 4.63 (1H, s, CH), 3.82 (3H, s, OCH_3), 1.46 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 170.5 and 152.9 (C=O), 137.8, 135.9, 128.6, 128.4, 128.3, 127.9, 127.3, 126.9, 126.0, 125.1, 121.5 and 105.7 (aromatic), 73.1 (OCH_3), 60.5 (C), 55.2 (^tBu), 53.6 (CH), 28.7 (^tBu); *m/z* (CI) 394 (65%, $M+NH_4^+$), 377 (100%, $M+H^+$); *m/z* (EI) 277 (70%, M-CO(N)^{t}Bu), 215 (60%, M-PhCH(N)^{t}Bu), 187 (100%, M-(CO)N(^{t}Bu)(CHPh)). [Found: $M+H^+$, 377.1856. $C_{23}H_{25}N_2O_3$ requires 377.1860].

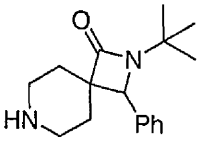
***2-tert-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nonane-7-carboxylic acid methyl ester* 236**



A stirred solution of 2-*tert*-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid methyl ester (**211b**) (101 mg, 0.31 mmol) and palladium on charcoal in ethanol (25 ml) was left at room temperature overnight under an atmosphere of hydrogen. The palladium on charcoal was removed by filtration through a pad of celite. The filtrate was concentrated to yield a colourless oil (100 mg, 0.30 mmol, 97%); ν_{max}/cm^{-1} (thin film) 1731 (lactam C=O), 1698 (amide C=O); δ_H (500 MHz; $CDCl_3$) 7.28–7.15 (5H, m, Ph-H), 4.23 (1H, s, Bn-H), 3.57–3.48 (5H, m, OCH_3 and CH_2), 3.23–3.48 (1H, m, CH_2), 3.11–2.98 (1H, br, CH_2), 1.87–1.80 (1H, m,

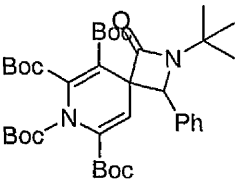
CH_2), 1.74–1.63 (1H, br, CH_2), 1.48–1.40 (1H, m, CH_2), 1.18 (9H, s, ^tBu), 0.99–1.86 (1H, br, CH_2); δ_C (125 MHz; $CDCl_3$) 173.5 (C=O), 156.2, 138.0, 128.8, 128.6, 128.4, and 129.0–128.3 (aromatic), 65.5, 56.0, 54.5, 52.9, 41.8, 41.2, 33.0–32.5, 28.5 and 28.1–27.6 (aliphatic); *m/z* (CI) 348 (20%, $M+NH_4^+$), 331 (100%, $M+H^+$). [Found: $M+H^+$, 331.2016. $C_{19}H_{27}N_2O_3$ requires 331.2016].

***2-tert-Butyl-3-phenyl-2,7-diaza-spiro[3.5]nonan-1-one* 237**



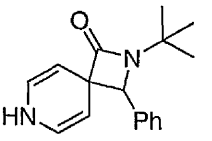
A stirred solution of 2-*tert*-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid benzyl ester (**211a**) (98 mg, 0.24 mmol) and palladium on charcoal in ethanol (25 ml) was left at room temperature overnight under an atmosphere of hydrogen. The palladium on charcoal was removed by filtration through a pad of celite. The filtrate was concentrated to yield a colourless oil (63 mg, 0.23 mmol, 98%); ν_{max}/cm^{-1} (thin film) 1734 (C=O); δ_H (500 MHz; $CDCl_3$) 7.35–7.02 (5H, m, Ph-H), 4.25 (1H, s, CH), 3.45–0.94 (8H, br-m, CH_2), 1.22 (9H, s, ^tBu); δ_C (125 MHz; $CDCl_3$) 174.3 and 173.9 (C=O), 138.5, 138.3, 130.9, 129.7, 128.7 (wide), 128.7, 128.4, 128.3, 128.0–126.9 (wide) and 126.3 (aromatic), 66.0, 65.7, 56.2, 56.1, 54.4, 54.4, 52.6, 50.8, 50.0, 43.6, 42.9, 33.5, 33.1, 28.6, 28.0 and 12.3 (aliphatic); *m/z* (CI) 301 (55%, $M+NH_4^+$), 273 (100%, $M+H^+$). [Found: $M+H^+$, 273.1961. $C_{17}H_{25}N_2O$ requires 273.1961].

***2-tert-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-5,6,7,8-tetracarboxylic acid tetra-tert-butyl ester* 243**



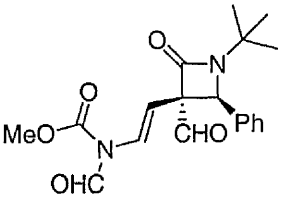
n-butyllithium solution (1.5 mmol) was added to a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of *N*-benzyl-*N*-*tert*-butyl-isonicotinamide (**201**) (134 mg, 0.5 mmol) in THF (5 ml) was added *via* cannula. After 30 min, the orange solution was quenched by addition of Boc anhydride (109 mg, 0.5 mmol) at –78 °C. Diethyl ether (60 ml) was added and the organics were washed with water (4 × 20 ml) and brine (20 ml), and the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the title compound as a colourless oil (70 mg, 0.105 mmol, 21%); silica gel TLC R_f 0.29 (9:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1758 (lactam C=O), 1732 (C=O); δ_H (300 MHz; $CDCl_3$) 7.36-7.20 (5H, m, Ph-H), 5.99 (1H, s, py-H), 5.08 (1H, s, CH), 1.53 (9H, s, ^{t}Bu-H), 1.50 (9H, s, ^{t}Bu-H), 1.40 (9H, s, ^{t}Bu-H), 1.32 (9H, s, ^{t}Bu-H), 1.30 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 167.7, 164.5, 161.1, 161.1 and 161.0 (C=O), 150.0, 137.1, 135.7, 128.7, 128.4, 127.2, 122.4 and 120.6 (aromatic and C=C), 83.6, 83.1, 82.3 and 81.7 (^{t}Bu-C), 68.2 (Bn-C), 59.8 (^{t}Bu-C), 55.3 ©, 28.4, 28.2, 28.1, 28.0 and 27.9 (^{t}Bu-CH_3); *m/z* (CI) 686 (100%, M+NH_4^+). [Found: M+NH_4^+, 686.3998. $C_{37}H_{56}N_3O_9$ requires 686.4011].

***2-tert-Butyl-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-dien-1-one* 240**



A stirred solution of 2-*tert*-butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid adamantan-1-yl ester (**211c**) in dichloromethane (9 ml) at room temperature was treated with trifluoroacetic acid (1 ml). After 30 min, the dichloromethane and trifluoroacetic acid were removed under reduced pressure to yield a light brown oil δ_H (400 MHz; $CDCl_3$) 7.42-7.26 (5H, m, Ph-H), 7.01 (1H, dd, *J* 9 and 2, py-H_2 and py-H_6), 6.73 (1H, dd, *J* 9 and 2, py-H_2 and py-H_6), 5.05 (1H, dd, *J* 8 and 3, py-H_3 and py-H_5), 4.57 (1H, dd, *J* 8 and 3, py-H_3 and py-H_5), 4.48 (1H, s, Bn-H), 1.32 (9H, s, ^{t}Bu-H).

***Methyl (E)-2-((3R,4S)-1-tert-butyl-3-formyl-2-oxo-4-phenylazetidin-3-yl)vinylformylcarbamate* 247**

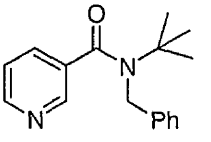


A solution of 2-*tert*-Butyl-1-oxo-3-phenyl-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid methyl ester (**211b**) (94 mg, 0.29 mmol) in dichloromethane (25 ml) at –78 °C was treated with ozone gas until the solution changed from colourless to a pale blue colour. The reaction was quenched with dimethylsulfide (1 ml) and allowed to warm to room temperature. The reaction mixture was concentrated to yield a colourless oil, which was purified by flash column chromatography (SiO_2; 7:3 petrol:EtOAc) to furnish the title compound as a colourless oil (60 mg, 0.17 mmol,

58%); ν_{max}/cm^{-1} (thin film) 1755 (C=O), 1714 (C=O); δ_H (300 MHz; $CDCl_3$) 9.66 (1H, s, CHO), 9.01 (1H, s, NCHO), 7.50–7.32 (5H, m, Ph-H), 6.16 (1H, d, *J* 9, CH), 5.39 (1H, d, *J* 9, CH), 5.00 (1H, s, Ph-H), 3.86 (3H, s, OCH_3), 1.27 (9H, s, ^tBu-H); δ_C (125 MHz; $CDCl_3$) 194.5 (CHO), 162.9 (C=O), 153.3 (NCHO), 136.6 (NC=O), 129.5, 129.2, 129.0 and 127.0 (aromatic), 124.7 and 120.5 (C=C), 74.1 (CH), 60.5 (^tBu-C), 55.8 (C), 54.6 (OCH_3), 28.6 (^tBu-CH_3); *m/z* (CI) 376 (100%, $M+NH_4^+$), 359 (65%, $M+H^+$). [Found: $M+H^+$, 359.1601. $C_{19}H_{23}N_2O_5$ requires 359.1601].

The relative configuration of **247** was confirmed by NOE studies, where irradiation of the benzyl proton returned an enhancement of 5.8% for the signal for the aldehyde proton. No enhancement of either signal for the alkene protons was detected.

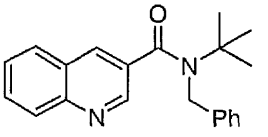
N-Benzyl-N-tert-butyl-nicotinamide 251



A solution of nicotinic acid (1.85 g, 15 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced prerssure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (100 ml), triethylamine (3.14 ml, 22.5 mmol) and *N-tert*-butylbenzylamine were added and the solution was stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml) and brine (40 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; ether) afforded the title compound as a white crystalline solid (2.40 g, 8.4 mmol, 56%); silica gel TLC R_f 0.23 (ether); ν_{max}/cm^{-1} (thin film) 1635

(C=O); δ_H (300 MHz; $CDCl_3$) 8.69 (1H, d, *J* 1, py-H2), 8.58 (1H, dd, *J* 3.5 and 1, py-H6), 7.72 (1H, dt, *J* 1.5 and 8, py-H4), 7.4–7.2 (6H, m, Ph-H and py-H5), 4.62 (2H, s, Bn-H), 1.56 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 171.0, 150.0, 147.1, 139.2, 134.9, 133.7, 128.6, 127.2, 126.0 and 123.1 (aromatic), 58.4 (^{t}Bu-C), 51.4 (CH_2), 28.6 (^{t}Bu-CH_3); *m/z* (CI, NH_4^+) [Found: M^+, 268.1577. $C_{17}H_{20}N_2O$ requires 268.1576].

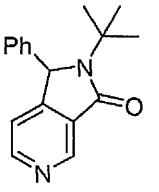
N-tert-Butyl-N-benzylquinoline-3-carboxamide 252



A solution of 3-quinoline-carboxylic acid (570 mg, 3.3 mmol) in thionyl chloride (50 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (50 ml), then triethylamine (0.69 ml, 4.95 mmol) and *N-tert*-butylbenzylamine (0.36 ml, 3.3 mmol) were added and stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml), brine (40 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 3:1 pet/EtOAc) afforded the title compound as a white crystalline solid (630 mg, 1.98 mmol, 60%); silica gel TLC R_f 0.10 (3:1 petrol/EtOAc); ν_{max}/cm^{-1} (thin film) 1632 (C=O); δ_H (300 MHz; $CDCl_3$) 8.98 (1H, d, J 2, qu-H_2), 8.17 (1H, d, J 2, qu-H_4), 8.05 (1H, d, J 9, qu-H_5 or qu-H_8), 7.7–7.6 (2H, m, qu-H_5 or qu-H_8 and qu-H_6 or qu-H_7), 7.48 (1H, td, J 1 and 6.5, qu-H_6 or qu-H_7), 7.31 (5H, m, Ph-H), 4.65 (2H, s, Bn-H), 1.56 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 171.1, 148.1, 147.8, 139.2, 133.3, 131.9, 130.2, 129.1, 128.6, 128.1, 127.2, 127.1, 126.8 and 126.0 (aromatic), 58.5 (^{t}Bu-C), 51.5 (CH_2), 28.6 (^{t}Bu-CH_3); *m/z* (CI, NH_4^+)

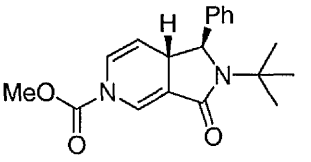
319 (100%, M+H$^+$); *m/z* (EI) 261 (45%, M–^{t}Bu), 156 (100%, M–^{t}BuNCH$_2$Ph). [Found: M+H$^+$, 319.1803. $C_{21}H_{23}N_2O$ requires 319.1805].

***2-tert-Butyl-1-phenyl-1,2-dihydro-pyrrolo[3,4-c]pyridin-3-one* 255**



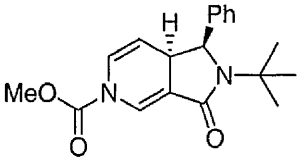
Lithium diisopropylamide solution (2.5 mmol) was added to a solution of *N*-benzyl-*N*-*tert*-butyl-nicotinamide (**251**) (134 mg, 0.5 mmol) in THF (20 ml) at –40 °C. After 10 min the reaction was quenched with aqueous ammonium chloride solution (1 ml). Ether was added (60 ml) and the aqueous layer was washed with water (3 × 20 ml) and brine (20 ml). The combined aqueous layers were further extracted with ether (20 ml), then dried ($MgSO_4$), filtered and concentrated to give a yellow oil that was a 5:1 mixture of **253** and **254**. On attempted purification with flash column chromatography (SiO_2; 1:1 petrol:EtOAc) this mixture rearomatised to furnish the title compound as a colourless oil (131 mg, 0.49 mmol, 98%); silica gel TLC R_f 0.1 (ether); ν_{max}/cm^{-1} (thin film) 1686 (C=O); δ_H (300 MHz; $CDCl_3$) 9.10 (1H, s, py-H$_2$), 8.63 (1H, d, *J* 5, py-H$_6$), 7.4–7.2 (5H, m, Ph-H) 7.04 (1H, dd, *J* 0.5 and 5, py-H$_5$), 5.75 (1H, s, Bn-H), 1.50 (9H, s, *t*-Bu-H); δ_C (125 MHz; $CDCl_3$) 168.6 (C=O), 155.0, 151.9, 146.1, 139.6, 129.8, 128.9, 128.3, 126.6 and 118.0 (aromatic), 65.2 (^{t}Bu-C), 56.8 (Bn-C), 28.9 (^{t}Bu-CH$_3$); *m/z* (CI) 267 (100%, M+H$^+$). [Found: M+H$^+$, 267.1487. $C_{17}H_{19}N_2O$ requires 267.1492].

***(1S/R,7aS/R)-Methyl 2-tert-butyl-2,3-dihydro-3-oxo-1-phenyl-1H-pyrrolo[3,4-c]pyridine-5(7aH)-carboxylate* 257**



Lithium diisopropylamide solution (2.5 mmol) was added to a solution of *N*-benzyl-*N*-*tert*-butyl-nicotinamide (**251**) (134 mg, 0.5 mmol) in THF (20 ml) at –40 °C. After 10 min the reaction was quenched with methyl chloroformate (0.194 ml, 2.5 mmol). Ether was added (60 ml), and the organic fraction was washed with water (3 × 20 ml) and brine (20 ml), and the combined aqueous layers were further extracted with ether (20 ml). The combined organics were dried (Na_2SO_4), filtered and concentrated to yield a brown oil. This was purified by column chromatography (SiO_2; 4:1 petrol:EtOAc) to give the title compound as the major product as a colourless oil (131 mg, 0.40 mmol, 80%); silica gel TLC R_f 0.44 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1735 (C=O), 1687 (lactam C=O); δ_H (300 MHz; $CDCl_3$) 7.70–7.50 (1H, br, py-H_2), 7.42–7.14 (5H, m, Ph-H), 6.64–6.49 (1H, br, py-H_6), 5.02 (1H, d, *J* 9, Bn-H), 4.39–4.22 (1H, br, py-H_5), 3.95 (1H, m, py-H_4), 3.84 (3H, s, OCH_3), 1.39 (9H, s, ^{t}Bu-H).

