Dearomatising Anionic Cyclisation onto Five-Membered Heterocycles

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Abstract

This thesis describes investigations into the dearomatising anionic cyclisation of five-membered heterocycles and the application of the cyclisation to the synthesis of biologically important molecules.

Chapter 2 describes the attempted dearomatising anionic cyclisation of *N*-protected pyrroles, furans, thiophenes, indoles and benzofurans. Efforts to use this methodology to synthesise analogues of the natural product Hinckdentine A are described. An investigation into diastereoselective deprotonation was also pursued. Also discussed are the problems we encountered during these investigations and the interesting observations that were made.

Finally chapter 3 describes the dearomatising cyclisation onto sulfone-activated naphthalenes and the application of these reactions towards the total synthesis of (±)-podophyllotoxin.

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

Acknowledgements

I would like to take this opportunity to thank Prof. Jonathan Clayden for his encouragement and support throughout the course of my Ph.D. I would also like to thank Dr Ivan Pinto at GlaxoSmithKline for his insight and guidance especially during my placement at Stevenage.

A mention must be made to the EPSRC and GlaxoSmithKline for funding this research and to the University of Manchester for providing the necessary facilities. I would also like to thank the technical staff in the Department of Chemistry, in particular Val for the mass spectrometry and Dr Madeleine Helliwell for the X-ray crystallography.

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Finally I would like to thank my mam, dad and family for their constant support, both financial and otherwise throughout my seemingly never-ending education and to David for his love, abundant wit and senseless humour.

Preface

The Author graduated from the University of Manchester Institute of Science and Technology in July 2001 with a First Class degree of Master of Chemistry (Honours) with industrial experience. She then engaged in research at the Department of Chemistry in the University of Manchester from October 2001 to September 2004 under the supervision of Prof. Jonathan Clayden. The results of the investigations carried out during this period are embodied in this thesis.

"Science is a wonderful thing if one does not have to earn one's living at it."

Albert Einstein, 1879-1955.

Abbreviations

Å	Angström
AcOH	acetic acid
AIBN	azo*iso*butyronitrile
Ar	aryl
aq	aqueous
Bn	benzyl
Boc	*t*-butoxycarbonyl
B.p.	boiling point
Bu	butyl
n-BuLi	*n*-butyllithium
s-BuLi	*sec*-butyllithium
t-BuLi	*tert*-butyllithium
c.	concentrated
C.I.	chemical ionisation
m-CPBA	*meta*-chloroperoxybenzoic acid
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereoisomeric excess
DEB	2,2-diethylbutyryl
DIBAL	diisobutyl aluminium hydride
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dppf	bis(diphenylphosphino)ferrocene
E^+	electrophile
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
E.I.	electron impact
equiv.	molar equivalent
Et	ethyl
Et_3N	triethylamine

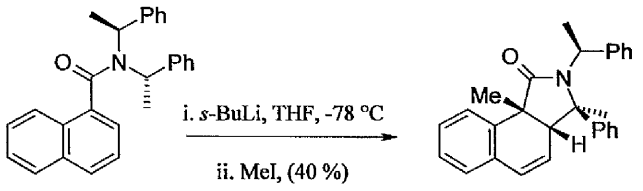
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram
h	hour
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
Lit.	literature
LTMP	lithium tetramethylpiperidine
m	meta
M	moles per cubic decimetre
M	parent molecule
M^+	molecular ion
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mg	milligram
$M+H^+$	protonated molecular ion
min.	minute
mL	millilitre
mmol	millimole
m.p.	melting point
m/z	mass to charge ratio
NaH	sodium hydride (60 % suspension in mineral oil)
NBS	*N*-Bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
o	ortho
O/N	overnight

p	para
Pd/C	activated palladium on charcoal (10 %)
PG	protecting group
Ph	phenyl
PhLi	phenyllithium
PMDTA	*N,N,N',N'',N''*-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
R_f	retardation factor
RT	room temperature
$SOCl_2$	thionyl chloride
TBAF	tetra-*n*-butylammoniumfluoride
TBDMS or TBS	*tert*-buyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tlc	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TosMIC	*p*-toluenesulfonylmethyl isocyanide
Ts	*p*-toluenesulfonyl
UV	ultraviolet/visible
ν_{max}	wavenumber

Chapter 1
Introduction

1.1 The Aim of the Project

In 1998 the Clayden group made a serendipitous discovery in connection with their work on atropisomeric amides.[1] Attempted ortholithiation of the naphthalene **1** resulted in the tricyclic isoindolone **2** *via* a dearomatising anionic cyclisation (Scheme 1.1).

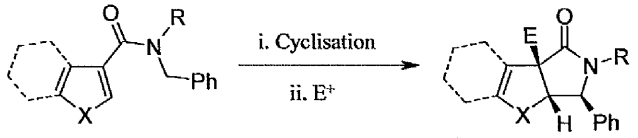


1 **2**

Scheme 1.1

Over the past 6 years the Clayden group has been involved in the generalisation, exploitation and development of the dearomatising anionic cyclisation reaction. Using simplified starting materials and procedures they have been able to study the mechanistic aspects of organolithium reactions in detail and apply this methodology to the synthesis of biologically important compounds.

To date these reactions have been confined to tertiary six-membered aromatic amides. We wished to investigate the dearomatising anionic cyclisation reaction of five-membered aromatic heterocycles **3** with a view to forming 5,5-fused heterocycles **4**, of the type found in a number of natural products, such as the indolizidine alkaloids (Scheme 1.2).[2]



3 **4**

Scheme 1.2

A variety of starting materials were synthesised; different heterocyclic rings both five-membered and six-five fused were incorporated, pyrrole protecting groups were explored, the amide substituents varied and chirality introduced. We also hoped to apply this methodology to the synthesis of analogues of biologically important targets.

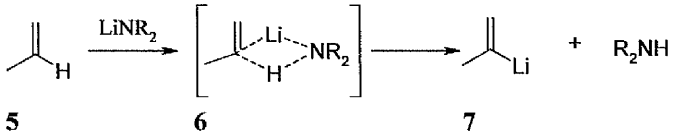
1.2 Heterocyclic Organolithium Derivatives[3]

Although Grignard reagents have been widely use in carbocyclic chemistry, the direct preparation of heterocyclic Grignard reagents by the standard route (halogenated compounds and magnesium metal) is often difficult, particularly if a basic nitrogen is involved. Haloimidazoles and halopyridines have been converted by exchange reactions with Grignard reagents to the corresponding magnesium species, but these are less reactive towards electrophiles than normal Grignard reagents.[4]

Lithio-heterocycles, which react as nucleophiles with the whole range of electrophiles in a manner exactly comparable with Grignard reagents, have proved to be more useful as they can often be prepared by direct metallation, as well as by halogen exchange between halo-heterocycle and alkyllithium. The use of lithiated species is the most convenient route to heterocyclic derivatives of less electropositive metals such as zinc,[5] boron,[6] silicon[7] and tin[8] which are widely used in coupling reactions.[9]

1.2.1 Direct Lithiation

Many heterocyclic systems react directly with alkyllithiums or with lithium amides to give the lithio-heterocycle *via* proton abstraction. Although a 'free' anion is never formed, the ease of lithiation correlates well with C-H acidity and with the stability of the corresponding conjugate base (carbanion).[10] Lithiations by deprotonation are therefore directly related to base-catalysed proton exchange.[11] The detail of the mechanism of metallation is under discussion, but it is thought to involve a four-centre transition state **6** (Scheme 1.3).[11]



5 **6** **7**

Scheme 1.3

The main factor giving increased acidity of heterocyclic C-H relative to benzenoid C-H is the inductive effect of the heteroatoms, thus metallation occurs at the carbon α to the heteroatom, where the inductive effect is strongest. This is the case unless other factors intervene:

Coordination of the metal counterion to the heteroatom

Stronger coordination between the metal of the base and a heteroatom leads to enhanced acidity of the adjacent C-H. This is due to increased inductive withdrawal of electron density and the effect is proportionately stronger for oxygen than for sulfur.

Lone pair interactions

Repulsion between the electrons in the orbital of the 'anion' and an adjacent heteroatom lone pair has a destabilising influence. This effect is thought to be important in pyridines and other azines.[12]

Substituent effects

Directed metallation,[13] just as in carbocyclic chemistry, is extremely useful in heterocyclic chemistry. Metallation *ortho* to the directing group is promoted by inductive effects, chelation or a combination of these, and may overcome the intrinsic regioselectivity of metallation of a particular heterocycle. This is by far the most important additional factor influencing the regioselectivity of lithiation.

Lithiating agents

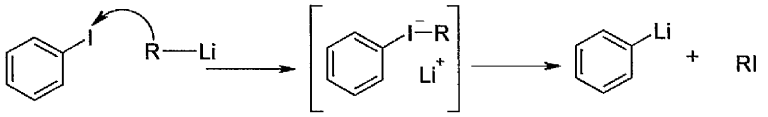
Lithiations are normally performed by alkyllithiums or lithium amides. The most widely used alkyllithium is *n*-butyllithium, but *t*- and *s*-butyllithium are used when more powerful reagents are required. Phenyllithium can be of value when a less reactive, more selective base is required.[14] Lithium diisopropylamine (LDA) and lithium 2,2,6,6-tertamethylpiperidine (LiTMP) are the most widely used lithium amides. LiTMP is more basic and less nucleophilic. Alkyllithiums are stronger bases than lithium amides, but usually react at slower rates. Metallations with lithium amides are reversible, so for efficient conversion the substrate must have a pK_a of two units lower than the base.

Solvents

Etheral solvents, Et_2O and THF, are normally used. THF is more strongly coordinating and increases the reactivity of the lithiating agent by increasing its dissociation. Trapp's solvent (a mixture of ether, THF and pentane) can be employed for very low temperature reactions as THF alone freezes at –100 °C. To increase the reactivity of the reagents even further, ligands such as HMPA or TMEDA can be added. HMPA strongly and specifically coordinates to the metal cation, increasing deaggregation of the organolithium. The role of TMEDA is uncertain and there is evidence that alkyllithiums are deaggregated just as much by THF alone as by TMEDA and THF.[15]

1.2.2 Halogen-Lithium Exchange

Bromo- and iodo-heterocycles react rapidly with alkyllithiums, even at low temperatures, to give the lithio-heterocycle. Where alternative exchanges are possible, the site of reaction is governed by the stability of the 'anion' formed, just as for direct lithiation by deprotonation. Exchange of fluorine is unknown and for chlorine it is rare enough to assume it is inert. Mechanistically, the exchange process may involve a four-membered transition state, or possibly proceed *via* an electron-transfer sequence. Direct nucleophilic attack has been demonstrated in the case of iodobenzene **8**, and is the most likely mechanism for aryl iodides (Scheme 1.4).[16]

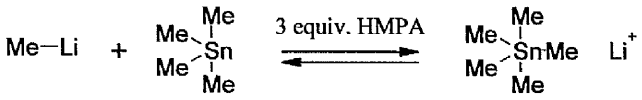


8 **9** **10**

Scheme 1.4

1.2.3 Tin-Lithium Exchange

Organolithiums react rapidly and reversibly with stannanes. The reaction is under thermodynamic control forming the most stable organolithium. There is considerable evidence that tin-lithium exchange proceeds *via* an ate complex as proposed by Still[17] and Seebach.[18] The reaction of methyllithium with tetramethylstannane in THF at –80 °C produces a peak in the ^{119} Sn NMR at δ 0 corresponding to Me_4Sn **11**. However, addition of HMPA causes a peak at δ –277 to appear, in which the ^{119} Sn nuclei are coupled equally to fifteen H nuclei. The upfield shift for tin is characteristic of a stannate complex. The addition of three equivalents of HMPA is sufficient to convert all of the stannane to lithium pentmethylstannate **12** (Scheme 1.5).[19]



11 **12**

Scheme 1.5

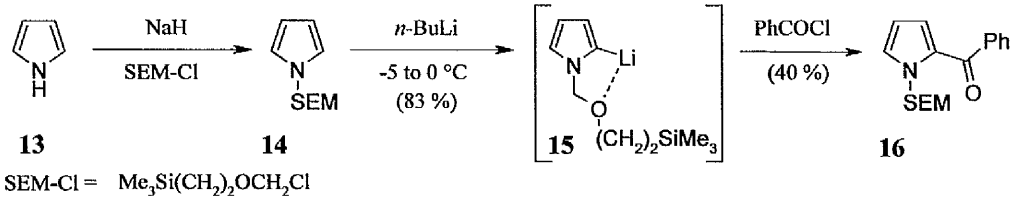
On warming the stannate to –20 °C coalescence is observed between the peaks in the ^{1}H NMR spectrum assigned to MeLi and Me_5SnLi indicating the exchange process is fast at this temperature even on the NMR timescale.

1.3 Lithiation of Five-Membered Aromatic Heterocycles

The inductive effect of the heteroatom allows direct α-lithiation of practically all five-membered aromatic heterocycles. Despite the lower electronegativity of sulfur, and hence weaker inductive effect, thiophene metallates as readily as furan, probably because the higher polarisability of sulfur allows more efficient charge distribution;[20] d-orbital participation is thought to be unimportant in the stabilisation of carbanionic centres adjacent to sulfur.

1.3.1 Pyrrole

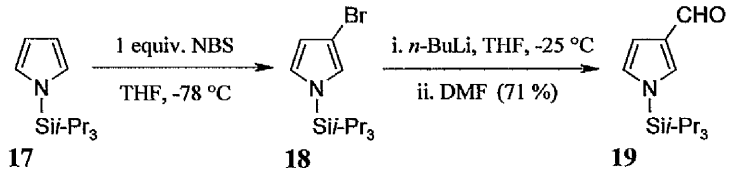
Lithiation of pyrroles is complicated by the presence of an acidic N-H (pK_a 17.5). The pyrryl anion generated by deprotonation is nucleophilic at the heteroatom, providing a means for the introduction of electrophilic groups on nitrogen. The C-deprotonation/lithiation of pyrroles requires the absence of the much more acidic N-H, i.e. the presence of an *N*-substituent. Alkyl[21] or removable protecting groups such as phenylsulfonyl,[22] carboxylate,[23] trimethylsilylethoxymethyl **14** (Scheme 1.6),[24] *t*-butylaminocarbonyl[25] and *t*-butoxycarbonyl[22] have been used successfully. The latter examples have the additional advantages of being easily removed, they are sufficiently electron-withdrawing to acidify the α-hydrogen further and they provide chelation assistance **15**.[26]



Scheme 1.6

Reactions of the species produced by the lithiation of *N*-substituted pyrroles are efficient for the introduction of groups to the 2-position, either by reaction with electrophiles or by coupling processes based on boron or palladium chemistry.[27]

Metal/halogen exchange using 3-bromo-*N*-triisopropylsilylpyrrole **18** allows the introduction of groups to the pyrrole β-position **19**. The intrinsic α-reactivity can be effectively completely blocked with a very large substituent such as TIPS (Scheme 1.7).[28]



17 **18** **19**

Scheme 1.7

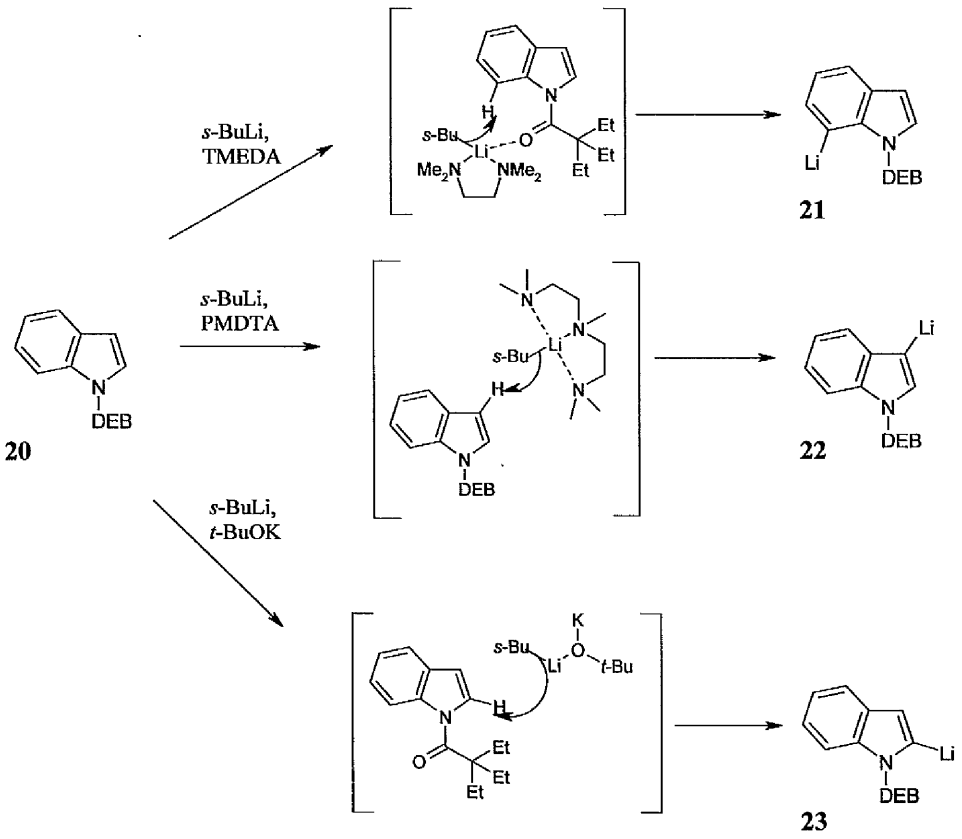
1.3.2 Indole

As with pyrroles, the indole N-H is much more acidic (pK_a 16.2) than that of an aromatic amine. Any strong base will effect complete conversion of an *N*-unsubstituted indole into the corresponding indolyl anion. Deprotonation of indole C-H requires the presence of an *N*-substituent such as an alkyl group.[29] Removable protecting groups such as phenylsulfonyl,[30] lithium carboxylate,[31] *t*-butoxycarbonyl,[22] dialkylaminomethyl,[32] trimethylsilylethoxymethyl[24] and methoxymethoxy[33] are widely employed. These removable substituents also assist lithiation by intramolecular chelation and in some cases by electron-withdrawal, reinforcing the intrinsic tendency for metallation to proceed at the α-position.

One of the most convenient *N*-protecting groups to be used in indole α-lithiation is carbon dioxide[31] because the protecting group is installed *in situ* and removed during work up.

3-Lithioindoles can be prepared by metal/halogen exchange[34] but the temperature must be kept low to prevent isomerism to the more stable 2-lithio species. 3-Lithiation has also been accomplished with *ortho* assistance from a 2-(2-pyridyl)[35] or a 2-carboxyl group.[36]

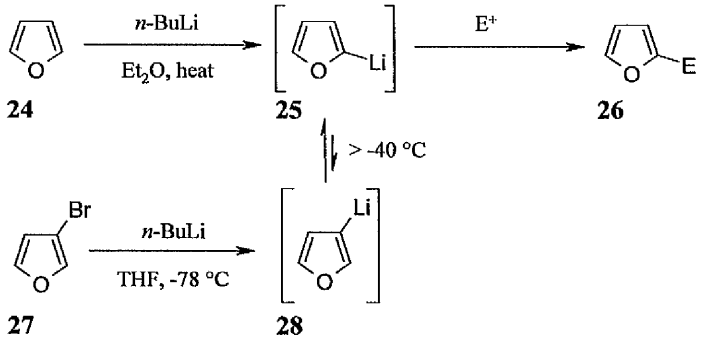
The lithiation at other positions of the simple *N*-protected indoles has scarcely been studied.[37] Recent investigations by Fukuda *et al.*[38] have discovered that the 2,2-diethylbutyryl (DEB) group **20** can promote unprecedented C-7 lithiation **21** under kinetically controlled conditions;[39] an example of regioselective lithiation *via* a complex-induced proximity effect.[40] C-3 **22** and C-2 **23** lithiation can also be achieved selectively with the DEB group.[38] These results are interesting because the regioselectivities are essentially controlled by the effects of the ligands employed (Scheme 1.8).



Scheme 1.8

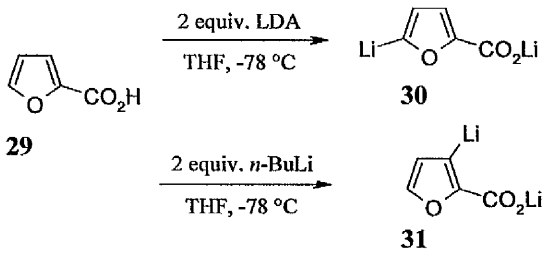
1.3.3 Furan

Furans are deprotonated by strong bases such as *n*-BuLi and LDA selectively at their α-positions to give anions (eg. **24** → **25**), which can then react with a range of electrophiles to afford α-substituted furans **26**. The metallation of furan was one of the earliest examples of the now familiar practice of aromatic ring-metallation.[41] The preference for α-lithiation is illustrated by the observation that 3-lithiofuran **28** equilibrates to the more stable 2-lithiofuran **25** if the temperature rises to greater than –40 °C (Scheme 1.9).[42]



Scheme 1.9

When furoic acid **29** is treated with two equivalents of LDA, selective formation of the 5-carbanion **30** is observed,[43] whereas treatment with *n*-butyllithium, *via ortho*-assistance, produces the lithium 3-carbanion **31** (Scheme 1.10).[44]



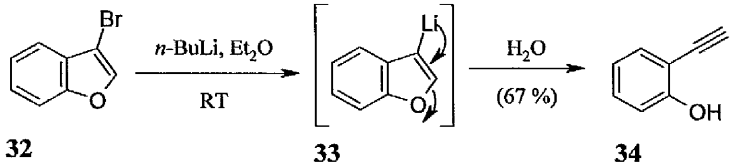
Scheme 1.10

Ortho direction of metallation to C-3 by 2-bisdimethylaminophosphate[45] and 2-oxazolidine[46] groups, and to C-2 by 3-hydroxymethyl,[47] have also been described.

Metallation at C-3 can be achieved *via* metal-halogen exchange.[48] There are many examples of the use of 2- and 3- lithiofurans in reactions with various electrophiles such as aldehydes, ketones and halides.[49,50] Furan-2- and 3-boronic acids (which are useful for palladium-catalysed coupling reactions) have been made by reaction of the lithiated species with tributyl borate.[51]

1.3.4 Benzofuran

In some of the earliest uses of *n*-butyllithium, 2-lithiobenzofuran was obtained by metal-halogen exchange between 2-bromobenzofuran and *n*-butyllithium,[52] or by deprotonation of benzofuran.[53] Lithiation at the other hetero-ring position (3-) can be achieved *via* halogen exchange of 3-bromobenzofuran **32,** but low temperatures must be maintained to prevent equilibration to the more stable 2-lithiated heterocycle.[34] The generation of 3-metallated benzofurans **33** generally results in fragmentation with the production of 2-hydroxyphenylacetylene **34** at room temperature (Scheme 1.11).[52, 54]

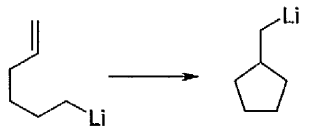


Scheme 1.11

1.4 Heterocycle Formation *via* Anionic Cyclisations

The preparation of heterocyclic compounds from acyclic precursors constitutes one of the most studied areas of research in organic chemistry.[55] Approximately two-thirds of known organic compounds have structures that incorporate at least one heterocyclic component. Heterocyclic compounds have a wide range of applications: they are predominant among the types of compounds used as pharmaceuticals, agrochemicals and are central to life processes. They are also used as optical brightening agents, as antioxidants, as dyestuffs and as corrosion inhibitors. Over the past two decades significant advances have been made in the exploitation of main group organo-metallics for this purpose.

The 5-*exo*-trig cyclisation of 5-hexenyllithiums **35** [56] has been extensively studied as a route to cyclopentyl-containing systems **36** (Scheme 1.12) and the preparation of carbocycles *via* cyclisation of unsaturated organolithiums has been reviewed.[57] Perhaps surprisingly, the development of this methodology for the preparation of heterocyclic compounds has received less attention.

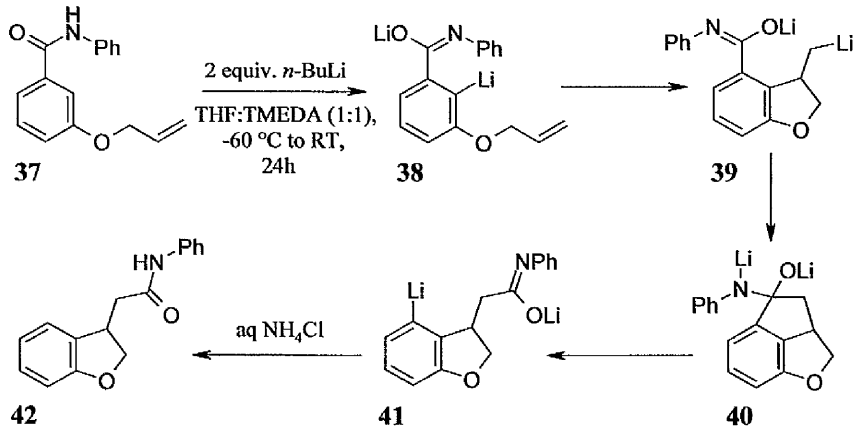


35 **36**

Scheme 1.12

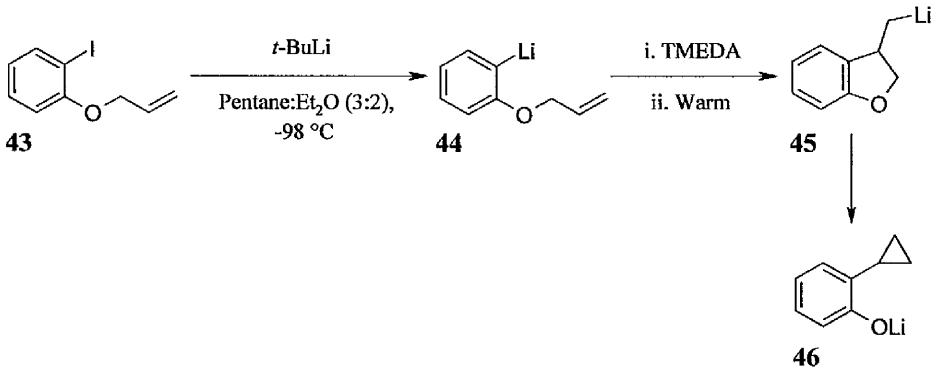
1.4.1 Oxygen Heterocycles

The first reports of carbolithiation of an unactivated carbon-carbon double bond for the preparation of a heterocycle were two brief accounts from the 1970s describing the intramolecular addition of α-oxyallylithiums[58] and α-oxybenzyllithiums[59] to the carbon-carbon π-bond of a norbornene. In 1980, Baldwin *et al.*[60] observed the novel rearrangement of **37** to benzofuran **42** upon *ortho*-lithiation (Scheme 1.13). The proposed mechanism for the transformation involved intramolecular addition of the aryllithium **38** to the tethered π-bond.



Scheme 1.13

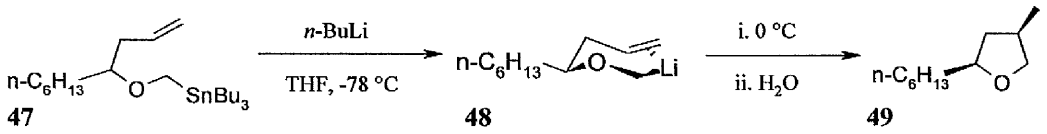
The parent system, 2-(2-propenoxy)-phenyllithium **44**, rearranges upon warming in the presence of TMEDA *via* 5-*exo*-cyclisation to give **45**, and subsequent γ-elimination affords the lithium salt of 2-cyclopropylphenol **46** (Scheme 1.14).[61]



Scheme 1.14

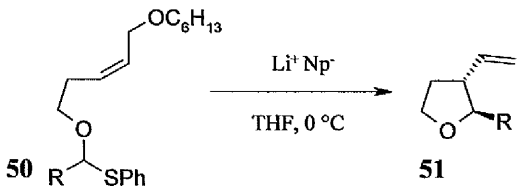
The first systematic studies of intramolecular carbolithiation for the preparation of heterocycles were the seminal reports by Broka *et al.*[62] detailing the preparation of substituted tetrahydrofurans by anionic cyclisation of olefinic α-alkoxy-organolithiums. These cyclisations were found to be highly stereoselective as a consequence of their progression through a rigid, chair-like transition state analogous to that observed in the cyclisation of the parent 5-hexenyllithium.[63, 64]

Broka and co-workers examined the cyclization of α-alkoxyorganolithiums derived from homoallylic (tri-*n*-butylstannyl)methyl ethers **47** with regard to a general route to 2,4-disubstituted tetrahydrofurans **49**.[62] Following generation of the organolithium by low temperature tin-lithium exchange in THF, the organolithiums **48** were observed to cyclise in a highly *cis*-selective manner upon warming (Scheme 1.15).



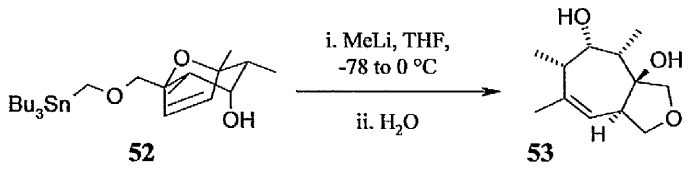
Scheme 1.15.

Using reductive lithiation of O,S-thioacetals **50** as a route to secondary alkoxy organolithiums, Broka and Shen[62] further demonstrated that *trans*-2,3-disubstituted tetrahydrofurans **51** could be prepared with good stereocontrol *via* intramolecular carbolithiation. Incorporation of a distal allylic leaving group improved both the chemical yield and the stereoselectivity of the reaction (Scheme 1.16).



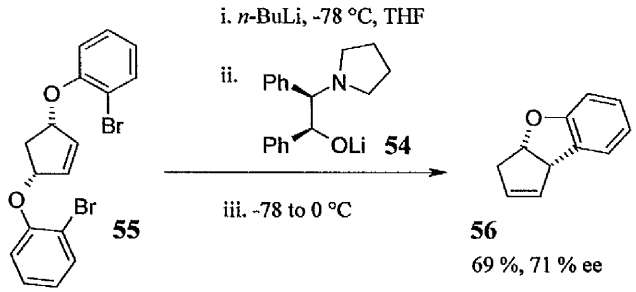
Scheme 1.16

More recently, Lautens and Kumanovic[65] extended the pioneering work of Broka to the synthesis of bicyclo[5.3.0] systems. Treatment of the oxabicyclo[3.2.1] substrate **52** with five equivalents of methyllithium in THF at –78 °C, followed by warming to 0 °C, afforded **53** in 75 % yield (Scheme 1.17). This elegant methodology leads to structures containing up to five contiguous stereocentres, a bridgehead tertiary alcohol, and the newly constructed ring. The intramolecular ring opening reaction is also applicable to the preparation of *N*-methylpyrrolidine and thiophene moieties in the bicyclo[5.3.0] systems.



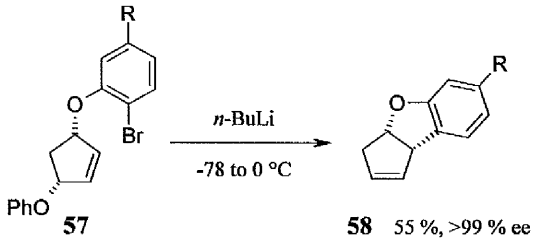
Scheme 1.17

Nishiyama and co-workers have conducted a related intramolecular S_N2 cyclisation in the presence of chiral lithium alkoxides **54** (Scheme 1.18).[66]



Scheme 1.18

In several instances, good chemical yields and modest enantioselectivites were obtained. They also reported the preparation of cyclopenta[b]benzofurans **58** from chiral precursors **57** (Scheme 1.19).[67]



Scheme 1.19

In the preparation of carbocycles, Hoppe and co-workers observed that the cyclisation of 6-phenyl-5-hexenyl-(α-carbamoyl)alkyllithiums proceeded with complete retention of configuration at the carbanionic centre.[68] Nakai demonstrated that cyclisation of enantio-enriched α-(homoallyloxy)alkyllithiums, prepared from the corresponding organostannanes **59**, also proceeds with complete retention of configuration at the carbanionic centre.[69,70] Thus, a 9:1 mixture of *trans*- and *cis*-2,3-disubstituted tetrahydrofurans **60** may be prepared with no loss of enantiomeric purity (Scheme 1.20). The β-elimination of lithium methoxide, pioneered by Broka, was employed to facilitate the reaction and increase the yield. The addition of a lithium halide also served to improve the yield: intramolecular chelation of the lithium with the oxygen atom of the substrate inhibits the lithium-alkene coordination essential for cyclisation (Figure 1.1). Thus addition of a lithium halide, which can coordinate to the substrate oxygen atom, leaves the lithium available for cyclisation (Figure 1.2).

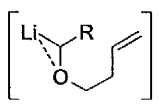


Figure 1.1

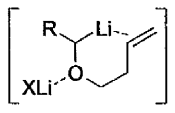
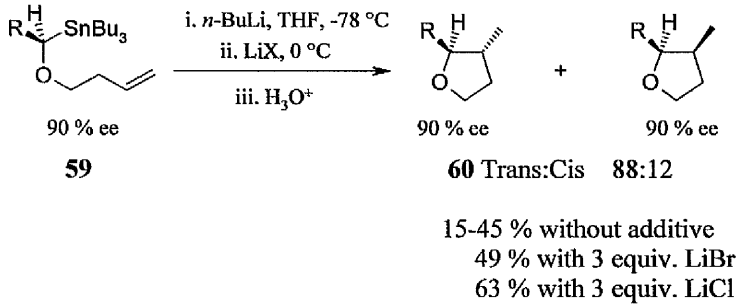


Figure 1.2

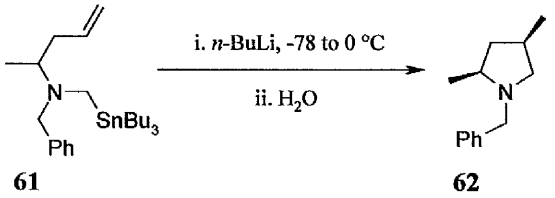


Scheme 1.20

1.4.2 Nitrogen Heterocycles

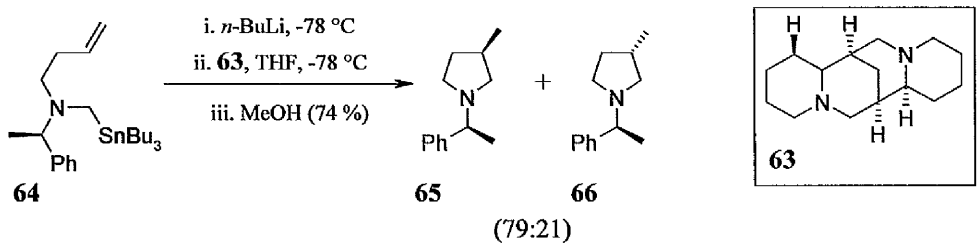
The extension of anionic cyclisation to the preparation of nitrogen-heterocycles has proved fruitful and recent work has demonstrated that this technique is an efficient method for diastereoselective and enantioselective synthesis of this compound class.

The Coldham group have extensively studied the preparation of pyrrolidines (Scheme 1.21).[71-74] Treatment of **61** with two equivalents of *n*-BuLi in THF leads to **62** in 46 % yield with >25:1 *cis:trans* selectivity. When the cyclisation is conducted in 10:1 hexane:diethyl ether the yields are increased but at the expense of stereoselectivity. This was attributed to the fact that tin-lithium exchange is not complete at –78 °C in hexane-ether solution and cyclisation occurs at a higher temperature in this case.[73]



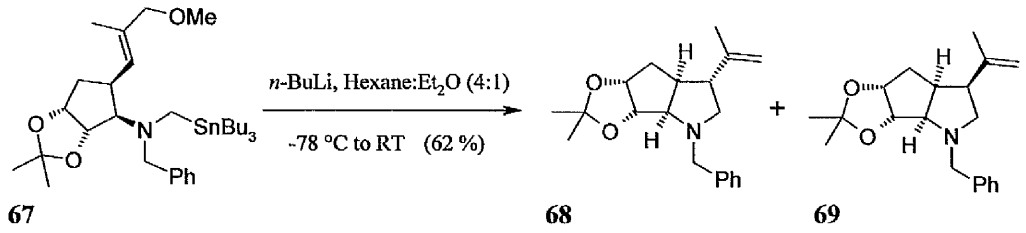
Scheme 1.21

The presence of a chiral auxiliary on nitrogen in the anionic cyclisation of the α-amino-organolithium was found to induce moderate enantioselectivity. Optimal conditions for the cyclisation involved transmetallation at –78 °C in THF, followed by addition of (–)-sparteine **63** dissolved in THF, which increased the diastereomeric ratio of **65:66** to 79:21 (Scheme 1.22). However, disappointingly low levels of enantioselectivity were observed in the (–)-sparteine-mediated cyclisation of achiral analogues of **64**.