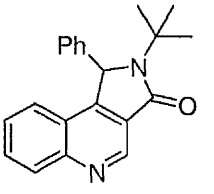
***(1S/R,7aR/S)-Methyl 2-tert-butyl-2,3-dihydro-3-oxo-1-phenyl-1H-pyrrolo[3,4-c]pyridine-5(7aH)-carboxylate* 258**



Lithium diisopropylamide solution (2.5 mmol) was added to a solution of *N*-benzyl-*N*-*tert*-butyl-nicotinamide (**251**) (134 mg, 0.5 mmol) in THF (20 ml) at –40 °C. After

10 min the reaction was quenched with methyl chloroformate (0.194 ml, 2.5 mmol). Ether was added (60 ml), and the organics were washed with water (3 × 20 ml), and brine (20 ml). The combined aqueous layers were re-extracted with ether (20 ml), dried (Na_2SO_4), filtered and concentrated to yield a brown oil. This was purified by column chromatography (SiO_2; 1:1 petrol:EtOAc) to give the title compound as the minor product as a colourless oil (13 mg, 0.04 mmol, 16%); silica gel TLC R_f 0.54 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1738 (C=O), 1693 (lactam C=O); δ_H (300 MHz; $CDCl_3$) 7.62–7.18 (6H, br-m, Ph-H and py-H_2), 6.99–6.84 (1H, br, py-H_6), 5.13–5.08 (1H, br, py-H_5), 4.44 (1H, d, *J* 7, Bn-H), 3.91 (3H, s, OCH_3), 3.13 (1H, m, py-H_4), 1.32 (9H, s, ^{t}Bu-H).

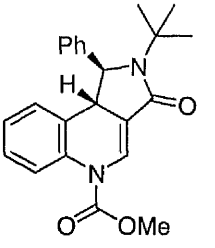
***2-tert-Butyl-1,2-dihydro-1-phenylpyrrolo[3,4-c]quinolin-3-one* 261**



Lithium diisopropylamide solution (0.75 mmol) was added to a solution of *N-tert*-butyl-*N*-benzylquinoline-3-carboxamide (**252**) (80 mg, 0.25 mmol) in THF (10 ml) at –40 °C. After 10 min, the reaction was quenched with saturated aqueous ammonium chloride solution (1 ml). Ether was added (30 ml) and the organic layer was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with ether (10 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to yield a pale yellow oil. This was purified by flash column chromatography (SiO_2; 7:3 petrol:EtOAc) to furnish the title compound as a white crystalline solid (56 mg, 0.18 mmol, 72%); mp 239–240 °C; silica gel TLC R_f 0.49 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1670 (C=O); δ_H (300 MHz; $CDCl_3$) 8.60 (1H,

s, qu-H_2), 8.05 (1H, d, *J* 8, qu-H_8), 7.98 (1H, dd, *J* 8 and 1, qu-H_5), 7.74 (1H, ddd, *J* 9, 7 and 2, qu-H_7), 7.57 (1H, ddd, *J* 8, 7 and 1, qu-H_6), 7.38–7.27 (5H, m, Ph-H), 5.89 (1H, s, CH), 1.55 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 167.9 (C=O), 164.3, 150.3, 139.7, 132.6, 131.3, 129.6, 129.6, 129.3, 128.4, 127.9, 127.2, 127.0 and 124.3 (aromatic), 66.7 (^{t}Bu), 56.8 (CH), 28.9 (^{t}Bu); *m/z* (CI) 317 (100%, $M+H^+$); *m/z* (EI) 316 (55%, M^+), 301 (100%, $M-CH_3$). [Found: $M+H^+$, 317.1651. $C_{21}H_{21}N_2O$ requires 317.1648].

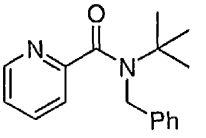
***2-tert-Butyl-2,3-dihydro-3-oxo-1-phenyl-1H-pyrrolo[3,4-c]quinoline-5(9bH)-carboxylate* 262**



Lithium diisopropylamide solution (0.354 mmol) was added to a solution of *N-tert*-butyl-*N*-benzylquinoline-3-carboxamide (**252**) (60 mg, 0.12 mmol) in THF (10 ml) at –40 °C. After 10 min, the reaction was quenched with methyl chloroformate (0.03 ml, 0.354 mmol). Ether was added (30 ml) and the organic layer was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with ether (10 ml) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield a pale yellow oil. This was purified by flash column chromatography (SiO_2; 4:1 petrol:EtOAc) to furnish the title compound as a colourless oil (59 mg, 0.16 mmol, 84%); silica gel TLC R_f 0.55 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1731 (lactam C=O), 1681 (C=O); δ_H (300 MHz; $CDCl_3$) 7.61 (1H, d, *J* 8, qu-H_8), 7.26 (5H, s, Ph-H), 7.17–7.06 (3H, m, qu-H_2, qu-H_5 and qu-H_7), 6.94 (1H, ddd, *J* 7, 7 and 1, qu-H_6), 5.44 (1H, d, *J* 7, CH), 5.34 (1H, dd, *J* 7 and 3, qu-

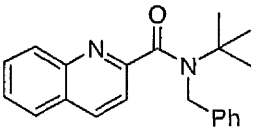
H_4), 3.80 (3H, s, OCH_3), 1.41 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 166.5 and 155.0 (C=O), 137.2, 130.9, 130.2, 129.6, 129.0, 128.6, 128.4, 125.2, 125.0, 123.4, 123.2 and 118.9 (aromatic and C=C), 65.6 (OCH_3), 58.6 (C), 56.0 (^tBu), 53.3 (CH), 28.3 (^tBu); *m/z* (CI) 377 (100%, $M+H^+$); *m/z* (EI) 187 (100%, M-PhCHN^{t}BuCO). [Found: $M+H^+$, 377.1856. $C_{23}H_{25}N_2O_3$ requires 377.1860].

***Pyridine-2-carboxylic acid benzyl-tert-butyl-amide* 265**



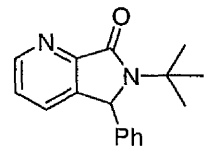
A solution of 2-picolinic acid (1.85 g, 15 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (100 ml), triethylamine (3.14 ml, 22.5 mmol) and *N-tert*-butylbenzylamine (2.78 ml, 22.5 mmol) were added and the solution was stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml) and brine (40 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; ether) afforded the title compound as an off white crystalline solid (2.53 g, 9.5 mmol, 63%); ν_{max}/cm^{-1} (thin film) 1626 (C=O); δ_H (300 MHz; $CDCl_3$) 8.54 (1H, ddd, *J* 1, 2 and 5, py-H6), 7.70 (1H, td, *J* 1.5 and 7.5, py-H_4), 7.52 (1H, dt, *J* 1 and 8, py-H_3), 7.35–7.20 (6H, m, Ph-H and py-H_5), 4.75 (2H, s, CH_2), 1.56 (9H, s, ^tBu-H); δ_C (75 MHz; $CDCl_3$) 171.1, 156.7, 148.3, 139.7, 136.8, 128.3, 126.8, 126.4, 123.6 and 122.5 (aromatic), 58.3 (^tBu-C), 50.5 (CH_2), 28.6 (^tBu-CH_3).

***N-tert-butyl-N-benzylquinoline-2-carboxamide* 266**



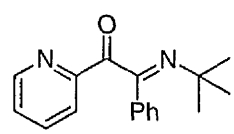
A solution of quinaldic acid (1.39 g, 8 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane (100 ml), triethylamine (1.7 ml, 12 mmol) and *N-tert*-butyl benzylamine were added and the solution was stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml) and brine (40 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 3:7, ether:petrol) afforded the title compound as an off white crystalline solid (1.69 g, 5.3 mmol, 66%); mp 132–133 °C; silica gel TLC R_f 0.76 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1634 (C=O); δ_H (300 MHz; $CDCl_3$) 8.07 (1H, d, *J* 8.5, qu-H4), 7.90 (1H, d, *J* 8.5, qu-H3), 7.69 (1H, d, *J* 8, qu-H8 or qu-H5), 7.59 (1H, t, *J* 8, qu-H6 or qu-H7), 7.53 (1H, d, *J* 8.5, qu-H8 or qu-H5), 7.45 (1H, t, *J* 8, qu-H6 or qu-H7) 7.3–7.1 (5H, m, Ph-H), 4.71 (2H, s, CH), 1.49 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 156.1, 140.0, 137.6, 130.3, 129.5, 128.6, 128.5, 127.9, 127.8, 127.5, 127.1, 126.9, 120.3 (aromatic), 59.0 (^{t}Bu-C), 51.0 (CH_2), 28.9 (^{t}Bu-CH_3); *m/z* (CI) 319 (100%, $M+H^+$), 263 (90%, M-^{t}Bu) [Found: $M+H^+$, 319.1812. $C_{21}H_{23}N_2O$ requires 319.1805].

***6-tert-Butyl-5-phenyl-5,6-dihydro-pyrrolo[3,4-b]pyridin-7-one* 267**



A solution of pyridine-2-carboxylic acid benzyl-*tert*-butyl-amide (**265**) (134 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (1 mmol) in THF (15 ml) at 0 °C *via* cannula. After stirring overnight at 0 °C the reaction was quenched with aqueous NH_4Cl. Water was added (20 ml) and this was extracted with ether (2 × 20 ml), the combined ether layers were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2; 3:7 petrol:EtOAc) to give the title compound as a brown oil (38 mg, 0.14 mmol, 28%); silica gel TLC R_f 0.24 (1:4 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1692 (C=O); δ_H (300 MHz; $CDCl_3$) 8.74 (1H, dd, *J* 1.5 and 4.5, py-H_6), 7.42 (1H, dd, *J* 0.5 and 1.5, py-H_4), 7.4–7.2 (6H, m, Ph-H and py-H_5), 5.73 (1H, s, Bn-H), 1.52 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 167.8 (C=O), 150.8, 149.6, 140.3, 139.6, 130.7, 129.2, 128.2, 126. and 125.3 (aromatic), 62.5 (^{t}Bu-C), 56.5 (CH), 28.3 (^{t}Bu-CH_3); *m/z* (CI) 267 (100%, $M+H^+$). [Found: M^+, 266.1420. $C_{17}H_{18}N_2O$ requires 266.1419].

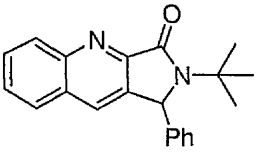
***(E)-2-(tert-butylimino)-2-phenyl-1-(pyridin-2-yl)ethanone* 268**



A solution of pyridine-2-carboxylic acid benzyl-*tert*-butyl-amide (**265**) (134 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (1 mmol) in THF (15 ml) at 20 °C *via* cannula. After stirring overnight at 20 °C the reaction was

quenched with aqueous NH_4Cl. Water was added (20 ml) and this was extracted with ether (2 × 20 ml), the combined ether layers were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2; 3:7 petrol:EtOAc) to give the title compound as a brown oil (36 mg, 0.14 mmol, 27%); silica gel TLC R_f 0.68 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1674 (C=O); δ_H (300 MHz; $CDCl_3$) 8.56 (1H, dd, *J* 5 and 2, py-H_6), 7.74–7.61 (3H, m, Ar-H), 7.47–7.41 (2H, m, Ar-H), 7.36–7.29 (2H, m, Ar-H), 1.28 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 195.0 (C=O), 162.2 (C=N), 148.9, 148.3, 137.1, 136.3, 136.1, 132.7, 129.0, 128.3 and 125.3 (aromatic), 51.0 (^{t}Bu-C), 28.5 (^{t}Bu-CH_3).

***2-tert-Butyl-1,2-dihydro-1-phenylpyrrolo[3,4-b]quinolin-3-one* 269**

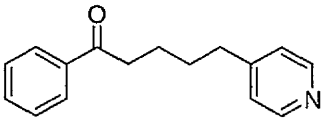


A solution of *N*-tert-butyl-*N*-benzylquinoline-2-carboxamide (**266**) (158 mg, 0.5 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (15 mmol) in THF (15 ml) at 0 °C *via* cannula. After stirring at 0 °C overnight, the reaction was quenched with aqueous NH_4Cl. Water was added (20 ml) and this was extracted with ether (2 × 20 ml), the combined ether layers were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2; 3:7 petrol:EtOAc) to give the title compound as a light brown oil (49 mg, 0.16 mmol, 31%); silica gel TLC R_f 0.18 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1682 (C=O); δ_H (300 MHz; $CDCl_3$) 8.38 (1H, d, *J* 9, qu-H_4), 7.86–7.72 (3H, m, qu-H_5, qu-H_7 and qu-

H_8), 7.62–7.55 (1H, t, *J* 7, qu-H_6), 7.42–7.28 (5H, m, Ph-H), 5.88 (1H, s, CH), 1.57 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 167.5 (C=O), 151.0, 149.4, 140.9, 136.0, 131.1, 130.7, 130.2, 129.6, 129.2, 128.5, 128.1, 128.0, 126.4 (aromatic), 62.8 (CH), 57.2 (^{t}Bu-C), 26.4 (^{t}Bu-CH_3); *m/z* (CI) 317 (100%, $M+H^+$). [Found: $M+H^+$, 316.1576. $C_{21}H_{20}N_2O$ requires 316.1570].

5.3 Experimental for Chapter Three

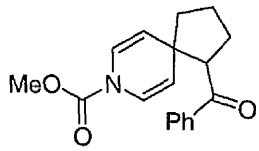
1-Phenyl-5-(pyridin-4-yl)pentan-1-one **281**



Methanesulphonyl chloride (11 mmol, 0.85 ml) was added to a stirred solution of 4-pyridine propanol (10 mmol, 1.37 g) and triethylamine (11 mmol, 1.55 ml) in dichloromethane (50 ml) at 0 °C. After 30 min, the reaction mixture was diluted with dichloromethane (50 ml), washed with water (3 × 30 ml) and brine (30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil which was not isolated due to polymerisation. The resulting oil was dissolved in acetone (50 ml) and sodium iodide was added (11 mmol, 1.65 g). This solution was stirred under reflux for 2 h. After this time the white precipitate was removed by filtration, the solvent was removed under reduced pressure, dichloromethane was added (100 ml) and the solution was washed with 10% sodium thiosulphate solution (30 ml), water (2 × 30 ml) and brine (30 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a brown oil that was not isolated due to rapid polymerisation. This oil was dissolved in acetone (50 ml) and ethyl 3-oxo-3-phenylpropanoate (11 mmol, 1.90 ml) was added followed by potassium carbonate (12 mmol, 1.66 g) and the mixture was refluxed overnight. The solvent was removed under reduced pressure and the product was decarboxylated by heating under reflux in a solution of 2 M sodium hydroxide (30 ml) and ethanol (15 ml) for 4 h. The ethanol was removed under reduced pressure, dichloromethane was added (100 ml), the solution was washed with water (3 × 40 ml) and brine (40 ml), and the combined aqueous layers were re-extracted with dichloromethane (40 ml). The combined

organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil that was purified by flash column chromatography (SiO_2, 1:1 petrol:EtOAc) to give the title compound as a pale yellow crystalline solid (1.07 g, 4.47 mmol, 45%); mp 42–44 °C; silica gel TLC R_f 0.18 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1685 (C=O); δ_H (300 MHz; $CDCl_3$) 8.51 (2H, dd, *J* 5 and 2, py-H_2 and py-H_6), 7.99–7.92 (2H, m, Ph-H), 7.64–7.45 (3H, m, Ph-H), 7.17 (2H, dd, *J* 5 and 2, py-H_3 and py-H_5), 3.03 (2H, t, *J* 7, CH_2), 2.71 (2H, t, *J* 8, CH_2), 1.89–1.69 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 200.2 (C=O), 151.5, 149.8, 137.2, 133.3, 128.9, 128.3 and 124.2 (aromatic), 38.4, 35.4, 30.1 and 24.0 (CH_2); *m/z* (CI) 240 (100%, $M+H^+$); *m/z* (EI) 105 (80%, PhCO), 77 (100%, C_6H_5). [Found: M^+, 239.1298. $C_{16}H_{17}NO$ requires 239.1305].

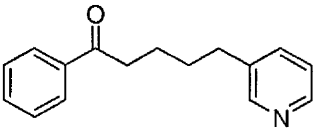
***1-Benzoyl-8-aza-spiro[4.5]deca-6,9-diene-8-carboxylic acid methyl ester* 283**



Lithium diisopropylamide solution (0.275 mmol) was added to a solution of 1-phenyl-5-(pyridin-4-yl)pentan-1-one (**281**) (60 mg, 0.25 mmol) in THF (10 ml) at –78 °C. After 10 min, the enolate was quenched with methyl chloroformate (0.021 ml, 0.275 mmol) and allowed to warm to room temperature. Diethyl ether was added (30 ml) and the solution was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with ether (10 ml) before the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow oil. This was purified using flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to give the title product as a colourless oil (14 mg, 0.047 mmol, 19%); silica gel TLC R_f 0.26 (petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1728 (ketone C=O), 1674

(amide C=O); δ_H (300 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8, Ph-H), 7.53 (3H, m, Ph-H), 6.79-6.40 (2H, br-m, py-H_2 and py-H_6), 5.07-4.70 (2H, br-m, py-H_3 and py-H_5), 3.76-3.62 (4H, m, OCH_3 and CH), 2.41-2.23 (1H, m, CH_2), 2.00-1.72 (5H, m, CH_2); *m/z* (CI, NH_4^+) 298 (100%, $M+H^+$), 240 (65%, $M-CO_2Me$). [Found: M^+, 297.1370. $C_{18}H_{19}NO_3$ requires 297.1365].

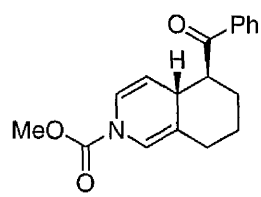
***1-Phenyl-5-(pyridin-3-yl)pentan-1-one* 292**



Methanesulphonyl chloride (22 mmol, 1.70 ml) was added to a stirred solution of 3-pyridine propanol (20 mmol, 2.74 g) and triethylamine (22 mmol, 3.09 ml) in dichloromethane (100 ml) at 0 °C. After 30 min, the reaction mixture was diluted with dichloromethane (100 ml), washed with water (3 × 60 ml) and brine (60 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil which was not isolated due to polymerisation. The resulting oil was dissolved in acetone (100 ml) and sodium iodide was added (22 mmol, 3.30 g), this solution was stirred under reflux for 2 h. After this time the white precipitate was removed by filtration, the solvent was removed under reduced pressure, dichloromethane was added (200 ml) and the solution was washed with 10% sodium thiosulphate solution (60 ml), water (2 × 60 ml) and brine (60 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a brown oil that was not isolated due to rapid polymerisation. This oil was dissolved in acetone (100 ml) and 3-oxo-3-phenylpropanoate (22 mmol, 3.81 ml) was added followed by potassium carbonate (24 mmol, 3.32 g) and the mixture was refluxed overnight. The solvent was removed under reduced pressure and the product was decarboxylated by heating under reflux in

a solution of 2 M sodium hydroxide (60 ml) and ethanol (30 ml) for 4 h. The ethanol was removed under reduced pressure, dichloromethane was added (200 ml), and the solution was washed with water (3 × 80 ml) and brine (80 ml). The combined aqueous layers were re-extracted with dichloromethane (80 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown oil that was purified by flash column chromatography (SiO_2, 1:1 petrol:EtOAc) to give the title compound as a pale yellow crystalline solid (1.62 g, 6.78 mmol, 34%); mp 44–47 °C silica gel TLC R_f 0.17 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1685 (C=O); δ_H (300 MHz; $CDCl_3$) 8.49 (2H, br, py-H_2 and py-H_6), 8.01–7.95 (2H, m, Ph-H), 7.62–7.45 (4H, m, Ph-H and py-H_4), 7.24 (1H, dd, *J* 8 and 5, py-H_5), 3.03 (2H, d, *J* 7, CH_2), 2.70 (2H, d, *J* 7, CH_2), 1.89–1.69 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 200.2 (C=O), 150.1, 147.5, 137.7, 137.2. 136.2, 133.3, 128.9, 128.3 and 123.6 (aromatic), 38.5, 33.2, 30.1 and 24.0 (CH_2); *m/z* (CI) 240 (100%, M+H^+); *m/z* (EI) 239 (5%, M^+), 105 (45%, PhCO), 77 (100%, C_6H_5). [Found: M^+, 239.1307. $C_{16}H_{17}NO$ requires 239.1305].

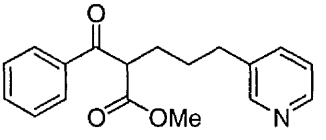
***(4aR/S,5S/R)-5-Benzoyl-5,6,7,8-tetrahydro-4aH-isoquinoline-2-carboxylic acid methyl ester* 293**



Methyl chloroformate (0.056 ml, 0.722 mmol) was added to a solution of 3-((Z)-5-phenyl-5-trimethylsilanyloxy-pent-4-enyl)-pyridine (**295**) (45 mg, 0.144 mmol) and triethylamine (0.02 ml, 0.144 mmol) in dichloromethane (5 ml) at –78 °C. After warming to room temperature, dichloromethane was added (30 ml), and the solution

was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with dichloromethane (10 ml) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to furnish a light yellow oil. This was purified using flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to yield the title compound as a colourless oil (40 mg, 0.135 mmol, 93%); silica gel TLC R_f 0.38 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1721 (amide C=O), 1677 (ketone C=O); δ_H (500 MHz; $CDCl_3$) 7.80 (2H, d, *J* 7, Ph-H), 7.41 (1H, t, *J* 8, Ph-H), 7.32 (2H, t, *J* 8, Ph-H), 6.67 (1H, br, py-H_2), 6.54 (1H, br, py-H6) 4.60 (2H, br, py-H_5); 3.64 (3H, br, OCH_3), 3.33 (2H, m, py-H_4 and CH), 2.1–1.3 (6H, br-m, CH_2) δ_C (125 MHz; $CDCl_3$) 202.9 (ketone C=O), 152.2 (amide C=O), 137.3, 133.6, 129.1 and 128.8 (aromatic), 123.4 and 123.0 (py-C_6), 120.9 and 119.9 (py-C_3), 117.1 and 116.8 (py-C_2), 108.1 and 107.7 (py-C_5), 60.8 (py-C_4), 53.8 and 53.7 (OCH_3), 38.0 and 37.8 (CH), 32.5 and 32.4 (CH_2), 31.7 and 31.6 (CH_2), 27.5 (CH_2); *m/z* (CI) 298 (100%, $M+H^+$), 238 (40%, M-CO_2Me); *m/z* (EI) 297 (10%, M^+). [Found: $M+H^+$, 298.1436. $C_{18}H_{20}NO_3$ requires 298.1438].

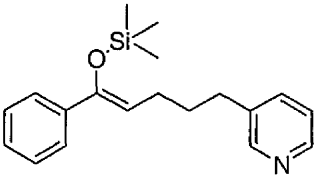
***2-Benzoyl-5-pyridin-3-yl-pentanoic acid methyl ester* 294**



Potassium hexamethyl disilazide (0.275 mmol) was added to a solution of 1-phenyl-5-(pyridin-3-yl)pentan-1-one (60 mg, 0.25 mmol) in THF (10 ml) at –78 °C. After stirring for 1 h at –78 °C, methyl chloroformate was added (0.021 ml, 0.275 mmol) before the solution was allowed to warm to room temperature. Ether was added (30 ml), and the solution was washed with water (3 × 10 ml) and brine (10 ml). The

combined aqueous layers were then re-extracted with ether (10 ml) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. This was purified by flash column chromatography (SiO_2; 7:3 petrol:EtOAc) to yield the title compound as a colourless oil (62 mg, 0.209 mmol, 84%); silica gel TLC R_f 0.30 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1762 (C=O); δ_H (500 MHz; $CDCl_3$) 8.45 (2H, br, py-H_2 and py-H_6), 7.54-7.23 (7H, Ph-H, py-H_3 and py-H_5), 5.71 (1H, t, *J* 7, CH), 3.77 (3H, s, OCH_3), 2.64 (2H, t, *J* 8, CH_2), 2.19 (2H, q, *J* 7, CH_2), 1.72 (2H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 153.9, 149.1, 147.5, 146.6, 137.3, 134.8, 128.9, 128.7, 124.7, 124.0 and 117.6 (C=O and aromatic), 55.8 (OCH_3), 32.8, 30.4 and 25.6 (CH_2); *m/z* (CI, NH_4^+) 298 (100%, $M+H^+$). [Found: $M+H^+$, 297.1360. $C_{18}H_{19}NO_3$ requires 297.1359].

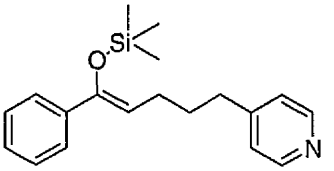
***3-((Z)-5-Phenyl-5-trimethylsilanyloxy-pent-4-enyl)-pyridine* 295**



n-Butyllithium solution (1.1 mmol) was added to a stirred solution of diisopropylamine (1.1 mmol, 0.16 ml) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –78 °C and a solution of the ketone 1-phenyl-5-(pyridin-3-yl)pentan-1-one (**292**) (1.0 mmol, 239 mg) in THF (5 ml) was added *via* cannula. After 10 min, chlorotrimethylsilane (1.2 mmol, 0.15 ml) was added and the solution was allowed to warm to room temperature. Diethyl ether was added (60 ml) and the organic fraction was washed with sat. sodium hydrogen carbonate solution (20 ml), water (2 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with diethyl ether (20 ml), the combined organic layers were dried (Na_2SO_4), filtered

and concentrated under reduced pressure to give a light yellow oil. This was purified by flash column chromatography (SiO_2, 4:1 petrol:EtOAc) to yield the title compound as a colourless oil (299 mg, 0.96 mmol, 96%); silica gel TLC R_f 0.51 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1648 (C=C), 1252 ($SiMe_3$), 1057 (Si–O), 844 ($SiMe_3$); δ_H (300 MHz; $CDCl_3$) 8.52 (1H, s, py-H_2), 8.48 (1H, d, *J* 5, py-H_6), 7.56 (1H, d, *J* 8, py-H_4), 7.51–7.47 (2H, m, Ph-H), 7.38–7.22 (4H, m, Ph-H and py-H_3), 5.28 (1H, t, *J* 7, CH), 2.72 (2H, t, *J* 8, CH_2), 2.28 (2H, dt, *J* 8 and 8, CH_2), 1.80 (2H, tt, *J* 8 and 8, CH_2), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 150.3, 149.9, 147.5, 139.3, 137.9, 136.2, 128.3, 127.8, 125.6, 123.5 and 110.6 (aromatic and C=C), 33.0, 31.4 and 25.9 (CH_2), 0.8 ($Si(CH_3)_3$); *m/z* (CI) 312 (80%, $M+H^+$), 240 (100%, hydrolysed). [Found: M^+, 311.1257. $C_{19}H_{25}NOSi$ requires 311.1705].

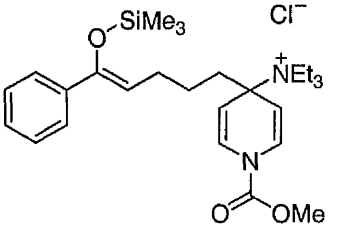
***4-((Z)-5-Phenyl-5-trimethylsilanyloxy-pent-4-enyl)-pyridine* 296**



n-Butyllithium solution (1.1 mmol) was added to a stirred solution of diisopropylamine (1.1 mmol, 0.16 ml) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –78 °C and a solution of the ketone 1-phenyl-5-(pyridin-4-yl)pentan-1-one (**281**) (1.0 mmol, 240 mg) in THF (5 ml) was added *via* cannula. After 10 min chlorotrimethylsilane (1.2 mmol, 0.15 ml) was added and the solution was allowed to warm to room temperature. After this time, diethyl ether was added (60 ml) and the organic layer was washed with sat. sodium hydrogen carbonate solution (20 ml), water (2 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with diethyl ether (20 ml), and the combined organic layers were

dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light yellow oil. This was purified by flash column chromatography (SiO_2, 4:1 petrol:EtOAc) to yield the title compound as a colourless oil (298 mg, 0.96 mmol, 96%); silica gel TLC R_f 0.22 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1647 (C=C), 1252 ($SiMe_3$), 1055 (Si–O), 843 ($SiMe_3$); δ_H (300 MHz; $CDCl_3$) 8.51 (2H, d, *J* 5, py-H_2 and py-H_6), 7.49–7.44 (2H, m, Ph-H), 7.36–7.22 (3H, m, Ph-H), 7.16 (2H, d, *J* 5, py-H_3 and py-H_5), 5.24 (1H, t, *J* 7, CH), 2.68 (2H, t, *J* 8, CH_2), 2.24 (2H, dt, *J* 8 and 8, CH_2), 1.78 (2H, tt, *J* 8 and 8, CH_2), 0.11 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 152.0, 150.0, 149.6, 139.2, 128.3, 127.8, 125.6, 124.3 and 110.5 (aromatic and C=C), 35.2, 30.5 and 25.9 (CH_2), 0.8 ($Si(CH_3)_3$); *m/z* (CI) 312 (10%, $M+H^+$), 240 (100%, M-$Si(CH_3)_3$); *m/z* (EI) 311 (60%, M^+), 105 (90%, PhCO), 77 (45%, C_6H_5), 73 (100%, $Si(CH_3)_3$). [Found: M^+, 311.1703. $C_{19}H_{25}NOSi$ requires 311.1700].

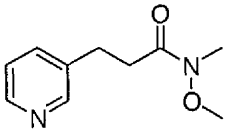
***Triethyl-[1-methoxycarbonyl-4((Z)-5-phenyl-5-trimethylsilanyloxy-pent-4-enyl)-1,4-dihydro-pyridin-4-yl]-ammonium chloride* 297**



Methyl chloroformate (0.056 ml, 0.722 mmol) was added to a solution of 4-((Z)-5-phenyl-5-trimethylsilanyloxy-pent-4-enyl)-pyridine (**296**) (45 mg, 0.144 mmol) and triethylamine (0.02 ml, 0.144 mmol) in dichloromethane (5 ml) at –78 °C. After warming to room temperature, the crude solution was concentrated under reduced pressure to furnish an impure sample of the title compound as an unstable light yellow oil δ_H (200 MHz; $CDCl_3$) 7.50–7.39 (2H, m, Ph-H), 7.36-7.20 (3H, m, Ph-H), 6.80

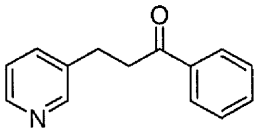
(2H, br, py-H_2 and py-H_6), 6.73 (2H, br, py-H_3 and py-H_5), 5.23 (1H, t, *J* 7, CH), 3.84 (3H, s, OCH_3), 3.70-3.52 (2H, m, CH_2), 3.08 (6H, q, *J* 8, CH_2), 2.31-2.18 (4H, m, CH_2), 0.11 (9H, s, $Si(CH_3)_3$).

***N-Methoxy-N-methyl-3-(pyridin-3-yl)propanamide* 299**



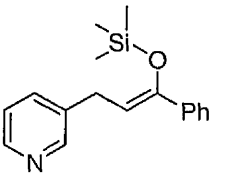
Thionyl chloride (50 ml) was added to 3-(3-pyridyl)propionic acid (1.33 g, 8.8 mmol) and the mixture was stirred overnight at room temperature. The thionyl chloride was then removed under reduced pressure and the resulting acid chloride was dissolved in dichloromethane (50 ml) and cooled to 0 °C. A solution of *N*-methoxymethanamine (0.95 g, 9.68 mmol) and triethylamine (3.67 ml, 26.4 mmol) in dichloromethane was added and the solution was allowed to warm to room temperature. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 50 ml) and brine (50 ml), then dried ($MgSO_4$) and concentrated to afford a light brown oil purified by column chromatography (SiO_2, 5% MeOH in EtOAc) to afford the title compound as a thick colourless oil (1.28 g, 6.58 mmol, 68%); silica gel TLC R_f 0.30 (5% MeOH in EtOAc); ν_{max}/cm^{-1} (thin film) 1660 (C=O); δ_H (300 MHz; $CDCl_3$) 8.53 (1H, s, py-H_2), 8.48 (1H, d, *J* 4, py-H_6), 7.61 (1H, d, *J* 8, py-H_4), 7.25 (1H, dd, *J* 8 and 5, py-H_5), 3.64 (3H, s, CH_3), 3.20 (3H, s, CH_3), 3.00 (2H, t, *J* 8, CH_2), 2.78 (2H, t, *J* 8, CH_2); δ_C (75 MHz; $CDCl_3$) 150.0, 147.7, 137.1, 136.6 and 123.7 (aromatic), 61.5 (O-CH_3), 33.5 (CH_2), 32.5 (N-CH_3), 28.0 (CH); *m/z* (CI, NH_4^+) 195 (100%, $M+H^+$); *m/z* (EI) 134 (100%, M-C_2H_6NO). [Found: $M+H^+$, 195.1126. $C_{10}H_{14}N_2O_2$ requires 195.1128].

1-Phenyl-3-(pyridin-3-yl)propan-1-one **300**



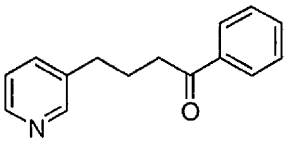
Phenyllithium (7.11 mmol) was added to a solution of *N*-methoxy-*N*-methyl-3-(pyridin-3-yl)propanamide (**301**) (920 mg, 4.74 mmol), in tetrahydrofuran (50 ml) at –78 °C. The reaction mixture was stirred at 0 °C for 1 h, then poured into 5% hydrochloric acid in ethanol at 0 °C (50 ml). After being stirred for 30 min, the mixture was neutralised ($NaHCO_3$) and the organics were removed under reduced pressure. The residue was diluted with dichloromethane (100 ml), washed with water (3 × 50 ml) and brine (50 ml), then the combined aqueous layers were re-extracted with dichloromethane (30 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a light brown oil, which was purified by flash column chromatography (SiO_2, 1:1 petrol:EtOAc) to afford the title compound as a colourless oil (732 mg, 3.46 mmol, 73%); silica gel TLC R_f 0.13 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1681 (C=O); δ_H (300 MHz; $CDCl_3$) 8.58 (1H, s, py-H_2), 8.49 (1H, dd, *J* 5 and 1, py-H_6), 8.01–7.96 (2H, m, Ph-H), 7.66–7.57 (2H, m, py-H and Ph-H), 7.53–7.45 (2H, m, Ph-H), 7.26 (1H, dd, *J* 8 and 5, py-H_5), 3.36 (2H, t, *J* 8, CH_2), 3.12 (2H, t, *J* 7, CH_2); δ_C (75 MHz; $CDCl_3$) 198.7 (C=O), 150.1, 147.8 and 137.0 (py), 136.9 (Ph), 136.5 (py), 133.6, 129.0 and 128.3 (Ph), 123.7 (py), 40.0 and 27.4 (CH_2); *m/z* (CI, NH_4^+) 212 (100%, $M+H^+$); *m/z* (EI) 105 (100%, PhCO), 77 (80%, C_6H_5). [Found: M^+, 211.0984. $C_{14}H_{13}NO$ requires 211.0992].