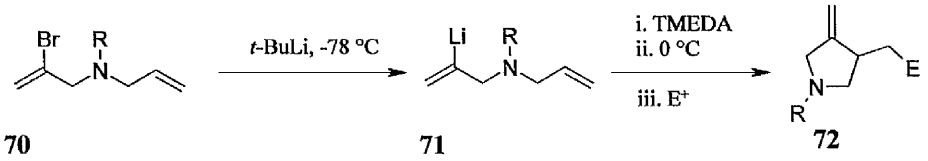
Scheme 1.22

In 2003 Coldham *et al.* extended this methodology to the stereoselective synthesis of complex cyclic amines, including those related to the kainoid natural products.[75] Tin-lithium exchange of the amino-stannane **67** afforded the pyrrolidine products **68** and **69** in 4:1 ratio and 62 % yield (Scheme 1.23).



Scheme 1.23

Barluenga and co-workers reported that cyclisation of the vinyl lithium **71** derived from *N*-protected substrates such as **70** delivers 3-methylene-4-pyrrolidines **72** in good yields (Scheme 1.24).[76]

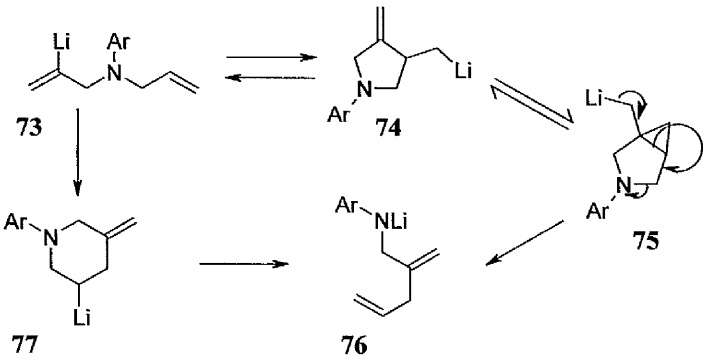


Scheme 1.24

The cyclic organolithium undergoes reaction with various electrophiles to provide highly functionalised pyrrolidine nuclei. The protective group on nitrogen plays a crucial role in the reaction, as rearranged products **76** were observed when the vinyllithium **77** was generated from an arylamine substrate. It was postulated that when the nitrogen bears an aryl group, the kinetically favoured 5-*exo* product, **74** may revert to the acyclic vinyllithium **73** which then undergoes a slower 6-*endo* cyclisation followed by irreversible cleavage to the lithium amide **76** (Scheme 1.25).[77]

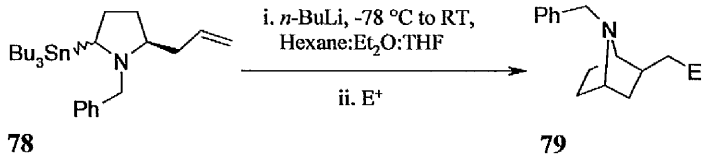
There are no examples of reversible 5-*exo* cyclisations of unsaturated organolithiums in the literature; an alternative explanation of the mechanistic aspects of these reactions is provided by Chamberlin *et al.*[78]

As shown (Scheme 1.25) a reversible 3-*exo* cyclisation of **74**, followed by rapid and irreversible fragmentation of the strained intermediate **75**, also accounts for the rearrangement favoured by aromatic amines.



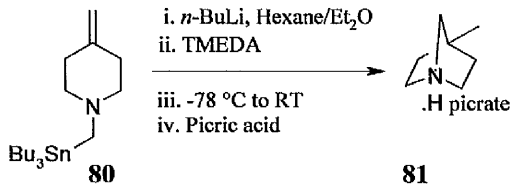
Scheme 1.25

Coldham *et al.*[79] have also demonstrated that bicyclic systems, such as 7-azabicyclo[2.2.1]heptanes can be prepared by cyclisation of pyrrolidinyllithiums tethered to a remote alkene (Scheme 1.26).[80] Thus, treatment of the organostannane **78** with an excess of *n*-butyllithium in a 4:1:1 mixture of hexane:diethyl ether:THF at –78 °C followed by warming to room temperature for 6 h afforded *exo*-2-substituted-7-azabicyclo[2.2.1]heptanes **79**. The bicyclic organolithium could subsequently be trapped with a variety of electrophiles.



Scheme 1.26

Of the three types of nitrogen-positional isomers of the azabicyclo[2.2.1] heptanes the 1-aza system was the most conveniently accessed, by transmetallation and cyclisation of the piperidinyl stannane **80**, and was isolated as the picrate salt **81** (Scheme 1.27).[80]

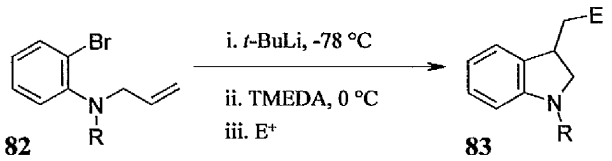


80 **81**

Scheme 1.27

TMEDA was required to facilitate the cyclisation of the organolithium derived from **80**. The analogous carbocyclic cyclisation is known to be rapid, but significant rate acceleration was observed upon the addition of TMEDA.[81]

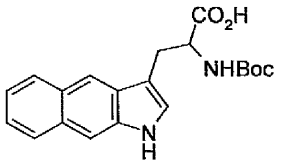
Indolines and indoles can be conveniently synthesised by a variety of anionic cyclisation techniques. As shown in Scheme 1.28, the aryllithium derived from an *N*-allyl-2-bromoaniline **82** by lithium-bromine exchange,[82] cyclises on warming to 0 °C in the presence of TMEDA and quenching with a variety of electrophiles affords three-substituted indolines **83** in good yield.[83]



82 **83**

Scheme 1.28

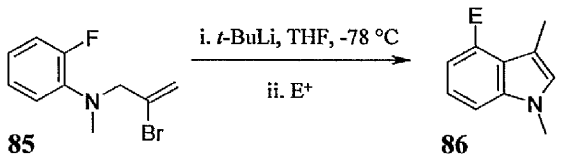
A similar approach was employed in the synthesis of *N*-α-*t*-Boc-benz[*f*]tryptophan **84**, a fluorescent amino acid probe, by Yokum and co-workers.[84]



84

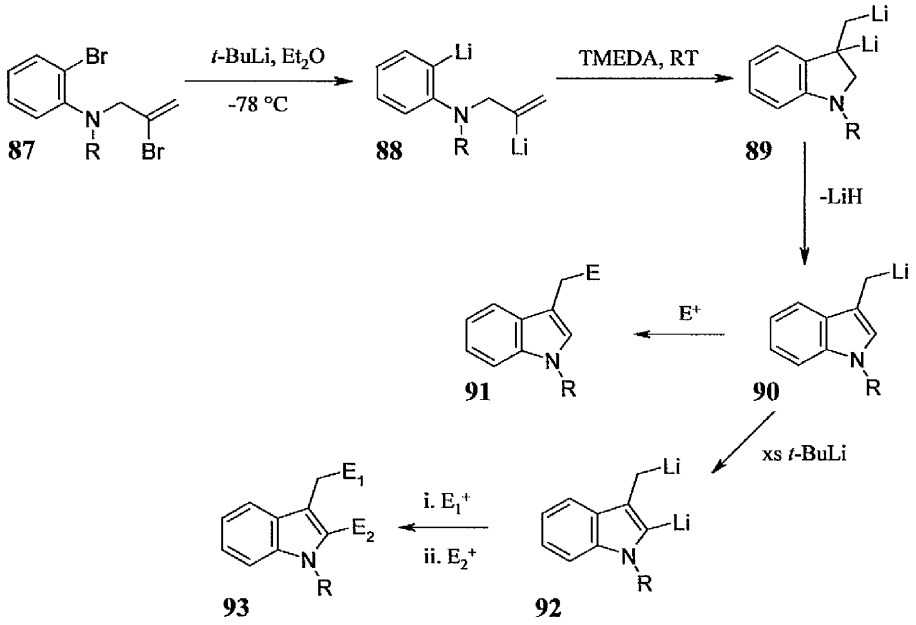
Metal-halogen exchange is not the sole means by which cyclisation to give indolines may be initiated. Bailey and Carson have described a novel cascade reaction that delivers 3,4-disubstituted indolines in modest yield.[85]

Barluenga *et al.* have demonstrated that 3,4-disubstituted indoles **86** may be prepared in one-pot (thus avoiding oxidation of the indoline) *via* an analogous cascade involving cyclisation of a vinyllithium-tethered benzyne derived from **85** (Scheme 1.29).[86]



Scheme 1.29

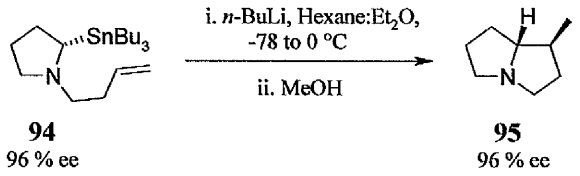
Indoles and pyrroles have also been prepared by cyclisation of dilithio-species such as **88**, prepared by low temperature lithium-bromine exchange. On treatment with TMEDA the dianion **88** underwent intramolecular carbometallation of the vinyllithium moiety by the aryllithium to afford the dilithiated indoline derivative **89**. Elimination of lithium hydride and electrophilic quench furnished the 3-alkylated indoles **91**. It was revealed that 2,3-bifunctional indoles **93** could be prepared by careful control of the organolithium stoichiometry (Scheme 1.30).[87, 88]



Scheme 1.30

In certain cases, a catalytic quantity of organolithium may be employed to effect a lithium-iodine exchange-mediated cycloisomerisation of an unsaturated iodide substrate.[89-91]

Anionic cyclization of chiral organolithiums has been exploited for the synthesis of a variety of nitrogen heterocycles. Coldham and co-workers found that transmetallation of optically active stannane **94** in 10:1 hexane:diethyl ether proceeded with retention of configuration at the carbanionic centre to give an organolithium that cyclised on warming to provide (+)-pseudoheliotridane **95** with complete stereocontrol (Scheme 1.31).[92]



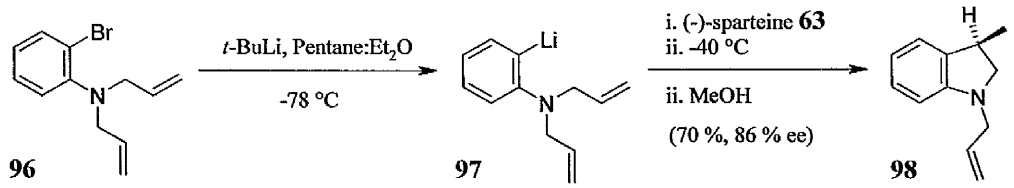
94
96 % ee

95
96 % ee

Scheme 1.31

Hoppe *et al.*[93] demonstrated that the powerful technique of asymmetric deprotonation may be coupled with the cyclisation of an unsaturated organolithium to afford functionalised indolizidines in high enantiomeric excess. Similar chemistry has been described for asymmetric deprotonation and cyclisation into allylic chlorides to prepare 3,4-divinylpyrrolidines in both good yield and enantiomeric excess.[94]

It has recently been shown that the ring closure of achiral organolithiums proceeds enantioselectively in the presence of (–)-sparteine **63**.[95, 96] Upon complexation with a chiral bidentate ligand, the lithium atom of the olefinic organolithium **97** is rendered stereogenic and may transmit this information in the cyclisation step to the product **98** (Scheme 1.32).



96

97

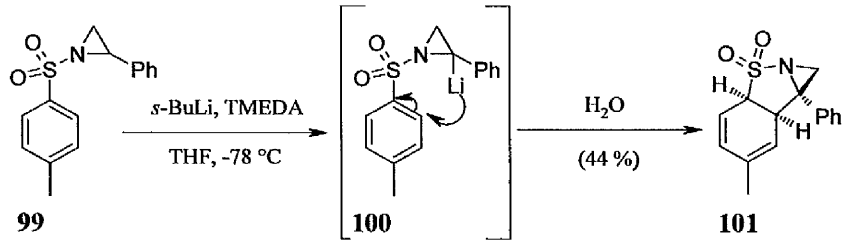
98

Scheme 1.32

1.5 Dearomatising Anionic Cyclisations

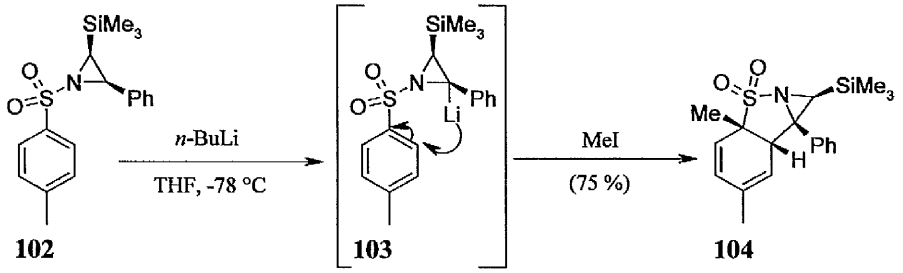
Although anionic cyclisations of organolithiums involving addition to alkenes and alkynes to form carbocycles[82] and heterocycles[71] are well documented in the literature, there are relatively few precedents of cyclisations of organolithiums onto an aromatic ring[58] and only a minority occur with dearomatisation.[97]

In 1991, Schaumann *et al.* reported a dearomatising anionic cyclisation whilst attempting a ring opening of an *N*-tosyl aziridine with allylic silyl anions.[98] The α-lithiation of sulfonamide **99** was facilitated by the stabilising effect of the phenyl group on the α-anion **100** and the additional acidity of the three-membered aziridine proton. The dearomatised tricyclic product **101** was also obtained in modest yield when α-lithiation was affected with *s*-BuLi and TMEDA (Scheme 1.33).



Scheme 1.33

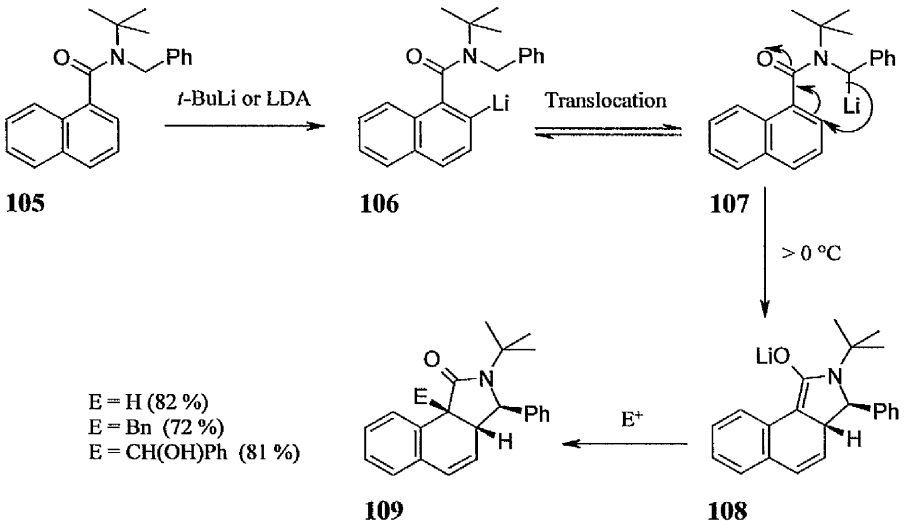
Recently Aggarwal *et al.* reported a similar reaction in which a *cis* di-substituted aziridine **102** was lithiated at the benzylic postion **103** rather than α- to the silicon.[99] The tricyclic product **104** was formed in good yield on methyl quench (Scheme 1.34).



Scheme 1.34

1.6 Dearomatising Anionic Cyclisation within the Clayden Group

Following the discovery of the novel dearomatising anionic cyclisation reaction (Scheme 1.1), investigation into the limitations and scope of this reaction were performed. Early reports indicated *t*-BuLi in the presence of HMPA or DMPU at –78 °C was required to effect lithiation,[100, 101] but later it became apparent that LDA at –20 °C with warming to 0 °C is sufficient to afford the lithiated product.[102] The reaction proceeds *via* a reactive α-lithiated species **107**, which attacks the aromatic ring to form an enolate intermediate **108.** This is quenched with electrophiles, usually stereoselectively, to give the dearomatised product **109**.[101] In the case of naphthamides **105**, the mechanism proceeds *via* lithiation *ortho* to the amide **106**, followed by *ortho*-α anion translocation **107** (Scheme 1.35).[103] Analogous cyclisations of sulfonamides[99] and phosphonamides[104] have been reported.



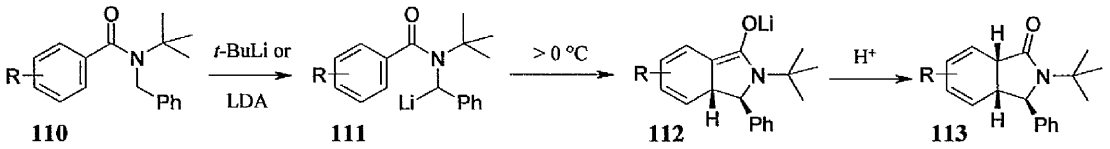
105 **106** **107** **109** **108**

Scheme 1.35

Similarly, benzamides **110** undergo dearomatising anionic cyclisation to form substituted isoindolones **113** (Scheme 1.36).[101,105] The scope for modification of the acceptor ring was explored and a variety of substituted benzamides were prepared and cyclised. The *N*-*t*-butyl group could also be replaced with the acid labile cumyl group.

All compounds were obtained as a single diastereoisomer with the phenyl group in a *cis*-position (on the *exo* face) to the *cis* 6,5-ring junction. This results from attack of the electrophile from the least hindered *exo* face of the enolate forming the more stable *cis* ring junction. The ring closure is also diastereoselective, with the phenyl group and the hydrogen lying *cis* to each other.

The cyclisation was tolerant to electron-withdrawing and electron-donating groups and the use of LDA allowed cyclisation of compounds containing functionality reactive towards *t*-BuLi such as bromo and nitrile (Table 1.1). This route provided access to a wide range of functionalised, substituted and partially saturated isoindolones.

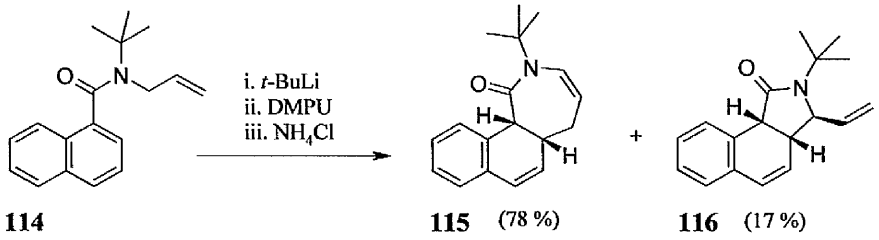


Scheme 1.36

R =	Yield	R =	Yield
4-Me	30 %	4-Br	59 %
4-OMe	62 %	6-OMe	60 %
4-Ph	80 %	5-Br	44 %
4-CN	20 %	4,6-OMe	62 %

Table 1.1

An allylic stabilising group has also been employed in the cyclisation of naphthamides **114**; this group was sufficient to stabilise the α-lithiated intermediate and resulted in the formation of both a seven-membered ring product **115** and a pyrrolidine ring product **116** (Scheme 1.37).[106] Structural similarity to the pharmaceutically important benzazepin-2-one series is apparent.[107]



Scheme 1.37

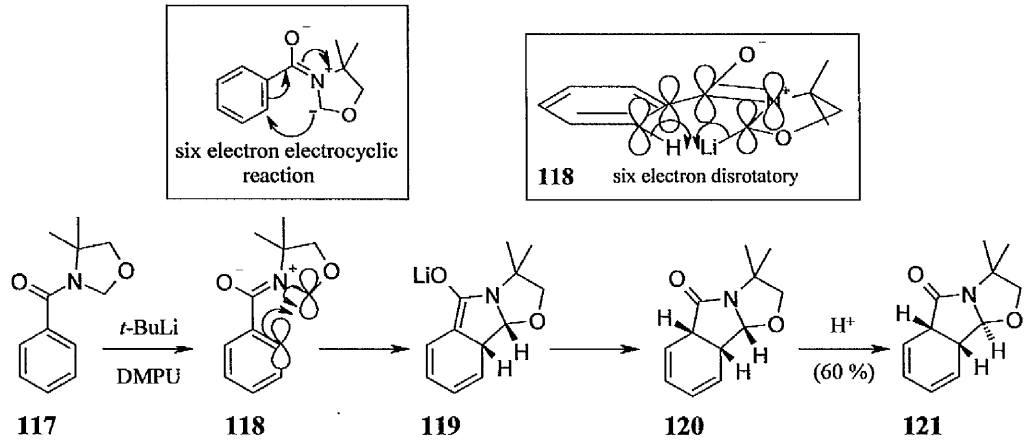
The major product is tetrahydroazepinone **115**, formed by attack at the γ-position of the lithiated allyl group. Typically, seven-membered rings are slow to form by cyclisation reactions and to our knowledge have never previously been made by organolithium cyclisation onto a carbon-carbon double bond.

1.6.1 Selectivity and Mechanism of the Cyclisation

The mechanism of the dearomatising anionic cyclisation was intriguing. As discussed previously (Scheme 1.35) three new stereogenic centres were generated in the cyclisation step and the products were obtained as single diastereoisomers. Two alternative pathways, ionic or pericyclic, could explain the source of the diastereoselectivity.

Initially the reaction was thought to proceed by an intramolecular conjugate addition reaction[108] of the benzylic anionic centre into the electron-deficient *ortho* position of the aromatic ring. The stereochemistry was presumed to arise from the preference of the phenyl group for the *exo* face of the forming bicyclic ring system. However, with this interpretation, the cyclisation of lithiated benzamides and naphthamides has 5-*endo-trig* character, which is Baldwin-disfavoured.[109]

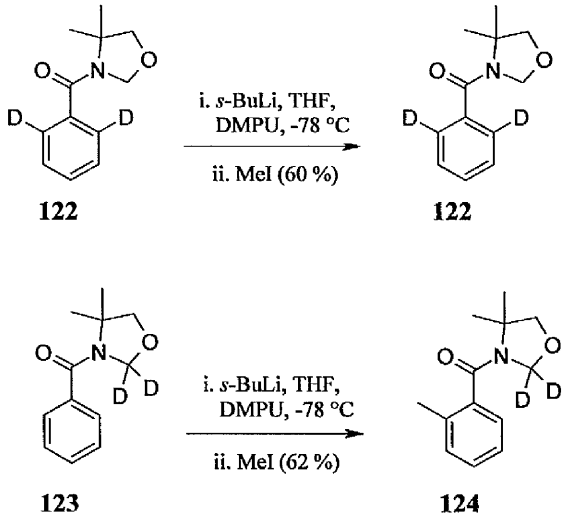
It has now been shown, for a related compound **117**, with known conformation that the mechanism is pericyclic and thus not subject to the usual stereoelectronic constraints proposed by Baldwin. The oxygen substituent of the oxazolidine ring in the α-lithiated intermediate **118** is forced to adopt a *cis* relationship with the bulky geminal dimethyl group on the nitrogen by virtue of the fact that it is constrained within a ring system.[110] The initial cyclisation produces a *cis*-fused tricyclic ring system **120** (established *via* X-ray crystallography), which is significantly less stable than the *trans*-fused system **121** formed after epimerisation of the *cis*-fused system with 2 M HCl, under thermodynamic control. A disrotatory thermal electrocyclic ring closure obeys the Woodward-Hoffmann rules[111] and leads to the observed product stereochemistry (Scheme 1.38).



Scheme 1.38

Conclusive proof of the exact reaction pathway came from deuterium labelling studies (Scheme 1.39).[110] It was shown that the di-orthodeuterated benzamide **122** failed to lithiate under the cyclisation conditions, recovering predominantly starting material, this indicated that cyclisation was not possible if ortholithiation was blocked.

When both α- positions were deuterated **123**, cyclisation was again prevented. Ortholithiation was observed, but the kinetic isotope effect prevented 'translocation' into the α-position. The ortholithiated intermediate was quenched with iodomethane to give **124** in good yield (Scheme 1.39). This indicated that translocation was necessary for cyclisation and the reaction pathway was elucidated: ortholithiation, anion translocation, cyclisation and quench.



122 **122**

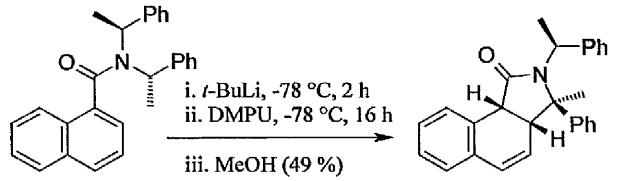
123 **124**

Scheme 1.39

1.6.2 Enantioselective Dearomatising Anionic Cyclisation

Following the successful mechanistic studies into this interesting reaction the next stage in its development was to make it enantioselective. Initially this was done in the naphthamide series by attachment of a chiral auxiliary to the amide nitrogen.[112, 113]

The cyclisation bearing chiral *N*-substituents **1**, proceeds with overall retention of configuration at the newly formed tetrasubstituted chiral centre **125** (Scheme 1.40). Overall, the cyclisation is stereospecific, with the configuration of the starting trisubstituted stereogenic centre controlling the stereochemistry of the product.

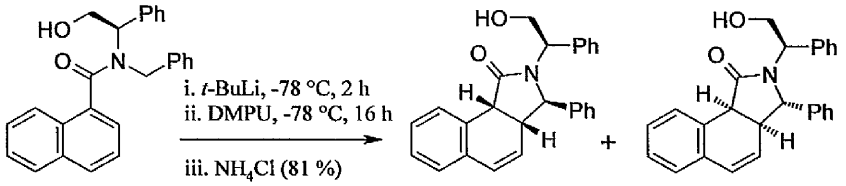


1 **125**

Scheme 1.40

The stereospecificity was thought to arise from either a configurationally stable organolithium intermediate or because the starting amide **1** exists as two atropisomers at –78 °C, of which only one is lithiated. The remaining material is recovered starting material, thus the overall yield is less than 50 %.

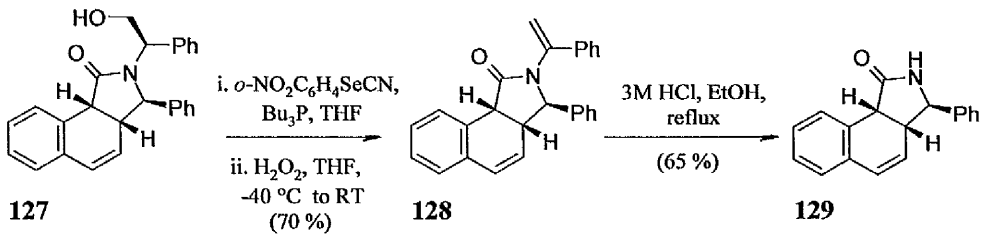
A phenylglycinol auxiliary[113,114] has also been employed to control selectivity of the reaction; naphthamide **126** gave the cyclised product **127** in 81 % yield with a 91:9 ratio of diastereoisomers (Scheme 1.41). It is postulated that the selectivity arises from co-ordination of lithium by the oxygen atom in the auxiliary.



126 **127** 91 : 9

Scheme 1.41

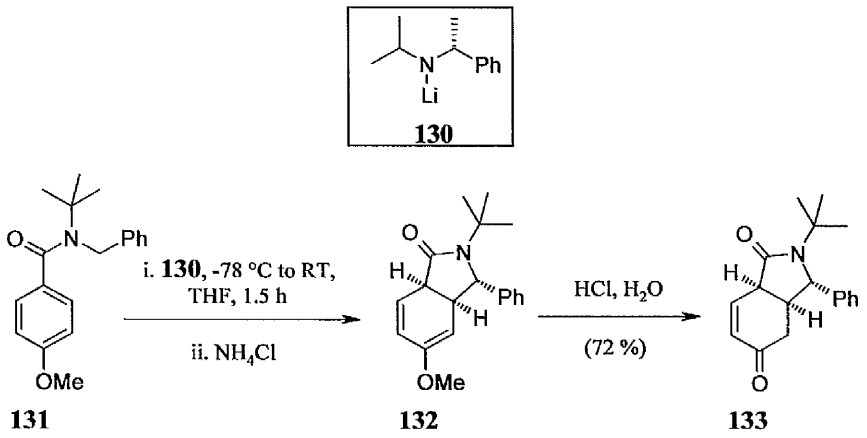
This stereoselective cyclisation of naphthamides was extremely versatile as both enantiomers of phenylglycine are commercially available and the auxiliary could be easily removed using a novel selenide oxidation-elimination protocol, therefore providing a handle for further functionalisation **129** (Scheme 1.42).[113]



127 **128** **129**

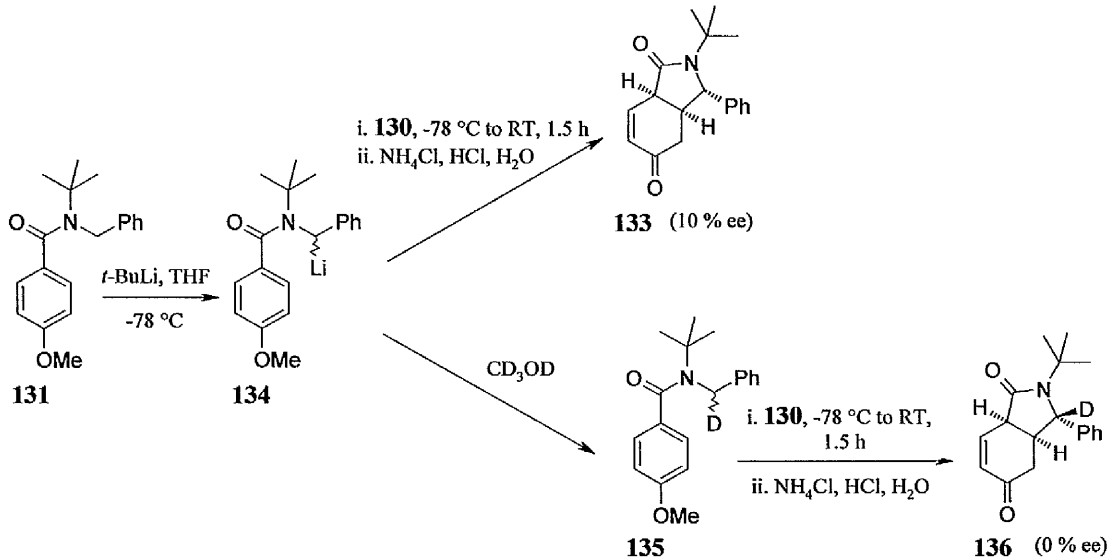
Scheme 1.42

More recently, a chiral version of LDA **130** was employed to effect the cyclisations asymmetrically.[115] Cyclisation of **131** achieved enantiomeric excesses greater than 80 % and a single recrystallisation was enough to return **133** with greater than 99 % ee (Scheme 1.43).



Scheme 1.43

It was shown that the enantioselectivity was determined before the cyclisation step. Treatment of **131** with *t*-BuLi generated the racemic α-lithiated intermediate **134**. Chiral amine **130** was added and after cyclisation, aqueous quench and acid work-up, it was found that **133** was essentially racemic (Scheme 1.44). On treatment of racemic, deuterium labelled **135** under the cyclisation conditions with chiral lithium amide **130** the reaction afforded >99 % deuterated **136** (Scheme 1.44).



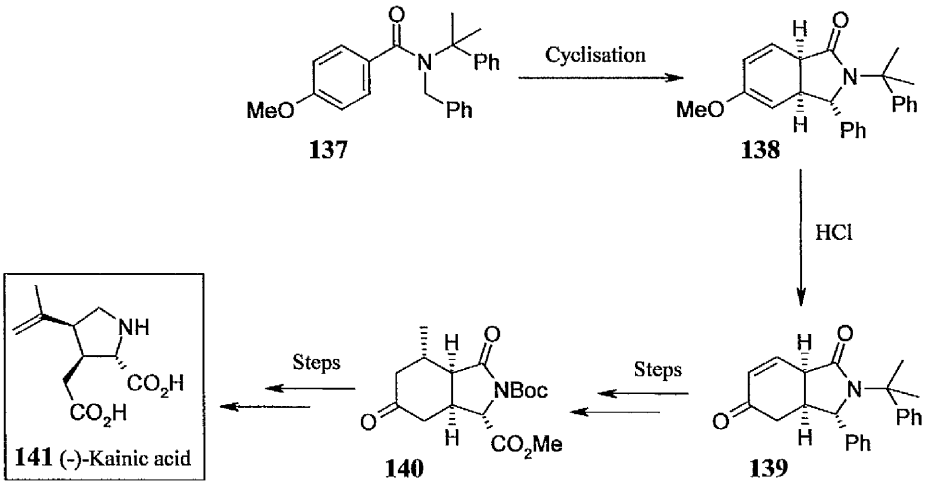
Scheme 1.44

This result is consistent with the primary kinetic isotope effect being of a high enough value (greater than 100)[116] to overturn the enantioselective effect of the chiral base, implying that deprotonation was the enantioselective step. Thus, it was concluded that the source of the enantioselectivity came from an asymmetric deprotonation of one of the pair of enantiotopic protons of **131**, giving a benzylic organolithium with sufficient configurational stability to cyclise stereospecifically.

1.6.3 Synthetic Application of the Cyclisation

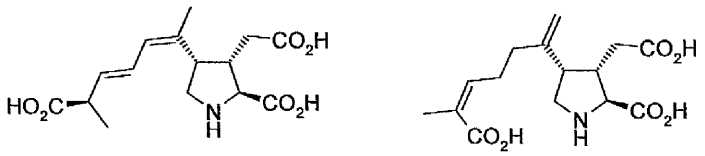
The enol ether product **138** from the dearomatising anionic cyclisation of methoxy-substituted amides may be cleanly hydrolysed to enones such as **139**[117] and these have proven to be versatile intermediates for the stereoselective synthesis of a range of important heterocycles, principally in the kainoid family of amino acids. Kainic acid itself is an extremely potent neuroexcitor which binds strongly to the kainite neurotransmitter receptors leading to specific neuronal death.[118] The neuroexcitory properties are dependent on the *cis* C-3-C-4 relative stereochemistry that is set up in the dearomatising anionic cyclisation step.

The general strategy for the synthesis of (–)-kainic acid **141** was to retain the new five-membered ring of **139** but to sacrifice the six-membered ring, while exploiting the *cis* ring junction as a means of ensuring the characteristic *cis* stereochemistry of the substituents at C-3 and C-4 (Scheme 1.45).[117]



Scheme 1.45

Current research within the group includes the use of dearomatising anionic cyclisation to target racemic and asymmetric versions of other members of the kainoid family, namely domoic acid **142** and isodomoic acid C **143** (Scheme 1.46).[119]



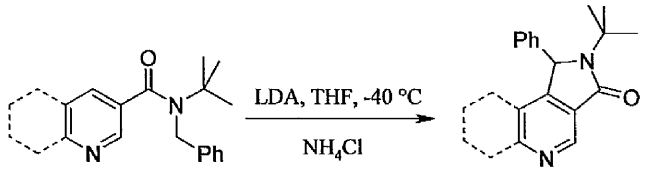
142
(-)-Domoic acid

143
Isodomoic acid C

Scheme 1.46

1.6.4 Dearomatising Anionic Cyclisation onto Aromatic Heterocycles

The cyclisation was also applied to six-membered aromatic heterocycles and it was shown that 3-substituted pyridines **144** and quinolines **145** act as acceptors but rearomatisation to the bicyclic **146** and tricyclic **147** was prevalent (Scheme 1.47).[120]

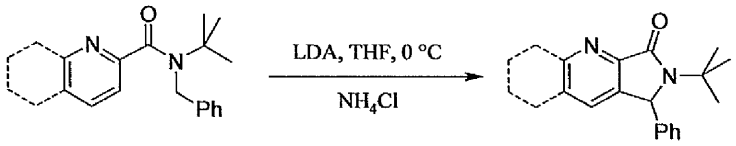


144
145

146 Pyridine (70 %)
147 Quinoline (72 %)

Scheme 1.47

The same rearomatisation was observed on attempted cyclisation of 2-substituted pyridines **148** and quinolines **149** resulting in the formation of the aromatic bicycle **150** and tricycle **151** (Scheme 1.48).

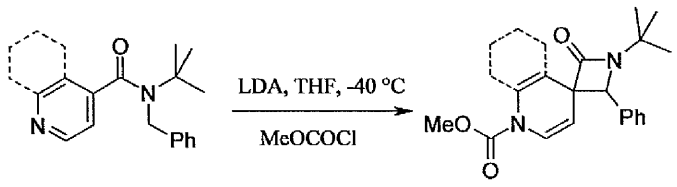


148
149

150 Pyridine (45 %)
151 Quinoline (31 %)

Scheme 1.48

Attempted cyclisation of 4-substituted pyridines **152** and quinolines **153** resulted in the formation of novel spirocyclic systems **154** and **155** (Scheme 1.49).



152
153

154 Pyridine (91 %)
155 Quinoline (72 %)

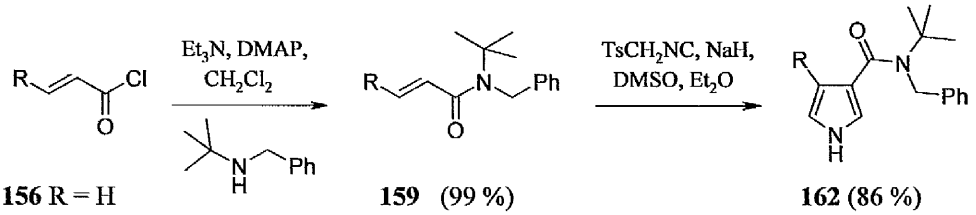
Scheme 1.49

Chapter 2

Dearomatising Anionic Cyclisation onto Five Membered Heterocycles

2.1 Pyrroles

Investigations into the cyclisation of *N*-protected pyrrole-3-carboxamides began with the synthesis of the 3-substituted pyrrole ring. The reaction of commercially available acyl chlorides **156-158** and *N-tert*-butylbenzylamine afforded the *N*-benzyl-*N-tert*-butylacrylamides **159-161,** in near quantitative yield. The acrylamides were subject to cycloaddition with an equimolar amount of tosylmethylisocyanide (TosMIC) and excess sodium hydride in DMSO and diethyl ether. Flash chromatography provided the 3-substituted pyrroles **162-164** in good yield (Scheme 2.1).



156 R = H
157 R = Me
158 R = Ph

159 (99 %)
160 (100 %)
161 (99 %)

162 (86 %)
163 (58 %)
164 (43 %)

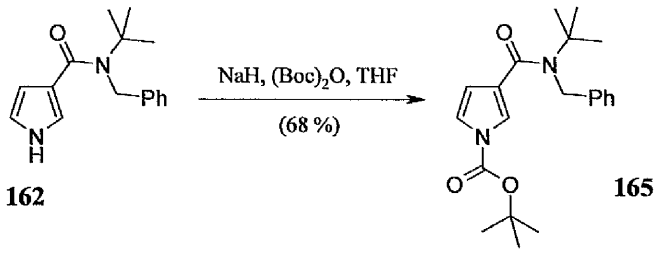
Scheme 2.1

The utility of TosMIC for the construction of heterocycles is well documented.[121] TosMIC reacts under basic conditions with α,β-unsaturated ketones, esters or nitriles to give, by concomitant loss of *p*-toluenesulfinic acid, 3-acylpyrroles, pyrrole-3-carboxylates and 3-cyanopyrroles.[122] It has also been shown that TosMIC reacts with acrylamides providing a short route to pyrrole-3-carboxamides.[123]

2.1.1 Protecting Group Study

Protection of the pyrrole N-H was necessary in order to prevent *N*-lithiation under the conditions required for the cyclisation reaction. It was initially proposed that *N*-acyl pyrroles would promote cyclisation due their electron deficiency and reduced nucleophilicity. The carbamate, *t*-butoxycarbonyl (Boc) protecting group was selected due to the ease of *N*-protection and deprotection.

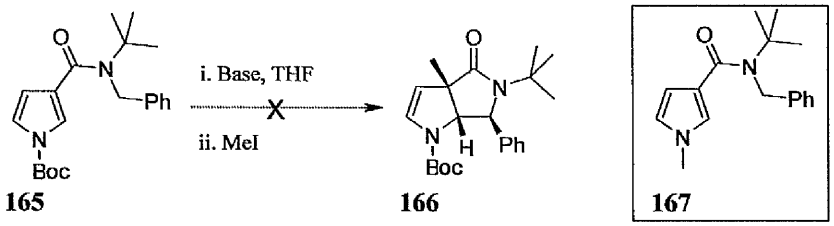
Thus, reaction of the pyrrole-3-carboxamide **162** with di-*tert*-butyldicarbonate and excess sodium hydride in THF afforded the Boc-protected pyrrole-3-carboxamide **165** in 68 % yield (Scheme 2.2).



162 **165**

Scheme 2.2

However, attempted cyclisation of the *N*-Boc protected pyrrole-3-carboxamide **165** under the conditions optimised by the Clayden group proved unsuccessful.[100-103] Efforts using both LDA and *t*-BuLi under various conditions (Table 2.1) did not afford the desired cyclised product **166**, instead the *N*-methyl compound **167** resulting from Boc deprotection was observed in all cases (Scheme 2.3).



165 **166** **167**

Scheme 2.3

Base	**Equiv.**	**Solvent**	**Temp. °C**	**Time**	**Yield (167)**	**SM Recovery**
LDA	1.5	THF	0	3 h	51 %	40 %
LDA	1.5	THF	-40	O/N	0 %	100 %
LDA	3.0	THF	-40	O/N	56 %	30 %
LDA	3.0	THF	0	3 h	57 %	15 %
t-BuLi	1.3	THF	-78 to RT	1 h then 2 h	54 %	20 %
t-BuLi	1.3	THF + DMPU	-78	O/N	52 %	15 %

Table 2.1

Deprotection could be accounted for by considering the reaction of the amide anion, $(i\text{-Pr})_2N^-$, formed during the reaction, or *t*-BuLi, with the starting material. It is believed that these species may be reacting with the Boc group in one of two ways:

i. Direct nucleophilic displacement at the electrophilic centre in the Boc group, displacing the pyrrole nucleus.

ii. A β-elimination process involving deprotonation of the *t*-butyl group of the Boc moiety, with elimination of CO_2 and 2-methylpropene, expelling the pyrrole anion as the leaving group (Figure 2.1).

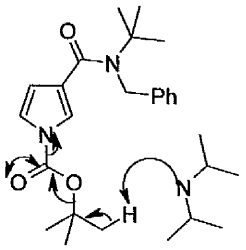
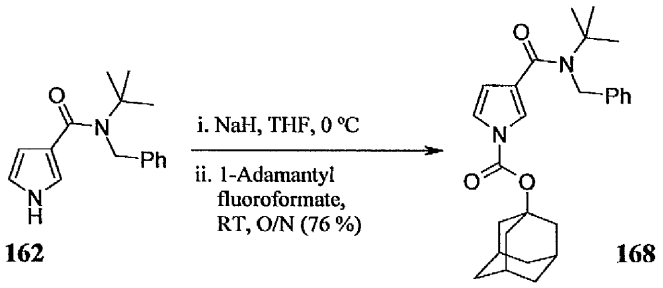


Figure 2.1

The relative instability of the Boc protected pyrrole prompted the investigation of alternative protecting groups. It was anticipated that an adamantyl protecting group could not undergo the β-elimination pathway based on the premise of Bredt's Rule.[124] This is a consequence of the strain induced by planar bridgehead carbon atoms. Thus the adamantyl-protected pyrrole-3-carboxamide **168** was prepared in 76 % yield from pyrrole **162** and 1-adamantyl fluoroformate (Scheme 2.4).

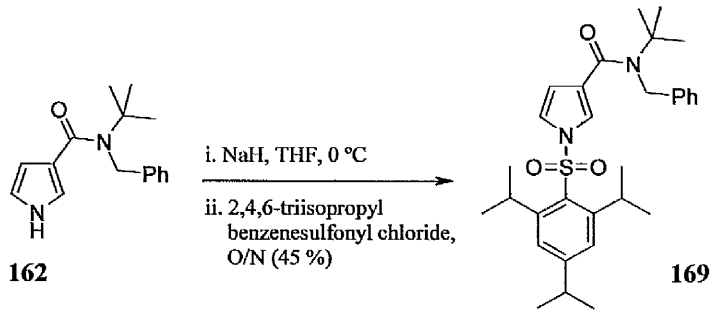


162 **168**

Scheme 2.4

Endeavours to cyclise the adamantyl protected pyrrole **168** using both LDA and *t*-BuLi resulted in formation of the *N*-methyl pyrrole **167**, no cyclised product was observed. It can be speculated that the deprotection mechanism is that of direct nucleophilic displacement and not a β-elimination process.

The trisyl *N*-sulfonyl protecting group was also investigated as it was proposed that the electron-withdrawing, arylsulfonyl group would stabilise negative charge at the 2-position in the pyrrole ring and could not be subject to the β-elimination pathway. The trisyl-protected pyrrole **169** was prepared in modest (45 %) yield, by reaction of pyrrole-3-carboxamide **162** with 2,4,6-triisopropylbenzenesulfonyl chloride (Scheme 2.5).



162 **169**

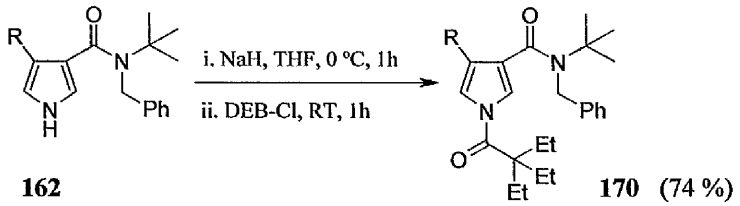
Scheme 2.5

Sulfonamide derivatives are amongst the most stable of the nitrogen protecting groups and they have the added bonus of being highly crystalline and are less susceptible to nucleophilic attack than carbamate protecting groups. They are frequently used to circumvent problems associated with nitrogen heterocycles; the powerful electron-withdrawing effect reduces the susceptibility of the pyrrole nucleus to electrophilic attack and oxidation, and replacement of the acidic N-H allows lithiation of the heterocyclic nucleus.

Attempted cyclisation of the *N*-trisyl protected pyrrole **169** using LDA and *t*-BuLi was unsuccessful and no cyclised product was obtained. Deprotection was not observed and starting material was recovered in all cases. This is potentially due to the sterically demanding, bulky isopropyl substituents in the protecting group, preventing lithiation at the pyrrole 2-position.

Efforts to effect cyclisation of the *N*-methyl pyrrole **167**, recovered from previous cyclisation attempts, using LDA and *t*-BuLi were not auspicious and starting material was recovered. It is postulated that cyclisation of the *N*-methyl pyrrole **167** is unfavourable owing to the electron-donating nature of the methyl group which prevents lithiation and subsequent cyclisation.

The diethyl butyryl (DEB) group was chosen as an alternative protecting group for the pyrrolecarboxamide **162**, as a conformationally restricted bulky acyl group had not previously been tested. It was anticipated that the DEB group would be stable to deprotection owing to the absence of β-hydrogen atoms, thus preventing the β-elimination pathway and the ethyl groups would be sufficiently bulky to prevent a direct nucleophilic displacement pathway. The acyl group should also provide sufficient electron-withdrawing character to encourage lithiation on the pyrrole ring. Thus, DEB-pyrrole-3-carboxamides **170-172** were synthesised in good yields (Scheme 2.6).

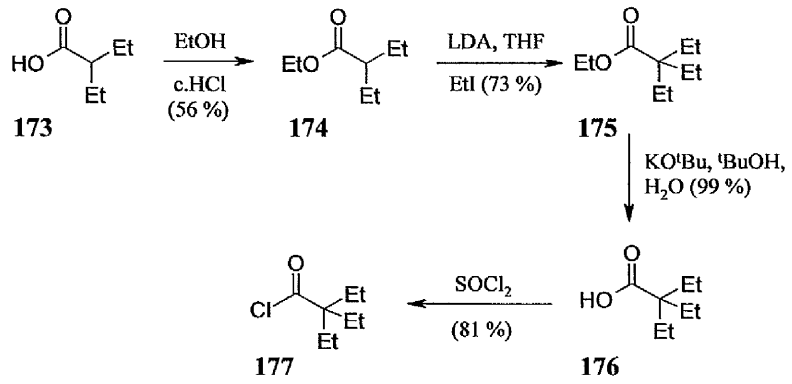


162
163
164

170 (74 %)
171 (84 %)
172 (89 %)

Scheme 2.6

The DEB-Cl protecting group **177** was prepared by a four-step procedure as outlined by Beak and Zajdel (Scheme 2.7).[125] Esterification of commercially available diethyl acetic acid **173**, followed by alkylation and ester elimination afforded the acid **176** which on treatment with refluxing thionyl chloride gave DEB-Cl **177** in excellent yield.



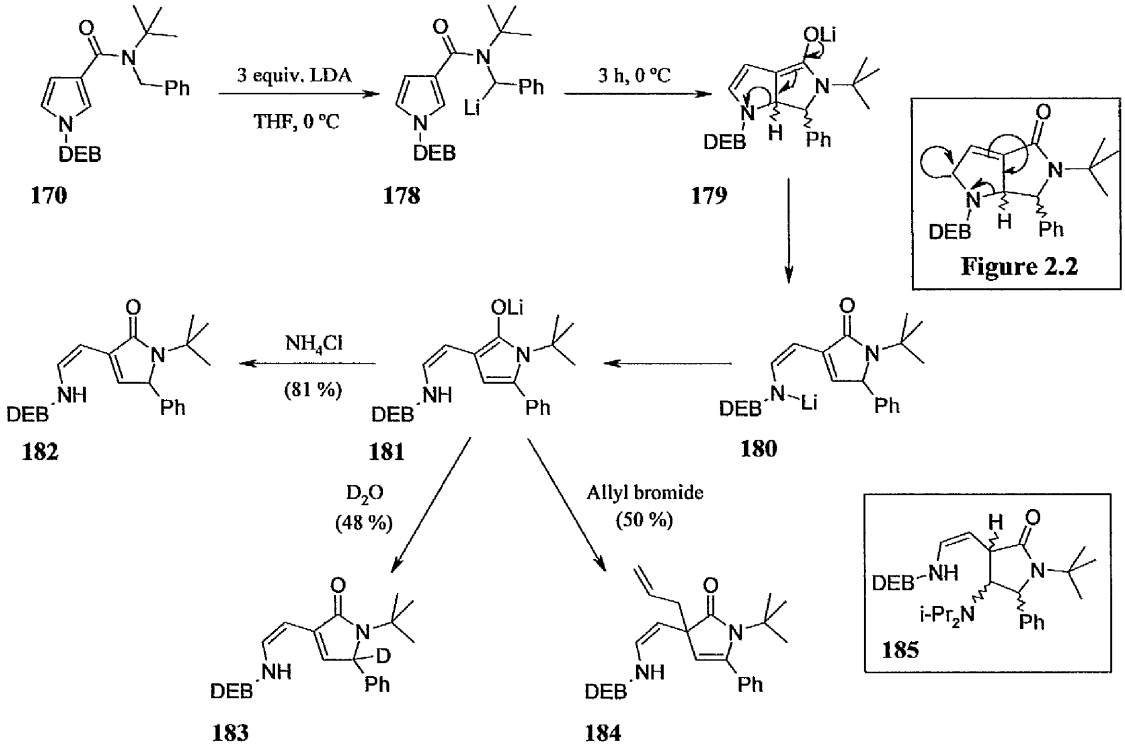
173 **174** **175** **176** **177**

Scheme 2.7

2.1.2 Attempted Cyclisation of DEB Protected Pyrrole-3-Carboxamides[126]

Attempted cyclisation of the pyrrole-3-carboxamide **170** using *t*-BuLi in THF at –78 °C resulted in decomposition, so the use of LDA was investigated. Interestingly, attempted cyclisation using 3 equivalents of LDA at 0 °C for 3 h did not give the desired cyclised product. Instead the 1,5-dihydropyrrol-2-one **182** was formed in 81 % yield. The cyclisation evidently followed the pathway shown in Scheme 2.8.

The expected benzylic lithiation gave **178**, which cyclised by nucleophilic attack on the 2-position of the pyrrole ring. The product, the extended enolate **179**, was unstable due to extensive saturation in the 5,5-fused system. A decomposition pathway, which can be rationalised as either a 5-*endo-trig* or an electrocyclic ring opening (Figure 2.2), relieves the strain to generate **180**. This product undergoes an intramolecular proton transfer yielding a new extended enolate **181**, which on proton quench generated **182**. The intermediacy of the extended enolate **181** was demonstrated by γ-deuteration, which gave **183**, or α-allylation, which gave **184**. It was important to avoid a large excess of LDA, because with 6 equivalents **185** was formed in 20 % yield due to conjugate addition of the LDA to the pyrrolinone ring system.



Scheme 2.8

This was an encouraging result as it was the first example of a dearomatising anionic cyclisation onto a pyrrole ring. Various conditions were applied in order to both optimise the yield of **182** and prevent the ring opening of the 5,5-bicyclic system (Table 2.2). Attempts to quench the cyclisations with different electrophiles (Me, Bn) were unsuccessful and only protonated products **182** were observed.

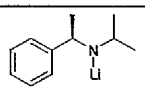
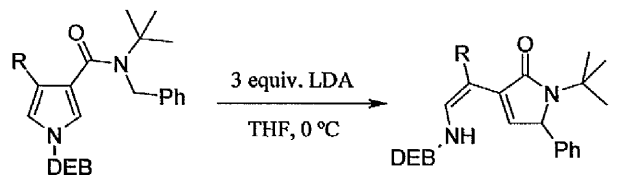
Base	Equiv.	E^+	°C	Time	Results 182	185
t-BuLi	2.0	MeI	-78	O/N	Decomposition	
LDA	6.0	NH_4Cl	0	3 h	56 %	20 %
LDA	3.0	NH_4Cl	0	3 h	81 %	
LDA	1.3	NH_4Cl	0	3 h	50 %	
LDA	3.0	NH_4Cl	0	10 min	55 %	
LDA	3.0	NH_4Cl	0	Immediate quench	35 %	
LDA	3.0	NH_4Cl	-40	3 h	48 %	
LDA	3.0	NH_4Cl	-40	Immediate quench	46 %	
LTMP	3.0	NH_4Cl	0	2 h	50 %	
 **130**	3.0	NH_4Cl	-78 to 0	4 h	90 %	

Table 2.2

As can be seen from Table 2, it proved impossible to isolate any cyclised product even at –40 °C followed by immediate quench, indicating that the ring opening occurs instantaneously. Although the chiral base lithium isopropyl-(1-phenylethyl)-amine **130** introduced no chirality into the molecule, it gave the highest yield of product **182**, without any adducts being formed. It is postulated that the hindered base was unable to form any adduct as the bulky DEB group shields its attack.

2.1.3 Investigation into Ring Opening

We wished to explore the scope of the novel ring opening reaction and the formation of 1,5-dihydropyrrol-2-ones **182**. The cyclisation (effectively a conjugate substitution of the pyrrole nitrogen by the benzyllithium) was repeated using the 4-substituted pyrrole carboxamides **171** and **172** and again good yields of the ring-opened products **186** and **187** were obtained (Scheme 2.9).

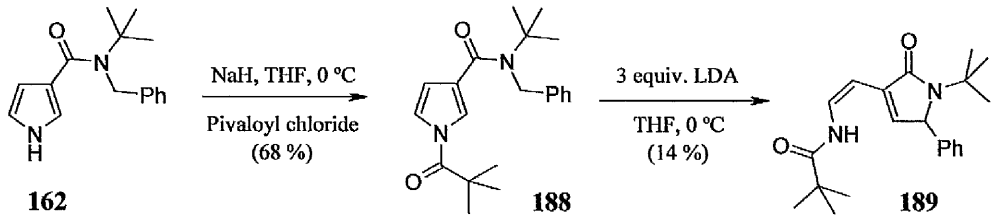


171
172

186 (R = Me, 59 %)
187 (R = Ph, 75 %)

Scheme 2.9

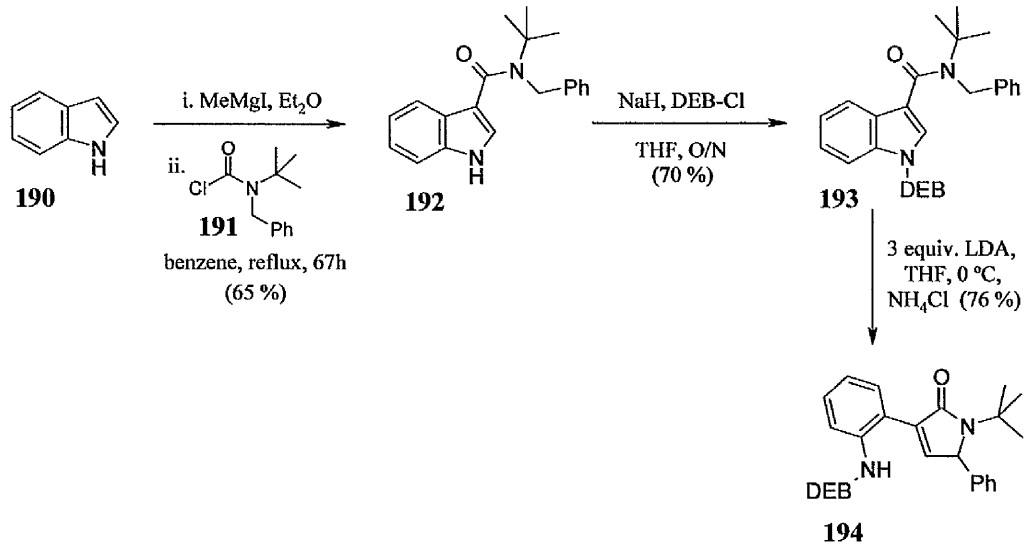
Changing the protecting group to the more readily available pivaloyl group **188** resulted in poorer yields of the 1,5-dihydropyrrol-2-one **189** (Scheme 2.10)



162 **188** **189**

Scheme 2.10

Incorporation of the pyrrole into an indole nucleus **193** produced the aminophenyl-substituted product **194** in high yield on cyclisation. Reaction of the indolyl Grignard reagent with carbamoyl chloride **191** afforded the 3-substituted carboxamide **192**, which was readily DEB protected **193** (Scheme 2.11).

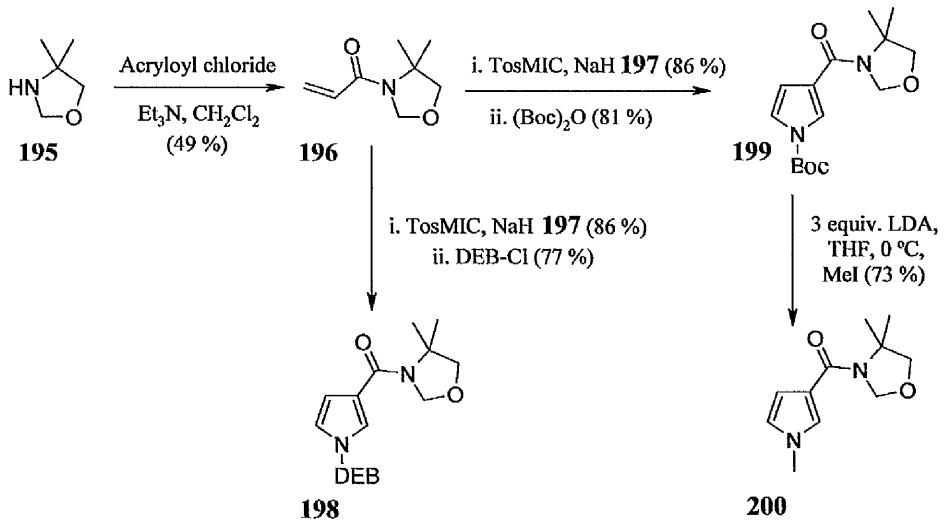


190 **191** **192** **193** **194**

Scheme 2.11

In order to investigate the effect of replacing the benzylic group, oxazolidine substituted pyrrolecarboxamide **198** was prepared in good yield from the acrylamide **196** (Scheme 2.12). The precedent for the use of the oxazolidine side chain arose because it was more versatile than the *N*-*t*-butyl benzamide and a better precursor to a CO_2H substituent. Its use in the benzamide cyclisations revealed some deeper mechanistic aspects of the reaction (Section 1.6.1).[110]

Replacement of the *N*-*tert*-butylbenzyl group by an oxazolidine moiety proved unsuccessful under the conditions required for cyclisation. When a DEB protecting group **198** was employed only starting material was recovered. However if a Boc protecting group **199** was used pyrrole deprotection followed by methylation to give **200** was observed. It was evident that the oxazolidine group did not undergo lithiation and was therefore an inappropriate replacement.



Scheme 2.12

Attempted cyclisation of the recovered *N*-methyl pyrrole oxazolidine **200** with both LDA and *t*-BuLi resulted in starting material recovery. Again, the electron-donating methyl group hindered lithiation of the pyrrole ring.

The dearomatising anionic cyclisation of pyrroles with subsequent ring opening to form the 1,5-dihydropyrrol-2-ones **182** can be regarded as belonging to the general class of rearrangements designated as 'monocyclic rearrangement of heterocycles' by Katritzky *et al.* (Figure 2.3).[127,128]

These reactions cover many possible interconversions but are generally limited to heterocycles containing an N-O bond; oxadiazoles, isoxazoles, triazoles, thiadiazoles, tetrazoles, imidazoles and pyrazoles have all been prepared by monocyclic rearrangement.[127] As far as we are aware ours is the first example in which there is a carbon atom where the old ring is broken and the new ring formed.

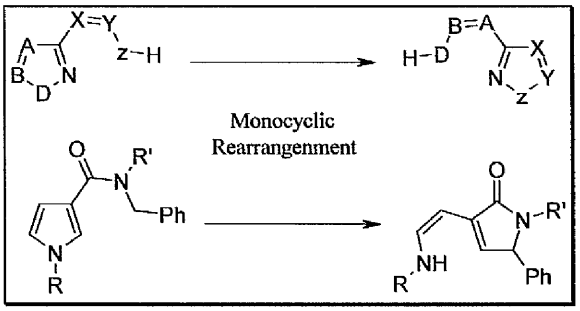
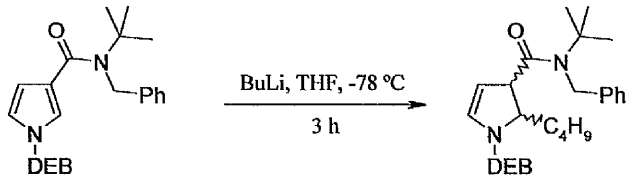


Figure 2.3

Whilst nucleophilic additions to, and substitution at, heteroaromatic rings are well documented for 6-membered heterocycles such as pyridines, pyrazines and pyrimidines[129] it is less established for the electron-rich family of 5-membered heterocycles.[130] The dearomatising anionic cyclisation of pyrroles can be regarded as an intramolecular nucleophilic attack by the organolithium.

It was also demonstrated throughout the investigation that nucleophilic butyllithiums could attack the pyrrole nucleus directly and treatment of the pyrrole-3-carboxamide **170** with *n*- and *s*- butyllithium in THF at –78 °C afforded the corresponding dearomatised 2-substituted carboxamides **201** and **202** (Scheme 2.13).



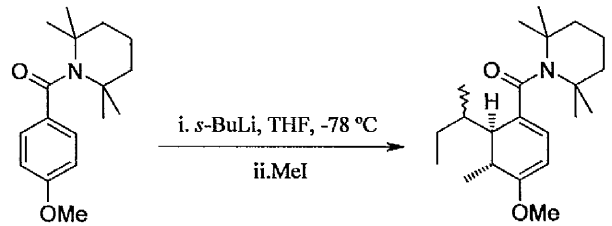
170

n-**201** (40 %)
s-**202** (40 %)

Scheme 2.13

Few methods achieve partial dearomatisation of heterocycles; Birch reduction[131-133] allows only electrophilic functionalisation of the ring, dearomatisation is usually achieved by nucleophilic addition to an electron-deficient aromatic ring lacking other points of electrophilic reactivity.

It was previously demonstrated within the Clayden group[134] that benzamides of 2,2,6,6-tetramethylpiperidine **203** allow the addition of an organolithium and an electrophile across a double bond of the aromatic ring to give the diene **204** (Scheme 2.14). However, the phenomenon has not previously been reported for an electron-rich system such as pyrrole.

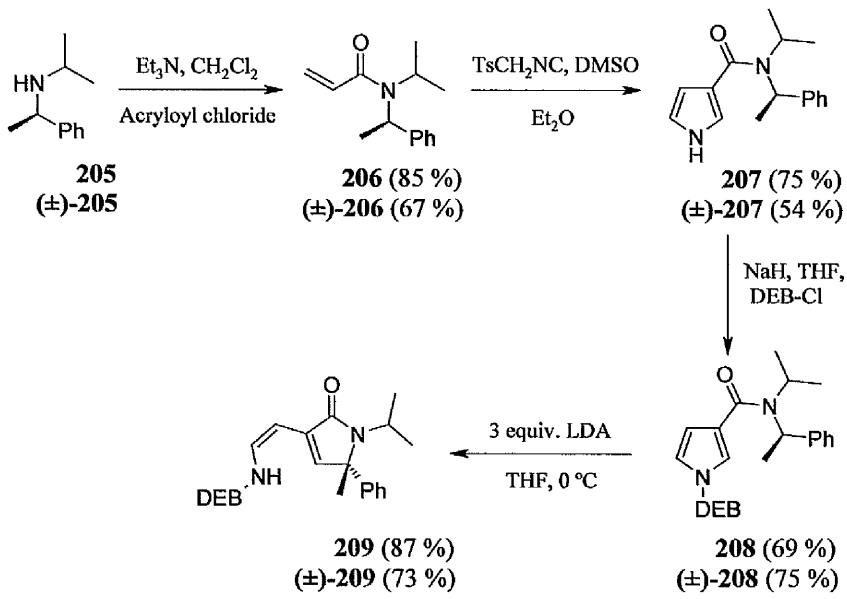


203 **204**

Scheme 2.14

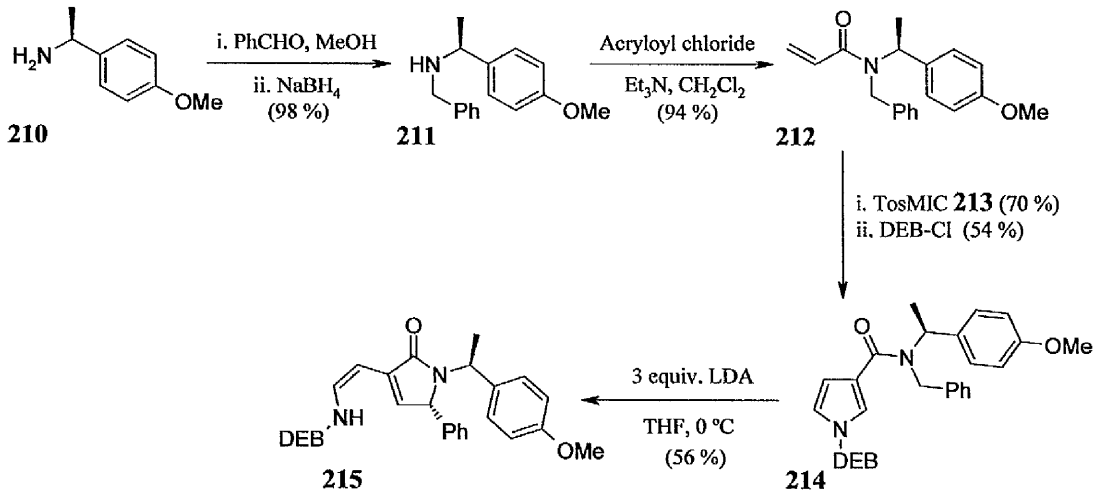
2.1.4 Selectivity within the Cyclisation

Although the cyclisation generates chiral products, an attempt to promote asymmetric cyclisations of pyrrolecarboxamides using a chiral lithium amide base **130** in place of LDA (a strategy which works well in the benzamide series)[115,135] was prevented by the unavoidable formation of the achiral enolate **181** (Scheme 2.8). However, with the chiral and enantiomerically pure amide **208**, the cyclisation product **209** cannot re-form an enolate, and indeed **209** is formed fully stereospecifically. The chiral pyrrole-3-carboxamide **207** was readily prepared from the acrylamide **206** and subsequent DEB protection gave **208** in good yield (Scheme 2.15). A fully substituted stereogenic centre is incorporated into the ring system with >99 % ee when compared to the racemic equivalent (±)-**209** by stationary phase chiral HPLC (Chiralpak OT(+) column at 5 °C). In agreement with previous reports of similar cyclisations,[135] we propose that both the lithiation and cyclisation of **208** are stereospecific, and the intermediate organolithium is configurationally stable on the timescale of the reaction. Configurational stability in similar tertiary *N*-substituted organolithiums is well documented.[136]



Scheme 2.15

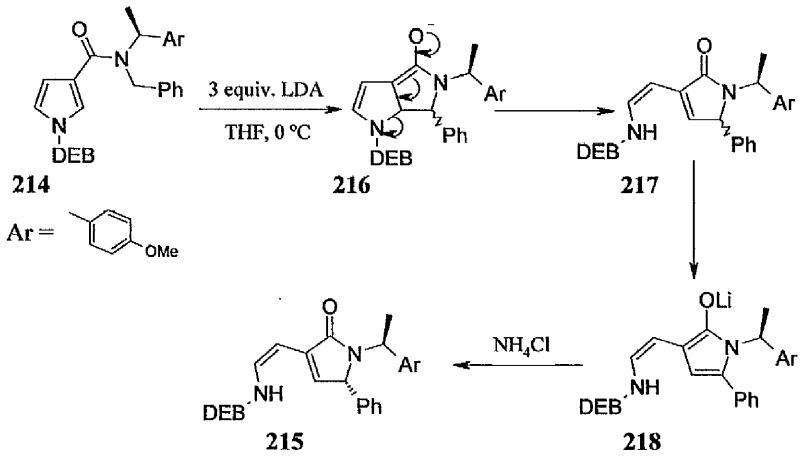
Remarkably it was also possible to cyclise **214** diastereoselectively, despite the late-stage deprotonation/reprotonation of the benzylic centre. Reductive amination afforded the chiral secondary amine **211**, which was subjected to acrylamide formation **212** followed by TosMIC cycloaddition to generate pyrrole **213**. Subsequent DEB protection gave the target compound **214** with good overall yield (Scheme 2.16).



Scheme 2.16

Attempts to quench the cyclisation of **214** with different electrophiles were unsuccessful and decomposition or the protonated product **215** prevailed.

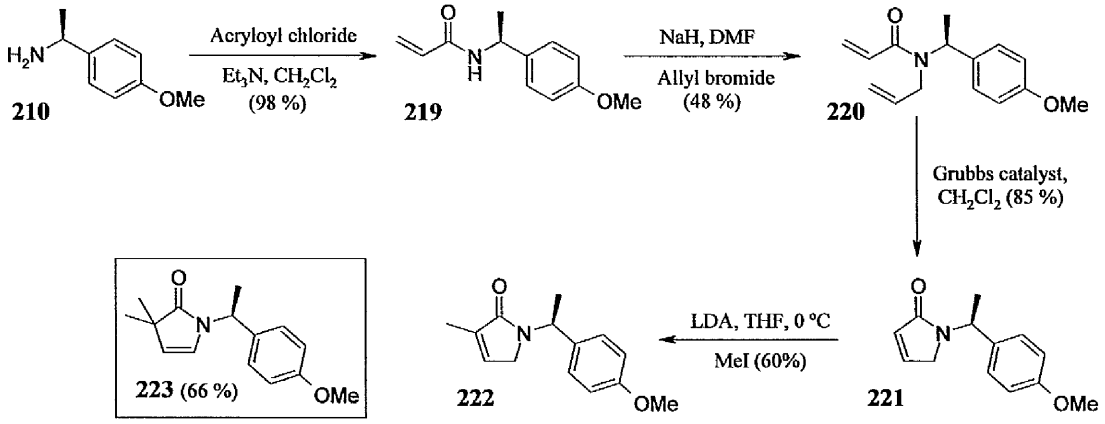
The 1,5-dihydropyrrol-2-one **215** was formed as a single diastereoisomer. The relative stereochemistry is predicted, with the phenyl group on the opposite face to the bulky chiral auxiliary. The 'auxiliary' α-methyl-*p*-methoxybenzyl substituent of **214** controls the facial selectivity of the final protonation of the extended enolate **218** (Scheme 2.17).[137]



Scheme 2.17

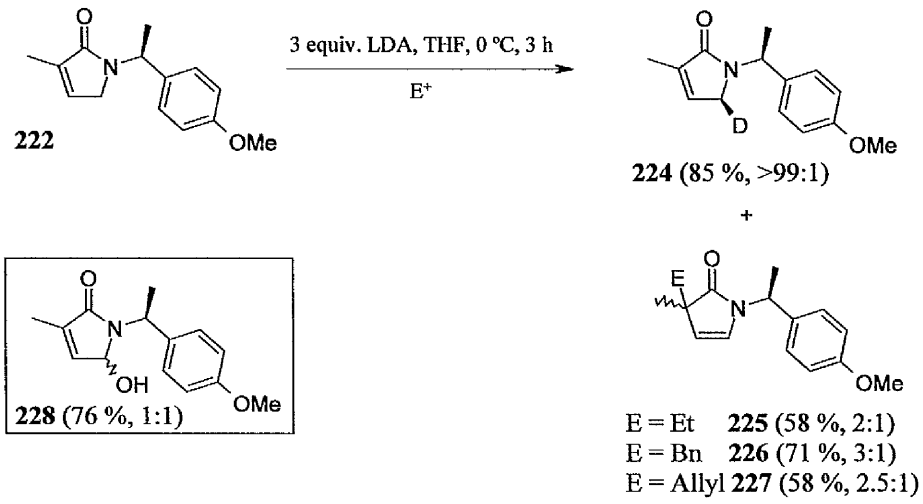
2.1.5 Diastereoselective Deprotonation/Reprotonation

We wished to investigate whether this chiral auxiliary was able to govern the selectivity of deprotonation/reprotonation of related pyrrolidinones. Allylation of the acrylamide **219** followed by ring closing metathesis[138] with the first-generation ruthenium based Grubbs catalyst[139] afforded the pyrrolidinone **221**, which was methylated α- to the carbonyl group to provide a more accurate model system **222** (Scheme 2.18). If a slight excess of LDA was used the by-product **223** was formed, indicating the electrophilic quench would occur α- to the carbonyl moiety.