3-((Z)-3-Phenyl-3-trimethylsilanyloxy-allyl)-pyridine **301**



n-Butyllithium solution (1.1 mmol) was added to a stirred solution of diisopropylamine (1.1 mmol, 0.16 ml) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –78 °C and a solution of 1-phenyl-3-(pyridin-3-yl)propan-1-one (**300**) (1.0 mmol, 211 mg) in THF (5 ml) was added *via* cannula. After 10 min chlorotrimethylsilane (1.2 mmol, 0.15 ml) was added and the solution was allowed to warm to room temperature. After this time, diethyl ether was added (60 ml) and the organics were washed with saturated sodium hydrogen carbonate solution (20 ml), water (2 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with diethyl ether (20 ml), then the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light yellow oil. This was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to yield the title compound as a colourless oil (265 mg, 0.94 mmol, 94%); silica gel TLC R_f 0.48 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1645 (C=C), 1253 ($SiMe_3$), 1097 and 1025 (Si–O_2), 847 ($SiMe_3$); δ_H (300 MHz; $CDCl_3$) 8.56 (1H, d, *J* 2, py-H_2), 8.47 (1H, dd, *J* 5 and 1, py-H_6), 7.60 (1H, dt, *J* 8 and 2, py-H_4), 7.54–7.48 (2H, m, Ph-H), 7.37–7.26 (3H, m, Ph-H), 7.22 (1H, dd, *J* 8 and 5, py-H_5), 5.38 (1H, t, *J* 7, CH), 3.58 (2H, d, *J* 7, CH_2), 0.17 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 151.0, 150.1, 147.6, 138.9, 137.1, 136.2, 128.4, 128.2, 125.9, 123.6, 108.5 (aromatic or C=C); *m/z* (CI, NH_4^+) 284 (5% $M+H^+$), 212 (60%, hydrolysed+H^+), *m/z* (EI) 283 (25%, M^+), 105 (100%, PhCO), 77 (90%, C_6H_5). [Found: $M+H^+$, 284.1461. $C_{17}H_{22}NOSi$ requires 284.1465].

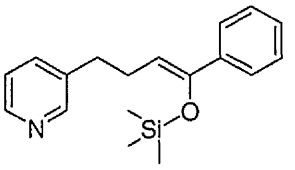
***1-phenyl-4-(pyridin-3-yl)butan-1-one* 305**



Methanesulphonyl chloride (22 mmol, 1.70 ml) was added to a stirred solution of 3-pyridine propanol (20 mmol, 2.74 g) and triethylamine (22 mmol, 3.09 ml) in dichloromethane (100 ml) at 0 °C. After 30 min, the reaction mixture was diluted with dichloromethane (100 ml), washed with water (3 × 60 ml) and brine (60 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil which was not isolated due to polymerisation. The resulting oil was dissolved in acetone (100 ml) and sodium iodide was added (22 mmol, 3.30 g), this solution was stirred under reflux for 2 h. The white precipitate was removed by filtration and the solvent was removed under reduced pressure, dichloromethane was added (200 ml) and the solution was washed with 10% sodium thiosulphate solution (60 ml), water (2 × 60 ml), brine (60 ml), dried ($MgSO_4$) and concentrated under reduced pressure to yield a brown oil that was not isolated due to rapid polymerisation. This oil was dissolved in THF (40 ml) and added to a solution of 2-lithio-2-phenyl-1,3-dithiane synthesised by adding *n*-butyllithium (11 mmol) dropwise to a solution of 2-phenyl-1,3-dithiane (1.96 g, 10 mmol) in THF (30 ml) at –40 °C. This mixture was then stirred at 2.5 h at –20 °C to furnish the solution of 2-lithio-2-phenyl-1,3-dithiane. Once the iodide had been added at –40 °C, the solution was stirred at this temperature for 2 h before being quenched by the addition of water (50 ml). The aqueous layer was extracted with dichloromethane (3 × 50 ml) and the combined organic layers were washed with water (2 × 150 ml), aqueous 7% sodium hydroxide (150 ml), water (150 ml), and brine (50 ml), then dried ($MgSO_4$), filtered and evaporated under

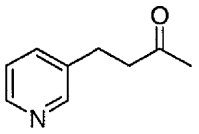
reduced pressure. The product of this reaction was inseparable from the iodide starting material. The product was dissolved in acetonitrile/water (150 ml, 8:2) and added to a mixture of mercuric chloride (5.97 g, 22 mmol) and mercuric oxide (2.38 g, 11 mmol) in acetonitrile/water (150 ml, 8:2) and heated for 4 h at 80 °C. This mixture was filtered, washed with 5 M aqueous ammonium acetate (100 ml), water (150 ml) and brine (150 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a dark brown oil. This was purified using flash column chromatography (SiO_2; 1:1 petrol:EtOAc) to yield the title compound as a colourless oil (603 mg, 2.68 mmol, 13%); silica gel TLC R_f 0.15 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1683 (C=O); δ_H (300 MHz; $CDCl_3$) 8.55–8.47 (2H, m, py-H_2 and py-H_6), 8.00–7.94 (2H, m, Ph-H), 7.63–7.57 (2H, m, Ph-H and py-H_4), 7.53–7.46 (2H, m, Ph-H), 7.31–7.24 (1H, m, py-H_5), 3.04 (2H, t, *J* 7, CH_2), 2.77 (2H, t, *J* 7, CH_2), 2.14 (2H, tt, *J* 7 and 7, CH_2); δ_C (75 MHz; $CDCl_3$) 199.8 (C=O), 150.0, 147.6, 137.3, 137.1, 136.4, 133.4, 129.0, 128.9, 128.2 and 123.7 (aromatic), 37.7, 32.5 and 25.5 (CH_2); *m/z* (CI) 226 (100%, $M+H^+$); *m/z* (EI) 105 (80%, PhCO), 77 (100%, C_6H_5). [Found: M^+, 225.1143. $C_{15}H_{15}NO$ requires 225.1148].

3-((Z)-4-Phenyl-4-trimethylsilanyloxy-but-3-enyl)-pyridine **306**



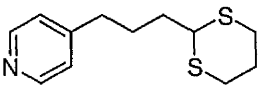
n-Butyllithium solution (1.5 mmol) was added to a stirred solution of diisopropylamine (1.5 mmol, 0.21 ml) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –78 °C and a solution of 1-phenyl-4-(pyridin-3-yl)butan-1-one (**305**) (1.0 mmol, 225 mg) in THF (5 ml) was added *via* cannula. After 10 min chlorotrimethylsilane (1.5 mmol, 0.19 ml) was added and the solution was allowed to warm to room temperature. After this time, diethyl ether was added (60 ml) and the organic fraction was washed with saturated sodium hydrogen carbonate solution (20 ml), water (2 × 20 ml) and brine (20 ml). The combined aqueous layers were re-extracted with diethyl ether (20 ml), then the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light yellow oil. This was purified by flash column chromatography (SiO_2; 4:1 petrol:EtOAc) to yield the title compound as a colourless oil (265 mg, 0.89 mmol, 89%); silica gel TLC R_f 0.39 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1648 (C=C), 1252 ($SiMe_3$), 1049 (Si–O), 844 ($SiMe_3$); δ_H (300 MHz; $CDCl_3$) 8.55 (1H, s, py-H_2), 8.50, (1H, dd, *J* 5 and 1, py-H_6), 7.60 (1H, d, *J* 8, py-H_4), 7.50–7.44 (2H, m, Ph-H), 7.37–7.24 (4H, m, Ph-H and py-H_5), 5.25 (1H, t, *J* 7, CH), 2.79 (2H, t, *J* 8, CH_2), 2.56 (2H, dt, *J* 8 and 7, CH_2), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 150.4, 150.1, 147.5, 139.2, 137.6, 136.3, 128.3, 127.9, 125.8, 123.6, 109.7 (aromatic and C=C), 33.3 and 27.9 (CH_2); *m/z* (CI) 298 (100%, $M+H^+$). [Found: $M+H^+$, 298.1623. $C_{18}H_{24}NOSi$ requires 298.1622].

4-(Pyridin-3-yl)butan-2-one **309**



1.4 M Methylmagnesium bromide (5.17 ml, 7.24 mmol) was added to a solution of *N*-methoxy-*N*-methyl-3-(pyridin-3-yl)propanamide (**299**) (1.28 g, 6.58 mmol), in tetrahydrofuran (65 ml) at –78 °C. The reaction mixture was stirred at 0 °C for 1 h, then poured into 5% hydrochloric acid in ethanol at 0 °C (50 ml). After being stirred for 30 min, the mixture was neutralised ($NaHCO_3$) and the organics were removed under reduced pressure. The residue was diluted with dichloromethane (100 ml), then washed with water (3 × 50 ml) and brine (50 ml), then the combined aqueous layers were re-extracted with dichloromethane (30 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a light brown oil. This was purified by flash column chromatography (SiO_2; 1:1 petrol:EtOAc) to afford the title compound as a colourless oil (844 mg, 5.7 mmol, 86%); silica gel TLC R_f 0.20 (1:4 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1714 (C=O); δ_H (300 MHz; $CDCl_3$) 8.48 (1H, s, py-H_2), 8.46 (1H, d, *J* 2, py-H_6), 7.54 (1H, d, *J* 8, py-H_4), 7.23 (1H, dd, *J* 8 and 2, py-H_5), 2.92 (2H, t, *J* 7, CH_2), 2.81 (2H, t, *J* 8, CH_2), 2.18 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 207.3 (C=O), 150.1, 147.9, 136.6, 136.2 and 123.6 (aromatic), 44.8 (CH_3), 30.3, 27.0 (CH_2); *m/z* (Electrospray) 150 (100%, $M+H^+$). [Found: $M+H^+$, 150.0912. $C_9H_{12}NO$ requires 150.0913].

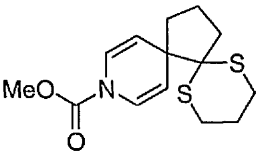
4-(3-(1,3-Dithian-2-yl)propyl)pyridine **319**



Methanesulphonyl chloride (13.2 mmol, 1.02 ml) was added to a stirred solution of 4-pyridine propanol (12 mmol, 1.65 g) and triethylamine (13.2 mmol, 1.84 ml) in dichloromethane (50 ml) at 0 °C. After 30 min, the reaction mixture was diluted with dichloromethane (50 ml), washed with water (3 × 30 ml) and brine (30 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a colourless oil which was not isolated due to polymerisation. The resulting oil was dissolved in acetone (50 ml) and sodium iodide was added (14.4 mmol, 2.16 g), this solution was stirred under reflux for 2 h. The resulting white precipitate was removed by filtration, the solvent was removed under reduced pressure, dichloromethane was added (100 ml) and the solution was washed with 10% sodium thiosulphate solution (30 ml), water (2 × 30 ml) and brine (30 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a brown oil that was not isolated due to rapid polymerisation. A stirred solution of 1,3-dithiane (1.2 g, 10 mmol) in THF (25 ml) was treated with butyllithium (12 mmol) at –25 °C. After 2 h, the previously prepared iodide was added by pipette to the solution at –78 °C, after 1 h, the solution was allowed to warm to –25 °C and held at this temeperature for 2 h. It was then left to warm to room temperature overnight. Diethyl ether (80 ml) was added and the organics were washed with water (3 × 30 ml) and brine (30 ml), then the combined aqueous layers were re-extracted with ether (30 ml). The combined organic layers were then dried ($MgSO_4$), filtered and concentrated to yield a thick dark brown oil. This was purified by flash column chromatography (SiO_2, 1:1 petrol:EtOAc) to afford the title compound as a pale yellow oil (610 mg, 2.56 mmol, 26%); silica gel TLC R_f

0.18 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2929 and 2857 (CH_2) δ_H (300 MHz; $CDCl_3$) 8.49 (2H, dd, *J* 4 and 2, py-H_2 and py-H_6), 7.11 (2H, dd, *J* 4 and 2, py-H_3 and py-H_5), 4.06 (1H, t, *J* 7, dithiane-H_2), 2.98–2.78 (4H, m, dithiane-$(CH_2)_4$ and dithiane-$(CH_2)_6$), 2.64 (2H, t, *J* 7, CH_2), 2.21–2.01 (2H, m, dithiane-$(CH_2)_5$), 2.00–2.76 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 150.3, 150.1, 149.9 and 149.3 (py-C_2 and py-C_6), 124.3, 124.2 and 124.0 (py-C_3 and py-C_5), 65.2, 54.3, 46.5, 44.1, 37.5, 35.9, 32.1, 31.3, 30.7, 30.5, 30.3, 29.7, 29.6, 29.1, 28.8, 27.8 and 26.1 (CH_2 and CH); *m/z* (CI) 240 (100%, $M+H^+$). [Found: M^+, 239.0799. $C_{12}H_{17}NS_2$ requires 239.0797].

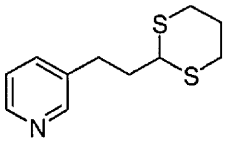
***1,5-Dithia-10-aza-dispiro[5.0.5.3]pentadeca-8,11-diene-10-carboxylic acid methyl ester* 320**



n-Butyllithium solution (0.275 mmol) was added to a stirred solution of diisopropylamine (0.04 ml, 0.275 mmol) in THF (7.5 ml) at 0 °C. After 10 min, a solution of 4-(3-(1,3-dithian-2-yl)propyl)pyridine (**318**) (60 mg, 0.25 mmol) in THF (5 ml) was added *via* cannula. After 30 min, the orange solution was quenched by addition of methyl chloroformate (0.019 ml, 0.25 mmol). Diethyl ether (30 ml) was added and the organic fraction was washed with water (3 × 10 ml) and brine (10 ml), and the combined aqueous layers were re-extracted with ether (10 ml). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated to yield a red/brown oil. This was purified by flash column chromatography (SiO_2, 4:1 petrol:EtOAc) to afford the title compound as a colourless oil (26 mg, 0.087 mmol, 35%); silica gel TLC R_f 0.43 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1727 (C=O),

1686 (C=C); δ_H (300 MHz; $CDCl_3$) 7.08–6.86 (2H, br, py-H_2 and py-H_6), 5.14–4.97 (2H, br, py-H_3 and py-H_5), 3.84 (3H, s, OCH_3), 3.01–3.82 (4H, m, dithiane-H_4 and dithiane-H_6), 2.51–2.47 (2H, m, cyclopentane-CH_2), 2.12–2.00 (1H, m, dithiane-H_5), 1.98–1.82 (5H, m, dithiane-H_5 and cyclopentane-CH_2); δ_C (75 MHz; $CDCl_3$) 151.8 (C=O), 122.8 and 122.5 (py-C_2 and py-C_6), 109.6 and 109.3 (py-C_3 and py-C_5), 65.7 (dithiane-C_2), 53.5 (OCH_3), 51.1 (py-C_4), 41.5 and 38.8 (cyclopentane-C), 27.8 (dithiane-C_4 and dithane-C_6), 25.3 (dithiane-C_5), 20.3 (cyclopentane-C); *m/z* (CI) 298 (100%, $M+H^+$); *m/z* (EI) 297 (20%, M^+). [Found: $M+H^+$, 298.0938. $C_{14}H_{20}NO_2S_2$ requires 298.0930].