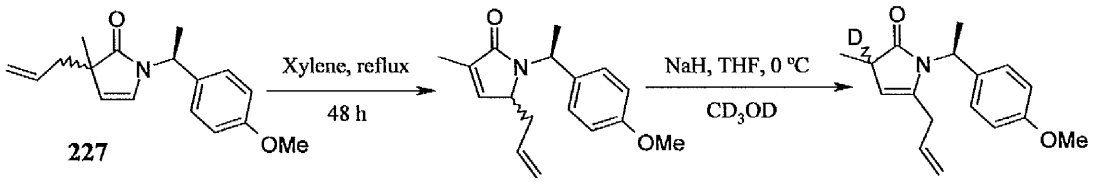
Scheme 2.18

The pyrrolidinone **222** was subjected to the standard deprotonation conditions (3 equiv. of LDA in THF at 0 °C) followed by an electrophilic quench (Scheme 2.19). With deuterium the quench occurred γ- to the carbonyl with complete diastereoselectivity **224**, which was consistent with previous results (Scheme 2.17). The carbon-carbon double bond of the product **224** is conjugated with the carbonyl group providing additional stability. However with other electrophilic quenches **225-227**, the quench occurred α- to the carbonyl group (due to steric encumbrance) with modest diastereoselectivity owing to the increased distance from the chiral auiliary. The relative stereochemistry was assumed, based on previous results. If the reaction mixture was not degassed the major product was the hydroxylated **228**.



Scheme 2.19

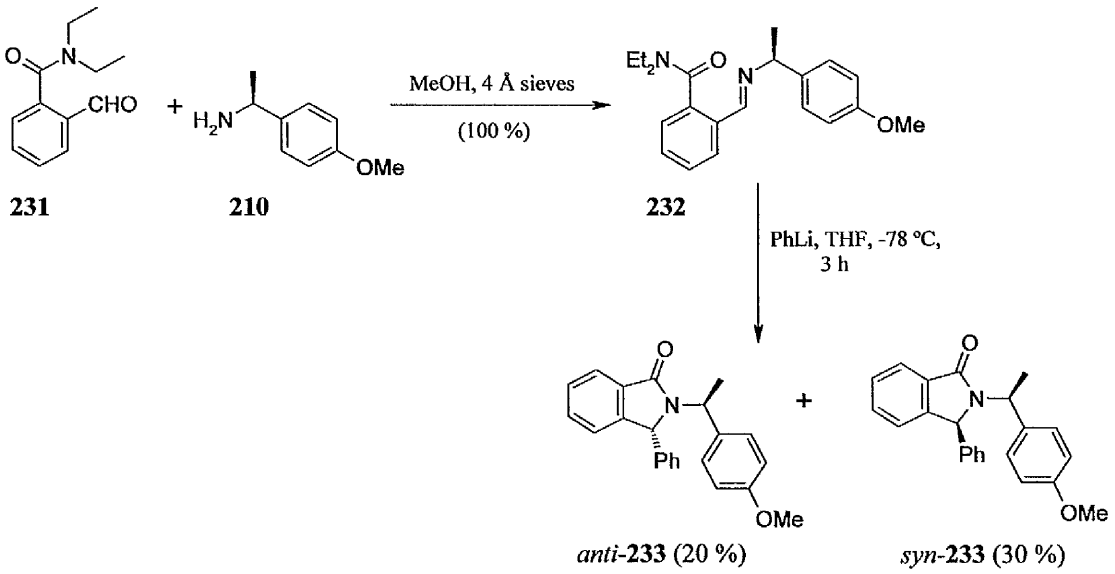
It was anticipated that modification of the model pyrrolidinone **222** to a more structurally similar system to the original **215** would increase the chance of a diastereoselective quench. Thus [3,3] sigmatropic rearrangement of **227** provided the 5-substituted pyrrolidinone **229** in good yield (Scheme 2.20). Deprotonation with LDA followed by deuterium quench resulted in starting material recovery; it was postulated that the protonated amine base provided an internal proton source.[140] When deprotonation was performed with sodium hydride (in order to remove the internal proton source) the deuterium quench occurred α- to the carbonyl with modest diastereoselectivity **230**. We postulate that steric hindrance from the allyl group causes the α-deuterium quench and the increased distance from the chiral auxiliary results in modest diastereoselectivity.



227 **229** (60 %, 2:1) **230** (99 %, 2.5:1)

Scheme 2.20

It was anticipated that the phenyl group in the 5-position of the pyrrolidinone ring system was an essential component for the diastereoselective control. It was envisaged that the 2,3-dihydroisoindolone system **233** would undergo diastereoselective quench in a comparable manner to the original system **215**. Reductive amination of the chiral amine **210** and *N,N*-diethyl-2-formylbenzamide **231**[141] gave the imine **232** which on treatment with phenyllithium afforded the dihydroisoindolone ***anti*-233** and ***syn*-233** (Figure 2.4) in a ratio of 1:1.5 (Scheme 2.21).[142] Attempts to control the diastereoselectivity of deprotonation of either a single diastereoisomer of **233** or a mixture of **233** followed by deuterium quench were unsuccessful and only the respective starting materials were recovered indicating that deprotonation had not occured.



231 **210** **232** *anti*-**233** (20 %) *syn*-**233** (30 %)

Scheme 2.21

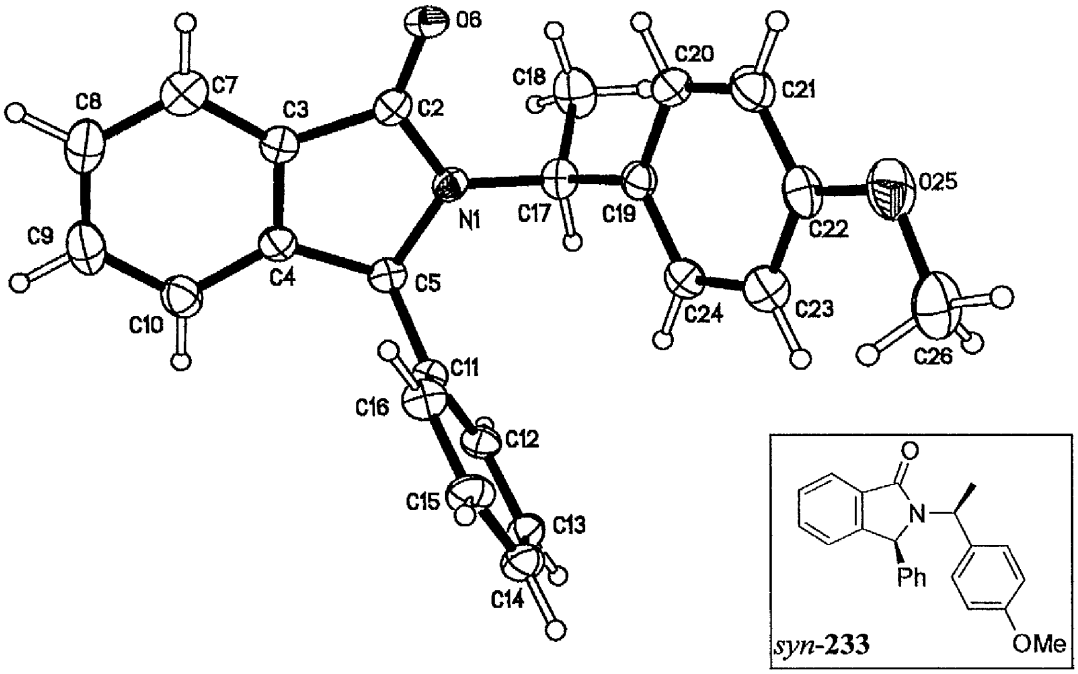
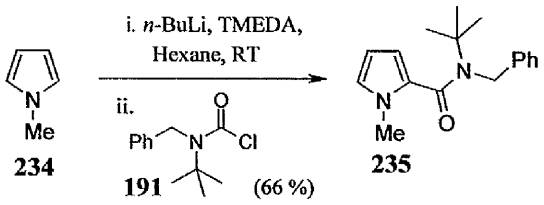


Figure 2.4 ORTEP representation of *syn*-**233** X-ray structure.

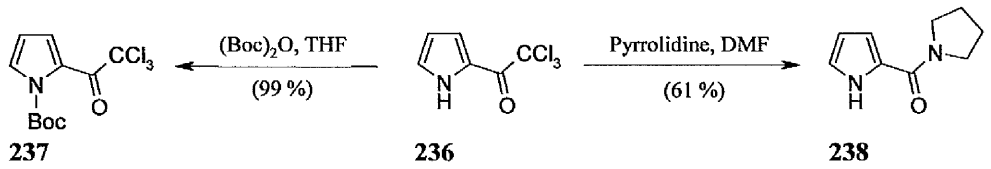
2.1.6 Pyrrole-2-Carboxamides

In order to investigate the dearomatising anionic cyclisation of pyrrole-2-carboxamides, **235** was prepared by lithiation of *N*-methylpyrrole **234** with *n*-BuLi in hexane at ambient temperature,[21] followed by reaction with carbamoyl chloride **191** (Scheme 2.22). The carbamoyl chloride **191** was prepared in excellent yield by reaction of *N*-*tert*-butylbenzylamine and diphosgene.



Scheme 2.22

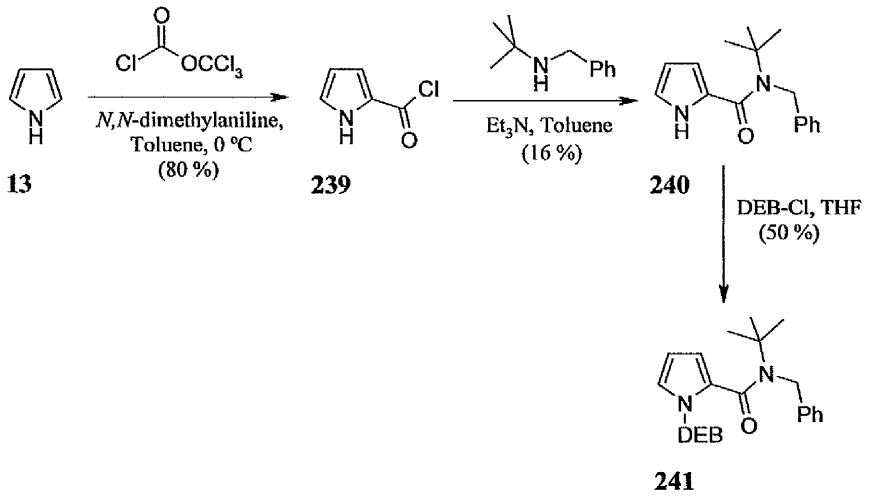
An alternative approach to the pyrrole-2-carboxamide allowing the introduction of an electron-withdrawing *N*-protecting group involved reaction of Boc protected 2-trichloroacetylpyrrole **237** and various amines in DMF. The precedent for this reaction was the observation that 2-trichloroacetyl pyrrole **236** reacts with pyrrolidine to form a pyrrole-2-amide **238** with the subsequent loss of $^{\ominus}CCl_3$ (Scheme 2.23).[143]



Scheme 2.23

However, attempts with both *N-tert*-butylbenzylamine and dibenzylamine in place of pyrrolidine afforded only starting material, even under forcing reaction conditions, due to greater steric hindrance in the amine nucleophiles.

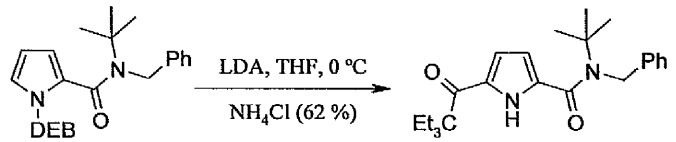
Another approach to the pyrrole-2-carboxamide **240**, *via* the pyrrole-2-carbonyl chloride **239** was attempted, allowing the introduction of a variety of protecting groups. Reaction of pyrrole with diphosgene in the presence of *N,N*-dimethylaniline afforded the pyrrole-2-carbonyl chloride **239**,[144] which was subject to reaction with the secondary amine albeit in poor yield to give **240** which was readily DEB protected **241** (Scheme 2.24).



Scheme 2.24

2.1.7 Attempted Cyclisation of Pyrrole-2-Carboxamides

Attempted cyclisation of the *N*-methyl protected pyrrole-2-carboxamide **235** using LDA or *t*-BuLi resulted in the recovery of starting material. When the electron-withdrawing DEB protecting group was in place attempted cyclisation resulted in the formation of the deprotected, rearranged product **242** (Scheme 2.25). The electronics of the pyrrole-2-carboxamide make it unsuitable for cyclisation onto the 3-position. Lithiation occurs preferentially at the 5-position due to the inductive effect of the nitrogen and the stabilising effect of chelation to the DEB carbonyl group. If lithiation and cyclisation did occur (as with the pyrrole-3-carboxamides) the 5,5 fused intermediate enolate would also be strained but no comparable ring-opening pathway is available.

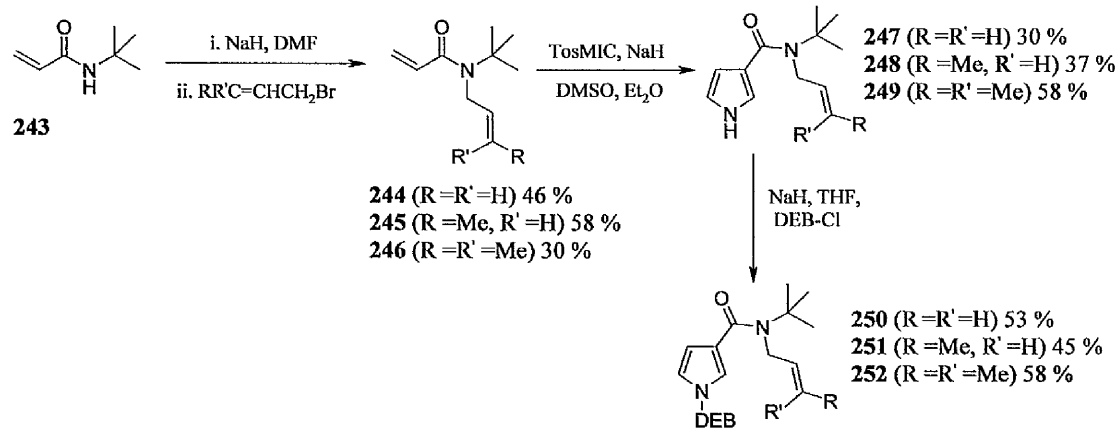


241 **242**

Scheme 2.25

2.1.8 N-Allyl Pyrrolecarboxamides

The ring opening of the pyrroles prevents the formation of the desired 5,5-fused systems. It was previously demonstrated that the cyclisation of *N*-allyl substituted naphthamides was able to generate a seven membered ring[106] and it seemed reasonable to suppose that a 7,5-fused ring system might be much less strained. Thus *N*-allyl pyrrolecarboxamides **247-249** were prepared by the cycloaddition of the acrylamides **244-246** with TosMIC followed by DEB protection to yield **250-252** (Scheme 2.26).



243

244 (R =R' =H) 46 %
245 (R =Me, R' =H) 58 %
246 (R =R' =Me) 30 %

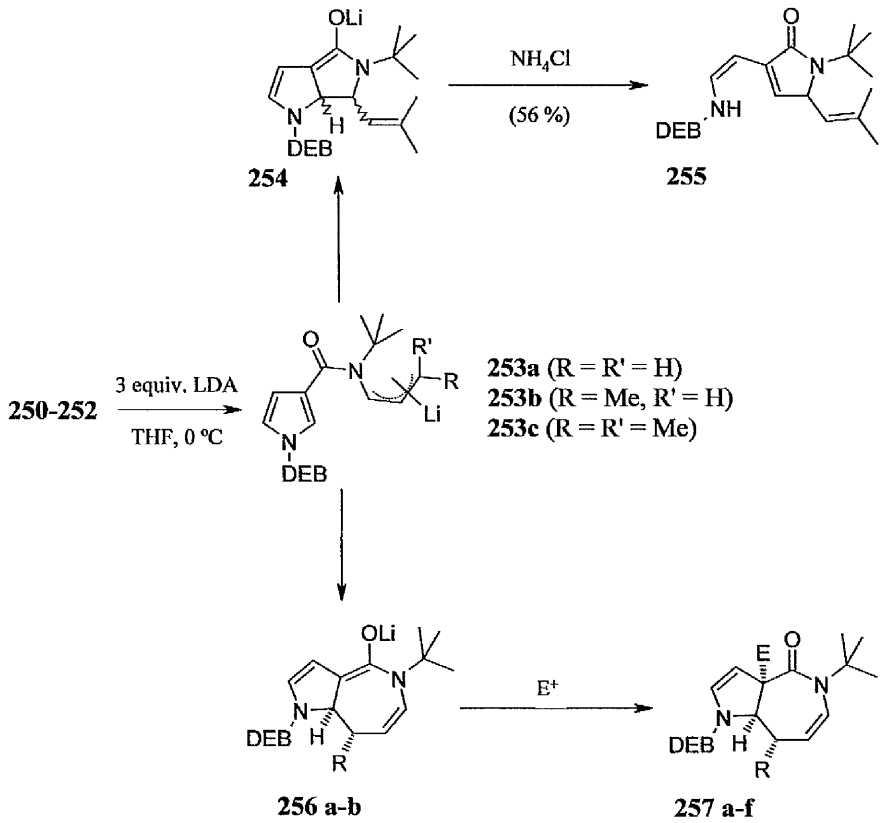
247 (R =R' =H) 30 %
248 (R =Me, R' =H) 37 %
249 (R =R' =Me) 58 %

250 (R =R' =H) 53 %
251 (R =Me, R' =H) 45 %
252 (R =R' =Me) 58 %

Scheme 2.26

Treatment of the *N*-allyl pyrrolecarboxamides **250-252** with LDA gave coloured allyllithiums **253a-c** which, with the exception of **253c**, cyclised over a period of 3 h at 0°C to yield the enolates **256a-b** (Scheme 2.27). As anticipated, these enolates were stable, and stereoselective alkylation yielded in every case essentially a single diastereoisomer of the 7,5-fused pyrroloazepinones **257a-f** (Table 2.3). The *cis* stereochemistry at the ring junction was proved by X-ray crystallography (Figures 2.5 and 2.6). The *cis* stereochemistry at the third stereocentre (where R = Me) was assumed due to the preference of larger groups for the exo face of the bicyclic system. Protonation of **256a** gave mainly the *cis*-fused 7,5-ring system (Figure 2.5), accompanied by a small amount of the *trans*-fused by-product *trans*-**257a**.

Cyclisation of *N*-prenyl substituted carboxamide **253c** gave no 7,5-fused products, presumably due to the steric hindrance at the far end of the allylic system. The isolated product was the pyrrolidinone **255**, which was analogous to the products **182** obtained from *N*-benzyl carboxamides (Scheme 2.8).



Scheme 2.27

	Cis-257	*Trans*-257	R	E
a	70 %	15 %	H	H
b	100 %	0 %	H	Me
c	65 %	0 %	H	Allyl
d	85 %	0 %	H	Bn
e	56 %	7 %	Me	H
f	62 %	0 %	Me	Me

Table 2.3

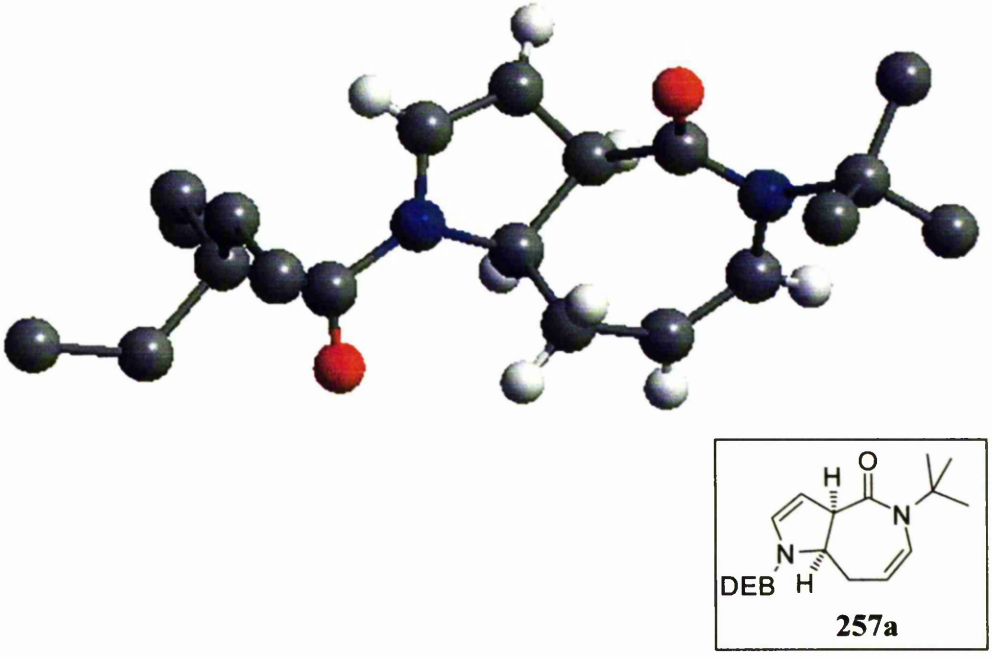
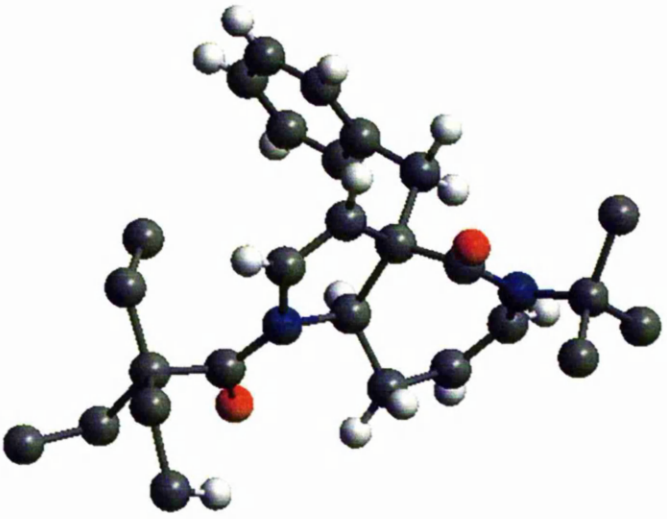
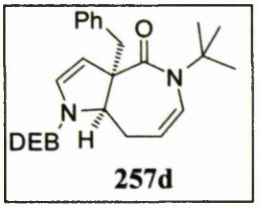


Figure 2.5 Chem 3D representation of **257a** X-ray structure.



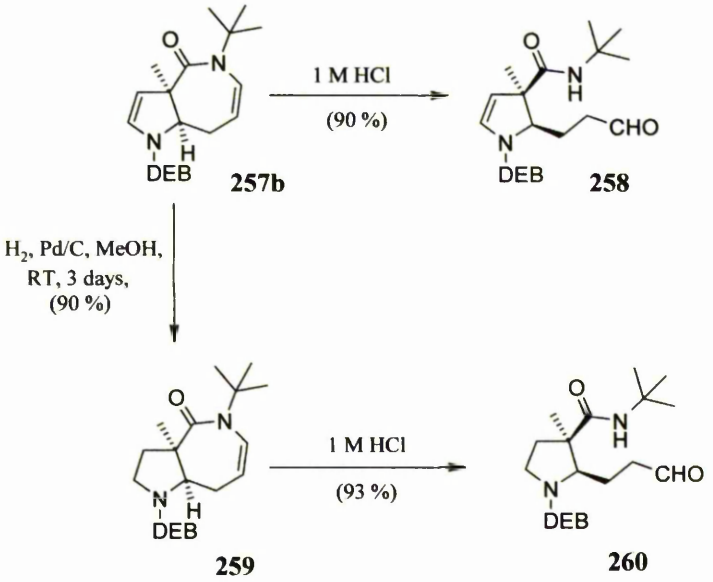


257d

Figure 2.6 Chem 3D representation of **257d** X-ray structure.

2.1.9 Chemistry of Products

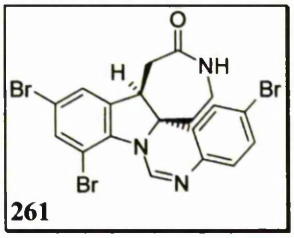
We wished to investigate the chemistry of these novel bisenamides **257**. Treatment of *cis*-**257b** with aqueous acid hydrolysed only one of the enamides to the amido aldehyde, yielding **258**. It is postulated that both enamides are subject to hydrolysis in an equilibrium process but the five-ring enamide is fastest to reform. Hydrogenation by contrast was selective for the more reactive double bond in the strained five-membered ring, giving **259**. Hydrolysis of **259** gave the pyrrolidine **260** (Scheme 2.28). Attempted DEB deprotection of **260** with a view to forming indolizidine alkaloid type structures[2] was unsuccessful and decomposition products prevailed.



Scheme 2.28

2.1.10 Studies Towards an Analogue of Hinckdentine A 261

We wanted to apply this synthetic methodology to a natural product synthesis but the novel ring systems are not prevalent in nature. It was envisaged that a structural isomer of the Hinckdentine A core **262** could be formed by cyclisation of the indole-*N*-allyl system **264** which could in turn be prepared from 5,7-dibromoindole **266** (Scheme 2.29).



261

Hinckdentine A is isolated from the bryozoan (a moss-like organism) *Hincksinoflustra denticulate* (Figure 2.7) off the coast of Tasmania.[145] The pharmacological properties of Hinckdentine A are yet to be determined, but biologically important dihydrotryptamine and dihydropyrimidine units are contained within the framework. Its unique structure makes it an interesting and challenging target.

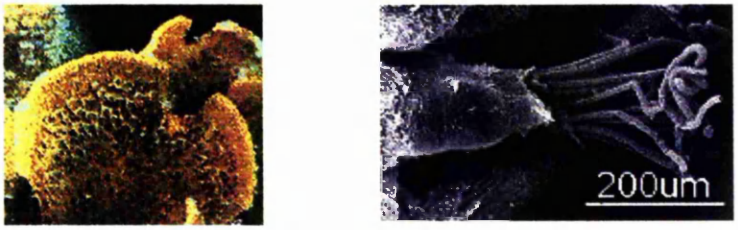
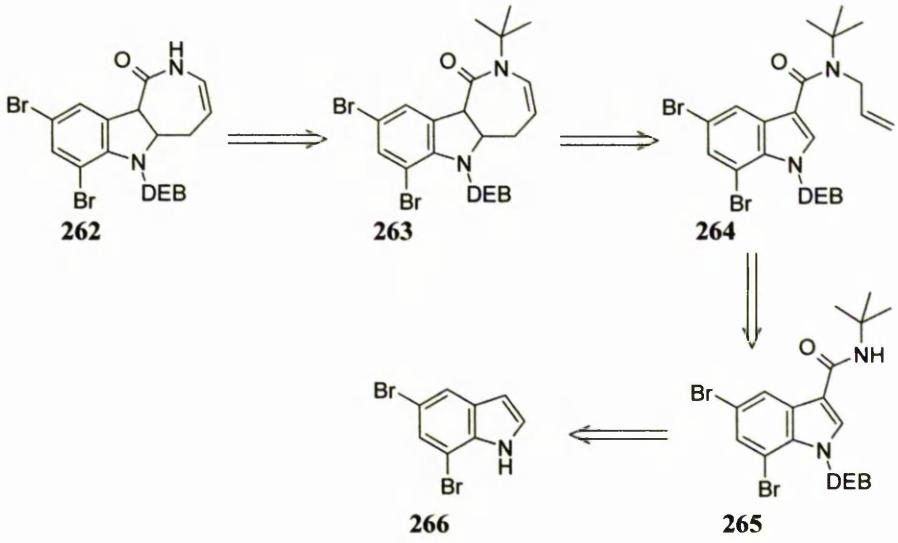
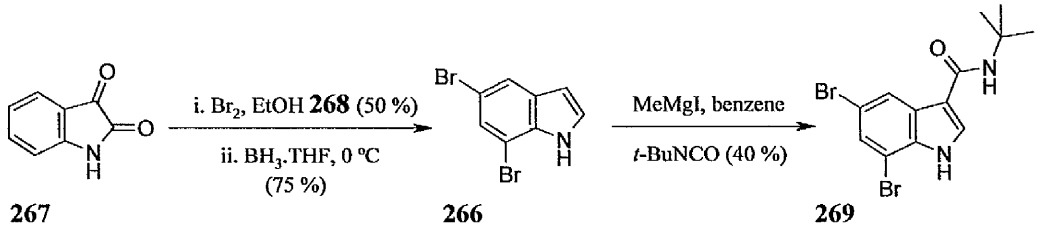


Figure 2.7



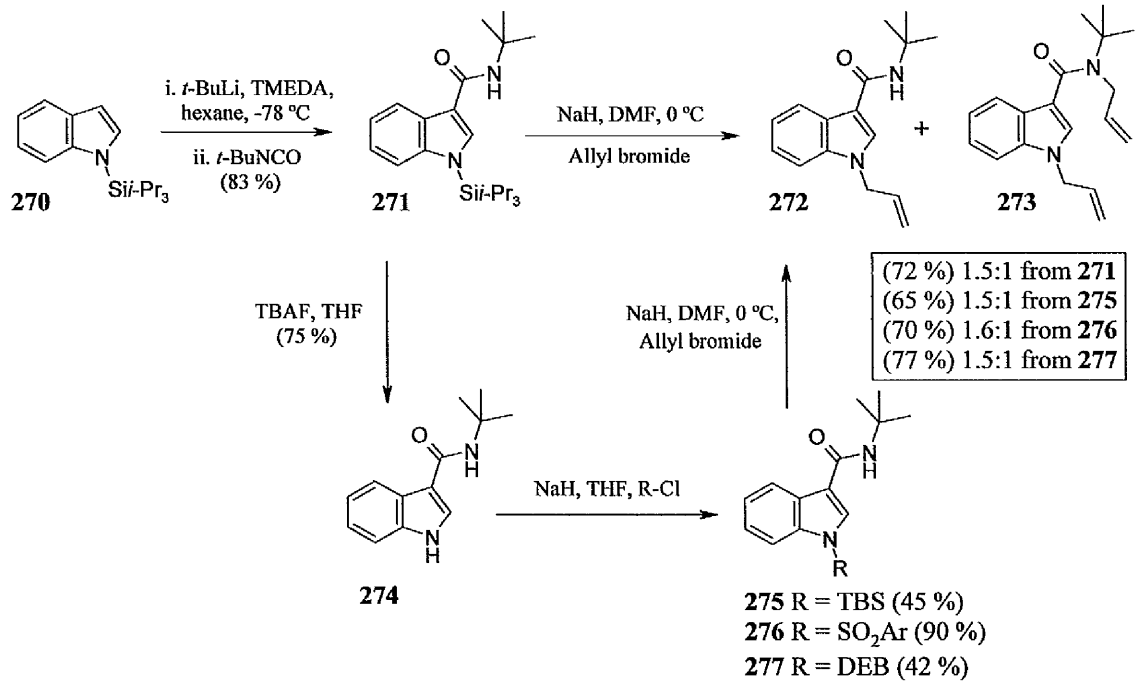
Scheme 2.29

5,7-Dibromoindole was prepared in a two-step procedure as outlined by Lindwall and Plieninger[146] and was subject to Grignard reaction with *N-tert*-butylisocyanate to afford the indole-3-carboxamide **269** (Scheme 2.30). These reactions were modest yielding and capricious so until a route to **264** was well established, reactions were performed on a model system without the two bromine atoms.



Scheme 2.30

The model intermediate **271** was prepared from TIPS protected indole **270**,[147] however attempted allylation resulted in deprotection to give the *N*-allyl indole **272** and di-allylated indole **273** in a ratio of 1.5:1. Alternative protecting groups including TBS **275**, arylsulfonyl **276** and the required DEB **277** again resulted in indole deprotection (Scheme 2.31).



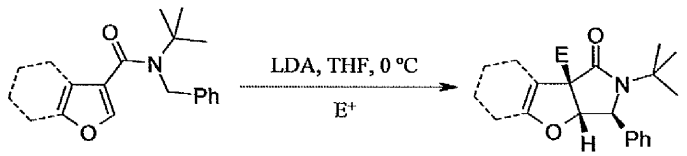
Scheme 2.31

Alternative routes to the *N*-allyl-indole-3-carboxamides were also unsuccessful. It was anticipated that introduction of the *N-tert*-butyl allyl group in a one-step procedure would overcome these problems, but we were unable to synthesise the *N-tert*-butyl allyl carbamoyl chloride required for Grignard reaction.

Unfortunately, we were unable to overcome the issue with protecting groups; shorter reaction times, varying the solvents, base and temperature also had no effect on the outcome. When the DEB protecting group was in place (**277**) LDA was used as throughout the cyclisations the DEB group had remained intact. However LDA was unable to deprotonate the amide, possibly due to steric encumbrance and only starting material was recovered. Based on these results it was anticipated that allylation of the DEB protected dibromo indole **265** required for cyclisation would also prove unsuccessful so work in this area was discontinued.

2.2 Furans and Benzofurans

We wished to apply our synthetic methodology to the dearomatising anionic cyclisation of furan 2- and 3-carboxamides and benzofuran-2-carboxamides, with a view to forming 5,5-fused bicycles **279** (Scheme 2.32)

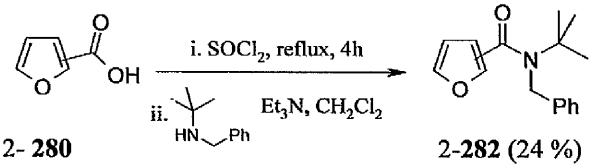


278 **279**

Scheme 2.32

2.2.1 Furancarboxamides

In order to investigate the dearomatising anionic cyclisation reaction on a furan nucleus, furan-2-carboxamide **282** and furan-3-carboxamide **283** were formed by reaction of the commercially available furoic acids **280** and **281**, with thionyl chloride followed by the amine (Scheme 2.33). It was anticipated that the modest yield arose due to steric hindrance in the reaction of the acyl chloride, with the bulky amine.



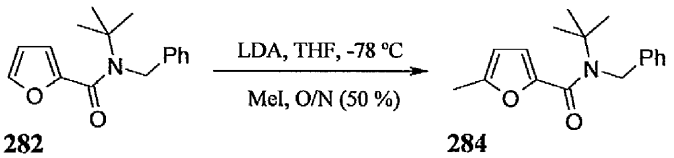
2- **280**
3- **281**

2-**282** (24 %)
3-**283** (40 %)

Scheme 2.33

2.2.2 Furan-2-Carboxamides

Attempted dearomatising cyclisation of the furan-2-carboxamide **282** proved unsuccessful. Treatment with LDA at –30 °C in THF, overnight, resulted in decomposition. However, if the temperature was reduced to –78 °C, lithiation and subsequent methylation at the 5-position of the furan ring was observed **284**, in 50 % yield after separation from the recovered starting material **282** (20 %) by preparative HPLC (Scheme 2.34).



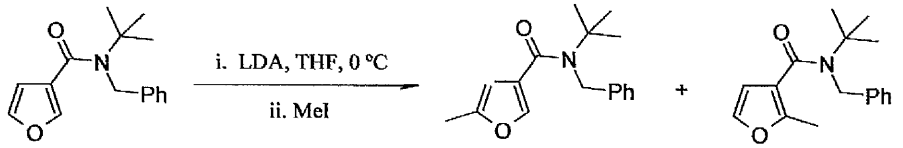
282 **284**

Scheme 2.34

Attempted cyclisation of furan-2-carboxamide **282** with 1.5 equivalents of *t*-BuLi, in the presence of DMPU, in THF at –78 °C overnight, afforded starting material only. The greater propensity for lithiation at the 5-position on the furan ring, as opposed to α- to the amide nitrogen, arises due to the increased electronegativity and inductive effect of the furan oxygen.

2.2.3 Furan-3-Carboxamides

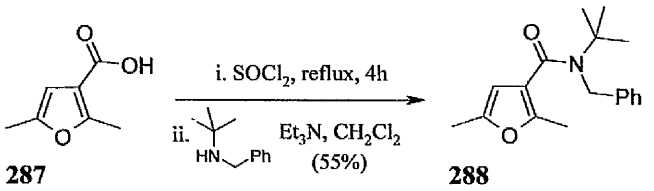
Attempted cyclisation of the furan-3-carboxamide **283** with LDA at both –30 and –78 °C in THF was also unsuccessful. We were unable to overcome the predisposition for lithiation α- to the furan oxygen and the major products were resulting from 5- **285** and 2- **286** methylation (Scheme 2.35). Although lithiation occurred no cyclised products were observed thus indicating the anion does not undergo translocation.[103]



283 **285** (30 %) **286** (25 %)

Scheme 2.35

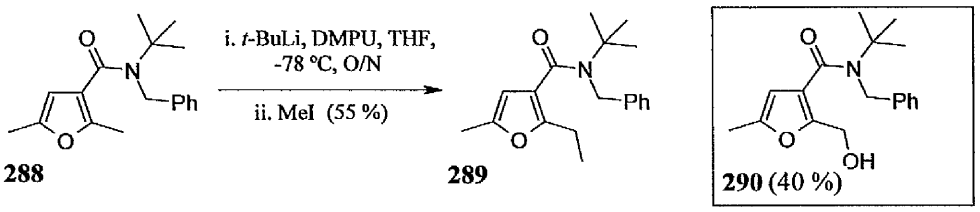
It was anticipated that cyclisation of the 2,5-disubstituted furancarboxamide **288** would be effective as the favoured positions for lithiation are blocked. The 2,5-dimethyl furan carboxamide **288** was readily accessible from the commercially available furoic acid **287** (Scheme 2.36).



287 **288**

Scheme 2.36

Endeavours to cyclise the 2,5-disubstituted furancarboxamide **288** with either LDA or *t*-BuLi were unproductive. The major product was **289**, resulting from lithiation of the 2-position methyl group. If the reaction mixture was not degassed prior to addition of the base the major product was the hydroxylated **290** (Scheme 2.37).

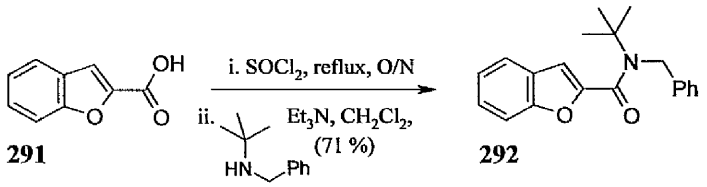


Scheme 2.37

We were unable to encourage lithiation α- to the amide due to a combination of the inductive effect of the O atom and the electron-withdrawing effect of the amide. Work with the furans was not pursued further.

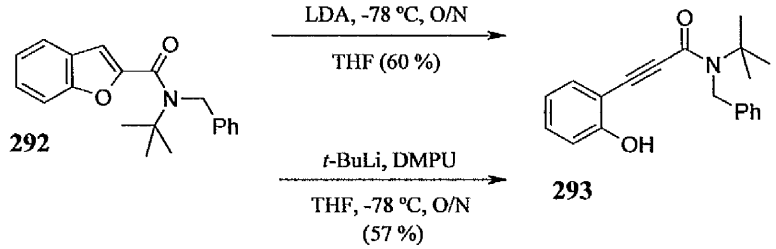
2.2.4 Benzofuran-2-Carboxamides

The reaction of commercially available benzo[b]furan-2-carboxylic acid **291** with thionyl chloride and the secondary amine furnished the desired benzofuran-2-carboxamide **292** in good yield (Scheme 2.38).



Scheme 2.38

Attempted cyclisation of benzofuran-2-carboxamide **292** with both LDA and *t*-BuLi, in THF at –78 °C overnight, resulted in the formation of 3-(2-hydroxyphenyl)-propynoic acid benzyl-*tert*-butylamide **293** in 60 % and 57 % yield, respectively (Scheme 2.39).



Scheme 2.39

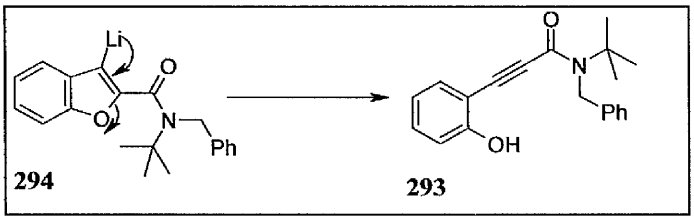
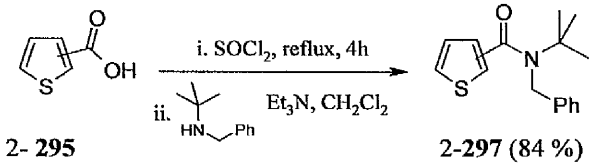


Figure 2.8

This alkyne product **293** arose from lithiation of the benzofuran ring at the 3-position **294**, followed by fragmentation to the alkyne (Figure 2.8). This phenomenon has been previously observed but only when ambient temperatures were reached.[52-54] The presence of the amide side chain at the 2-position must lower the energy barrier to fragmentation, which is now able to occur at lower than ambient temperatures. The product formed is conjugated and ring strain has been removed, both of which favour the fragmentation reaction. It was postulated that lithiation was unlikely to occur at temperatures lower than –78 °C, thus attempted cyclisation of the benzofuran-2-carboxamides was not pursued.

2.3 Thiophenes

We wished to extend the synthetic methodology of the dearomatising anionic cyclisation to the thiophene nucleus. It was anticipated that ring opening, as observed with the pyrrolecarboxamides (Scheme 2.8) would be avoided owing to the reduction in the 5,5-ring strain on account of the larger bonding radius of sulfur. The bonding angles of thiophene are larger than that of pyrrole and the angle strain is somewhat relieved, in addition a contribution to the stabilisation involving the sulfur d-orbital participation may be significant.[20] The thiophene 2- and 3- carboxamides **297** and **298** were readily accessible from the commercially available carboxylic acids **295** and **296** in good yields (Scheme 2.40).



2- **295**
3- **296**

2-**297** (84 %)
3-**298** (50 %)

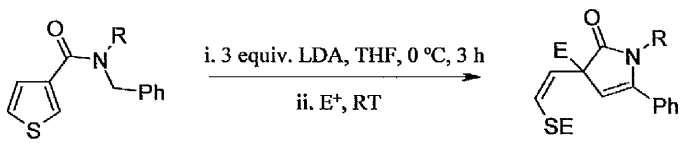
Scheme 2.40

2.3.1 Thiophene-2-Carboxamides

We were unable to provoke the dearomatising cyclisation of thiophene-2-carboxamide **297**, treatment with either LDA or *t*-BuLi in THF resulted exclusively in the recovery of starting material. Varying the reaction conditions (temperature, solvent, time and base) had no positive effect. This avenue of research was not continued as it was anticipated that the cyclisation of thiophene-3-carboxamides would be more successful owing to the inherent C-2 reactivity of thiophenes towards lithiation.[148]

2.3.2 Thiophene-3-Carboxamides[149]

To our surprise dearomatising anionic cyclisation of thiophene-3-carboxamides **298** and **299** resulted in the formation of the ring-opened vinyl sulfides **300a-f** and **301a-e** (Scheme 2.41). A variety of electrophilic quenches were applied in good yield (Table 2.4).



298 (R = *t*-Bu)
299 (R = *i*-Pr)

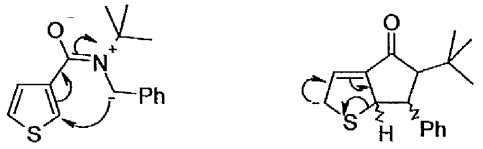
300 a-f
301 a-e

Scheme 2.41

300	E	Yield	301	E	Yield
a	Me	60 %	**a**	Me	65 %
b	Et	65 %	**b**	Et	62 %
c	Allyl	60 %	**c**	Allyl	60 %
d	Bn	55 %	**d**	Bn	67 %
e	4-BrBn	50 %	**e**	4-BrBn	58 %
f	4-PhBn	65 %			

Table 2.4

Mechanistically the reaction is similar to that of the pyrrolecarboxamides (Scheme 2.8). Treatment of the thiophene-3-carboxamide **298** with LDA at –78 °C followed by methylation (*via* the ortholithiated intermediate **302**) resulted in the formation of the 2-methylated thiophenecarboxamide **303** in 60 % yield.[150] It was assumed therefore that **302** is the kinetically favoured lithiation product from **298**. However, treatment of **298** with an excess (3 equiv.) of LDA at 0 °C gave, after electrophilic quench, good yields of the rearranged products **300a-f**. We propose the mechanism outlined in Scheme 2.42 for the formation of **300**: where the benzylic organolithium **304** formed from the ortholithiated **302** by "anionic translocation"[103,151] undergoes dearomatising cyclisation into the 2-position of the thiophene ring, by an electrocyclic mechanism (Figure 2.9a). The bicyclic 5,5-fused enolate **305** is evidently strained and another electrocyclic reaction (Figure 2.9b) gives the pyrrolinone **306**. Excess LDA forms the dianion **307**, and alkylation yields the final products **300**. Attempted protonation of **307** gave only a complex mixture of products, arising from decomposition of the resulting thioaldehyde.

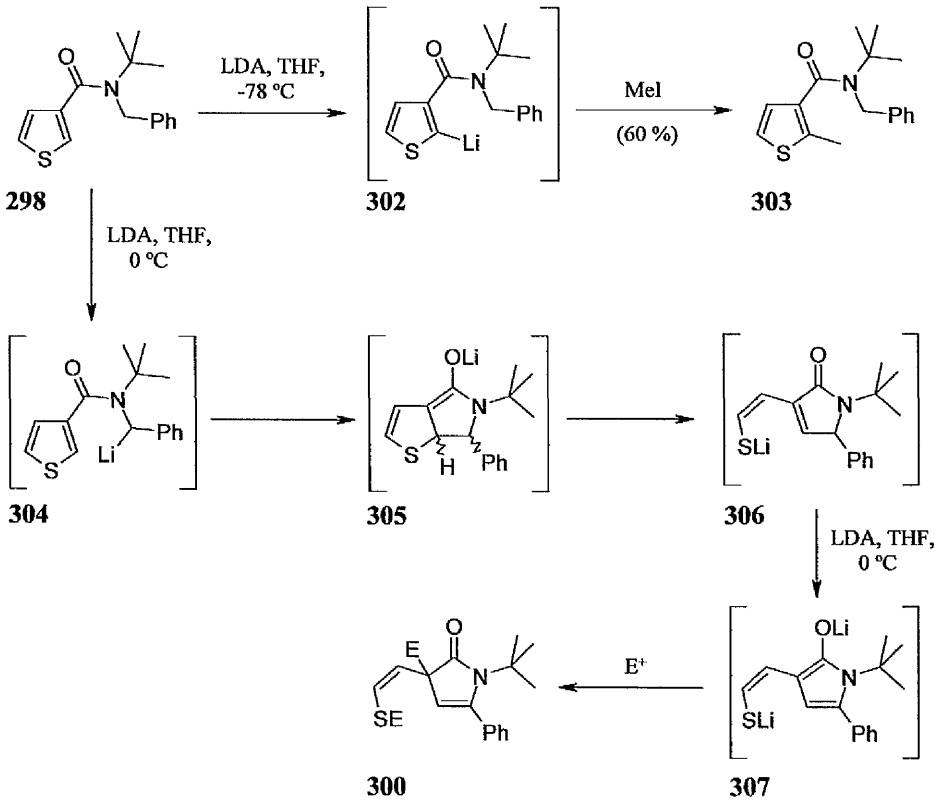


a. 6 π electron, dis **b.** 6 π electron, dis

Figure 2.9

The regiochemistry of the final quench was in accord with previous alkylations of related extended enolates.[101] Evidence that the electrophilic quench occurred α- to the carbonyl and not γ- came from direct comparison of **301a** and **311a** (Scheme 2.43).

The *cis* stereochemistry of the vinyl sulfide, preserved from the thiophene, was evident from the coupling constants obtained by ^{1}H NMR spectra.

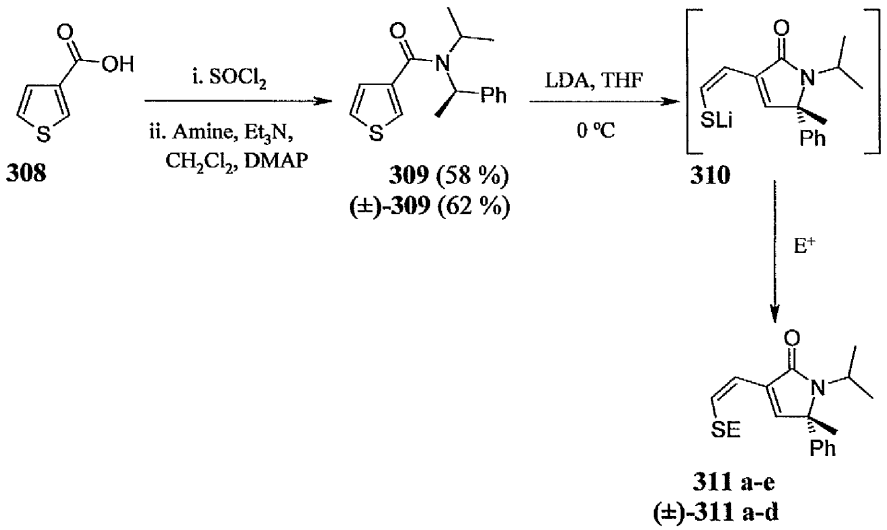


Scheme 2.42

Although this was not the desired outcome the heterocyclic compounds obtained were unique and we wished to explore the scope of the reaction.

2.3.3 Stereospecific Cyclisation

It was possible to form an alternative regioisomeric series of pyrrolinones by dearomatising cyclisation of **309**, the benzylic methyl group prevented formation of the equivalent enolate to **307** thus electrophilic quench occurs only once. In accordance with previous results,[135] we propose that the cyclisation is stereospecific and must proceed *via* an intermediate organolithium which can be represented as **310** and which has configurational stability on the timescale of the cyclisation (Scheme 2.43).[152] The products **311a-e** all have enantiomeric excesses >99 % when compared to the racemic equivalents **(±)-311a-d** by chiral stationary phase HPLC (Chiralpak OT(+) column at 5 °C). A variety of electrophilic quenches were applied in good yield (Table 2.5).



308 **309** (58 %) (±)-**309** (62 %) **310** **311 a-e** (±)-**311 a-d**

Scheme 2.43

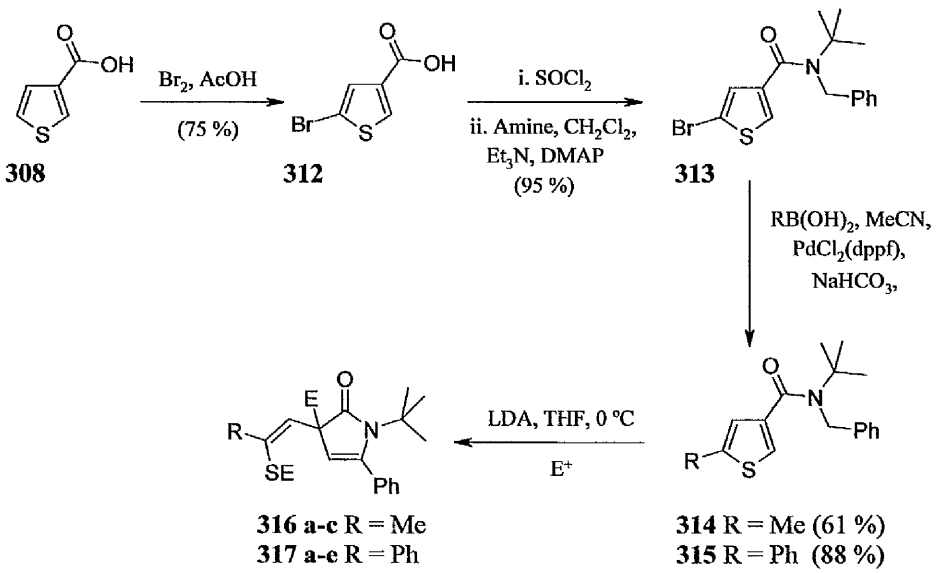
311	E	Yield	(±)-311	E	Yield
a	Me	50 %	**a**	Me	60 %
b	Et	60 %	**b**	Et	60 %
c	Allyl	70 %	**c**	Allyl	60 %
d	Bn	55 %	**d**	Bn	55 %
e	4-BrBn	70 %			

Table 2.5

Dearomatising anionic cyclisation of achiral thiophene-3-carboxamides **298** with the chiral base **130** used in the pyrrole series offered no advantages. Chirality was not introduced into the products and the resulting yields were similar to those with LDA.

2.3.4 5-Substituted Thiophenes

In order to increase the complexity of the ring-opened products, we wished to introduce a substituent into the 5-position of the thiophene ring thus providing cyclisation products with a structure similar to the kainoid family. The 5-position substituent was introduced *via* Suzuki coupling between the bromide **313** and methyl or phenylboronic acid (Scheme 2.44). Dearomatising cyclisation of **314** and **315** followed by electrophilic quench formed the pyrolinones **316a-c** and **317a-e** in good yield (Table 2.6).



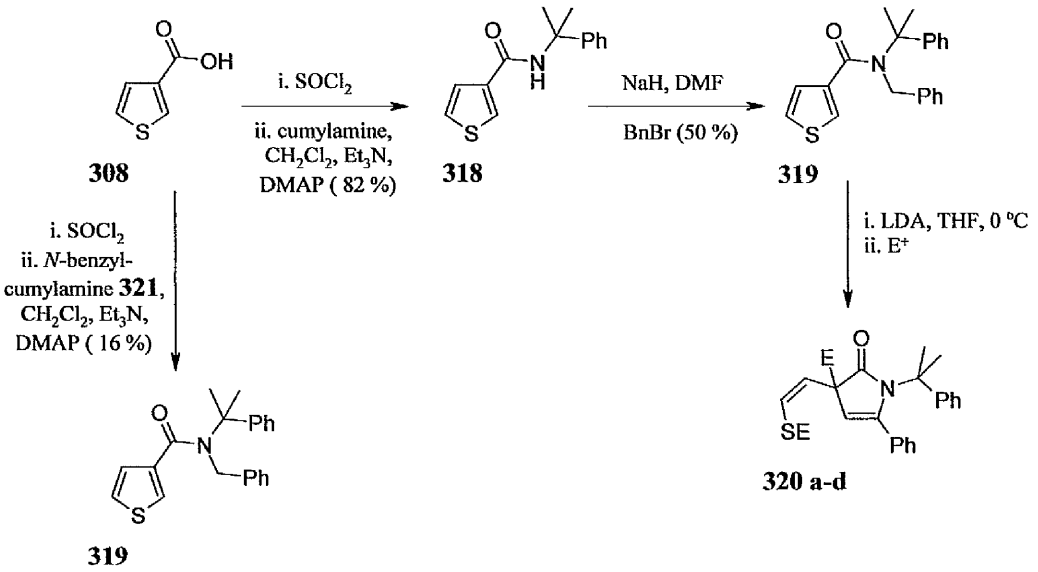
Scheme 2.44

316	E	Yield	317	E	Yield
a	Me	66 %	**a**	Me	60 %
b	Allyl	75 %	**b**	Et	61 %
c	Bn	56 %	**c**	Allyl	71 %
			d	Bn	50 %
			e	4-BrBn	60 %

Table 2.6

2.3.5 N-Cumyl Thiophenecarboxamides

It was anticipated that an *N*-cumyl group would be more readily removed than the *N-t*-butyl group, thus providing a handle for further modification of the ring-opened products.[153] Benzylation of the cumyl-3-carboxamide **318** provided the precursor to cyclisation **319**. Direct reaction of thiophene-3-carboxylic acid with the secondary amine **321** was low yielding thus a two-step procedure was utilized (Scheme 2.45). Dearomatising anionic cyclisation and electrophilic quench afforded the ring-opened products **320a-d** in excellent yields (Table 2.7).



Scheme 2.45

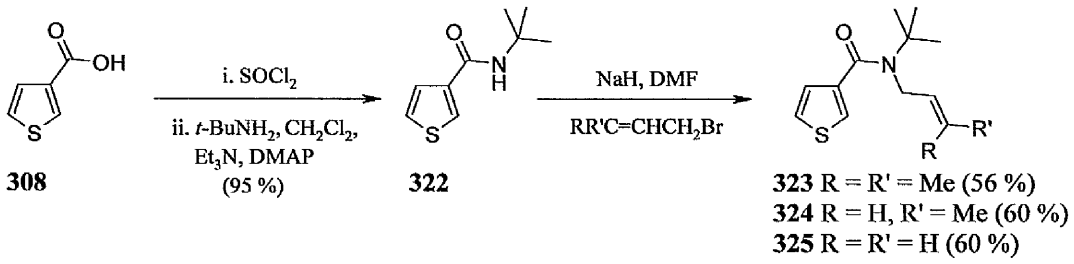
320	E	Yield	320	E	Yield
a	Me	62 %	**c**	Allyl	66 %
b	Et	75 %	**d**	Bn	62 %

Table 2.7

Unfortunately we were unable to remove the cumyl group of **320**. Attempts using concentrated hydrochloric acid, TFA or the milder formic acid[153] proved unsuccessful and decompostion was prevalent even when dilute solutions and short reaction times were employed. It was postulated that the thiol moiety was unstable to the acidic conditions.

2.3.6 N-Allyl Thiophenecarboxamides

The original intention was to retain the thiophene ring and form bicyclic products containing both nitrogen and sulfur. We therefore alkylated the amide **322** to form a series of substituted *N*-allyl thiophenecarboxamides **323-325**, which we speculated would undergo dearomatising cyclisation to yield less strained seven-membered rings (Scheme 2.46).[106] We were unable to prepare the cinnamyl equivalent of **323** (where R = H, R' = Ph); harsher reaction conditions and longer reaction times did not provide the desired product and only starting amide **322** was recovered.

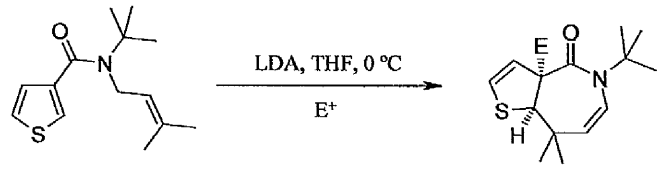


308 **322**

323 R = R' = Me (56 %)
324 R = H, R' = Me (60 %)
325 R = R' = H (60 %)

Scheme 2.46

Exposure of the *N*-prenyl substituted thiophenecarboxamide **323** to the usual cyclisation conditions (3 equiv. LDA, THF, 0 °C, 3 h) gave the 5,7-fused heterocycles **326a-f** in excellent yield (Scheme 2.47, Table 2.8).



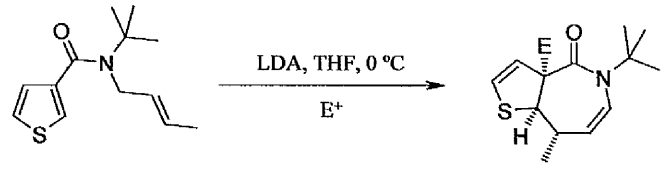
323 **326 a-f**

Scheme 2.47

326	E	Yield	326	E	Yield
a	H	71 %	**d**	Allyl	55 %
b	Me	51 %	**e**	Bn	55 %
c	Et	60 %	**f**	4-BrBn	50 %

Table 2.8

A similar result was obtained for *N*-crotyl substituted thiophenecarboxamides **324**, thus cyclisation and electrophilic quench afforded good yields of the 5,7-fused bicycle **327a-e** (Scheme 2.48, Table 2.9). *Cis* stereochemistry was predicted by analogy to the equivalent *N*-crotyl pyrrolecarboxamide cyclisations (Scheme 2.27).



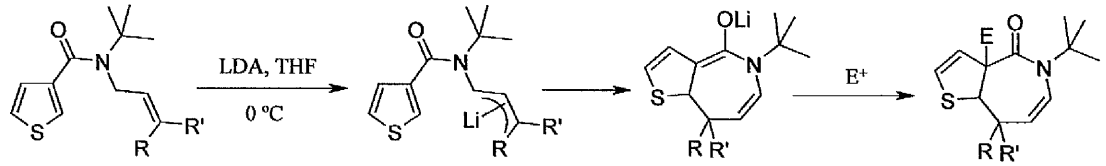
324 **327 a-e**

Scheme 2.48

327	E	Yield	327	E	Yield
a	H	65 %	**d**	Allyl	65 %
b	Me	52 %	**e**	Bn	50 %
c	Et	55 %			

Table 2.9

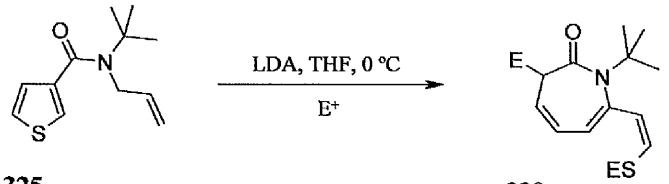
Mechanistically, allylic deprotonation yields **328**. Subsequent cyclisation gives the dearomatised enolate **329**, which is sufficiently free of strain to be stable. Quenching with electrophiles yields **326** and **327** without further rearrangement (Scheme 2.49).



323 and **324** **328** **329** **326** and **327**

Scheme 2.49

Cyclisation of the *N*-allyl thiophenecarboxamide **325** under the same reaction conditions resulted in a product **330** in which the thiophene ring was no longer intact (Scheme 2.50, Table 2.10).



325 **330 a-e**

Scheme 2.50

330	E	Yield	330	E	Yield
a	Me	61 %	**d**	Bn	45 %
b	Et	70 %	**e**	4-BrBn	50 %
c	Allyl	65 %			

Table 2.10

X-ray crystallography (Figure 2.10) proved that **330** was not merely the result of thiophene ring opening instead a [3H]-azepinone was formed by a remarkable 1,5-shift of the thiovinyl group from C-3 to C-7. It has previously been reported that [1,5]-shifts of unsaturated groups are relatively fast.[154]

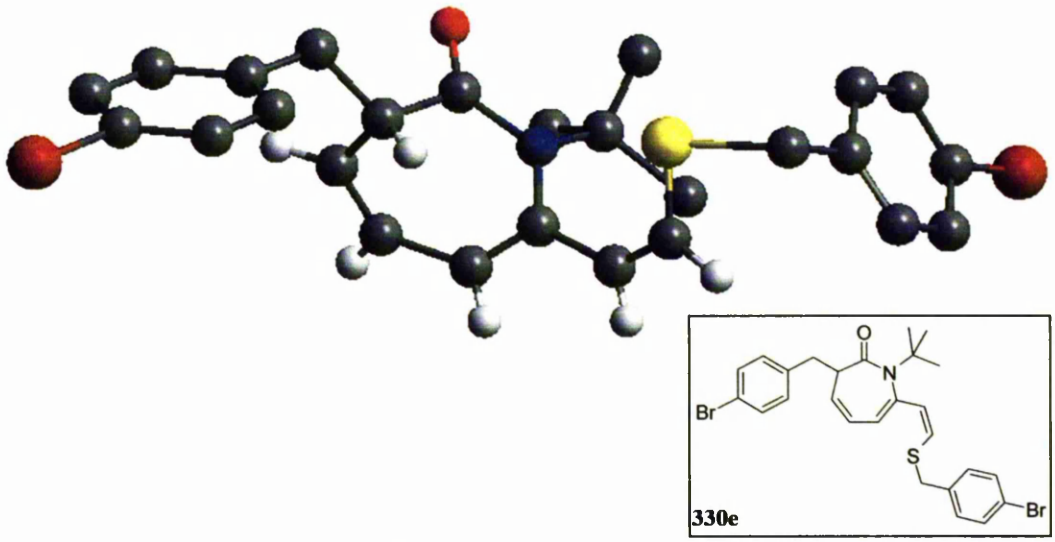
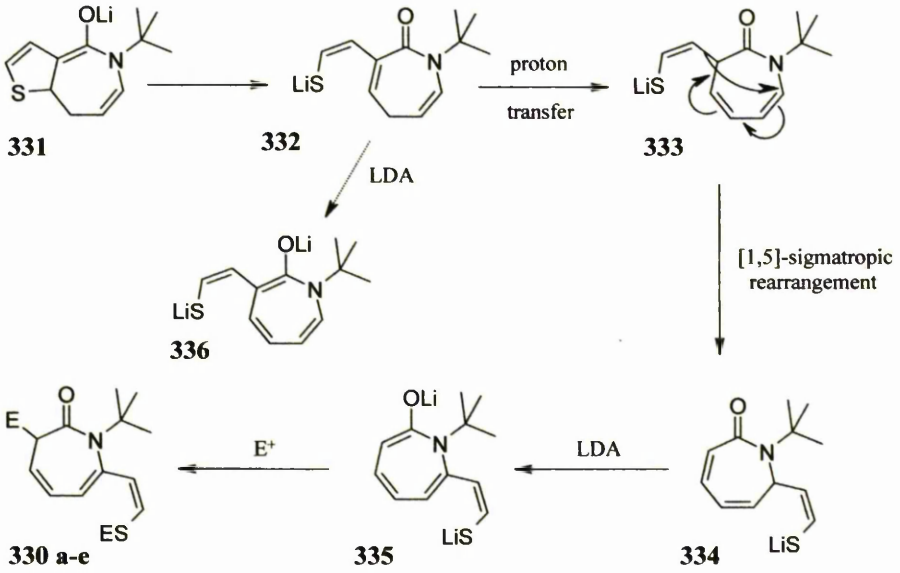


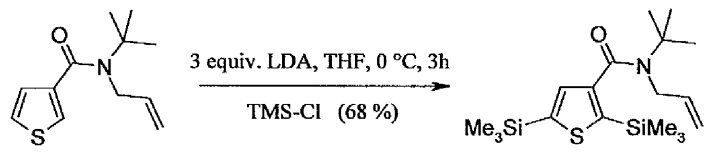
Figure 2.10 Chem 3D representation of **330e** X-ray structure.

Scheme 2.51 suggests a mechanism for the rearrangement, in which a proton shift (presumably mediated by LDA, and less favourable or impossible in prenyl **323** and crotyl **324** derivatives) sets up the π-array **333** required to allow [1,5]-sigmatropic rearrangement to give **334**. Excess LDA results in further deprotonation to afford the anionic azepine **335**, which was alkylated to give **330a-e**.



Scheme 2.51

Attempts to trap the intermediate enolate **335** with TMS-Cl in order to further elucidate the mechanism were unsuccessful and **337** was formed in good yield (Scheme 2.52). This is further evidence that the initial lithiation occurs α- to the heteroatom and that 'translocation' is required for dearomatising anionic cyclisation.



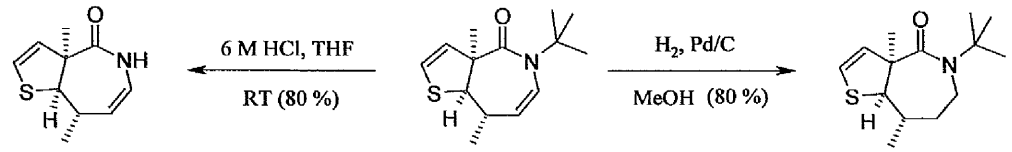
325 337

Scheme 2.52

It is known that protons at the 3-position of azepinones lack the usual acidity associated with positions α- to a carbonyl group[155] and it is proposed that rearrangement takes place in preference to formation of the anti-aromatic azepinoxy anion **336**. However, an azepinoxy anion **335** must be formed at some point in the sequence in order to allow α-alkylation. It is possible that the rearrangement may occur after alkylation but we were unable to verify either reaction pathway.

2.3.7 Chemistry of Products

In contrast to the pyrrole series, hydrogenation of **327b** was selective to the more electron-rich 7-membered enamide **338** and aqueous hydrolysis resulted in *N*-*t*-butyl deprotection **339** (Scheme 2.53). *t*-Butyl deprotection under aqueous acidic conditions is not commonplace and usually much harsher conditions are required.[156] We were unable to achieve desulfurisation of the products with Raney nickel. A variety of literature conditions were applied but decomposition products prevailed.[157]

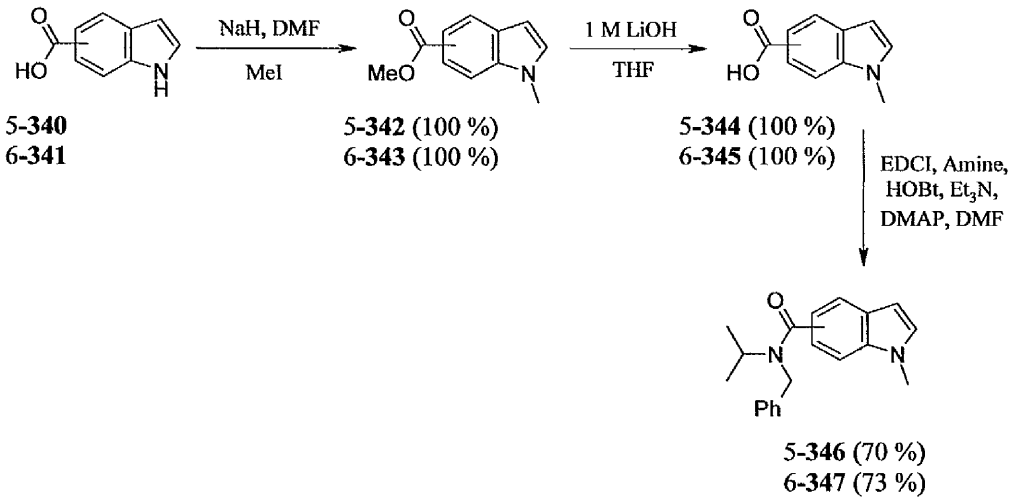


339 327b 338

Scheme 2.53

2.4 Indoles

We wished to investigate whether we could affect dearomatising anionic cyclisation onto the six-membered ring of the indole nucleus. It was anticipated that the susbsequent ring opening would be avoided due to the reduction in strain of the 5,6 fused system as compared to the 5,5 fused system. The starting *N*-methyl indole 5- and 6- carboxamides were prepared from the commercially available 5- and 6- carboxylic acids **340** and **341**. Methylation followed by ester hydrolysis gave the *N*-methyl carboxylic acids **344** and **345**.[158] EDCI coupling with *N*-isopropylbenzylamine furnished the desired carboxamides **346** and **347** in good yield (Scheme 2.54).[158] Interestingly, EDCI coupling with *N-tert*-butylbenzylamine (the standard amine used throughout the cyclisations) was unsuccessful, presumably due to increased steric encumbrance.



5-**340**
6-**341**

5-**342** (100 %)
6-**343** (100 %)

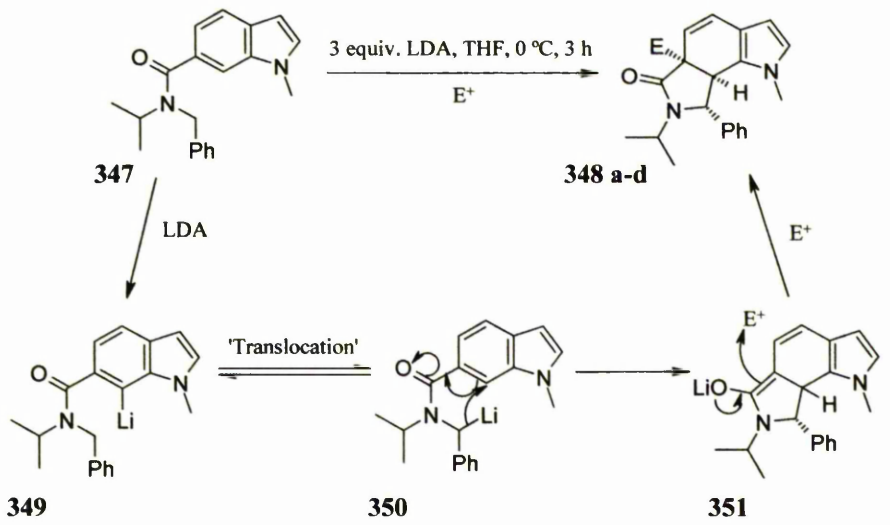
5-**344** (100 %)
6-**345** (100 %)

5-**346** (70 %)
6-**347** (73 %)

Scheme 2.54

2.4.1 Indole-6-Carboxamides

As anticipated dearomatising anionic cyclisation of the indole-6-carboxamides **347** with LDA at 0 °C was successful, yielding the 5,6,5-fused tricycles **348a-d** essentially as single diastereoisomers with a variety of electrophilic quenches (Scheme 2.55, Table 2.11). Only in the case of E = methyl was the *trans* ring junction observed as a by-product. X-ray crystallography confirmed the stereochemistry of the ring junction as *cis* (Figure 2.11). When a benzaldehyde quench was applied, the cyclisation afforded a single diastereoisomer with *cis* stereochemistry (Figure 2.12).