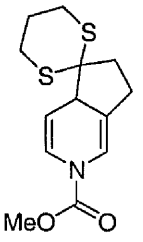
***3-(2-(1,3-Dithian-2-yl)ethyl)pyridine* 330**



Dimethyl sulfoxide (3.41 ml, 48 mmol) was added to a stirred solution of oxalyl chloride (1.92 ml, 22 mmol) in dichloromethane (80 ml) at –60°C over 5 min. After 10 min stirring, 3-(pyridin-3-yl)propan-1-ol (2.58 ml, 20 mmol) was added over 5 min. After 15 min triethylamine (13.92 ml, 100 mmol) was added over 5 min. The solution was allowed to warm to room temperature, water was added (60 ml), then after stirring for 10 min, the organic layer was separated, and the aqueous phase was re-extracted with dichloromethane (40 ml). The solution was concentrated under reduced pressure to yield the aldehyde as pale yellow oil. Acetyl chloride (5 ml, 70.31 mmol) was added dropwise to methanol (50 ml) at 0 °C and the mixture stirred for 5 min. The ice bath was removed and the aldehyde was added, followed by propane-1,3-dithiol (2.21 ml, 22 mmol) After 10 min, the solvent was removed under reduced pressure, dichloromethane was added (80 ml), and the solution was washed with sat

$NaHCO_3$ solution (20 ml), water (2 × 20 ml) and brine (20 ml) before the combined aqueous layers were re-extracted with dichloromethane (20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a light brown oil which was purified by flash column chromatography (SiO_2, 1:1 petrol:EtOAc) to give the title compound as a colourless oil (3.12 g, 13.85 mmol, 69%); silica gel TLC R_f 0.30 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2930 and 2900 (CH_2); δ_H (300 MHz; $CDCl_3$) 8.49 (1H, d, *J* 2, py-H_2), 8.47 (1H, d, *J* 5, py-H_6), 7.53 (1H, d, *J* 8, py-H_4), 7.22 (1H, dd, *J* 8 and 5, py-H_5), 3.97 (1H, t, *J* 7, dithiane-H_2), 2.90–2.80 (4H, m, CH_2), 2.19–2.02 (4H, m, CH_2), 1.96–1.80 (2H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 150.1 (py-C_2), 147.7 (py-C_6), 136.1 (py-C_3), 135.9 (py-C_4), 123.4 (py-C_5), 46.3 (dithiane-C_2), 36.5 (CH_2), 30.2 (dithiane-$(CH_2)_3$ and dithiane-$(CH_2)_5$), 29.6 (CH_2), 25.9 (dithiane-$(CH_2)_4$); *m/z* (CI) 226 (100%, $M+H^+$); *m/z* (EI) 225 (50%, M^+). [Found: M^+, 225.0634. $C_{11}H_{15}NS_2$ requires 225.0640].

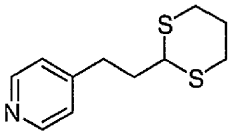
***Methyl 4a,5,6,7-tetrahydro-5-(1,3-dithian-2-yl)cyclopenta[c]pyridine-2-carboxylate* 331**



n-Butyllithium (1.5 mmol) was added to a stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (15 ml) at 0 °C. After 10 min, the solution was cooled to –40 °C and a solution of 4-(3-(1,3-dithian-2-yl)propyl)pyridine (**330**) (60 mg, 0.25 mmol) in THF (5 ml) was added *via* cannula. After 3 h, the orange solution was quenched by addition of methyl chloroformate (0.12 ml, 1.5 mmol). Diethyl ether (60

ml) was added and the organic fraction was washed with water (3 × 20 ml) and brine (20 ml), before the combined aqueous layers were re-extracted with ether (20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield a red/brown oil. This was purified by flash column chromatography (SiO_2, 9:1 petrol:EtOAc) to afford the title compound as a colourless oil (86 mg, 0.30 mmol, 61%); silica gel TLC R_f 0.69 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1718 (C=O), 1636 (C=C); δ_H (300 MHz; $CDCl_3$) 7.00 (0.5H, d, *J* 8, py-H_6 (rotamer A)), 6.89 (0.5H, d, *J* 8, py-H_6 (rotamer B)), 6.81 (0.5H, s, py-H_2 (rotamer A)), 6.60 (0.5H, s, py-H_2 (rotamer B)), 5.14 (0.5H, d, *J* 8, py-H_5 (rotamer A)), 5.05 (0.5H, d, *J* 8, py-H_5 (rotamer B)), 3.82 (3H, s, OCH_3), 3.32 (10H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 152.3, 148.6 and 146.9 (C=O rotamers), 125.6, 125.2, 121.1, 120.7, 119.3, 118.6, 118.3, 103.7 and 103.3 (C=C rotamers), 60.6, 58.6, 53.6, 49.9, 49.7, 43.1, 39.3, 28.8, 28.4, 27.0, 26.0. 25.9, 25.1, 21.3 and 14.5 (CH_2 and CH conformers); *m/z* (CI) 284 (10%, $M+H^+$), 240 (100%, M-$(CH_2)_3$), 224 (100%, M-CO_2Me), 120 (65%, M-(CO_2Me+1,3-dithiane)). [Found: M^+, 283.0698. $C_{13}H_{17}NO_2S_2$ requires 283.0695].

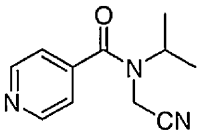
***4-(2-(1,3-Dithian-2-yl)ethyl)pyridine* 333**



Dimethyl sulfoxide (1.70 ml, 24 mmol) was added to a stirred solution of oxalyl chloride (0.96 ml, 11 mmol) in dichloromethane (25 ml) at –60 °C over 5 min. After 10 min stirring, 3-(pyridin-4-yl)propan-1-ol (1.37 g, 10 mmol) was added over 5 min. After 15 min triethylamine (6.96 ml, 50 mmol) was added over 5 min. The solution was allowed to warm to room temperature, water was added (30 ml), then after stirring for 10 min, the organic layer was separated, and the aqueous phase was re-

extracted with dichloromethane (20 ml). The solution was concentrated under reduced pressure to yield the aldehyde as pale yellow oil. Acetyl chloride (5 ml, 70.31 mmol) was added dropwise to methanol (50 ml) at 0 °C and the mixture stirred for 5 min. The ice bath was removed and the aldehyde was added, followed by propane-1,3-dithiol (1.11 ml, 11 mmol) After 10 min, the solvent was removed under reduced pressure, dichloromethane was added (80 ml), and the solution was washed with sat $NaHCO_3$ solution (20 ml), water (2 × 20 ml) and brine (20 ml), before the combined aqueous layers were re-extracted with dichlromethane (20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a light brown oil which was purified by flash column chromatography (SiO_2, 3:7 petrol:EtOAc) to give the title compound as a colourless oil (1.30 g, 5.78 mmol, 58%); silica gel TLC R_f 0.22 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3025 and 2900 (CH_2); δ_H (300 MHz; $CDCl_3$) 8.51 (2H, dd, *J* 4 and 2, Py-H_2 and py-H_6), 7.15 (2H, dd, *J* 4 and 2, py-H_3 and py-H_5), 3.96 (1H, d, *J* 7, CH), 2.92–2.77 (6H, m, dithiane CH_2), 2.18–1.81 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 149.9, 149.8 and 123.9 (aromatic), 46.3, 35.7, 31.8, 30.2 and 25.9 (CH_2); *m/z* (CI) 242 (100%, M+NH_4^+), 226 (75%, M+H^+), *m/z* (EI) 225 (65%, M^+), 119 (60%, $(CH)S_2(CH_2)_3$). [Found: M^+, 225.0636. $C_{11}H_{15}NS_2$ requires 225.0640].

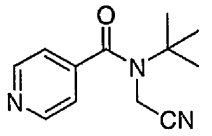
***N-(Cyanomethyl)-N-isopropylisonicotinamide* 369**



Isopropylamine (17.6 mmol, 1.5 ml) and bromoacetonitrile (8 mmol, 0.54 ml) was added to stirred acetonitrile (20 ml) at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat.

$NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organics were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. Thionyl chloride (50 ml) was added to isonicotinic acid (8 mmol, 0.98 g) and the solution was allowed to stir overnight at room temperature. The thionyl chloride was removed under reduced pressure and to the resulting acid chloride was added dichloromethane (50 ml). The mixture was cooled to 0 °C and triethylamine (12 mmol, 1.67 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml) and brine (25 ml), before being dried ($MgSO_4$), filtered and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, EtOAc) to afford the title compound as a tan crystalline solid (1.00 g, 4.94 mmol, 62%); mp 54–56 °C silica gel TLC R_f 0.25 (EtOAc); ν_{max}/cm^{-1} (thin film) 1646 (C=O), 2253 (CN); δ_H (300 MHz; $CDCl_3$) 8.79 (2H, d, *J* 6, py-H_2 and py-H_6), 7.35 (2H, d, *J* 5, py-H_3 and py-H_5), 4.30 (2H, br, CH_2), 4.02 (1H, br, ^iPr), 1.32 (6H, d, *J* 7, ^iPr); δ_C (75 MHz; $CDCl_3$) 169.3 (C=O), 150.7, 142.9 and 120.9 (aromatic), 116.4 (CN), 51.0 (CH), 28.3 (CH_2), 21.0 (CH_3); *m/z* (CI) 204 (100%, $M+H^+$), *m/z* (EI) 203 (5%, M), 163 (25%, M-CH_2CN), 106 (100%, M-$N(CH_2CN)(^iPr)$), 78 (80%, M-$(C=O)N(CH_2CN)(^iPr)$). [Found: M, 203.1059. $C_{11}H_{13}N_3O$ requires 203.1053].

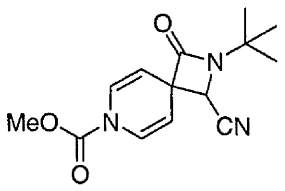
N-tert-Butyl-N-(cyanomethyl)isonicotinamide **371**



t-Butylamine (21 mmol, 2.21 ml) and bromoacetonitrile (10 mmol, 0.67 ml) was added to stirred acetonitrile (20 ml) at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organics were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. Thionyl chloride (50 ml) was added to isonicotinic acid (11 mmol, 1.35 g) and the solution was allowed to stir overnight at room temperature. The thionyl chloride was removed under reduced pressure and to the resulting acid chloride was added dichloromethane (50 ml). The mixture was cooled to 0 °C and triethylamine (15 mmol, 2.09 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml) and brine (25 ml), then dried ($MgSO_4$), filtered and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, 1:4 petrol:EtOAc) to afford the title compound as a tan crystalline solid (1.40 g, 6.44 mmol, 64%); mp 98–101 °C silica gel TLC R_f 0.32 (EtOAc); ν_{max}/cm^{-1} (thin film) 1658 (C=O), 2251 (CN); δ_H (300 MHz; $CDCl_3$) 8.76 (2H, d, *J* 4, py-H_2 and py-H_6), 7.38 (2H, dd, *J* 5 and 2, py-H_3 and py-H_5), 4.10 (2H, s, CH_2), 1.65 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 170.6 (C=O), 151.0, 144.7, 120.6 (aromatic), 117.0 (CN), 59.4 (^{t}Bu), 36.0 (CH_2), 28.4 (^{t}Bu); *m/z* (CI) 218 (100%,

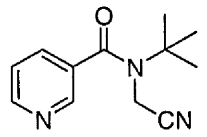
M+H$^+$), *m/z* (EI) 217 (30%, M$^+$) 162 (100%, M-CH_2CN), 106 (50%, M-$N(CH_2CN)(^iPr)$). [Found: M, 217.1209. $C_{12}H_{15}N_3O$ requires 217.1210].

***2-tert-Butyl-1-cyano-3-oxo-2,7-diaza-spiro[3.5]nona-5,8-diene-7-carboxylic acid methyl ester* 372**



Lithium diisopropylamide solution (0.25 mmol) was added to a stirred solution of *N*-*tert*-butyl-*N*-(cyanomethyl)isonicotinamide (0.25 mmol, 54 mg) in THF (10 ml) at –78 °C. After 1 min the reaction was quenched with methyl chloroformate (0.275 mmol, 0.021 ml), the cold bath was removed and the reaction allowed to warm to room temperature. After 4 h, diethyl ether was added (30 ml) and the organic fraction was washed with water (3 × 10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the title compound as a colourless oil (54 mg, 0.196 mmol, 78%); silica gel TLC R_f 0.39 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2239 (CN), 1756 (lactam C=O), 1687 (amide C=O); δ_H (300 MHz; $CDCl_3$) 7.20 (2H, br, py-H_2 and py-H_6), 5.03 (2H, br, py-H_3 and py-H_5), 3.99 (1H, s, CH), 3.91 (3H, s, CH_3O), 1.48 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 168.3 (C=O), 151.4 (C=O), 127.7 and 127.2 (py-H_2 and py-H_6), 116.1 (CN), 102.3 and 100.9 (py-H_3 and py-H_5), 58.9 (^{t}Bu), 55.7, 55.6, 54.4, 28.1 (^{t}Bu); *m/z* (CI) 293 (90%, M+NH_4), 276 (100%, M), 176 (40%, M-CON^{t}Bu. [Found: M, 276.1345. $C_{14}H_{18}O_3N_3$ requires 276.1343].

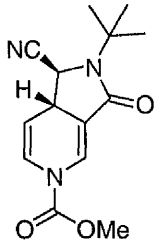
N-tert-Butyl-N-(cyanomethyl)nicotinamide **373**



t-Butylamine (21 mmol, 2.21 ml) and bromoacetonitrile (10 mmol, 0.67 ml) were added to stirred acetonitrile (20 ml) at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organics were washed with water (2 × 20 ml), brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. Thionyl chloride (50 ml) was added to nicotinic acid (11 mmol, 1.35 g) and the solution was allowed to stir overnight at room temperature. The thionyl chloride was removed under reduced pressure and to the resulting acid chloride was added dichloromethane (50 ml). The mixture was cooled to 0 °C and triethylamine (15 mmol, 2.09 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, 9:1 petrol:EtOAc) to afford the title compound as a white crystalline solid (1.52 g, 7.00 mmol, 70%); mp 63–67 °C; silica gel TLC R_f 0.28 (3:7 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2250 (CN), 1652 (C=O); δ_H (300 MHz; $CDCl_3$) 8.79 (1H, d, *J* 2, py-H_2), 8.76 (1H, dd, *J* 5 and 2, py-H_6), 7.89 (1H, m, py-H_4), 7.46 (1H, ddt, *J* 8, 5 and 1, py-H_5), 4.15 (2H, s, CH_2), 1.65 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 170.8 (C=O), 151.7, 147.8, 134.5, 133.3 and 124.0 (aromatic), 117.2 (CN), 59.3 (^tBu), 36.3 (CH_2), 28.4 (^tBu); *m/z* (CI) 218 (15%, $M+H^+$), 123

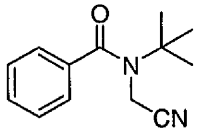
(100%, M-^{t}Bu and CH_2CN), 116 (80%, M-^{t}Bu(N)CH_2CN). [Found: M+H$^+$, 218.1293. $C_{12}H_{16}N_3O$ requires 218.1288].

***(1S/R,7aS/R)-Methyl 2-tert-butyl-1-cyano-2,3-dihydro-3-oxo-1H-pyrrolo[3,4-c]pyridine-5(7aH)-carboxylate* 374**



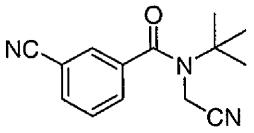
Lithium diisopropylamide solution (0.25 mmol) was added to a stirred solution of *N*-*tert*-butyl-*N*-(cyanomethyl)nicotinamide (**373**) (0.25 mmol, 54 mg) in dry THF (10 ml) at –78 °C. After 4 h the reaction was quenched with methyl chloroformate (0.275 mmol, 0.021 ml), the cold bath was removed and the reaction allowed to warm to room temperature. Diethyl ether was added (30 ml) and the organics were washed with water (3 × 10 ml) and brine (10 ml), then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown/red oil was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the title compound as a colourless oil (43 mg, 0.156 mmol, 62%); silica gel TLC R_f 0.25 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1742 (lactams C=O), 1686 (amide C=O), 1636 (C=C); δ_H (300 MHz; $CDCl_3$) 7.68 (1H, br, py-H_2), 7.11 (1H, br, py-H_6), 5.12 (1H, br-d, *J* 7, py-H_4), 4.70 (1H, d, *J* 8, CH), 3.92 (3H, s, CH_3O), 3.77 (1H, ddd, *J* 8, 5 and 2, py-H_4, 1.57 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 167.9 (lactam C=O), 152.2 (C=O), 127.6 (py-C_2), 126.5 (py-C_6), 116.9 (CN), 102.6 (py-C_5), 56.2 (^{t}Bu), 54.7 (OCH_3), 52.4 (lactam-C_2), 34.8 (lactam-C_3), 28.1 (^{t}Bu); *m/z* (CI) 276 (35%, M+H$^+$). [Found: M+H$^+$, 276.1354. $C_{14}H_{18}N_3O_3$ requires 276.1343].

N-tert-Butyl-N-(cyanomethyl)benzamide **375**



t-Butylamine (21 mmol, 2.21 ml) and bromoacetonitrile (10 mmol, 0.67 ml) were added to stirred acetonitrile (20 ml) at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organics were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. A solution of benzoyl chloride (11 mmol, 1.28 ml) in dichloromethane (50 ml) was cooled to 0 °C and triethylamine (15 mmol, 2.09 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml) and brine (25 ml), then dried ($MgSO_4$), filtered and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, 4:1 petrol:EtOAc) to afford the title compound as a white crystalline solid (1.95 g, 9.04 mmol, 90%); mp 84–88 °C; silica gel TLC R_f 0.60 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2243 (CN), 1651 (C=O); δ_H (300 MHz; $CDCl_3$) 7.56–7.47 (5H, m, Ar-H), 4.13 (2H, s, CH_2), 1.65 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 173.5 (C=O), 137.4, 130.7, 129.3 and 126.8 (aromatic), 117.8 (CN), 58.7 (^tBu), 36.5 (CH_2), 28.3 (^tBu); *m/z* (CI) 217 (100%, $M+H^+$) *m/z* (EI) 105 (100%, M-$^tBuNCH_2CN$), 77 (65%, M-$^tBuN(C=O)(CH_2CN)$. [Found: $M+H^+$, 217.1335. $C_{13}H_{16}N_2O$ requires 217.1335].