Scheme 2.55

	E	*Cis*-348	*Trans*-348
a	H	67 %	0 %
b	Me	60 %	10 %
c	Bn	66 %	0 %
d	PhCH(OH)	60 %	0 %

Table 2.11

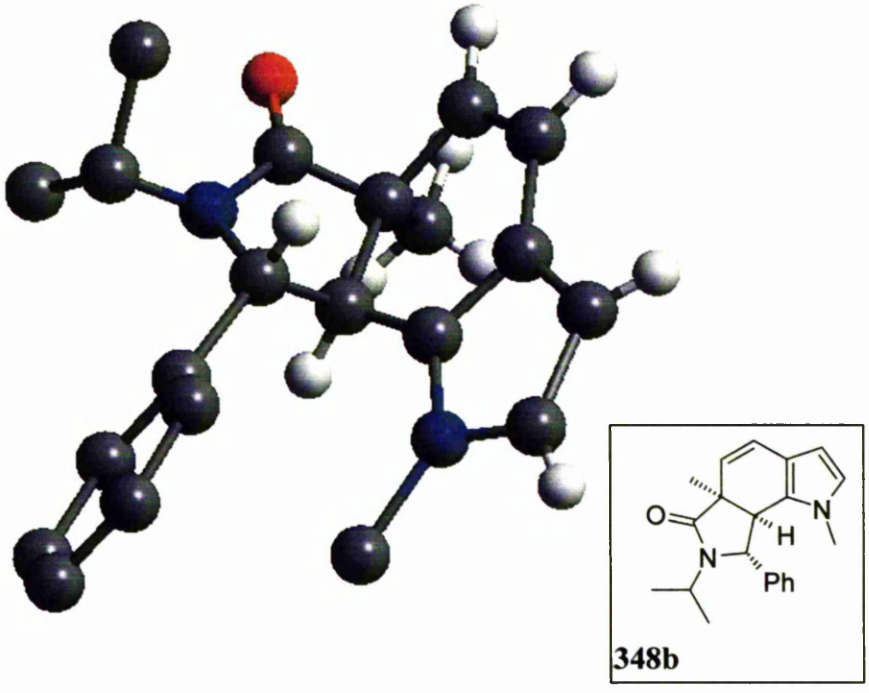


Figure 2.11 Chem 3D representation of **348b** X-ray structure.

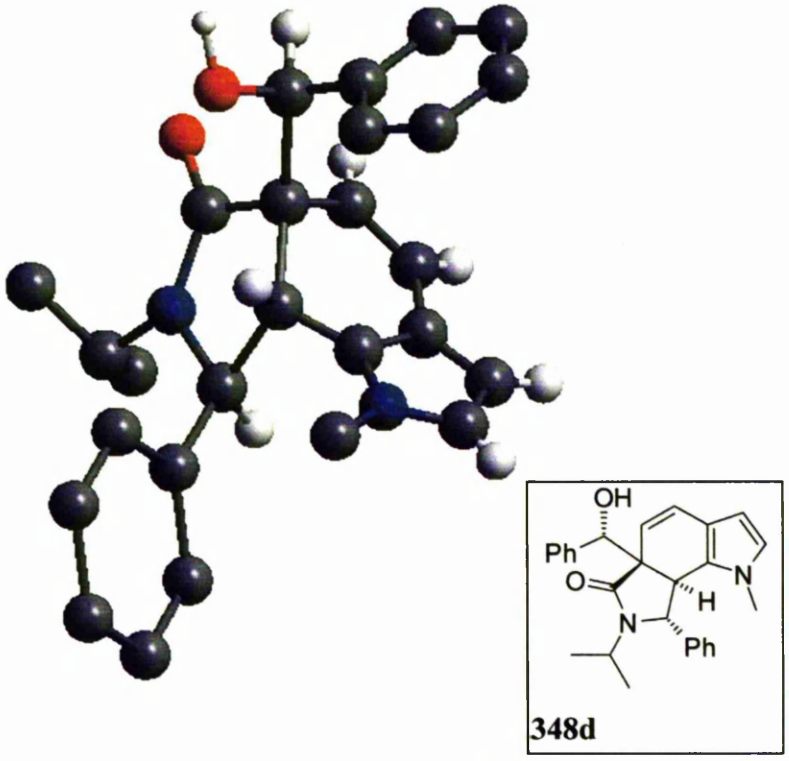
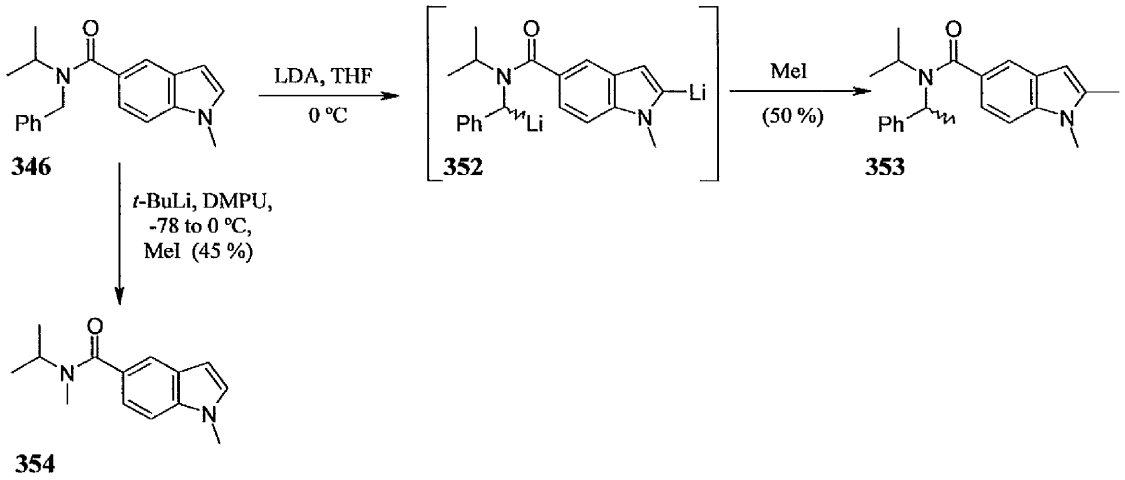


Figure 2.12 Chem 3D representation of **348d** X-ray structure.

2.4.2 Indole-5-Carboxamides

We were unable to initiate dearomatising anionic cyclisation of indole-5-carboxamides **346**. It was evident from the isolated product **353** that the di-lithiated intermediate **352** had formed but not cyclised and that the inherent C-2 reactivity of indoles towards lithiation was greater than the benzylic lithiation when in the 5-position as compared to the 6-position. Altering the conditions (base, temperature and time) had no positive effect and the dimethylated product **353** was predominant.

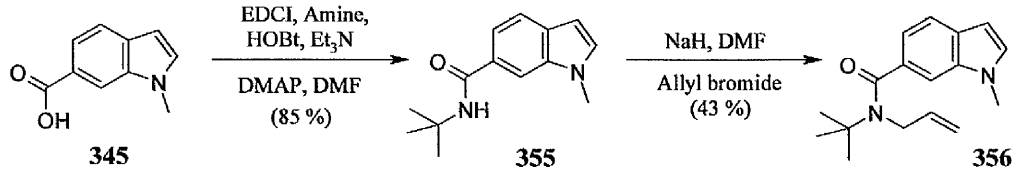
However, when *t*-BuLi and DMPU were used an interesting benzylic deprotection followed by methylation **354** was observed (Scheme 2.56). Attempts to cyclise the dimethylated indole-5-carboxamide **353** were also unsuccessful and only starting material was recovered.



Scheme 2.56

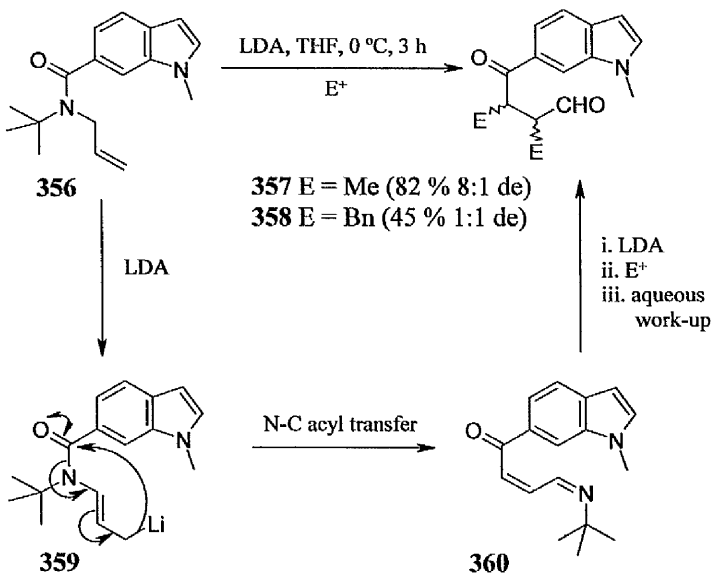
2.4.3 N-Allyl Indole-6-Carboxamides

It was anticipated that dearomatising anionic cyclisation of *N*-allyl indole-6-carboxamides **356** would result in the formation of 7,6,5-fused tricycles. The *N*-allyl indole-6-carboxamide **355** was prepared by EDCI coupling of *N-tert*-butylamine and the indole-6-carboxylic acid **345**, followed by allylation (Scheme 2.57).



Scheme 2.57

Attempted cyclisation of **356** did not afford the desired tricyclic heterocycles but instead a novel transformation was observed (Scheme 2.58). We postulate that the aldehyde of **357** and **358** is formed by a nitrogen to carbon acyl transfer where the organolithium **359** attacks the amide carbonyl group instead of the aromatic ring. This forms an imine **360**, which is hydrolysed on work-up, after further deprotonation and electrophilic quench. With a methyl quench **357**, moderate diastereoselectivity was observed and the diastereoisomers were separable by column chromatography. However with a benzyl quench **358** an inseparable 1:1 mixture of diastereoisomers resulted. A similar rearrangement was observed in the naphthamide series.[106]



Scheme 2.58

2.5 Conclusions

We have thoroughly investigated the methodology surrounding the dearomatising anionic cyclisation of five-membered and some six-five-fused heterocycles. A variety of substituted pyrroles, furans, thiophenes, indoles and benzofurans were examined and numerous electrophilic quenches applied. Chirality was introduced into the starting materials and was retained in the novel ring-opened heterocyclic products.

With *N*-DEB protected pyrrole and thiophene 3-carboxamides a novel ring opening reaction occured after cyclisation in order to relieve the 5,5-ring strain from cyclisation intermediates. This ring opening generated a variety of new and interesting heterocyclic products. The dearomatising anionic cyclisation of *N*-allyl and *N*-crotyl pyrrole and thiophene 3-carboxamides resulted in the formation of novel 5,7-bicyclic systems, with the exception of *N*-allyl-thiophenecarboxamides, which underwent unusual rearrangements to form substituted azepinones. Pyrrole and thiophene-2-carboxamides were unreactive towards dearomatising anionic cyclisation.

Unfortunately we were unable to overcome the inherent C-2 reactivity of furans towards lithiation and attempted dearomatising anionic cyclisation of both furan 2- and 3-carboxamides was unsuccessful.

The cyclisation was also successfully applied to the six-membered ring of an *N*-methyl indole nucleus, with a variety of electrophilic quenches. This was the first example of dearomatising anionic cyclisation onto an *N*-benzyl substituted heterocyclic system without concomitant ring opening. We wished to explore the chemistry of these cyclisation products and we anticipate that chirality could be introduced into the starting materials, but due to time constraints this chemistry was not fully realised.

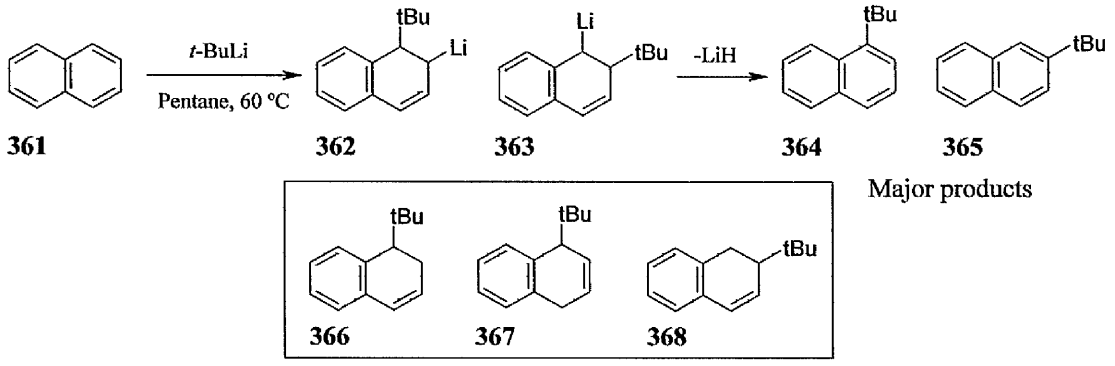
Application of the dearomatising anionic cyclisation of *N*-allyl indole-3-carboxamides to the synthesis of Hinckdentine A analogues was hindered by the incompatibility of protecting groups with the conditions required for *N*-allylation. If this problem was circumvented we envisage the remaining steps to the analogues would be facile.

Chapter 3
Towards Podophyllotoxin

3.1 Organolithium Addition to Naphthalenes

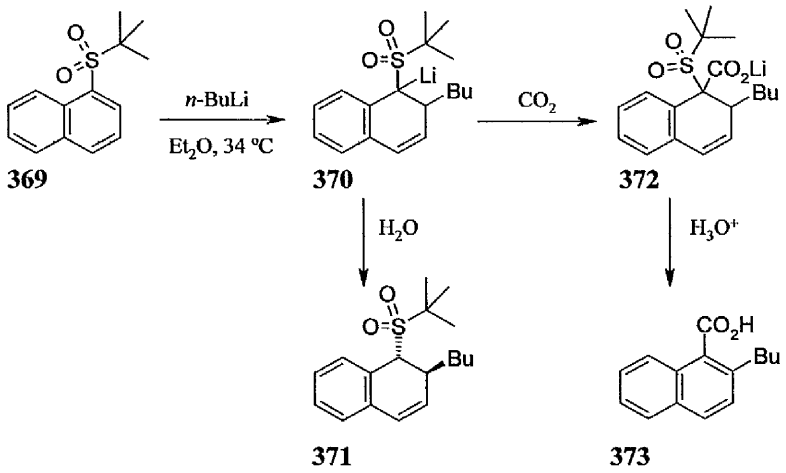
Dihydronaphthalene derivatives have been extensively used in the synthesis of biologically important targets.[159] The development of organolithium addition to activated naphthalenes, delivering dihydronaphthalene systems has been of great interest over the past 20 years.

The first published report on the addition of organolithiums to naphthalene came in 1964 from Dixon *et al.*[160] A pentane solution of naphthalene **361** and *t*-butyllithium were heated at 60 °C for 28 h. On work up a mixture of alkylated naphthalenes **364** and **365** and dihydronaphthalenes **366-368** were observed. The result was explained by addition of the organolithium to the naphthalene nucleus, forming the anions **362** and **363**, which eliminated LiH forming the rearomatised naphthalenes **364** and **365** as major products (Scheme 3.1).



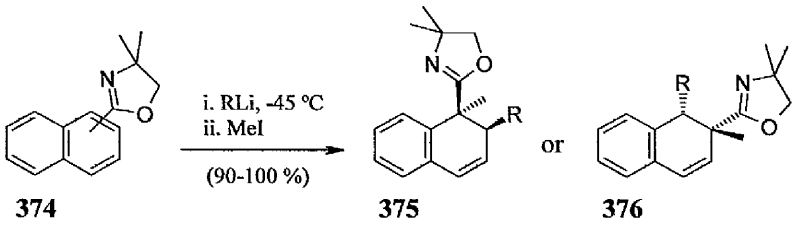
Scheme 3.1

Stoyanovich *et al.* published the first example of organolithium addition to activated naphthalenes.[161] Sulfone **369** reacted with *n*-butyllithium at 34 °C forming the sulfone stabilised anion **370** arising from butyl addition to the 2-position of the naphthalene. The anion could be quenched with water forming the dihydronaphthalene **371**, or carbon dioxide resulting in the naphthoic acid **373** by elimination of *t*-butylsulfinate (Scheme 3.2). At –78 °C it was noted that *ortho*-lithiation was observed instead of addition.



Scheme 3.2

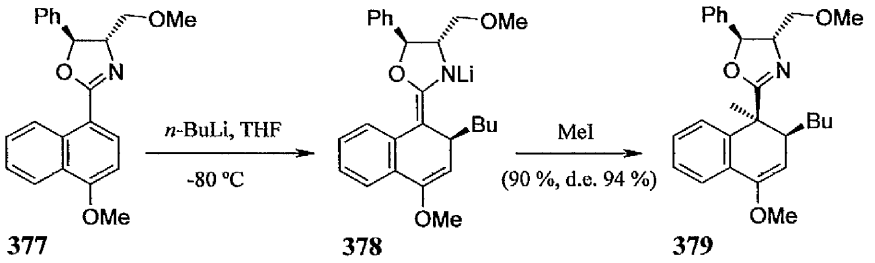
Meyers *et al.* reported dihydronaphthalene synthesis *via* organolithium addition to oxazoline-activated naphthalenes in 1984.[162] Addition of *n*-, *s*- and *t*-butyllithium to 1- and 2-oxazoline substituted naphthalenes **374** proceeded in excellent yields (Scheme 3.3). An effective 1,2-tandem addition to naphthalene was achieved with excellent diastereoselectivity when the reaction was quenched with an electrophile.



R = *n*-Bu, *s*-Bu, *t*-Bu

Scheme 3.3

Good diastereomeric excess was achieved when a chiral oxazoline was employed. The oxazoline **377** gave superior diastereomeric excess due to the methoxy substituents' ability to coordinate (Scheme 3.4).[163] Cleavage of the oxazoline from the dihydronaphthalene gave adducts with high enantiomeric excess. Meyers applied this methodology to the total synthesis of (–)-podophyllotoxin (see section 3.5[164]).

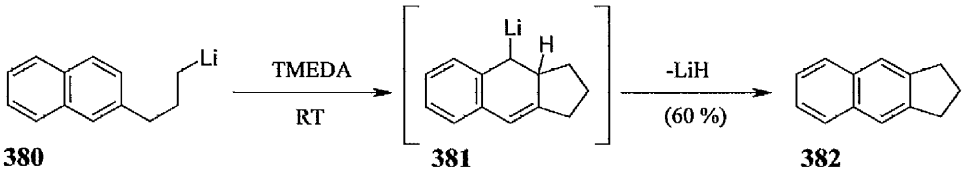


377 **378** **379**

Scheme 3.4

3.2 Dearomatising Cyclisations onto Naphthalenes

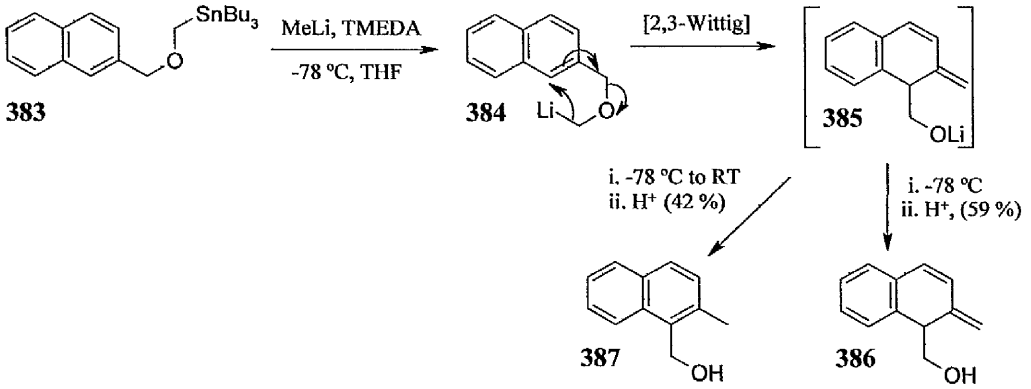
Previous results within the Clayden group[165,166] have shown that activation of the naphthalene ring is required for dearomatising cyclisation. Attempted dearomatising cyclisation of a carbon-tethered organolithium onto an unactivated naphthalene **380** resulted in rearomatisation (Scheme 3.5) due to the instability of the cyclised anion **381** under the conditions of the reaction.



380 **381** **382**

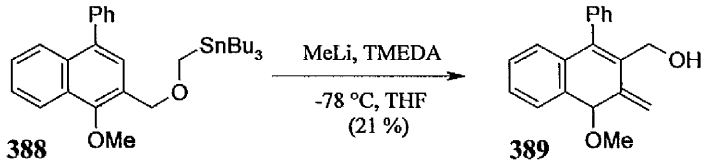
Scheme 3.5

When an oxygen-tethered stannane **383** was used a 2,3-Wittig rearrangement[167-172] of the organolithium **384** prevailed (Scheme 3.6). Attempts to inhibit 2,3-Wittig rearrangement with a 'blocking' methoxy group in the *ortho* position **388** were unsuccessful and the 2,3-Wittig rearrangement product **389** was predominant (Scheme 3.7).



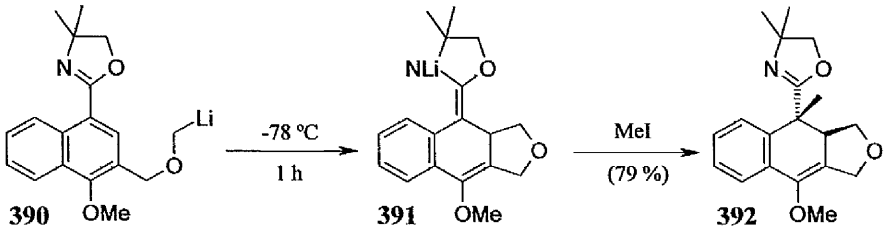
383 **384** **385** **387** **386**

Scheme 3.6



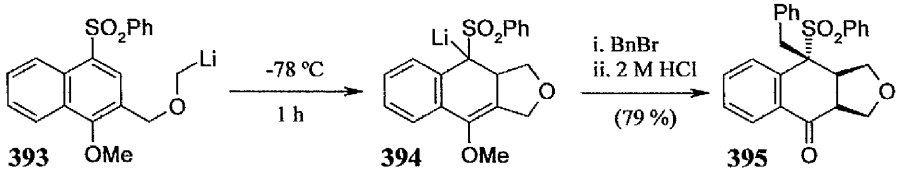
Scheme 3.7

It was demonstrated that activating groups such as oxazolines and sulfones could be used to mediate dearomatising anionic cyclisation of *meta*-tethered organolithiums. The reactions were generally very stereoselective, forming linear fused tricyclic products. For instance, dearomatising anionic cyclisation of oxazoline activated naphthalene **390** with methyl iodide quench resulted in a single diastereoisomer of **392** (Scheme 3.8).[165] The stereochemistry was assigned after cleavage of the oxazoline.



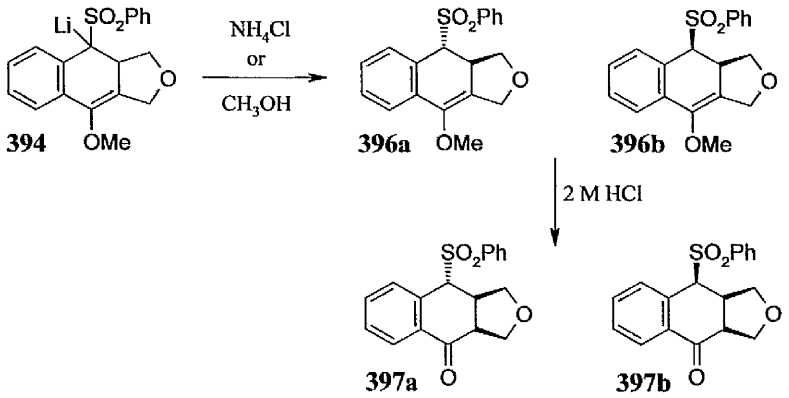
Scheme 3.8

Dearomatising anionic cyclisation of sulfone-activated naphthalene **393** resulted in a single diastereoisomer of **395**. The sulfone-stabilised anion **394** was subject to benzyl bromide quench. The initial alkylated methyl enol ether products were unstable so hydrolysis with 2 M HCl to the stable ketone **395** was undertaken before purification (Scheme 3.9).[166] The stereochemistry was assigned from X-ray crystallography. A major benefit of the use of sulfone activating groups is the ability of sulfones to be easily synthetically manipulated.[173]



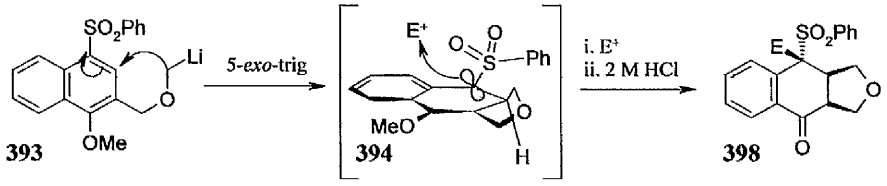
Scheme 3.9

The sulfone cyclisation gave different diastereoisomers dependent on the proton source and conditions used. When an ammonium chloride quench was applied the sulfone was found to be on the *exo* face of the bicycle with a *cis* ring-junction **397a**. With a methanol quench and warming to room temperature the product had a *cis* ring-junction but the sulfone was on the *endo* face of the bicycle **397b** (Scheme 3.10).[166]



Scheme 3.10

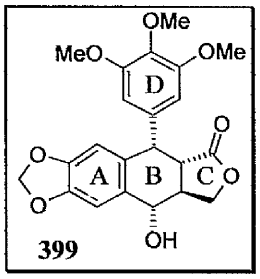
It was anticipated that the *exo* enol ether **396a** arose from a kinetic protonation of the sulfone-stabilised anion **394** by ammonium chloride, whereas the *endo* enol ether product **396b** was presumed to arise from epimerisation of the kinetic *exo* enol ether **396a** on warming. This must proceed *via* deprotonation/reprotonation of the sulfone by lithium methoxide produced after quenching. The selectivity of both kinetic protonation and alkylation of the sulfone-stabilised anion **394** showed that both reacted on the *endo*-face of the bicycle. This can be explained when considering the structure of sulfone anions, which have the potential to be chiral. Due to the benzylic nature of the sulfone-stabilised anion **394** it is anticipated that the structure is planar sp^2. The anion **394** is formed on 5-*exo*-trig cyclisation, which then reacts with electrophiles from the top face **398** (Scheme 3.11). The kinetic *exo* sulfone enol ether, obtained from ammonium chloride protonation, must be unstable when warmed in the presence of lithium methoxide. This is presumably due to the epimeric *endo* sulfone **396b** being less sterically hindered.



Scheme 3.11

3.3 Podophyllotoxin from Dearomatising Cyclisation

The products obtained from dearomatising cyclisation of oxygen-tethered organolithiums onto sulfone and oxazoline activated naphthalenes contain the naphthofuran skeleton present in lignan natural products, such as podophyllotoxin **399**.[174] We wished to investigate whether we could synthesise podophyllotoxin using the sulfone-activation approach. The synthetic strategy is shown in section 3.6.



399

3.4 Biological Activity of Podophyllotoxin

Podophyllotoxin **399** is a natural lignan of the aryltetralin class,[175] which has a long history of use in medicine and was originally used in ointments for the topical treatment of genital warts. The chemotherapeutic properties of podophyllotoxin were investigated and were attributed to inhibition of microtubule assembly. The adverse side effects including nausea, fever, seizures and kidney failure prevented further development and application of the treatment.

These toxicity problems were overcome with the development of novel derivatives. Epipodophyllotoxin (the C-4 epimer of podophyllotoxin) is currently being used as a precursor to semi-synthetic anti-cancer drugs etoposide **400** and teniposide **401** (Figure 3.1). These compounds have been used for the treatment of lung and testicular cancers as well as certain leukaemias. Etoposide and teniposide both block the cell cycle in two specific places: between the last division and the start of DNA replication (the G1 phase) and they block the replication of DNA (the S phase). They are topoisomerase II inhibitors that induce cell death by enhancing the topoisomerase II-mediated DNA cleavage through the stabilization of the transient DNA/topoisomerase II cleavage complex.

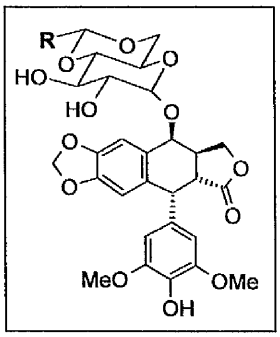


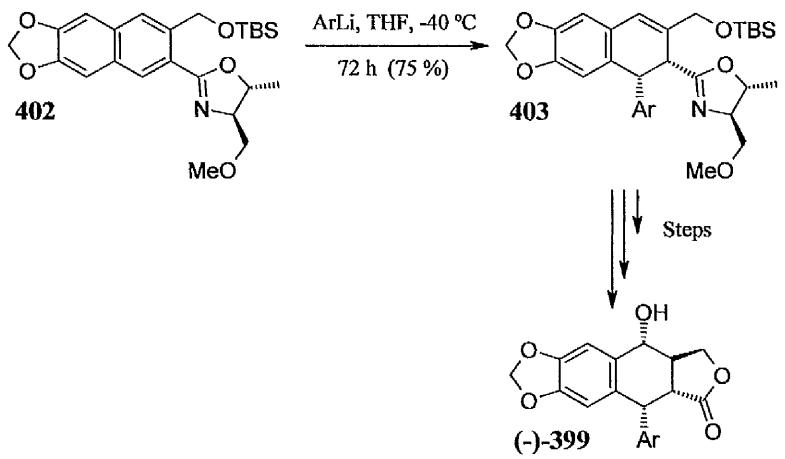
Figure 3.1 Etoposide (**R** = Me) **400**, Teniposide (**R** = 2-thiophene) **401**

In addition, the podophyllotoxin skeleton is the precursor to over 200 new derivatives, both natural and semi-synthetic that are being tested for the treatment of a variety of conditions including rheumatoid arthritis, psoriasis and malaria.[176]

The total synthesis of podophyllotoxin on a commercial scale is an expensive process and availability of the compound from natural resources is an important issue. Currently, the commercial source of podophyllotoxin is the rhizomes and roots of *Podophyllum emodi*, an endangered species from the Himalayas. Recent findings concluded that the leaf blades of the North American mayapple (*P. peltatum L.*) might serve as an alternative source, since the leaves are renewable organs that store lignans as glucopyranosides.[177]

3.5 Previous Syntheses of Podophyllotoxin and its Analogues

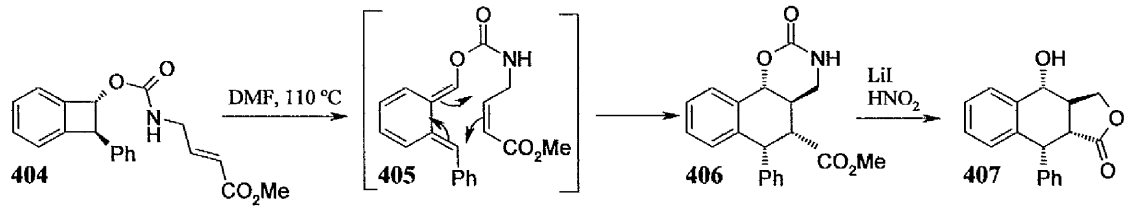
The first asymmetric synthesis of (–)-podophyllotoxin **399**, was achieved by Meyers *et al.*[164] The synthesis involved a diastereoselective addition of an aryl lithium to a chiral oxazoline-activated naphthalene **402** which provided the dihydronaphthalene **403** in excellent yield and diastereoselectivity 98:2 (Scheme 3.12). This was transformed into (–)-podophyllotoxin **399** in 5 % yield over 24 steps. This approach to podophyllotoxin is the only to use a dearomatising reaction in the synthesis of an advanced intermediate. The modular introduction of the aryl D ring provides an opportunity to explore structure-activity relationships.[178]



Scheme 3.12

Many groups have been concerned with flexible approaches to the podophyllotoxin skeleton, allowing synthesis of simplified analogues of the natural product which provide an insight into the importance of specific fragments of the skeleton by structure-activity relationships.[178]

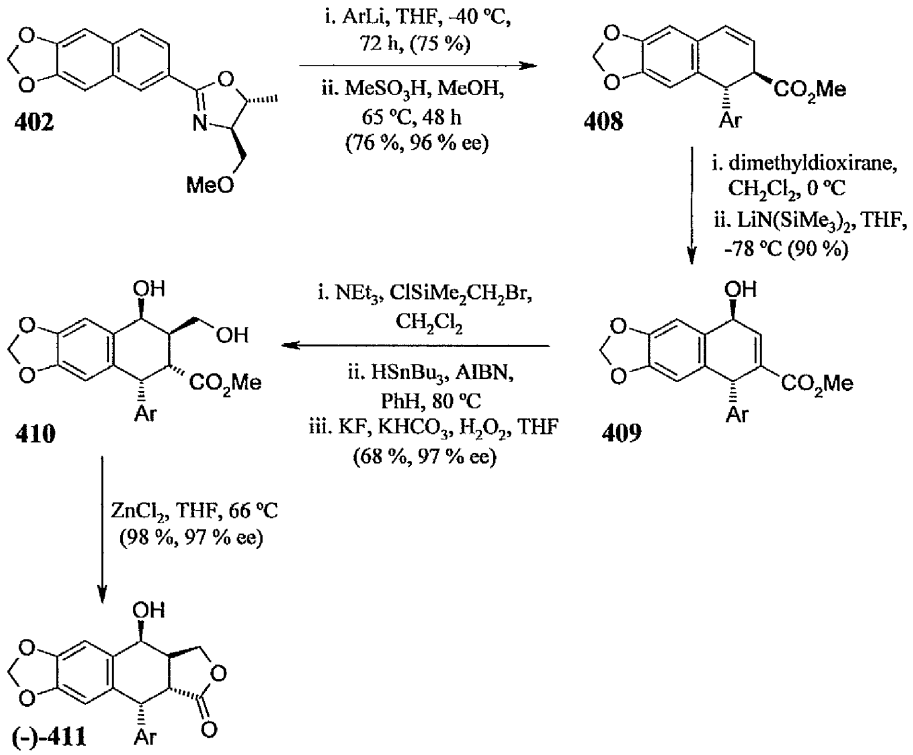
A Diels-Alder reaction was used to synthesise the simplified podophyllotoxin analogue **407**. Durst *et al.* developed an intramolecular Diels-Alder reaction between an *o*-quinodimethane and a crotonate moiety (Scheme 3.13).[179] Thermolysis of the cyclobutane **404** provided *o*-quinodimethane **405** which underwent a Diels-Alder reaction forming the adduct **406**. Cleavage of the methyl ester and urethane of **406** followed by diazotisation of the subsequent amine resulted in the analogue **407** in 35 % yield from **404**.



Scheme 3.13

The most recently synthesised podophyllotoxin analogue is (–)-epipodophyllotoxin **411**, the C-4 epimer of (–)-podophyllotoxin by Linker *et al.*[180] The strategy was based on the stereoselective introduction of the OH group at C-4 and the carbon substituent at C-3 in the later steps of the synthesis, allowing 1,2-dihydronaphthalenes **408** to be employed as precursors (Scheme 3.14). The elegant oxazoline strategy developed by Meyers[164] was used to introduce the aryl substituent at C-1.

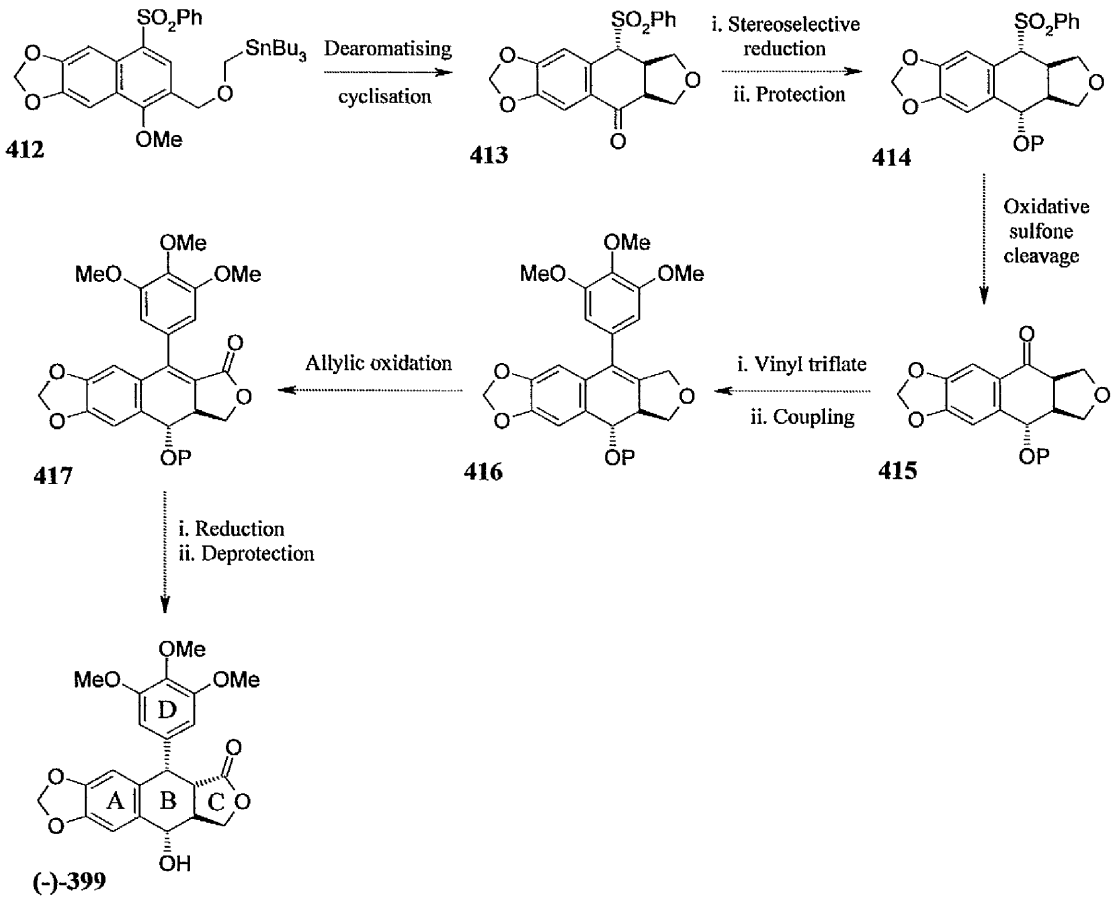
The crucial step of the total synthesis was the regio- and stereoselective introduction of a hydroxymethylene group **410** at C-3 using a silicon-tethered radical reaction.[181] The synthesis was completed in 12 steps, with high stereoselectivities in 30 % overall yield.



Scheme 3.14

3.6 Strategy for the Synthesis of Podophyllotoxin

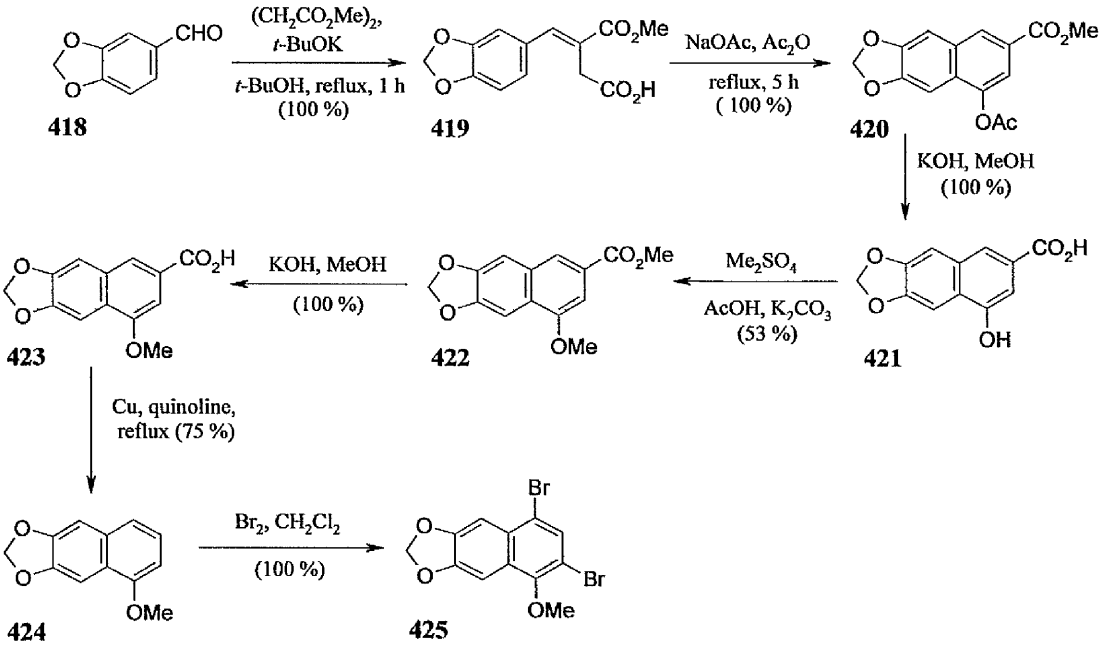
The synthetic strategy we envisaged for the synthesis of podophyllotoxin **399** is outlined in Scheme 3.15. Dearomatising cyclisation of the oxygen-tethered sulfone-activated naphthalene **412** would provide the naphthofuran skeleton **413** required for the natural product. It was anticipated that stereoselective reduction and protection would give **414**. Oxidative cleavage of the sulfone would provide ketone **415**, which could be used in a palladium catalysed coupling procedure *via* a vinyl triflate to introduce the aryl D-ring. Allylic oxidation would introduce the α,β-unsaturated system **417** which could be reduced and deprotected to form podophyllotoxin **399**.



Scheme 3.15

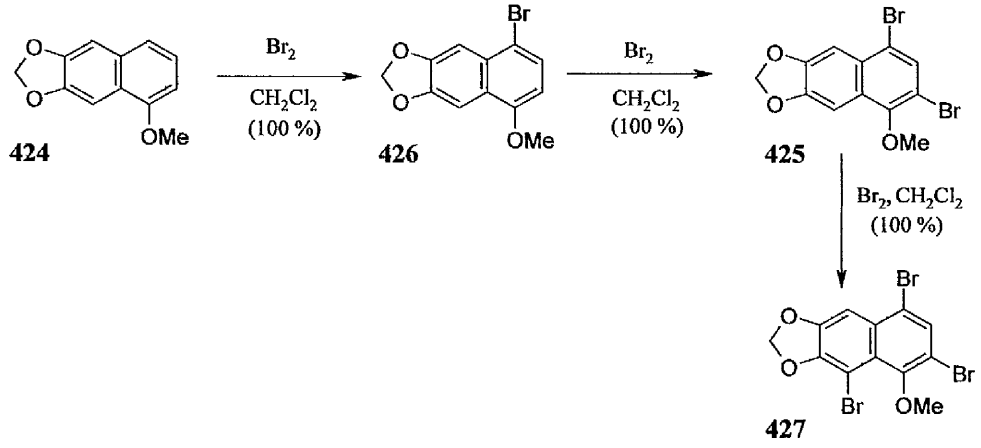
3.7 Synthesis of the Oxygen-Tethered Sulfone-Activated Naphthalene 412

The starting material **412** for the cyclisation was prepared from the 2,4-dibromonaphthalene **425** (Scheme 3.16). The methylenedioxy substituted naphthalene **424** was prepared by a six-step procedure as outlined by El-Assal *et al.*[182] from Stobbe condensation of commercially available piperonal **418** and dimethyl succinate. Cyclisation of **419** followed by ester hydrolysis furnished the phenol **421**, which was methylated to give **422**. Ester hydrolysis followed by decarboxylation in refluxing quinoline afforded the naphthalene **424** in 88 % yield over the six steps.

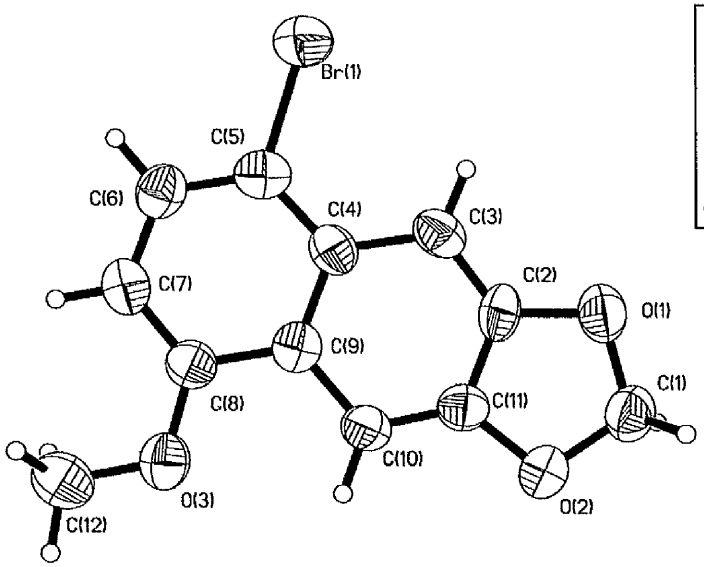


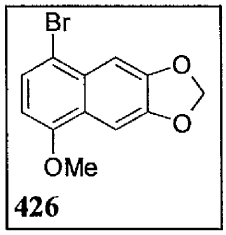
Scheme 3.16

The bromination step was regioselective; if only one equivalent of bromine was added the 4-position was brominated **426** (Figure 3.2), the second bromination occurred at the 2- position to give **425** due to the activating methoxy group. Only when excess bromine was added did bromination occur in the ring closest to the methylenedioxy group, to give the tribromo **427** (Figure 3.3, Scheme 3.17).



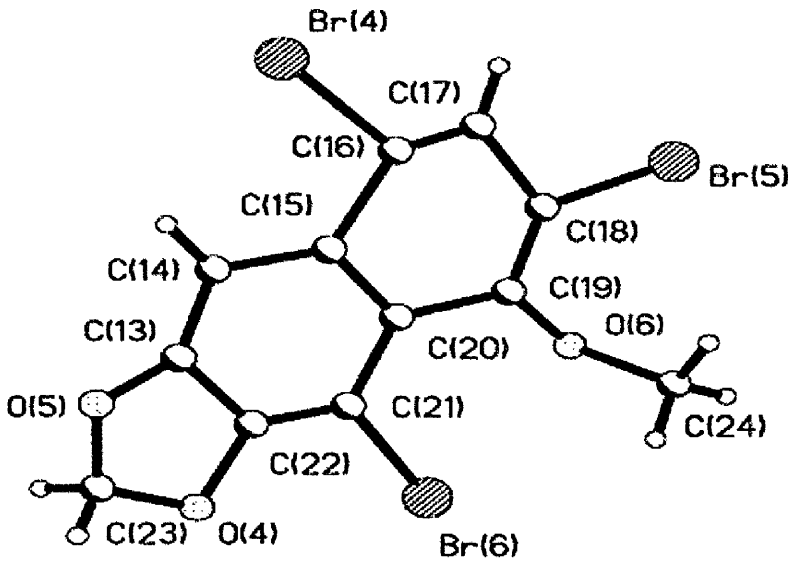
Scheme 3.17

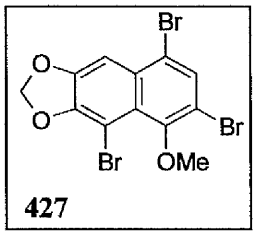




426

Figure 3.2 ORTEP representation of **426** X-ray structure.

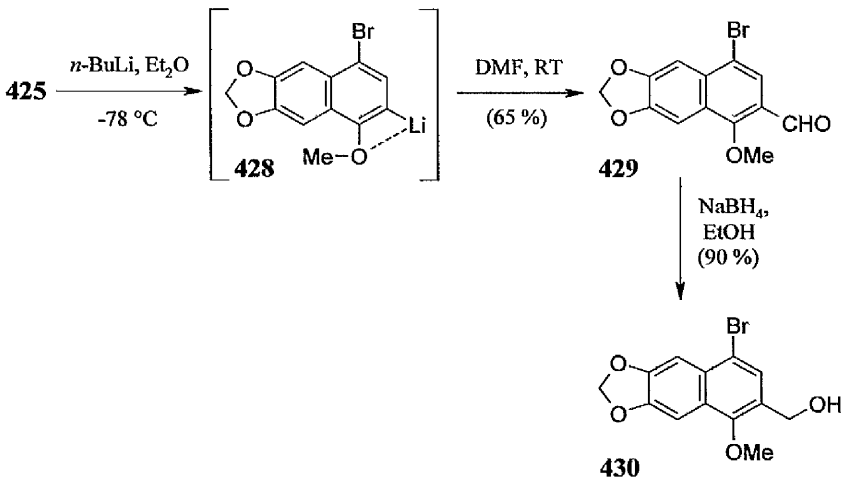




427

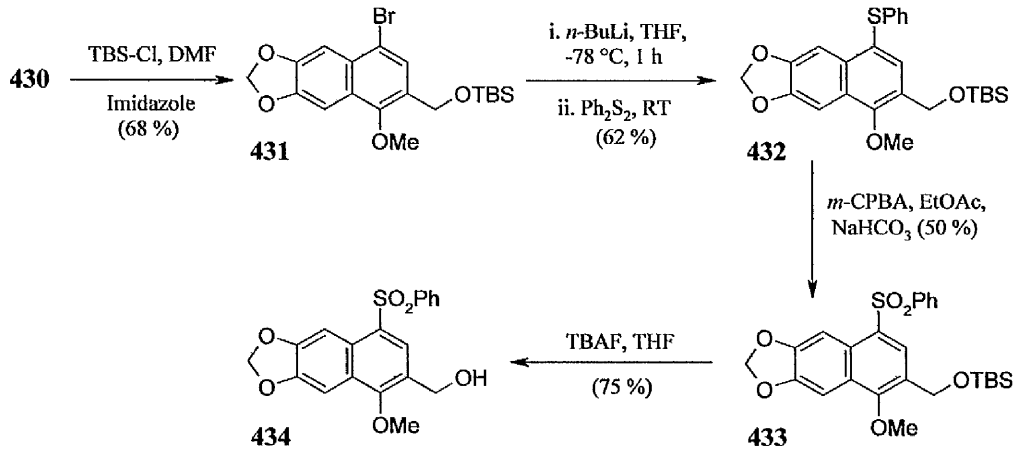
Figure 3.3 ORTEP representation of **427** X-ray structure.

A regioselective bromine-lithium exchange with *n*-butyllithium in diethyl ether at –78 °C provided the thermodynamic lithio-intermediate **428**, with the methoxy group stabilising the *ortho* organolithium.[183] The organolithium **428** reacted with DMF to give the aldehyde **429**, which was subsequently reduced to furnish the alcohol **430** (Scheme 3.18).



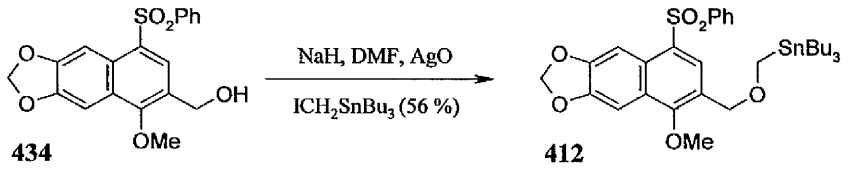
Scheme 3.18

TBS protection of the alcohol to give the silyl ether **431** was required to allow the second bromine-lithium exchange to take place. Diphenyldisulfide quench formed the sulfide **432**, which was oxidised with *m*-CPBA to the sulfone **433**. Deprotection with TBAF provided the required alcohol **434** (Scheme 3.19).



Scheme 3.19

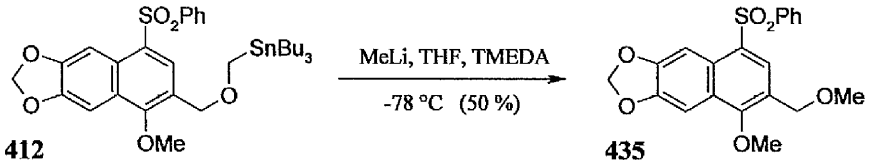
Alkylation of the alcohol **434** with iodomethyltributyltin[184] in DMF at room temperature resulted in the recovery of starting material. However when silver oxide was added the desired stannane **412** was formed in good yield (Scheme 3.20). It is postulated that the sodium hydride required for anion formation coordinates to both the methoxy and hydroxy groups thus preventing deprotonation. The presence of silver oxide prevents the coordination allowing the desired deprotonation.[185]



434 **412**

Scheme 3.20

Tin-lithium exchange was attempted using methyllithium and TMEDA in THF at –78 °C. It was obvious from the protodestannylated product **435** that the Sn-Li exchange had taken place but no cyclisation had occurred (Scheme 3.21).



412 **435**

Scheme 3.21

No improvement was observed when different temperatures (–40 °C), different additives (DMPU and HMPA) or different reaction times (both longer and shorter) were employed. The reason for the failure of **412** to undergo cyclisation (5-*exo-trig*) is unclear; we anticipate that the introduction of a more electron-withdrawing group to the sulfone moiety would increase the chance of cyclisation by increasing the stability of the organolithium intermediate and decreasing the chance of rearomatisation.

3.8 Introduction of an Electron-Withdrawing Group to the Sulfone

In order to increase the likelihood of cyclisation we wished to introduce an electron-withdrawing group to the sulfone moiety. Three groups were chosen to replace the benzene ring of the sulfone; *m*-fluorobenzene **a**, pentafluorobenzene **b** and 3,5-di(trifluoromethyl)benzene **c** (Figure 3.4).

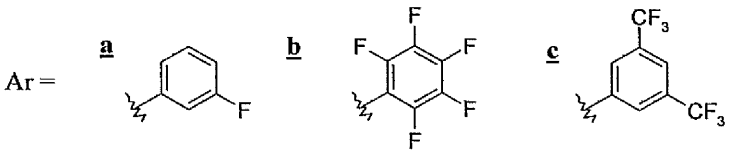
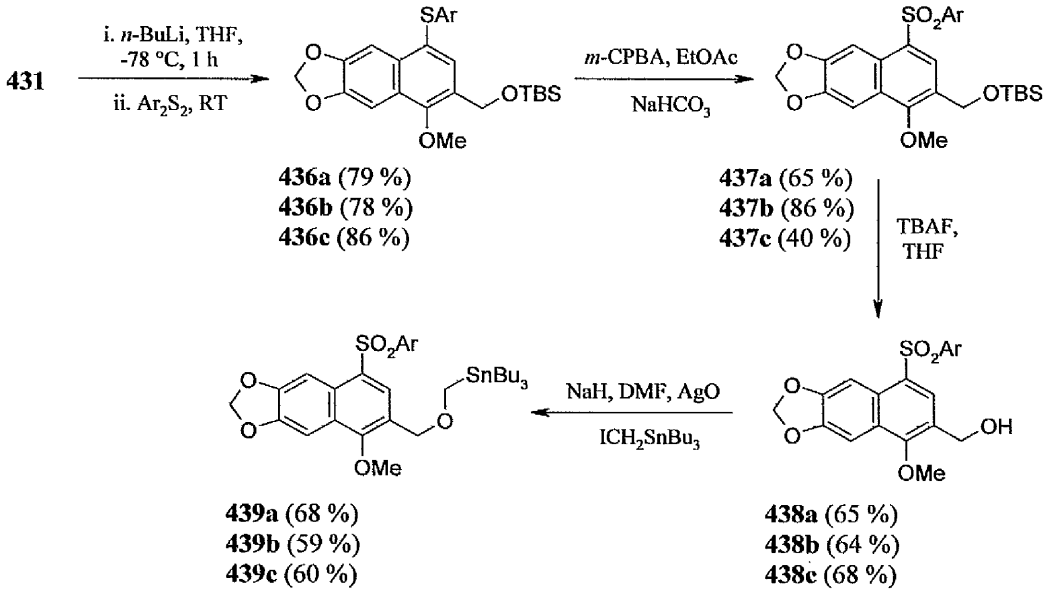


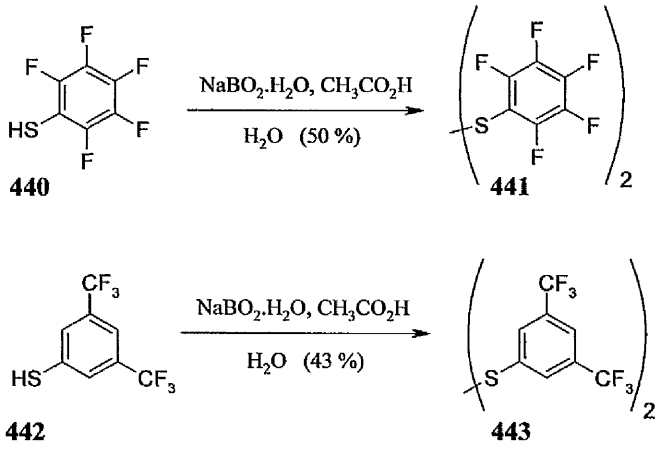
Figure 3.4

The stannanes required for cyclisation were prepared as shown previously by bomine-lithium exchange and disulfide quench **436a-c**. Oxidation to the sulfone **437a-c**, silyl deprotection **438a-c** and addition of the tin protecting-group provided the precursors to cyclisation **439a-c** (Scheme 3.22).



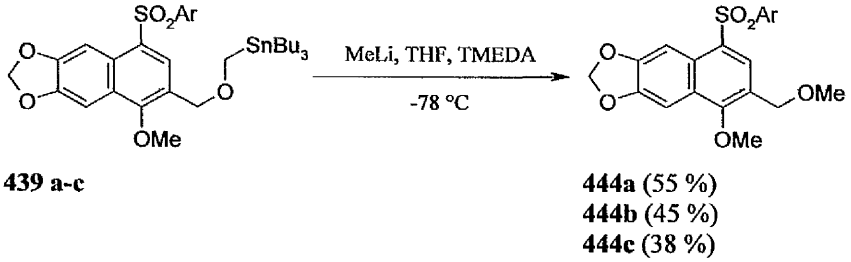
Scheme 3.22

The *m*-fluorophenyl disulfide was commercially available and the pentafluorophenyl disulfide **441** and 3,5-di(trifluoromethyl)phenyl disulfide **443** were readily accessible by oxidation of the commercially available thiols with sodium perborate (Scheme 3.23).[186]



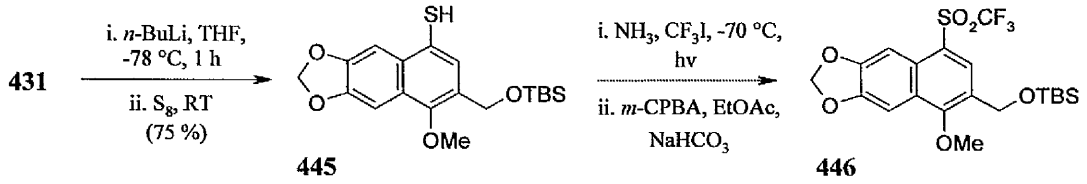
Scheme 3.23

Unfortunately attempted cyclisation by tin-lithium exchange was futile and in all cases the protodestannylated material **444a-c** was recovered (Scheme 3.24).



Scheme 3.24

Attempts were made to synthesise an alternative non-aromatic sulfone substituent **446**, unfortunately the thiol **445** was unreactive towards the CF_3 substitution and this route was not continued (Scheme 3.25).



Scheme 3.25

3.9 Conclusions and Future Work

We were unable to promote dearomatising cyclisation by tin-lithium exchange on the podophyllotoxin nucleus thus our route to (–)-podophyllotoxin was inaccessible. We postulate that the presence of the methylenedioxy group significantly alters the electronics of the ring and prevents dearomatising anionic cyclisation. We were unable to overcome this inherent lack of reactivity by increasing the electron-withdrawing groups on the sulfone moiety-one of the only groups on the podophyllotoxin nucleus that could be modified without significantly altering the core structure or introducing more steps to the synthesis. The identification of a suitable electron-withdrawing group on the sulfone moiety is required in order for successful cyclisation. It is anticipated that the subsequent steps in the synthesis of (–)-podophyllotoxin would be relatively straightforward.

Chapter 4

Experimental Section

4.1 General Experimental

Melting points (m.p.) were measured using a Gallenkamp melting point apparatus and are uncorrected. Optical rotations $[\alpha]_D^T$ were measured with a Perkin-Elmer 241 Polarimeter using a cell with a path length of 0.25 dm. Concentrations (c.) are given in grams per 100 mL.

Infra-red spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Spectrometer (225 to 4400 cm^{-1}). The samples were prepared as evaporated films on sodium chloride disks. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

^1H and ^{13}C NMR spectra were recorded on a Varian Inova 300 Spectrometer operating at ambient probe temperature using an internal deuterium lock (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR). Chemical shifts are reported in parts per million (δ) at lower frequencies relative to tetramethylsilane (TMS). They are reported as; position, multiplicity, coupling constant (Hz) and assignment. Standard abbreviations are used throughout (s-singlet, d-doublet, dd-doublet of doublets, t-triplet, q-quartet, m-multiplet, br-broad).

Mass spectra including chemical ionisation (C.I.) and electron impact (E.I.) were recorded on a Micromass VG Trio 2000 quadrupole mass spectrometer. Accurate mass measurements were recorded on a Kratos Concept-1S mass spectrometer and are correct to $\pm$ 0.001.

The solvents used were either distilled over appropriate drying agents, or of analytical grade. Petrol refers to the fraction of light petroleum ether boiling between 40-60 °C. All other commercially available reagents were purified as necessary following standard procedures.[187]

Flash chromatography[188] was performed using Apollo silica gel (40-63 microns). Analytical thin layer chromatography (TLC) was carried out using ALUGRAM® SIL G/UV_{254} plates with visualisation using either UV light or alkaline potassium permanganate.

4.2 General Procedures

Method A- *Acrylamide formation.*

Triethylamine (6.0 mmol, 2.0 equiv.), amine (6.1 mmol, 2.2 equiv.) and DMAP (0.3 mmol, 0.1 equiv.) in CH_2Cl_2 (10 mL) were stirred at 0 °C under a nitrogen atmosphere for 15 min. A solution of the acryloyl chloride (3.0 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C over 10 min and the solution stirred at room temperature for 14 h. 2 M HCl was added and the layers were separated. The organic layer was washed with 2M HCl and water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method B- *Pyrrole formation using TosMIC.*[121]

A solution of the acrylamide (0.9 mmol, 1.0 equiv.) and tosylmethylisocyanide (0.9 mmol, 1.0 equiv.) in DMSO (2 mL) and diethyl ether (5 mL) was added dropwise to a stirred suspension of sodium hydride (1.2 mmol, 1.3 equiv. of a 60 % suspension in oil) in diethyl ether (2 mL) at 0 °C, under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h, and quenched with water and 1 M potassium hydroxide solution. The mixture was extracted with diethyl ether and the combined organic layers were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product.

Method C- *Cyclisation using t-Butyllithium.*

t-Butyllithium (1.32 mmol, 2.5 equiv. of a 1.5 M solution in hexane) was added dropwise to a stirred solution of the amide (0.53 mmol, 1.0 equiv.) and DMPU (3.2 mmol, 6.0 equiv.) in THF (5 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred at this temperature overnight and quenched with the electrophile (0.78 mmol, 1.5 equiv.). The temperature was maintained at –78 °C for a further 10 minutes and allowed to warm to room temperature. Water was added and the organic phase separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts washed with water then brine, dried ($MgSO_4$), and solvents removed under reduced pressure to yield the crude product.

Method D- *Cyclisation using LDA.*

n-Butyllithium (1.1 mmol, 3.0 equiv. of a 2.5 M solution in hexane) was added dropwise to a stirred solution of diisopropylamine (1.1 mmol, 3.0 equiv.) in THF (2 mL) at 0 °C under a nitrogen atmosphere. The LDA solution was allowed to stir at this temperature for 20 minutes, and a solution of the amide (0.38 mmol, 1.0 equiv.) in THF (3 mL) was added *via* cannula at 0 °C. The mixture was stirred at 0 °C for 3 hours and quenched with the electrophile (2.3 mmol, 6.0 equiv.). Water was added and the organic phase separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts washed with water then brine, dried ($MgSO_4$), and solvents removed under reduced pressure to yield the crude product.

Method E- *DEB protection.*

A solution of the amide (3.7 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise to a suspension of sodium hydride (11.0 mmol, 3.0 equiv. of 60 % suspension in oil) in THF (10 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h then cooled to 0 °C. A solution of DEB-Cl[125] (5.0 mmol, 1.35 equiv.) in THF (10 mL) was added dropwise and the reaction stirred at room temperature for 16 h and quenched with ammonium chloride. Water was added and the organic phase separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts washed with water then brine, dried ($MgSO_4$), and the solvents removed under reduced pressure to yield the crude product.

Method F- *Cyclisation using s-BuLi.*

s-Butyllithium (1.8 mmol, 3.0 equiv. of a 1.5 M solution in hexane) was added dropwise to a stirred solution of amide (0.59 mmol, 1.0 equiv.) in THF (15 mL) at –78 °C under a nitrogen atmosphere. The mixture was stirred at –78 °C for 3 h and quenched with the electrophile (3.5 mmol, 6.0 equiv.). After 10 min water was added and the mixture extracted with EtOAc. Combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method G- *Cyclisation using chiral base **130**.*

n-Butyllithium (25 mmol, 6.0 equiv.) was added dropwise to a stirred solution of chiral base **130** (12.5 mmol, 3.0 equiv.) in THF (25 mL) at –78 °C, under a nitrogen atmosphere, and the mixture allowed to warm to room temperature for 15 min.

The solution was cooled to –78 °C and the amide (4.2 mmol, 1.0 equiv.) in THF (25 mL) added dropwise. The mixture was gradually allowed to warm to 0 °C over 5 h and quenched by the addition of saturated aqueous NH_4Cl solution. After 10 min water was added and the mixture was extracted with Et_2O. Combined organics were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product.

Method H- *Allylation.*

Amide (1.9 mmol, 1.0 equiv.) in DMF (2 mL) was added dropwise to a suspension of sodium hydride (2.9 mmol, 1.5 equiv. of a 60 % suspension in oil) in DMF (2 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 30 min and a solution of the appropriate allyl bromide (2.4 mmol, 1.2 equiv.) in DMF (2 mL) was added dropwise at 0 °C. The solution was stirred at room temperature for 1 h and quenched by the addition of water. The mixture was extracted with EtOAc and the combined organic fractions washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method I- *Deprotonation and selective quench with LDA.*

n-Butyllithium (0.69 mmol, 1.0 equiv. of a 2.4 M solution in hexane) was added dropwise to a solution of diisopropylamine (0.69 mmol, 1.0 equiv.) in THF (2.5 mL) at 0 °C under a nitrogen atmosphere. The LDA solution was stirred at 0 °C for 20 min and a solution of the 1,5-dihydropyrrol-2-one (0.69 mmol, 1.0 equiv.) in THF (2.5 mL) added dropwise. The solution was degassed and stirred at 0 °C for 3 h and quenched by the addition of the electrophile (1.4 mmol, 2.0 equiv.). The mixture was allowed to warm to room temperature for 30 min and water added. The mixture was extracted with EtOAc and the combined organic layers washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method J- *Amide formation from an acid chloride.*

A solution of the carboxylic acid (27 mmol, 1.0 equiv.) in thionyl chloride (30 mL) was heated at reflux for 16 h, under a drying tube. The thionyl chloride was removed *in vacuo,* the residue dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. A solution of the amine (40 mmol, 1.5 equiv.), Et_3N (46 mmol, 1.7 equiv.) and DMAP (2.7 mmol, 0.1 equiv.) in CH_2Cl_2 (10 mL) was added dropwise and the mixture stirred at room temperature for 3 days.

CH_2Cl_2 (20 mL) was added and the mixture washed with 2M HCl and water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method K- *EDCI coupling procedure.*[158]

Triethylamine (10.8 mmol, 6.0 equiv.) and hydroxybenzotriazole (2.7 mmol, 1.5 equiv.) were added to a solution of the carboxylic acid (1.8 mmol, 1.0 equiv.) in DMF (20 mL) at room temperature under a nitrogen atmosphere. EDCI (2.0 mmol, 1.1 equiv.) was added and the mixture stirred at room temperature for 20 min. The amine (2.7 mmol, 1.5 equiv.) and DMAP (0.2 mmol, 0.1 equiv.) were added and the mixture was stirred at room temperature for 24 h. EtOAc (10 mL) was added and the mixture washed with 10 % $NaHSO_4$ solution, saturated aqueous sodium hydrogen carbonate solution and water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method L- *Bromine-lithium exchange with disulfide quench.*

n-Butyllithium (2.6 mmol, 1.1 equiv. of a 2.4 M solution in hexane) was added dropwise to a solution of (8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **431** (2.4 mmol, 1.0 equiv.) in THF (10 mL) at –78 °C under a nitrogen atmosphere. The solution was maintained at –78 °C for 1 h and a solution of the disulfide (2.9 mmol, 1.25 equiv.) in THF (5 mL) was added dropwise. The solution was allowed to warm to room temperature over 12 h and quenched by the addition of saturated ammonium chloride solution. Water was added and the mixture extracted with EtOAc. Combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method M- *m-CPBA oxidation.*

m-CPBA (0.98 mmol, 2.7 equiv.) was added portionwise to a solution of the sulfide (0.37 mmol, 1.0 equiv.) and sodium hydrogen carbonate (2.4 mmol, 6.5 equiv.) in EtOAc (10 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 12 h and quenched by the addition of saturated sodium thiosulfate solution. The mixture was extracted with EtOAc. Combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

Method N- *TBAF deprotection.*

Tetra-*n*-Butylammonium fluoride (0.26 mmol, 1.1 equiv.) was added dropwise to a solution of the sulfone (0.24 mmol, 1.0 equiv.) in THF (10 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 1 h and quenched by the addition of water. The mixture was extracted with EtOAc. Combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product.

Method O- *Trialkylstannylmethyl ether formation.*

The alcohol (0.15 mmol, 1.0 equiv.) in DMF (2 mL) was added dropwise to a suspension of sodium hydride (1.0 equiv. of a 60 % suspension in oil) in DMF (2 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 20 min. and a solution of iodomethyltributyltin[184] (0.18 mmol, 1.2 equiv.) in DMF (2 mL) was added dropwise followed by silver oxide (0.15 mmol, 1.0 equiv.). The solution was stirred at room temperature for 12 h and water added. The mixture was extracted with EtOAc. Combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

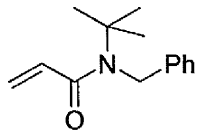
Method P- *MeLi promoted anionic cyclisation.*

Methyllithium (0.15 mmol, 1.1 equiv.) was added dropwise to a solution of the stannane (0.14 mmol, 1.0 equiv.) and TMEDA (0.15 mmol, 1.5 equiv.) in THF (5 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred at –78 °C for 2 h, at 0 °C for 2 h and quenched by the addition of methanol. The solution was allowed to warm to room temperature and 2M HCl added dropwise. The mixture was stirred at room temperature for 16 h and water added. The mixture was extracted with EtOAc. Combined organic layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product.

4.3 Experimental Procedures

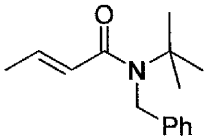
4.3.1 Experimental Details for Chapter 2.1

N-Benzyl-*N-tert*-butylacrylamide 159



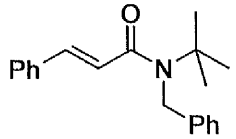
N-tert-Butylbenzylamine (6.0 mL, 32.6 mmol, 2.2 equiv.) and acryloyl chloride (1.2 mL, 14.8 mmol, 1.0 equiv.) were treated according to **Method A** to afford the *title compound* (3.2 g, 99 %) as white needles: m.p. 56.2-57.4 °C; R_f(1:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 1648 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40-7.43 (2H, m, Ar*H*), 7.28-7.29 (3H, m, Ar*H*), 6.37 (2H, dd, *J* 9.0 and 3.0, CHCH_2), 5.56 (1H, dd, *J* 9.0 and 3.0, C*H*CH_2), 4.66 (2H, s, CH_2Ph), 1.44 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.4, 139.3, 131.5, 128.7, 127.1, 126.9, 125.6, 57.6, 48.8, 28.4; *m/z* (C.I.) 218 (100 %, M + H^+); (Found: M^+, 217.1078. $C_{14}H_{19}NO$ requires 217.1066).

But-2-enoic acid benzyl-*tert*-butylamide 160



N-tert-Butylbenzylamine (3.87 mL, 21.0 mmol, 2.2 equiv.) and *trans*-crotonyl chloride (1.0 g, 9.6 mmol, 1.0 equiv.) were treated according to **Method A** to afford the *title compound* (2.22 g, 100 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1660 (C=O); δ_H(300 MHz, $CDCl_3$) 7.21-7.32 (5H, m, Ar*H*), 6.92 (1H, dq, *J* 13.0 and 7.0, C*H*CH_3), 6.1 (1H, d, *J* 13.0, C*H*C(O)), 4.63 (2H, s, CH_2), 1.80 (3H, dd, *J* 7.0 and 1.5, CH_3), 1.47 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.2, 141.2, 140.1, 139.6, 129.1, 128.9, 127.3, 126.0, 125.8, 57.8, 49.3, 28.8, 18.3; *m/z* (C.I.) 232 (100 %, M + H^+); (Found: M^+, 231.1623. $C_{15}H_{21}N_2O$ requires 231.1623).

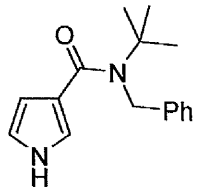
N-Benzyl-*N-tert*-butyl-3-phenylacrylamide 161



N-tert-Butylbenzylamine (1.21 mL, 6.6 mmol, 2.2 equiv.) and *trans*-cinnamoyl chloride (0.50 g, 3.0 mmol, 1.0 equiv.) were treated according to **Method A** to afford the *title*

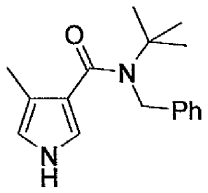
compound (0.87 g, 99 %) as an off white solid: m.p. 108-109 °C; R_f(1:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2962, 2360 (CH), 1651 (C=O); δ_H(300 MHz, $CDCl_3$) 7.73 (1H, d, *J* 15.5, C*H*Ph), 7.29-7.48 (10H, m, Ar*H*), 6.72 (1H, d, *J* 15.5, C*H*C(O)), 4.88 (2H, s, CH_2Ph), 1.58 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.1, 142.4, 139.9, 135.7, 131.3, 130.8, 129.6, 129.2, 128.9, 128.5, 127.9, 127.4, 126.1, 58.2, 28.9; *m/z* (C.I.) 294 (100 %, $M + H^+$); (Found: M^+, 293.1778. $C_{20}H_{23}NO$ requires 293.1779).