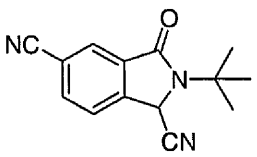
N-tert-Butyl-3-cyano-N-(cyanomethyl)benzamide **379**

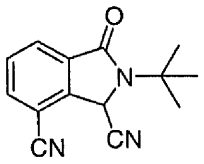


t-Butylamine (21 mmol, 2.21 ml) and bromoacetonitrile (10 mmol, 0.67 ml) were added to stirred acetonitrile (20 ml)at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organics were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. Thionyl chloride (50 ml) was added to 3-cyanobenzoic acid (10 mmol, 1.47 g) and the solution was allowed to stir overnight at room temperature. The thionyl chloride was removed under reduced pressure and to the resulting acid chloride was added dichloromethane (50 ml). The mixture was cooled to 0 °C and triethylamine (15 mmol, 2.09 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml) and brine (25 ml), then dried ($MgSO_4$), filtered and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, 4:1 petrol:EtOAc) to afford the title compound as a white crystalline solid (1.96 g, 8.13 mmol, 81%); mp 106–109 °C; silica gel TLC R_f 0.45 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2233 (CN), 1660 (C=O); δ_H (300 MHz; $CDCl_3$) 7.77–7.83 (3H, m, Ar-H), 7.64 (1H, m, Ar-H), 4.10 (2H, s, CH_2). 1.65 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 170.9 (C=O), 138.7, 134.1, 130.8, 130.6 and 130.3 (aromatic), 117.8 and 117.1 (CN), 113.9 (aromatic), 59.4 (^tBu), 36.2 (CH_2), 28.4

(^{t}Bu); *m/z* (CI) 259 (60%, M+NH_4), 242 (100%, M+H^+); *m/z* (EI) 130 (100%, M-^{t}BuNCH_2CN), 102 (50%, M-^{t}BuN(C=O)(CH_2CN)). [Found: M+H^+, 242.1286. $C_{14}H_{16}N_3O$ requires 242.1288].

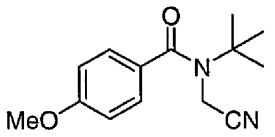
***2-tert-butyl-3-oxoisoindoline-1,5-dicarbonitrile* 380 *and 2-tert-butyl-3-oxoisoindoline-1,7-dicarbonitrile* 381**





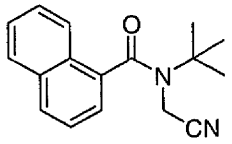
Lithium diisopropylamide solution (0.275 mmol) was added to a stirred solution of *N-tert*-Butyl-3-cyano-*N*-(cyanomethyl)benzamide (**379**) (0.25 mmol, 60 mg) in dry THF (10 ml) at –40 °C. After 4 h the reaction was quenched with methyl chloroformate (0.275 mmol, 0.021 ml), the cold bath was removed and the reaction allowed to warm to room temperature. Diethyl ether was added (30 ml) and the organics were washed with water (3 × 10 ml) and brine (10 ml), then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the two title compounds as an inseperable 1:1 mixture (30 mg, 0.125 mmol, 50%); silica gel TLC R_f 0.70 (1:1 petrol:EtOAc); δ_H (200 MHz; $CDCl_3$) 8.16–8.02 (2H, m, Ar-H), 7.99–7.88 (2H, m, Ar-H), 7.80–7.69 (2H, m, Ar-H), 5.60 (1H, s, CH), 5.51 (1H, s, CH), 1.68 (9H, s, ^{t}Bu), 1.67 (9H, s, ^{t}Bu) *m/z* (CI) 257 (55%, M+NH_4^+), 215 (35%, M-CN), 58 (100%, ^{t}Bu).

***N-tert-Butyl-N-(cyanomethyl)-4-methoxybenzamide* 382**



t-Butylamine (21 mmol, 2.21 ml) and bromoacetonitrile (10 mmol, 0.67 ml) were added to stirred acetonitrile (20 ml) at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organic fraction was washed with water (2 × 20 ml) and brine (20 ml), before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. A solution of anisoyl chloride (10 mmol, 1.35 ml) in dichloromethane (50 ml) was cooled to 0 °C and triethylamine (15 mmol, 2.09 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, 20:1 petrol:EtOAc) to afford the title compound as a colourless oil (1.92 g, 7.8 mmol, 78%); silica gel TLC R_f 0.48 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1648 (C=O); δ_H (300 MHz; $CDCl_3$) 7.54 (2H, d, *J* 9, py-H_2 and py-H_6), 6.99 (2H, d, *J* 9, py-H_3 and py-H_5), 4.16 (2H, s, CH_2), 3.89 (3H, s, OCH_3), 1.63 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 173.6 (C=O), 161.7, 129.5 and 129.2 (aromatic), 118.1 (CN), 114.5 (aromatic), 58.5 (^tBu), 55.7 (OCH_3), 36.7 (CH_2), 28.3 (^tBu); *m/z* (CI) 247 (100%, $M+H^+$), 191 (30%, M-^tBu), 135 (25%, M-$^tBuNCH_2CN$); *m/z* (EI) 135 (100%, M-$^tBuNCH_2CN$). [Found: $M+H^+$, 247.1443. $C_{14}H_{19}N_2O_2$ requires 247.1441].

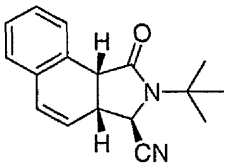
N-tert-Butyl-N-(cyanomethyl)-1-naphthamide **384**



t-Butylamine (17.6 mmol, 1.85 ml) and bromoacetonitrile (8 mmol, 0.54 ml) were added to stirred acetonitrile (20 ml) at room temperature. After 5 h, the solution was concentrated under reduced pressure. The residue was partitioned between sat. $NaHCO_3$ solution (40 ml), brine (40 ml) and chloroform (30 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 30 ml). The combined organic fraction was washed with water (2 × 20 ml) and brine (20 ml), before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting amine was not isolated due to its volatility. A solution of 1-naphthoyl chloride (8.8 mmol, 1.33 ml) in dichloromethane (50 ml) was cooled to 0 °C and triethylamine (12 mmol, 1.67 ml) was added, followed by the previously prepared amine. After stirring overnight, the solution was diluted with dichloromethane (50 ml), washed with water (3 × 25 ml) and brine (25 ml), then dried ($MgSO_4$) and concentrated to afford a colourless oil purified by flash column chromatography (SiO_2, 9:1 petrol:EtOAc) to afford the title compound as a white crystalline solid (1.35 g, 5.07 mmol, 63%); mp 84–86 °C; silica gel TLC R_f 0.62 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1655 (C=O); δ_H (300 MHz; $CDCl_3$) 7.98–7.90 (2H, m, qu-H), 7.89–7.82 (1H, m, qu-H), 7.63–7.52 (4H, m, qu-H), 4.06 (2H, br, CH_2), 1.77 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 172.1 (C=O), 135.1, 133.9, 129.9, 129.2, 128.9, 127.8, 127.1, 125.7, 124.5 and 123.6 (aromatic), 117.2 (CN), 59.1 (^{t}Bu), 36.0 (CH_2), 28.7 (^{t}Bu); *m/z* (CI) 267 (100%, $M+H^+$); *m/z* (EI) 266 (15%, M^+), 155 (100%, M-

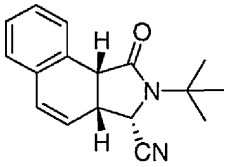
^{t}BuNCH$_2$CN), 126 (40%, M-^{t}BuN(C=O)(CH$_2$CN)). [Found: M+H$^+$, 267.1487. $C_{17}H_{18}N_2O$ requires 267.1492].

***(3R/S,3aR/S,9bR/S)-2-tert-Butyl-2,3,3a,9b-tetrahydro-1-oxo-1H-benzo[e]isoindole-3-carbonitrile* 385**



Potassium hexamethyldisilazide solution (0.5 mmol) was added to a stirred solution of *N*-tert-butyl-*N*-(cyanomethyl)-1-naphthamide (**384**) (67 mg, 0.25 mol) in THF (10 ml) at 0 °C. After 140 min, the reaction was quenched with saturated aqueous NH_4Cl (1 ml). Diethyl ether was added (30 ml) and the organic fraction was washed with water (3 × 10 ml) and brine (10 ml), the combined aqueous layers were re-extracted with ether (10 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown/red oil was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the title compound as a colourless oil (25 mg, 0.094 mmol, 36%); silica gel TLC R_f 0.63 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1695 (C=O); δ_H (300 MHz; $CDCl_3$) 7.37–7.24 (3H, m, Aryl-H), 7.09 (1H, d, *J* 6, Aryl-H), 6.60 (1H, dd, *J* 10 and 3, C=CH), 5.62 (1H, dd, *J* 10 and 2, C=CH), 4.52 (1H, s, NC-CH), 3.91 (1H, d, *J* 9, lactam-H_5), 3.78 (1H, ddd, *J* 8, 2 and 2, lactam-H_4), 1.53 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 172.7 (C=O), 131.7, 130.8, 130.4, 128.9, 128.8, 128.6, 127.4 and 124.1 (aromatic and C=C), 119.0 (CN), 56.2 (^{t}Bu), 52.3, 45.8 and 40.2 (CH), 27.9 (^{t}Bu); *m/z* (CI) 284 (50%, M+NH_4^+), 267 (100%, M+H$^+$); *m/z* (EI) 57 (100%, ^{t}Bu). [Found: M+NH_4^+, 284.1756. $C_{17}H_{22}N_3O$ requires 284.1757].

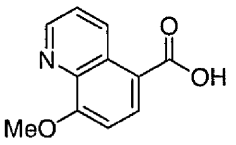
***(3S/R,3aR/S,9bR/S)-2-tert-Butyl-2,3,3a,9b-tetrahydro-1-oxo-1H-benzo[e]isoindole-3-carbonitrile* 386**



Potassium hexamethyldisilazide solution (0.5 mmol) was added to a stirred solution of *N-tert*-butyl-*N*-(cyanomethyl)-1-naphthamide (**384**) (67 mg, 0.25 mol) in THF (10 ml) at 0 °C. After 140 min, the reaction was quenched with saturated aqueous NH_4Cl (1 ml). Diethyl ether was added (30 ml) and the organic fraction was washed with water (3 × 10 ml) and brine (10 ml), the combined aqueous layers were re-extracted with ether (10 ml). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown/red oil was purified by flash column chromatography (SiO_2; 9:1 petrol:EtOAc) to afford the title compound as a colourless oil (15 mg, 0.056 mmol, 23%); silica gel TLC R_f 0.49 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1693 (C=O); δ_H (300 MHz; $CDCl_3$) 7.36–7.26 (3H, m, aryl-H), 7.21–7.16 (1H, m, aryl-H), 6.87 (1H, d, *J* 10, C=CH), 5.89 (1H, dd, *J* 10 and 6, C=CH), 4.68 (1H, d, *J* 8, NC-CH), 3.88 (1H, d, *J* 10, lactam-H_5), 3.50–3.42 (1H, m, lactam-H_4), 1.55 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 175.0 (C=O), 133.1, 131.9, 129.3, 128.3, 127.9, 127.3, 127.1 and 119.8 (aromatic and C=C), 56.2 (^{t}Bu), 52.5, 43.5 and 36.1 (CH), 28.0 (^{t}Bu); *m/z* (CI) 284 (50%, $M+NH_4^+$), 267 (100%, $M+H^+$) *m/z* (EI) 57 (100%, ^{t}Bu). [Found: $M+NH_4^+$, 284.1751. $C_{17}H_{22}N_3O$ requires 284.1757].

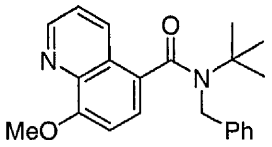
5.4 Experimental for Chapter Four

8-Methoxy-quinoline-5-carboxylic acid 395



A solution of 3-amino-4-methoxybenzoic acid (5.0 g, 29.9 mmol), glycerol (4.16 g, 45.2 mmol) and iodine (135 mg, 0.73 mmol) in concentrated sulphuric acid (5 ml) was heated at 180 °C for 2 h. The reaction was allowed to cool, diluted with water (170 ml), made basic to pH8/9 with 0.88 ammonia and stirred with activated charcoal (2.0 g). The mixture was filtered through Celite and the filtrate acidified to pH 4/5 with acetic acid. The precipitate was obtained by filtration and dried in a dessicator to yield the title compound as a brown powder (3.71 g, 18.3 mmol, 61%); δ_H (300 MHz; D_6-DMSO) 9.44 (1H, dd, *J* 1.5 and 9, nap-H_8), 8.91 (1H, dd, *J* 1.5 and 4, nap-H_6), 8.32 (1H, d, *J* 8.5, nap-H_4), 7.69 (1H, dd, *J* 4 and 9, nap-H_7), 7.28 (1H, d, *J* 8.5, nap-H_3), 4.06 (3H, s, OCH_3); δ_C (75 MHz; D_6-DMSO) 168.0, 159.2, 149.3, 139.8, 134.3, 133.0, 128.2, 123.4, 118.7, 107.3, 56.4.

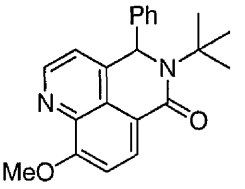
8-Methoxyquinoline-5-carboxylic acid benzyl-tert-butyl-amide 396



A solution of 8-methoxy-quinoline-5-carboxylic acid (**395**) (2.03 g, 10 mmol) in thionyl chloride (100 ml) was heated overnight at 85 °C under a calcium chloride drying tube. After this time the thionyl chloride was removed under reduced pressure to give the acid chloride as an off white solid. This was dissolved in dichloromethane

(100 ml), triethylamine (2.09 ml, 15 mmol) and *N-tert*-butylbenzylamine (1.90 ml, 10 mmol) were added and stirred overnight at room temperature. The resulting solution was washed with 3 M hydrochloric acid (40 ml), water (2 × 40 ml) and brine (40 ml), then dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (SiO_2; 100% EtOAc) afforded the title compound as a light brown crystalline solid (1.48 g, 4.25 mmol, 43%); mp 160–162 °C; silica gel TLC R_f 0.16 (EtOAc); ν_{max}/cm^{-1} (thin film) 1631 (C=O), δ_H (300 MHz; $CDCl_3$) 8.98 (1H, dd, *J* 1 and 4, nap-H_8), 8.30 (1H, dd, *J* 1 and 8, nap-H_6), 7.53 (1H, dd, *J* 4 and 8, nap-H_7), 7.47 (1H, d, *J* 8, nap-H_4), 7.4-7.1 (5H, m, Ph-H), 6.89 (1H, d, *J* 8, nap-H_3), 4.06 (3H, s, OCH_3), 1.65 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 171.6 (C=O), 155.5, 149.4, 139.7, 139.5, 133.0, 128.6, 128.4, 128.3, 126.9, 126.1, 125.9, 124.1, 122.3, 106.5 (aromatic), 58.5 (^{t}Bu-C), 56.0 (OCH_3), 51.4 (Bn-C), 28.8 (^{t}Bu-CH_3). *m/z* (CI) 349 (100%, $M+H^+$). [Found: $M+H^+$, 349.1910. $C_{22}H_{25}N_2O_2$ requires 349.1911].

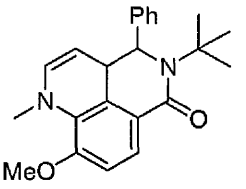
***5-tert-Butyl-9-methoxy-4-phenyl-4,5-dihydro-1,5-diaza-phenalen-6-one* 398**



A solution of 8-Methoxy-quinoline-5-carboxylic acid benzyl-*tert*-butyl-amide (**396**) (134 mg, 0.38 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamide (1 mmol) in THF (15 ml) at 0 °C *via* cannula. This solution was allowed to warm up overnight before it was quenched with excess aqueous ammonium chloride. Water was added (20 ml) and the aqueous layer was extracted with ether (2 × 20 ml), the combined ether layers were washed with water (2 × 20 ml)

and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated to yield a brown oil. This was purified by column chromatography (SiO_2; 1:4 petrol:EtOAc) to give a brown oil (48 mg, 0.18 mmol, 48%); δ_H (300 MHz; C_6D_6) 8.47 (1H, d, *J* 8, nap-H_2), 8.28 (1H, d, *J* 4, nap-H_7), 6.86 (2H, s, Ph-H), 6.59–6.52 (3H, m, Ph-H), 6.38 (1H, d, *J* 4, nap-H_6), 6.28 (1H, d, *J* 8, nap-H_3), 5.56 (1H, s, CH), 3.10 (3H, s, OCH_3) 1.25 (9H, s, ^{t}Bu-H); δ_C (75 MHz; $CDCl_3$) 163.9 (C=O), 158.0, 149.3, 143.6, 138.3, 129.1, 128.2, 128.0, 125.7, 123.0, 119.3, 118.3, 118.3 and 108.2 (aromatic), 62.4 (OCH_3), 59.2 (^{t}Bu-C), 56.2 (Bn-C), 28.9 (^{t}Bu-CH_3). *m/z* (CI) 347 (100%, M+H$^+$). [Found: M+H$^+$, 347.1754. $C_{22}H_{23}N_2O_2$ requires 347.1754].

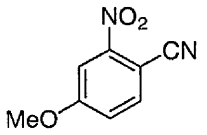
***5-tert-Butyl-9-methoxy-1-methyl-4-phenyl-1,3c,4,5-tetrahydro-1,5-diaza-phenalen-6-one* 399**



A solution of 8-Methoxy-quinoline-5-carboxylic acid benzyl-*tert*-butyl-amide (**396**) (87 mg, 0.25 mmol) in THF (5 ml) was added to a solution of LDA (0.5 mmol) in THF (15 ml) at 0 °C *via* cannula After 10 min this solution was quenched with excess methyl iodide (0.25 ml). Water was added (20 ml) and this was extracted with ether (2 × 20 ml), the combined ether layers were washed with water (2 × 20 ml) and brine (20 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. An attempt was made to purify the resulting brown oil by chromatography (SiO_2), but the compound decomposed δ_H (200 MHz; $CDCl_3$) 7.71 (1H, d, *J* 7.5, qu-H_7), 7.8–7.2 (5H, m, Ph-H), 6.78 (1H, d, *J* 7.5, qu-H_6), 5.71 (1H, dd, *J* 6 and 1, qu-H_2), 4.88 (1H, d, *J* 4.5, Bn-H),

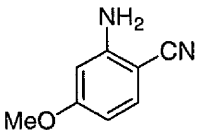
4.50 (1H, dd, *J* 6 and 1), 4.12 (1H, d, *J* 4.5, qu-H_3), 3.79 (3H, s, OCH_3), 3.06 (3H, s, N-CH_3), 1.47 (9H, s, ^tBu-CH_3).

***4-Methoxy-2-nitrobenzonitrile* 403**[97]



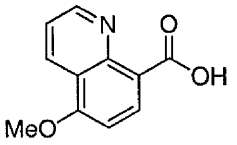
A solution of $NaNO_2$ (1.52 g, 22 mmol) in water (8 ml), was added, with stirring, to a cold (0 °C) solution of 2-nitroanisidine (3.36 g, 20 mmol) in concentrated HCl (30 ml) and ice (40 g). The mixture was stirred at 0 °C for 30 min. The resulting diazonium salt was neutralised by the slow addition of solid Na_2CO_3. This solution was slowly added, with stirring, to a suspension of CuCN (1.88 g, 21 mmol) and NaCN (2.06 g, 42 mmol) in water (8 ml) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The solution was extracted with dichloromethane (3 × 30 ml) and the organic layer washed with water (3 × 30 ml) and brine (30 ml), before being dried ($MgSO_4$), filtered and concentrated to yield the title compound as an orange solid (1.58 g, 8.87 mmol, 44%); silica gel TLC R_f 0.38 (3:2 petrol/EtOAc); ν_{max}/cm^{-1} (thin film) 2230 (CN), 1532 (NO_2); δ_H (300 MHz; $CDCl_3$) 7.82 (1H, d, *J* 6, H_2), 7.80 (1H, s, H_5), 7.28 (1H, dd, *J* 8 and 3, H_3), 3.99 (3H, s, OCH_3); δ_C (75 MHz; $CDCl_3$) 163.5 (C_4), 136.9 (C_6), 120.3 (C_5), 115.5 (CN), 111.3 (C_3), 99.7 (C_1); *m/z* (CI) 196 (100%, $M+NH_4^+$). [Found: M^+, 178.0366. $C_8H_6N_2O_3$ requires 178.0373].

2-Amino-4-methoxybenzonitrile **404**[98]



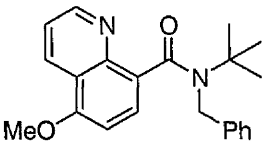
A solution of *m*-anisidine (4.47 ml, 40 mmol) in dichloromethane (40 ml), trichloroacetonitrile (4.81 ml, 48 mmol) and $AlCl_3$ (5.33 g, 40 mmol) were added successively to a stirred solution of 2.0 M BCl_3-CH_2Cl_2 (22 ml, 44 mmol) under ice cooling. The resulting mixture was stirred for 20 h. After cooling the mixture was added to a suspension of K_2CO_3 (64 g, 0.48 mol) in MeOH (120 ml) under ice cooling. The dichloromethane was removed and the suspension in methanol was refluxed for 2.5 h with stirring. After cooling, the insoluble material was removed by filtration and the filtrate was concentrated. Water was added to the residue (100 ml) and the mixture was extracted with ether (3 × 40 ml). The combined organic layers were washed with 2 M HCl (30 ml), water (3 × 30 ml) and brine (3 × 30 ml) then dried ($MgSO_4$) and filtered. The solvent was removed to yield the title compound as a yellow solid (2.22 g, 14.96 mmol, 37%); ν_{max}/cm^{-1} (thin film) 3373 (N-H), 2216 (CN); δ_H (300 MHz; $CDCl_3$) 7.34 (1H, d, *J* 9; H_6), 6.35 (1H, dd, *J* 9 and 2, H_5), 6.24 (1H, d, *J* 2, H_3); 4.5-4.1 (2H, br, NH_2), 3.83 (3H, s, OCH_3); δ_C (75 MHz; $CDCl_3$) 164.4 (C_4), 151.6 (C_2), 134.1 (C_6), 118.3 (CN), 106.0 (C_5), 99.6 (C_3), 89.0 (C_1), 55.6 (OCH_3); *m/z* (CI, NH_4^+) 166 (70%, $M+NH_4^+$), 149 (100%, $M+H^+$). [Found: $M+H^+$, 149.0715. $C_8H_9N_2O$ requires 149.0709].

5-Methoxyquinoline-8-carboxylic acid **405**[94]



A solution of 2-amino-4-methoxybenzonitrile (**404**) (2.20 g, 14.82 mmol), glycerol (2.05 g, 22.22 mmol) and iodine (74 mg, 0.293 mmol) in concentrated sulphuric acid (3 ml) was heated at 180 °C for 2 h. The reaction was allowed to cool, diluted with water (80 ml), made basic to pH8/9 with 0.88 ammonia and stirred with activated charcoal (1 g). The mixture was filtered through Celite and the filtrate acidified to pH 4/5 with acetic acid. The resulting solution was extracted with dichloromethane (3 × 20 ml), washed with water (3 × 20 ml) and brine (20 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the title compound as a brown solid (1.64 g, 8.22 mmol, 55%); ν_{max}/cm^{-1} (thin film) 1719 (C=O); δ_H (300 MHz; D_6-DMSO) 9.12 (1H, dd, *J* 4 and 2, qu-H_2), 8.81 (1H, dd, *J* 9 and 2, qu-H_3), 8.59 (1H, d, *J* 8, qu-H_7), 7.80 (1H, dd, *J* 9 and 4, qu-H_3), 7.33 (1H, d, *J* 8, qu-H_6) 4.12 (3H, s, OCH_3); δ_C (75 MHz; D_6-DMSO) 166.9 (C=O), 159.5, 150.5, 146.0, 137.1, 134.4, 122.3, 120.5, 116.5 and 106.6 (aromatic), 57.5 (OCH_3); *m/z* (CI) 204 (100%, $M+H^+$). [Found: $M+H^+$, 204.0660. $C_{11}H_{10}NO_3$ requires 204.655].

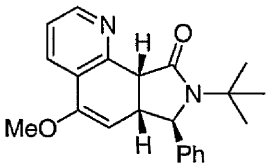
N-tert-Butyl-N-benzyl-5 methoxyquinoline-8-carboxamide **407**



Thionyl chloride (0.24 ml, 3.30 mmol) was added to a solution of 5-methoxyquinoline-8-carboxylic acid (**405**) (610 mg, 3.00 mmol) in dichloromethane (25 ml) at room temperature. After being left to stir overnight, the thionyl chloride

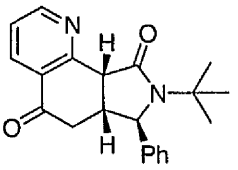
and dichloromethane were removed under reduced pressure. To the resulting acid chloride was added dichloromethane (25 ml). The solution was then cooled to 0 °C and triethylamine (0.69 ml, 4.95 mmol) was added followed by *t*-butylbenzylamine (0.92 ml, 4.95 mmol). After being left to stir overnight at room temperature, the reaction mixture was diluted with dichloromethane (25 ml), washed with water (3 × 10 ml) and brine (10 ml), before the combined aqueous layers here re-extracted with dichloromethane (10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a light brown oil. This was purified by flash column chromatography to afford the title compound as a white crystalline solid (532 mg, 1.53 mmol, 51%); mp 148-151 °C; silica gel TLC R_f 0.44 (1:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1638 (C=O); δ_H (300 MHz; $CDCl_3$) 8.99 (1H, dd, *J* 4 and 2, qu-H_8), 8.54 (1H, dd, *J* 9 and 2, qu-H_6), 7.58 (1H, d, *J* 8, qu-H_3), 7.40 (1H, dd, *J* 8 and 4, qu-H_7), 7.32-7.17 (5H, m, Ph-H), 6.73 (1H, d, *J* 8, qu-H_4), 4.53 (2H, m, CH_2), 3.97 (3H, s, OCH_3), 1.65 (9H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 172.7 (C=O), 155.4, 151.3, 146.0, 140.8, 131.6, 130.8, 128.5, 126.9, 126.9, 126.5, 120.8, 110.0 and 103.8 (aromatic), 58.5 (^{t}Bu), 56.0 (OCH_3), 51.6 (CH_2), 29.2 (^{t}Bu); *m/z* (CI) 349 (100%, $M+H^+$), 293 (40%, M-^{t}Bu); *m/z* (EI) 292 (20%, M-^{t}Bu), 186 (100%, M-$PhCH_2N^tBu$). [Found: $M+H^+$, 349.1916. $C_{22}H_{25}N_2O_2$ requires 349.1911].

***(6aR/S,7R/S,9aR/S)-8-tert-Butyl-7,8-dihydro-5-methoxy-7-phenyl-6aH-pyrrolo[3,4-h]quinolin-9(9aH)-one* 408**



Lithium diisopropylamide solution (0.646 mmol) was added to a stirred solution of *N*-tert-butyl-*N*-benzyl-5 methoxyquinoline-8-carboxamide (**407**) (75 mg, 0.215 mmol) in THF (10 mmol) at 0 °C. After 10 min, the reaction was quenched with saturated aqueous ammonium chloride solution (1 ml). Diethyl ether was added (30 ml) and the organic layer was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with diethyl ether (10 ml) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a brown oil. This was purified using flash column chromatography (SiO_2; EtOAc) to yield the title compound as a colourless oil (66 mg, 0.19 mmol, 88%); silica gel TLC R_f 0.08 (EtOAc); ν_{max}/cm^{-1} (thin film) 1687 (C=O), 1651 (C=C); δ_H (300 MHz; $CDCl_3$) 8.60 (1H, dd, *J* 5 and 2, qu-H_2), 7.46-7.41 (1H, m, qu-H_4), 7.40-7.30 (1H, br-m, Ph-H), 7.25-7.17 (1H, br-m, Ph-H), 7.11-6.98 (2H, m, qu-H_3 and Ph-H), 6.81-6.72 (1H, br-m, Ph-H), 6.59-6.51 (1H, br-m, Ph-H), 5.01 (1H, d, *J* 8, Bn-H), 4.62 (1H, d, *J* 6, C=CH), 3.99-3.91 (1H, m, qu-H_8), 3.69-3.59 (1H, m, qu-H_7), 3.49 (3H, s, OCH_3), 1.42 (9H, s, ^{t}Bu); δ_C (75 MHz) 174.2 (C=O), 152.3, 151.9, 148.9, 140.7, 129.4, 129.0, 127.9, 127.5, 127.3, 126.6, 121.9 and 93.4 (aromatic and C=C), 67.0 (Bn-C), 55.8 (^{t}Bu-C), 55.0 (OCH_3), 47.1 (qu-C_9), 38.0 (qu-C_8), 28.9 and 28.6 (^{t}Bu-CH_3); *m/z* (CI, NH_4^+) 347 (100%, rearomatised M+H$^+$); *m/z* 346 (50%, rearomatised M$^+$), 290 (35%, rearomatised M–^{t}Bu). [Found: rearomatised M+H$^+$, 347.1748. $C_{22}H_{23}N_2O_2$ requires 347.1754].

***(6aR/S,7R/S,9aR/S)-8-tert-Butyl-6,6a,7,8-tetrahydro-7-phenyl-9aH-pyrrolo[3,4-h]quinoline-5,9-dione* 409**



To a stirred solution of *N*-tert-butyl-*N*-benzyl-5 methoxyquinoline-8-carboxamide (**407**) (43 mg, 0.123 mmol) in THF (5 mmol) at 0 °C, was added lithium diisopropylamide solution (0.0.370 mmol). After 10 min, the reaction was quenched with saturated aqueous ammonium chloride solution (1 ml). 2 M aqueous hydrochloric acid (2 ml) was added and the solution was stirred overnight. The solution was neutralised by the addition of solid sodium carbonate. Diethyl ether was added (30 ml) and the organic layer was washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were re-extracted with diethyl ether (10 ml) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a brown oil. This was purified using flash column chromatography (SiO_2; EtOAc) to yield the title compound as a colourless oil (27 mg, 0.077 mmol, 63%); silica gel TLC R_f 0.10 (EtOAc); ν_{max}/cm^{-1} (thin film) 1684 (C=O); δ_H (300 MHz; $CDCl_3$) 8.93 (1H, dd, *J* 5 and 2, qu-H_2), 7.85 (1H, dd, *J* 8 and 2, qu-H_4), 7.37-7.17 (4H, m, qu-H_3 and Ph-H), 6.79 (1H, td, *J* 6 and 1, Ph-H), 6.39 (1H, d, *J* 8, Ph-H), 5.04 (1H, d, *J* 8, Bn-H), 4.12 (1H, d, *J* 9, qu-H_8), 3.57 (1H, sept, *J* 5, qu-H_7), 2.73 (2H, d, *J* 5, CH_2), 1.39 (9H, s, ^tBu); δ_C (75 MHz; $CDCl_3$) 193.1 (C=O), 172.3 (lactam C=O), 157.4, 154.3, 139.2, 133.9, 129.0, 128.6, 128.4, 128.0, 127.7 and 122.7 (aromatic), 64.9 (Bn-C), 56.1 (^tBu-C), 47.3 (qu-C_9), 37.0 (CH_2), 36.6 (qu-C_8), 28.4 (^tBu-CH_3); *m/z* (CI, NH_4^+) 335 (100%, $M+H^+$). [Found: $M+H^+$, 335.1757. $C_{21}H_{23}N_2O_2$ requires 335.1754].

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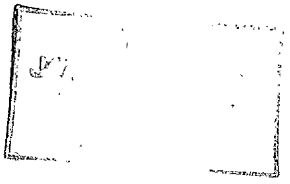

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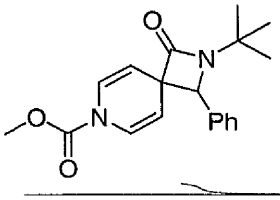
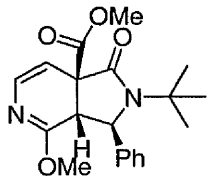
Appendix

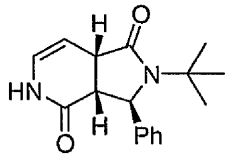
A1 Selected ^{1}H NMR spectra



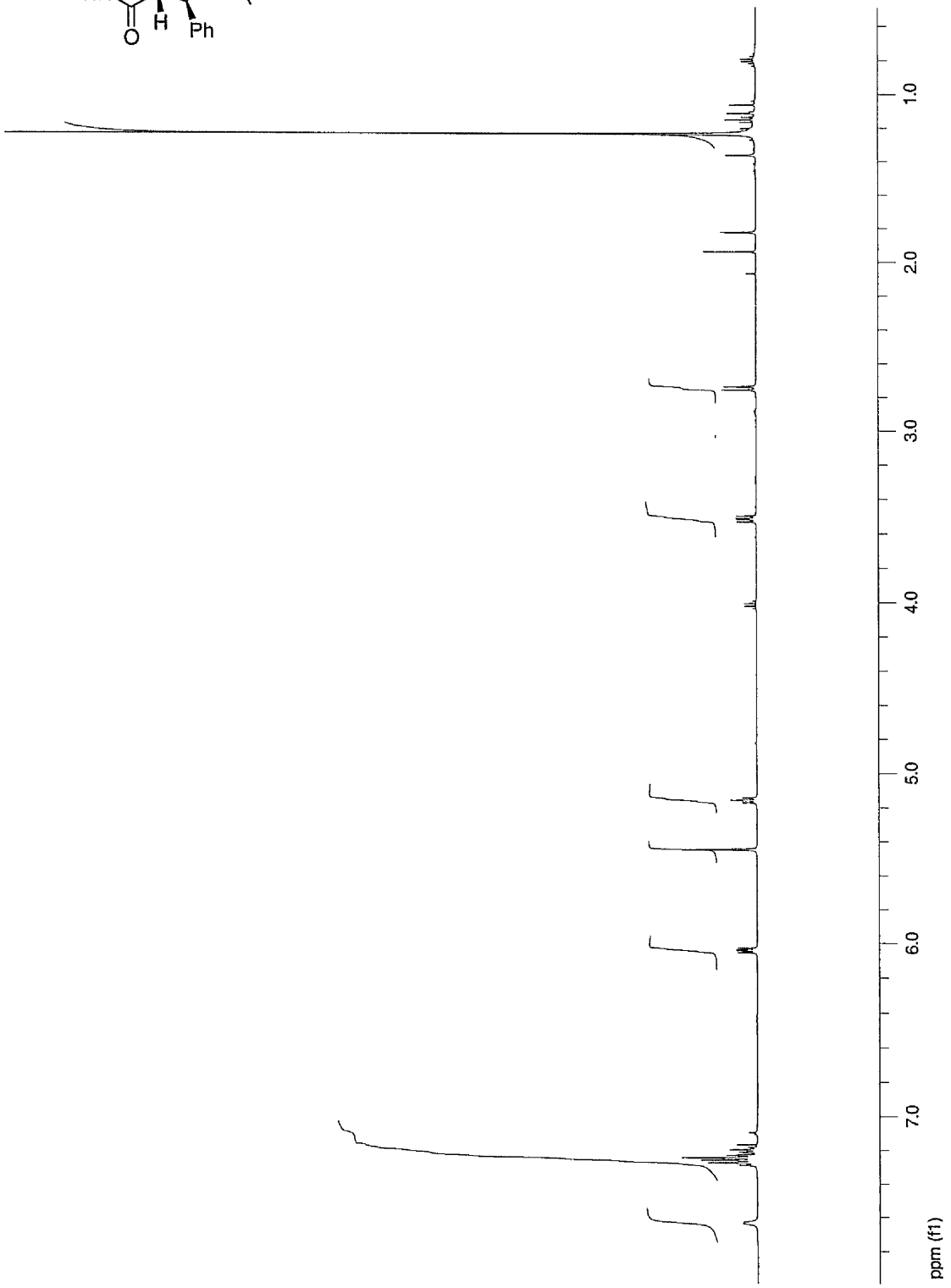
300 MHz ^{1}H NMR spectrum of **211b**

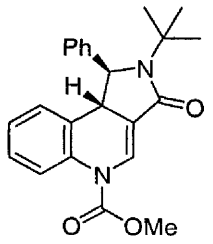


500 MHz ^{1}H NMR spectrum of **223**

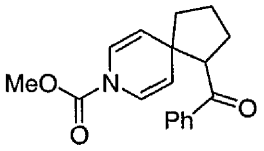


500 MHz ^{1}H NMR spectrum of **226**

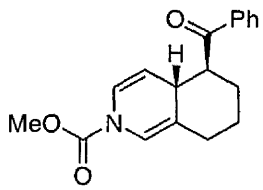




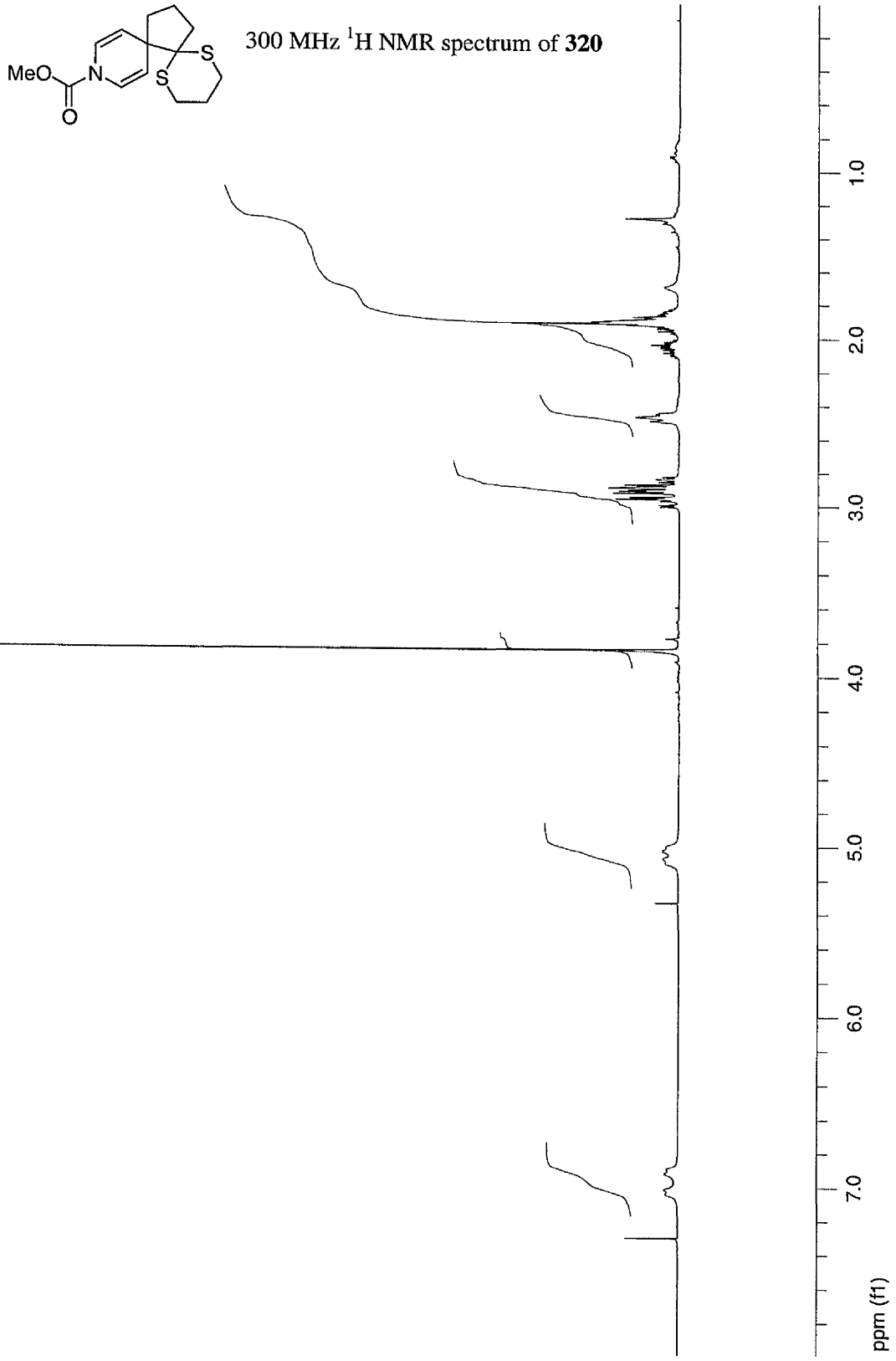
300 MHz ^{1}H NMR spectrum of **262**

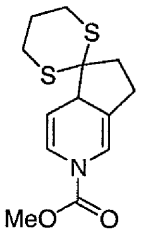


300 MHz ^{1}H NMR spectrum of **283**

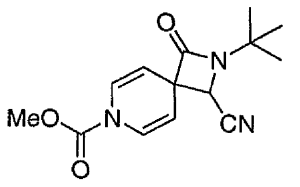


500 MHz ^{1}H NMR spectrum of **293**

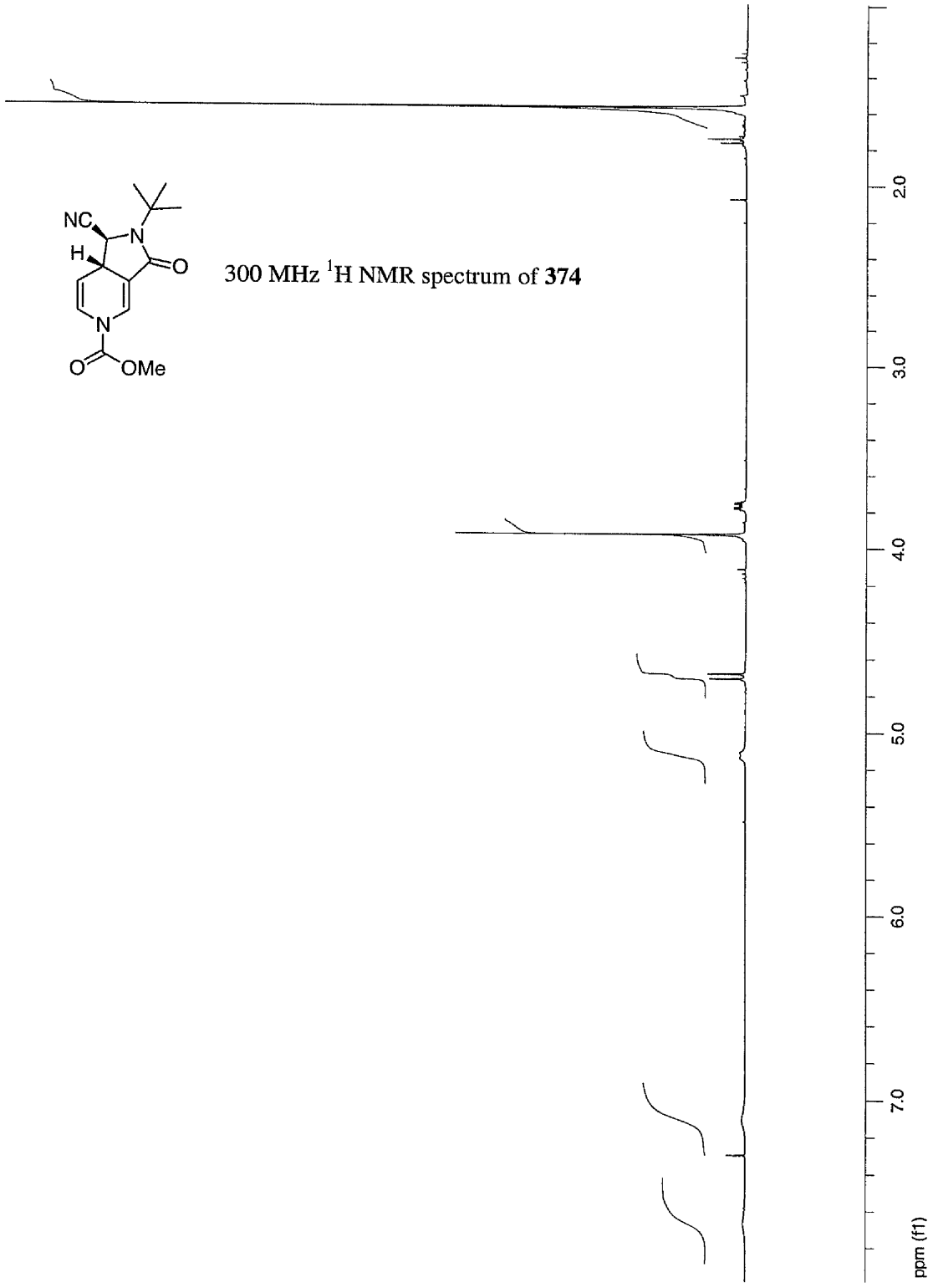

MeO
O
N
S
S
300 MHz ^{1}H NMR spectrum of **320**
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)



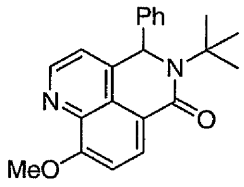
500 MHz ^{1}H NMR spectrum of **331**



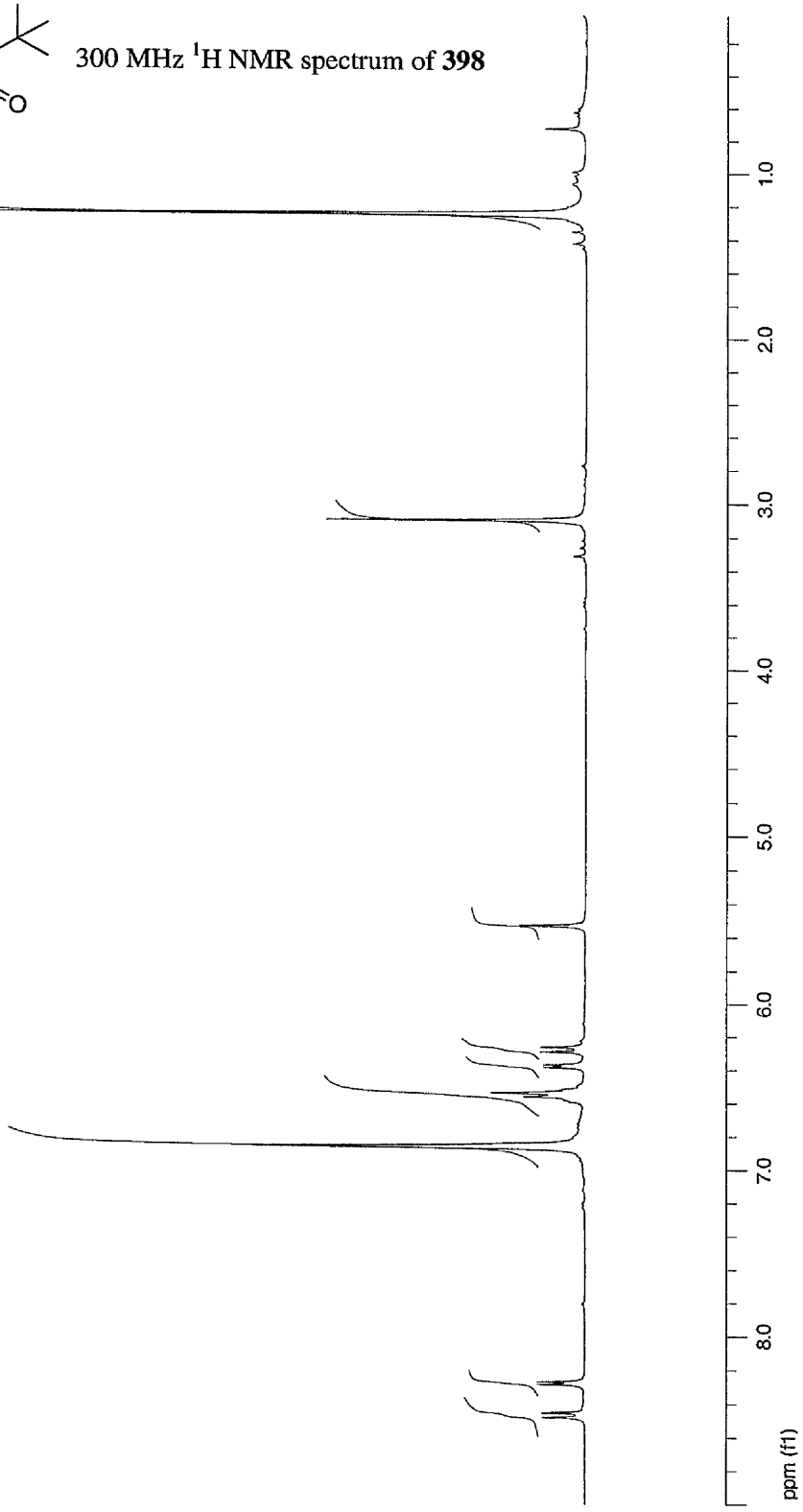
300 MHz ^{1}H NMR spectrum of **372**

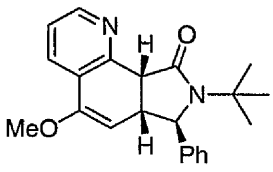


300 MHz ^{1}H NMR spectrum of **374**

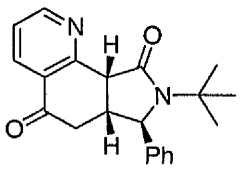


300 MHz ^{1}H NMR spectrum of **398**





300 MHz ^{1}H NMR spectrum of **408**



500 MHz ^{1}H NMR spectrum of **409**

A2 X-Ray Crystallography Data for 214a

Crystal data and structure refinement for s1343m.

Identification code	s1343m
Empirical formula	C19 H20 Cl2 N2 O3
Formula weight	395.27
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 14.3969(17) A alpha = 90 deg. b = 7.2480(8) A beta = 111.413(2) deg. c = 19.347(2) A gamma = 90 deg.
Volume	1879.5(4) A^3
Z, Calculated density	4, 1.397 Mg/m^3
Absorption coefficient	0.367 mm^-1
F(000)	824
Crystal size	0.40 x 0.30 x 0.04 mm
Theta range for data collection	1.52 to 28.55 deg.
Limiting indices	-18<=h<=17, -9<=k<=8, -25<=l<=19
Reflections collected / unique	11422 / 4410 [R(int) = 0.0535]
Completeness to theta = 28.55	92.3 %
Absorption correction	None
Max. and min. transmission	0.9855 and 0.8671
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4410 / 0 / 270
Goodness-of-fit on F^2	0.956
Final R indices [I>2sigma(I)]	R1 = 0.0398, wR2 = 0.0914
R indices (all data)	R1 = 0.0565, wR2 = 0.1091
Largest diff. peak and hole	0.367 and -0.339 e.A^-3