1*H*-Pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 162



N-Benzyl-*N*-*tert*-butylacrylamide **159** (2.0 g, 9.17 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) to afford the *title compound* (2.0 g, 86 %) as a white solid: m.p. 168.5-168.9 °C; R_f(1:1 Petrol:EtOAc) 0.40; $\nu_{max}(CHCl_3)/cm^{-1}$ 3192 (NH), 2963 (CH), 1598 (C=O); δ_H(300 MHz, $CDCl_3$) 8.62 (1H, brs, N*H*), 7.24-7.26 (5H, m, Ar*H*), 6.98 (1H, dd, *J* 5.0 and 2.5, *H*-5), 6.50 (1H, dd, *J* 5.0 and 2.5, *H*-2), 6.24 (1H, dd, *J* 5.0 and 2.5, *H*-4), 4.81 (2H, s, CH_2), 1.39 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 141.4, 128.5, 126.5, 126.1, 117.6, 108.9, 57.8, 51.4, 28.6 (CH_3); *m/z* (C.I.) 257 (100 %, $M + H^+$); (Found: M^+, 256.1575. $C_{16}H_{20}N_2O$ requires 256.1575).

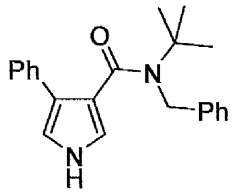
4-Methyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 163



But-2-enoic acid benzyl-*tert*-butylamide **160** (2.22 g, 9.61 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 6:1 Petrol/EtOAc) to afford the *title compound* (1.49 g, 58 %) as a white solid: m.p. 96.8-97.2 °C; R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 3201 (NH), 2910 (CH), 1665 (C=O); δ_H(300 MHz, $CDCl_3$) 8.56 (1H, brs, N*H*), 7.25-7.38 (5H, m, Ar*H*), 6.71 (1H, dd, *J* 4.5 and 2.5, *H*-5), 6.43 (1H, brs, *H*-2), 4.80 (2H, s, CH_2), 2.18 (3H,

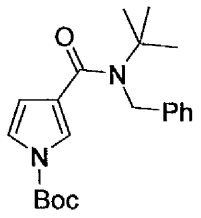
s, C*H*$_3$), 1.71 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 171.3, 141.3, 128.7, 127.0, 126.7, 125.6, 121.4, 117.6, 116.5, 57.9, 51.8, 29.2, 10.9; *m/z* (C.I.) 271 (100 %, M + H$^+$); (Found: M$^+$, 270.1728. $C_{17}H_{22}N_2O$ requires 270.1732).

4-Phenyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 164



N-Benzyl-*N*-*tert*-butyl-3-phenylacrylamide **161** (0.87 g, 2.97 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) to afford the *title compound* (0.42 g, 43 %) as a white solid: m.p. 124-125 °C; R_f(1:1 Petrol:EtOAc) 0.50; ν_{max}($CHCl_3$)/cm^{-1} 3336 (NH), 2922 (CH), 1601 (C=O); δ_H(300 MHz, $CDCl_3$) 8.56 (1H, brs, N*H*), 7.38 (2H, d, *J* 7.5, Ar*H*), 7.29 (2H, t, *J* 7.5, Ar*H*), 7.1-7.23 (4H, m, Ar*H*), 7.05 (2H, d, *J* 7.5, Ar*H*), 6.88 (1H, s, *H*-2), 6.71 (1H, s, *H*-5), 4.37 (2H, s, C*H*$_2$), 1.37 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 170.9, 140.7, 135.4, 128.6, 128.5, 127.7, 126.8, 126.4, 123.3, 120.8, 119.4, 115.8, 58.3, 51.2, 28.9; *m/z* (C.I.) 333 (100 %, M + H$^+$); (Found: M$^+$, 332.1889. $C_{22}H_{24}NO$ requires 332.8888).

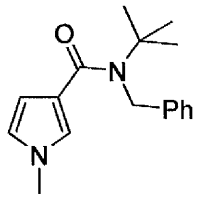
3-(Benzyl-*tert*-butylcarbamoyl)-pyrrole-1-carboxylic acid-*tert*-butyl ester 165



1*H*-Pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **162** (0.20 g, 0.78 mmol, 1.0 equiv.) in THF (5 mL), was slowly added to a suspension of sodium hydride (70 mg, 1.56 mmol, 2.0 equiv.) in THF (10 mL) at room temperature and the mixture stirred for 30 min. Di-*tert*-butyldicarbonate (0.18 g, 0.74 mmol, 0.95 equiv.) was added portion-wise and the reaction heated at 45 °C for 18 h. The mixture was diluted with water (3 mL) and extracted into EtOAc (4 × 5 mL), combined organic layers were washed with water (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) to

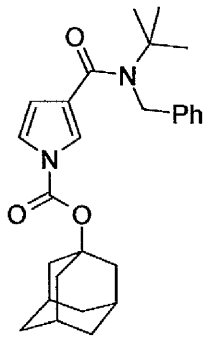
afford the *title compound* (0.12 g, 68 %) as a yellow solid: m.p. 144.0-144.6 °C; R_f (5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2976 (CH), 1747 (C=O), 1619 (C=O); δ_H(300 MHz, $CDCl_3$) 7.44 (1H, dd, *J* 4.0 and 2.0, *H*-5), 7.34-7.37 (5H, m, Ar*H*), 7.12 (1H, dd, *J* 3.0 and 2.0, *H*-2), 6.36 (1H, dd, *J* 3.0 and 2.0, *H*-4), 4.80 (2H, s, CH_2), 1.54 (9H, s, *t*Bu),1.52 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.4, 140.7, 128.6, 126.9, 125.9, 124.8, 121.2, 119.4, 111.2, 84.1, 77.4, 58.1, 28.5, 27.7; *m/z* (C.I.) 357 (100 %, M + H^+); (Found: M^+, 356.2099. $C_{21}H_{28}N_2O_3$ requires 356.2099).

1-Methyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 167



Attempts to cyclise various *N*-protected pyrrole-3-carboxamides using **Method C** and **Method D** resulted in the formation of the *title compound* as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.45; ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2923 (CH), 1622 (C=O); δ_H(300 MHz, $CDCl_3$) 7.42-7.24 (5H, m, Ar*H*), 6.98 (1H, dd, *J* 5.0 and 2.5, *H*-2), 6.41 (1H, dd, *J* 5.0 and 2.5, *H*-5), 6.22 (1H, dd, *J* 5.0 and 2.5, *H*-4), 4.86 (2H, s, CH_2), 2.58 (3H, s, NCH_3), 1.45 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 157.7, 142.9, 128.3, 127.7, 127.6, 127.1, 126.2, 107.5, 105.8, 74.4, 56.4, 30.4, 29.6, 29.4; *m/z* (C.I.) 271 (100 %, M + H^+); (Found: M^+, 270.1713 $C_{17}H_{22}N_2O$ requires 270.1732).

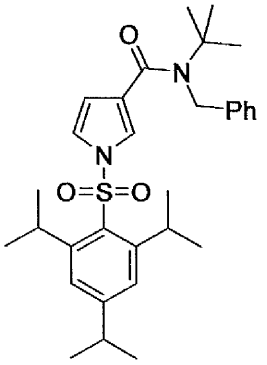
***N*-(1-adamantyloxycarbonyl)-3-(Benzyl-*tert*-butylcarbamoyl)-pyrrole 168**



A suspension of pyrrole-3-carboxamide **162** (0.25 g, 0.98 mmol, 1.0 equiv.) in THF (10 mL) at 0 °C under a nitrogen atmosphere, was treated with sodium hydride (0.12 g of a 60% suspension in mineral oil, 3.03 mmol, 3.1 equiv.). The suspension was stirred at

room temperature for 45 min then cooled to 0 °C and treated with 1-adamantyl fluoroformate (0.29 g, 1.32 mmol, 1.35 equiv.). After stirring at room temperature overnight (18 h), water (1.5 mL) was added dropwise and the THF removed under reduced pressure. The resultant residue was dissolved in CH_2Cl_2 (20 mL), washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) furnished the *title compound* (0.65 g, 76 %) as a white solid; m.p. 170.8-108.7 °C: R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2918 (CH), 1740 (C=O), 1620 (C=O); δ_H(300 MHz, $CDCl_3$) 7.38 (1H, dd, *J* 4.0 and 2.0, *H*-5), 7.26-7.29 (5H, m, Ar*H*), 6.98 (1H, dd, *J* 4.0 and 2.0, *H*-2), 6.20 (1H, dd, *J* 4.0 and 2.0, *H*-4), 4.72 (2H, s, CH_2), 2.12 (3H, brs, 3 × C*H*), 2.05 (6H, brs, 3 × CH_2), 1.60 (6H, brs, 3 × OCCH_2), 1.40 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.4, 147.6, 140.7, 128.5, 126.8, 125.9, 124.7, 121.2, 119.4, 111.7, 84.2, 58.0, 51.1, 41.0, 36.2, 36.0, 35.8, 30.8, 29.6, 28.4, 22.6; *m/z* (C.I.) 435 (100 %, M + H^+); (Found: M^+, 434.2565. $C_{27}H_{34}N_2O_3$ requires 434.2569).

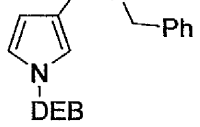
1-(2,4,6-Triisopropylbenzenesulfonyl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 169



A suspension of pyrrole-3-carboxamide **162** (0.20 g, 0.78 mmol, 1.0 equiv.) in THF (5 mL) at 0 °C under a nitrogen atmosphere was treated with sodium hydride (0.10 g of a 60% suspension in mineral oil, 2.42 mmol, 3.1 equiv.). The suspension was stirred at room temperature for 45 min, cooled to 0 °C and treated with 2, 4, 6-triisopropyl benzenesulfonylchloride, (0.32 g, 1.01 mmol, 1.35 equiv.). After stirring at room temperature overnight (18 h) water (1.5 mL) was added dropwise and the solvent removed under reduced pressure. The resultant residue was dissolved in CH_2Cl_2 (15 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) furnished the *title*

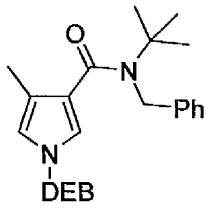
compound (0.18 g, 45 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.85; ν_{max} ($CHCl_3$)/cm^{-1} 2961 (CH), 1630 (C=O), 1174 (S=O); δ_H(300 MHz, $CDCl_3$) 7.38 (H, dd, *J* 3.5 and 2.0, *H*-4), 7.29-7.32 (5H, m, Ar*H*), 7.19 (2H, s, Ar*H*), 6.98 (1H, dd, *J* 3.5 and 2.0, *H*-2), 6.35 (H, dd, *J* 3.5 and 2.0, *H*-5), 4.78 (2H, s, CH_2), 4.03 (2H, q, *J* 6.5, $CH(CH_3)_2$), 2.94 (1H, dt, *J* 6.5, $CH(CH_3)_2$), 1.49 (9H, s, *t*Bu), 1.28 (6H, d, *J* 6.5, $CH(CH_3)_2$), 1.14 (12H, d, *J* 6.5, 2 × $CH(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 172.4, 154.8, 154.7, 151.5, 151.3, 140.4, 140.3, 139.0, 133.9, 128.6, 126.8, 125.8, 125.4, 122.3, 111.6, 111.1, 51.1, 34.2, 29.5, 28.4, 24.3; *m/z* (C.I.) 523 (100 %, M + H^+); (Found: M^+, 522.2767. $C_{31}H_{42}N_2SO_3$ requires 522.2759).

1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 170



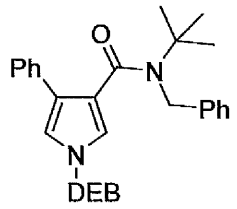
1*H*-Pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **162** (0.5 g, 1.95 mmol, 1.0 equiv.) was treated according to **Method E**. The crude product was purified by flash column chromatography (SiO_2; 8:1 Petrol/EtOAc) to afford the *title compound* (0.54 g, 74 %) as an off-white solid: m.p.72.2-72.5 °C; R_f(1:1 Petrol:EtOAc) 0.80; ν_{max} ($CHCl_3$)/cm^{-1} 2968 (CH), 1709, 1630 (C=O); δ_H(300 MHz, $CDCl_3$) 7.53 (1H, d, *J* 4.0, *H*-5), 7.25-7.43 (6H, m, *H*-2 and Ar*H*), 6.39 (1H, dd, *J* 4.0 and 1.5, *H*-4), 4.82 (2H, s, CH_2), 1.54 (9H, s, *t*Bu), 1.25 (6H, q, *J* 7.5, 3 × CH_2), 0.67 (9H, t, *J* 7.5, 3 × CH_3); δ_C(75 MHz, $CDCl_3$) 174.7, 170.9, 168.4, 140.8, 128.7, 126.8, 125.7, 124.6, 120.1, 119.9, 111.7, 58.1, 28.3, 14.0, 8.2; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2631. $C_{24}H_{34}N_2O_2$ requires 382.2620).

1-(2,2-Diethylbutyryl)-4-methyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 171



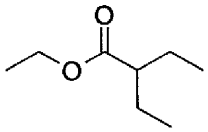
4-Methyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **163** (1.0 g, 3.7 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (1.22 g, 84 %) as a white solid: m.p. 123-124 °C; R_f(1:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1702, 1638 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.41 (6H, m, Ar*H* and *H*-5), 7.19 (1H, m, *H*-2), 4.75 (2H, s, CH_2Ph), 2.18 (3H, s, CH_3), 1.48 (9H, s, *t*Bu), 0.9 (6H, q, *J* 7.5, 3 × CH_2CH_3), 0.64 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 174.8, 169.4, 140.9, 128.9, 127.2, 126.1, 125.2, 121.4, 118.5, 52.4, 51.5, 28.9, 26.8; *m/z* (C.I.) 397 (100 %, M + H^+); (Found: M^+, 396.2784. $C_{25}H_{36}N_2O_2$ requires 396.1776).

1-(2,2-Diethylbutyryl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 172



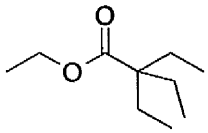
4-Phenyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **164** (0.42 g, 1.27 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.52 g, 89 %) as a white solid: m.p. 148.9-149.7 °C; R_f(5:1 Petrol:EtOAc) 0.75; ν_{max} $(CHCl_3)/cm^{-1}$ 2967 (CH), 1705, 1628 (C=O); δ_H(300 MHz, $CDCl_3$) 7.2-7.58 (12H, m, Ar*H*, *H*-2 and *H*-5), 4.52 (2H, s, CH_2Ph), 1.54 (9H, s, *t*Bu), 0.88 (6H, q, *J* 7.5, 3 × CH_2CH_3), 0.68 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 174.9, 169.1, 140.3, 133.6, 128.8, 128.7, 127.5, 127.4, 127.1, 126.0, 124.5, 119.1, 117.6, 58.5, 52.6, 50.9, 28.8, 26.3, 8.5; *m/z* (C.I.) 459 (100 %, M + H^+); (Found: M^+, 458.2940. $C_{30}H_{38}N_2O_2$ requires 458.2933).

2-Ethylbutyric acid ethyl ester 174[125]



A solution of diethyl acetic acid (20 mL, 0.16 moles, 1.0 equiv.) in ethanol (80 mL) and catalytic c.HCl was heated at reflux overnight. The reaction was allowed to cool to room temperature, water (50 mL) added and the mixture extracted with diethyl ether (4 × 25 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the *title compound* (12.2 g, 56 %) as a colourless oil: b.p. 150-152 °C (lit.,[125] 148-151 °C) ; R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972 (CH), 1749 (C=O); δ_H(300 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.0, OCH_2), 2.18-2.20 (1H, m, $CH(Et)_2$), 1.56 (4H, dq, *J* 7.0 and 14.5, 2 × CH_2CH_3), 1.25 (3H, t, *J* 7.0, CH_3), 0.89 (6H, t, *J* 7.0, 2 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.2, 59.7, 48.8, 24.9, 14.1, 11.6; *m/z* (C.I.) 162 (80 %, $M^+ + NH_4$); (Found: M^+, 144.1156 $C_8H_{16}O_2$ requires 144.1150).

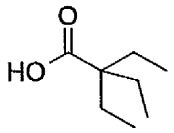
2,2-Diethylbutyric acid ethyl ester 175[125]



n-Butyllithium (21 mL of 2.5 M solution in hexane, 52.1 mmol, 1.5 equiv.) was added dropwise to a stirred solution of diisopropylamine (7.3 mL, 52.1 mmol, 1.5 equiv.) in THF (60 mL) at 0 °C, under a nitrogen atmosphere. The solution was stirred for 30 min and then cooled to –78 °C. To this LDA solution was added a pre-cooled solution of 2-ethylbutyric acid ethyl ester **174** (5.0 g, 34.7 mmol, 1.0 equiv.) in THF (40 mL) and the mixture stirred at –78 °C for 4 h. The reaction was quenched by the addition of ethyl iodide (6.0 mL, 69.4 mmol, 2.0 equiv.) and after stirring for 30 min, water (25 mL) was added. The mixture was extracted with diethyl ether (4 × 25 mL). The combined organic layers were washed with water (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave the *title compound* (4.34 g, 73 %) as a colourless oil: b.p. 177 °C (lit.,[125] 176-178 °C); R_f(1:1 Petrol:EtOAc) 0.75; ν_{max} $(CHCl_3)/cm^{-1}$ 2968, 2880 (CH), 1743 (C=O); δ_H(300 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7.5, OCH_2), 1.60 (6H, q, *J* 8.0, 3 × CH_2), 1.26 (3H, t, *J* 7.0, CH_3), 0.78 (9H, t, *J* 8.0, 3 × CH_3); δ_C(75 MHz,

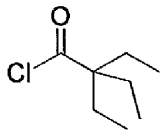
$CDCl_3$) 177.1, 59.8, 49.6, 25.9, 14.2, 8.1; *m/z* (C.I.) 173 (80 %, M + H^+); (Found: M^+, 172.1458. $C_{10}H_{20}O_2$ requires 172.1463).

2,2-Diethylbutyric acid 176[125]



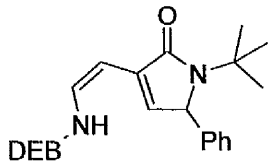
Water (0.63 mL, 34.9 mmol, 2.0 equiv.) was added to a stirred suspension of potassium *tert*-butoxide (19.6 g, 174 mmol, 10 equiv.) in *tert*-butanol (100 mL) at 0 °C and the mixture stirred for 20 min. 2,2-Diethylbutyric acid ethyl ester **175** (3.0 g, 17.4 mmol, 1.0 equiv.) was added portionwise and the slurry stirred at room temperature for 30 min. The mixture was heated at reflux for 3 days, cooled to room temperature and diluted with CH_2Cl_2 (50 mL) and water (20 mL). The organic layer was separated and the aqueous layer acidified with c.HCl (20 mL). The acidified solution was extracted with EtOAc (4 × 50 mL) and the combined organics dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (2.51 g, 99 %) as a yellow oil: R_f (5:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 3102 (OH), 2970, 2644 (CH), 1701 (C=O); δ_H(300 MHz, $CDCl_3$) 11.4 (1H, brs, O*H*), 1.63 (6H, q, *J* 7.5, 3 × CH_2), 0.84 (9H, t, *J* 7.5, 3 × CH_3); δ_C(75 MHz, $CDCl_3$) 177.1, 59.8, 49.6, 25.9, 14.2, 8.1; *m/z* (C.I.) 162 (100 %, M + NH_4^+); (Found: M^+, 144.1145. $C_8H_{16}O_2$ requires 144.1150).

2,2-Diethylbutyryl chloride 177[125]



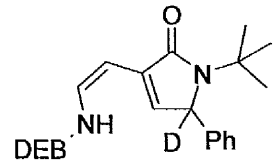
2,2-Diethylbutyric acid **176** (2.51 g, 17.4 mmol, 1.0 equiv.) in thionyl chloride (20 mL) was heated at reflux, under drying tube, overnight (18 h). The solution was cooled to room temperature and the thionyl chloride removed under reduced pressure to afford the *title compound* (2.26 g, 81 %) as a brown oil: b.p. 172 °C/14 mmHg (lit.,[125] 172 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 2961, 2872 (CH), 1792 (C=O); δ_H(300 MHz, $CDCl_3$) 1.73 (6H, q, *J* 7.5, 3 × CH_2), 0.87 (9H, t, *J* 7.5, 3 × CH_3); δ_C(75 MHz, $CDCl_3$) 177.1, 59.8, 14.2; *m/z* (C.I.) 162.5 (100 %, M + NH_4^+); (Found: M^+, 162.1002. $C_8H_{15}OCl$ requires 162.0811).

_N_-[2-(1-_tert_-Butyl-2-oxo-5-phenyl-2,5-dihydro-1_H_-pyrrol-3-yl)vinyl]-2,2-diethylbutyramide 182



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **170** (0.15 g, 0.39 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.12 g, 81 %) as needles: m.p. 120.8-121.4 °C; R_f(1:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$3210 (NH), 2964 (CH), 1677, 1641 (C=O); δ_H(300 MHz, $CDCl_3$) 12.2 (1H, d, *J* 10.5, N*H*), 7.38-7.22 (5H, m, Ar*H*), 7.05 (1H, t, *J* 10.5, NHC*H*CH), 6.48 (1H, d, *J* 2.5, C*H*C(H)Ph), 5.30 (1H, d, *J* 2.5, CHC(*H*)Ph), 5.09 (1H, d, *J* 10.5, NCHC*H*), 1.75 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.40 (9H, s, *t*Bu), 0.80 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.6, 172.2, 141.6, 137.9, 134.3, 128.9, 127.9, 126.3, 125.8, 98.1, 65.7, 56.1, 49.8, 28.0, 26.1, 25.7, 8.2; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2626. $C_{24}H_{34}N_2O_2$ requires 382.2620).

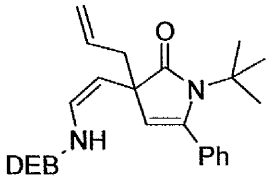
_N_-[2-(5-Deutero-1-_tert_-butyl-2-oxo-5-phenyl-2,5-dihydro-1_H_-pyrrol-3-yl)vinyl]-2,2-diethylbutyramide 183



sec-Butyllithium (0.67 mL of a 1.18 M solution in hexane, 0.78 mmol, 1.5 equiv.) was added dropwise to a stirred solution of 1-(2,2-diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **170** (0.20 g, 0.52 mmol, 1.0 equiv.) and potassium *tert*-butoxide (1.15 mL, 1.15 mmol, 2.2 equiv.) in THF (5 mL) at –78 °C, under a nitrogen atmosphere. The solution was stirred at –78 °C for 1 h and quenched by the addition of deuterated methanol (0.10 mL, 2.4 mmol, 5.0 equiv.). The mixture was stirred for 30 min and saturated aqueous ammonium chloride solution added (5 mL). The mixture was allowed to warm to room temperature and extracted EtOAc (4 × 5 mL). Combined organic layers were washed with water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) to afford the *title compound* (0.093 g, 48 %) as a clear oil:

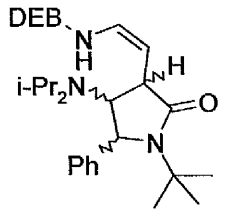
R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3205 (NH), 2976 (CH), 1692, 1639 (C=O); δ_H(300 MHz, $CDCl_3$) 11.98 (1H, d, *J* 9.0, N*H*), 7.20-7.41 (5H, m, Ar*H*), 7.0 (1H, t, *J* 9.0, NHC*H*), 6.41 (1H, s, C*H*CDPh), 5.05 (1H, d, *J* 9.0, NHCHC*H*), 1.78 (6H, q, *J* 7.5, 3 × CH_2CH$_3$), 1.60 (9H, s, *t*Bu), 0.65 (9H, t, *J* 7.5, 3 × CH$_2$CH_3); δ_C(75 MHz, $CDCl_3$) 175.7, 168.4, 140.8, 134.4, 128.7, 128.2, 127.5, 126.6, 125.7, 120.1, 119.6, 111.7, 105.6, 101.3, 98.2, 58.1, 51.3, 50.8, 29.0, 28.3, 27.6, 8.2; *m/z* (C.I.) 383 (100 %, M + H$^+$); (Found: M$^+$, 383.2685. $C_{24}H_{33}N_2O_2D$ requires 383.2683).

_N_-[2-(5-Allyl-1-*tert*-butyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)vinyl]-2,2-diethylbutyramide 184



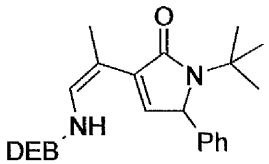
1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **170** (0.15 g, 0.39 mmol, 1.0 equiv.) was treated according to **Method G** with allyl bromide (0.40 mL, 4.72 mmol, 12 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 50 %) as needles: m.p. 112.6-113 °C; R_f(5:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 3268 (NH), 2967 (CH), 1679, 1646 (C=O); δ_H(300 MHz, $CDCl_3$) 10.63 (1H, d, *J* 10.0, N*H*), 7.65-7.80 (5H, m, Ar*H*), 6.95 (1H, t, *J* 10.0, NHC*H*CH), 5.75-5.77 (1H, m, CH$_2$C*H*CH$_2$), 5.13-5.15 (2H, m, CH$_2$CHCH_2), 5.10 (1H, s, C*H*CPh), 4.50 (1H, d, *J* 9.5, NHCHC*H*), 2.56 (2H, d, *J* 7.0, CH_2CHCH$_2$), 1.72 (6H, q, *J* 7.5, 3 × CH_2CH$_3$), 1.34 (9H, s, *t*Bu), 0.84 (9H, t, *J* 7.5, 3 × CH$_2$CH_3); δ_C(75 MHz, $CDCl_3$) 183.2, 175.6, 145.7, 136.3, 132.9, 129.3, 128.7, 128.3, 125.2, 118.9, 116.3, 104.9, 58.7, 54.7, 50.0, 41.3, 30.3, 26.3, 8.5; *m/z* (C.I.) 423 (100 %, M + H$^+$); (Found: M$^+$, 422.2940. $C_{27}H_{38}N_2O_2$ requires 422.2933).

_N_-[2-(1-*tert*-Butyl-4-diisopropylamino-2-oxo-5-phenylpyrrolidin-3-yl)vinyl]-2,2-diethylbutyramide 185



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **170** (0.15 g, 0.39 mmol, 1.0 equiv.) was treated according to **Method D** (with 6.0 equiv. of LDA) with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.04 g, 20 %) as a colourless oil in a 1:1 mixture: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3258 (NH), 2958 (CH), 1675, 1640 (C=O); δ_H(300 MHz, $CDCl_3$) 10.55 (1H, d, *J* 9.0, N*H*CHCH$_A$), 10.25 (1H, d, *J* 9.0, N*H*CHCH$_B$),7.38-7.21 (10H, m, Ar*H*$_{A+B}$), 6.92 (1H, td, *J* 9.0 and 2.5, NHC*H*CH$_A$), 6.88 (1H, td, *J* 9.0 and 2.5, NHC*H*CH$_B$), 4.88 (1H, s, C(*H*)Ph$_A$), 4.76 (1H, dd, *J* 9.0 and 4.0,NHCHC*H*$_A$), 4.62 (1H, s, C(*H*)Ph$_B$), 4.45 (1H, dd, *J* 9.0 and 4.0,NHCHC*H*$_B$), 3.90 (1H, ddd, *J* 4.0, 2.5 and 1.0, C*H*C(H)N-*i*Pr$_{2\ A}$), 3.80 (1H, ddd, *J* 4.0, 2.5 and 1.0, C*H*C(H)N-*i*Pr$_{2\ B}$), 3.20-3.10 (2H, m, 2 × CHC(*H*)N-*i*Pr$_2$), 1.88 (4H, m, 4 × C*H*(CH$_3$)$_2$), 1.70 (12H, q, *J* 7.5, 6 × C*H*$_2$CH$_3$), 1.40 (18H, s, *t*Bu), 1.26 (12H, d, *J* 7.0, 2 × CH(C*H*$_3$)$_2$), 1.00 (12H, d, *J* 7.0, 2 × CH(C*H*$_3$)$_2$), 0.85 (18H, t, *J* 7.5, 6 × CH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 178.7, 172.3, 138.8, 128.6, 128.3, 127.6, 127.2, 125.8, 125.3, 123.2, 122.9, 122.5, 112.3, 49.6, 49.2, 46.2, 44.8, 44.0, 43.4, 28.9, 26.7, 24.5, 22.6, 9.2, 8.9; *m/z* (C.I.) 484 (100 %, M + H$^+$); (Found: M$^+$, 483.7412. $C_{30}H_{49}N_3O_2$ requires 483.7408).

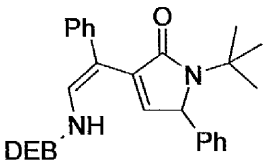
_N_-[2-(1-*tert*-Butyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)propenyl]-2,2-dimethylpropionamide 186



1-(2,2-Diethylbutyryl)-4-methyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **171** (0.15 g, 0.38 mmol, 1.0 equiv.) was treated according to **Method D** and quenched with saturated aqueous ammonium chloride. Purification by column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.088 g, 59 %) as a colourless

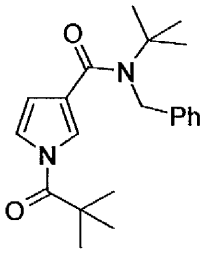
oil: R_f(6:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 3472 (NH), 2967 (CH), 1650, 1638 (C=O); δ_H(300 MHz, $CDCl_3$) 12.2 (1H, d, *J* 10.5, N*H*), 7.13-7.28 (5H, m, Ar*H*), 6.88 (1H, d, *J* 10.5, C*H*NH), 6.43 (1H, d, *J* 2.5, C*H*CHPh), 5.23 (1H, d, *J* 2.5, CHC*H*Ph), 1.76 (3H, s, CH_3), 1.63 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.33 (9H, s. *t*Bu), 0.76 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.6, 144.3, 141.3, 138.2, 130.1, 129.1, 128.0, 126.4, 124.8, 104.8, 65.8, 56.3, 49.9, 28.1, 25.9, 21.1, 8.4; *m/z* (C.I.) 397 (100 %, M + H^+); (Found: M^+, 396.2770. $C_{25}H_{36}N_2O_2$ requires 396.2776).

_N_-[2-(1-*tert*-Butyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)-2-phenylvinyl]-2,2-dimethylpropionamide 187



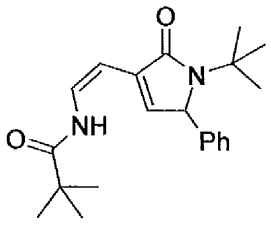
1-(2,2-Diethylbutyryl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **172** (0.15 g, 0.33 mmol, 1.0 equiv.) was treated according to **Method D** and quenched with saturated aqueous ammonium chloride. Purification by column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.113 g, 75 %) as a colourless oil: R_f(6:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 3584 (NH), 2966 (CH), 1655, 1627 (C=O); δ_H(300 MHz, $CDCl_3$) 12.0 (1H, d, *J* 10.0, N*H*), 7.28 (1H, d, *J* 10.0, C*H*NH), 7.10-7.26 (10H, m, Ar*H*), 6.25 (1H, d, *J* 2.5, C*H*CHPh), 5.22 (1H, d, *J* 2.5, CHC*H*Ph), 1.68 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.39 (9H, s. *t*Bu), 0.83 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.9, 168.2, 144.5, 137.7, 136.1, 129.5, 129.1, 128.9, 128.2, 128.1, 127.8, 126.7, 126.4, 125.9, 65.9, 56.4, 50.1, 28.2, 26.0, 8.4; *m/z* (C.I.) 459 (100 %, M + H^+); (Found: M^+, 458.2929. $C_{30}H_{38}N_2O_2$ requires 458.2776).

1-(2,2-Dimethylpropionyl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 188



1*H*-Pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **162** (0.40 g, 1.56 mmol, 1.0 equiv.) in THF (5 mL) was slowly added to a suspension of sodium hydride (0.19 g, 4.69 mmol, 3.0 equiv.) in THF (5 mL) at room temperature and the mixture stirred for 30 min. A solution of 2,2-dimethyl-propionyl chloride (0.25 g, 2.11 mmol, 1.35 equiv.) in THF (5 mL) was added dropwise and the reaction stirred at room temperature for 18 h. The mixture was diluted with water (3 mL) and extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with water (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) to afford the *title compound* (0.34 g, 68 %) as a white solid: m.p. 98.4-98.9 °C; R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2962 (CH), 1709, 1625 (C=O); δ_H(300 MHz, $CDCl_3$) 7.57 (1H, dd, *J* 4.5 and 2.5, *H*-5), 7.42 (1H, dd, *J* 4.5 and 2.5, *H*-2), 7.29-7.40 (5H, m, Ar*H*), 6.44 (1H, dd, *J* 4.5 and 2.5, *H*-4), 4.84 (2H, s, CH_2), 1.78 (9H, s, *t*Bu), 1.24 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$)164.2, 141.1, 129.1, 127.2, 126.1, 125.0, 121.0, 112.3, 58.3, 51.5, 28.7, 28.4; *m/z* (C.I.) 341 (100 %, $M + H^+$); (Found: M^+, 340. 2149. $C_{21}H_{28}N_2O_2$ requires 340.2150).

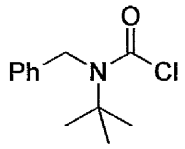
***N*-[2-(1-*tert*-Butyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)vinyl]-2,2-dimethylpropionamide 189**



1-(2,2-Dimethyl-propionyl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **188** (0.20 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method G** with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (28.0 mg, 14 %) as a yellow oil:

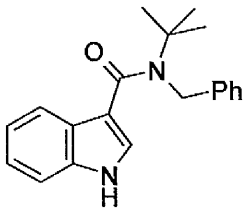
R_f(10:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 3429 (NH), 2968 (CH), 1686, 1643 (C=O); δ_H(300 MHz, $CDCl_3$) 12.25 (1H, d, *J* 10.0, N*H*), 7.26-7.38 (3H, m, Ar*H*), 7.19 (2H, d, *J* 4.5, Ar*H*), 6.88 (1H, t, *J* 10.0, C*H*NH), 6.44 (1H, d, *J* 2.5, C*H*CHPh), 5.24 (1H, d, *J* 2.5, C*H*Ph), 5.10 (1H, d, *J* 10.0, *H*C=CHNH), 1.39 (9H, s, *t*Bu), 1.30 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 177.3, 172.6, 142.2, 138.3, 131.6, 129.3, 128.7, 128.3, 126.8, 126.6, 126.1, 98.8, 66.1, 56.5, 39.5, 28.4, 27.6; *m/z* (C.I.) 341 (100 %, $M + H^+$); (Found: M^+, 340. 2149. $C_{21}H_{28}N_2O_2$ requires 340.2150).

N-tert-butyl-_N_-benzyl carbamoyl chloride 191[189]



N-benzyl *tert*-butylamine (2.28 mL, 12 mmol, 1.0 equiv.) and triethylamine (1.48 mL, 11 mmol, 0.87 equiv.) were added dropwise to a stirring solution of diphosgene (0.86 mL, 7.12 mmol, 0.57 equiv.) in toluene (20 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 h before refluxing (110 °C) overnight (16 h). After cooling to room temperature the slurry was poured onto 1M HCl (20 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the *title compound* (2.60 g, 97 %) as an off-white solid: m.p. 85.4-87.8 °C (lit.,[189] 85-89 °C); R_f(5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1648 (C=O); δ_H(300 MHz, $CDCl_3$) 7.24-7.27 (2H, m, Ar*H*), 7.18-7.20 (3H, m, Ar*H*), 4.79 (2H, s, CH_2), 1.35 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 164.3, 137.8, 128.6, 127.2, 125.8, 52.3, 48.1, 28.3; *m/z* (C.I.) 190 (80 %, M^+-Cl).

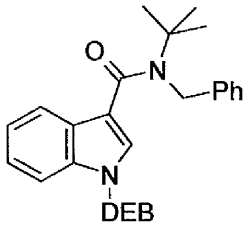
1*H*-Indole-3-carboxylic acid benzyl-*tert*-butylamide 192



A solution of indole (0.21 g, 1.77 mmol, 2.0 equiv.) in benzene (2.5 mL) was added dropwise to a stirring solution of methyl magnesium iodide (0.60 mL of 3 M solution in

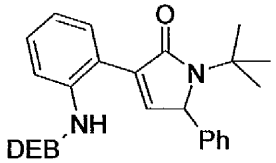
diethyl ether, 2.0 equiv.) in benzene (2.5 mL) at room temperature under a nitrogen atmosphere. The reaction was stirred for 10 min and a solution of *N*-*tert*-butyl-*N*-benzyl carbamoyl chloride **191** (0.20 g, 0.88 mmol, 1.0 equiv.) in benzene (2 mL) added dropwise. The mixture was heated under reflux for 67 h and cooled to room temperature. EtOAc (5 mL) was added and the layers separated. The combined organic layers were washed with water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO_2; 3:1 Petrol/EtOAc) afforded the *title compound* (0.19 g, 65 %) as a white solid: m.p. 216-217 °C; R_f(2:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3387 (NH), 2963 (CH), 1654 (C=O); δ_H(300 MHz, $CDCl_3$) 8.22 (1H, brs, N*H*), 7.82 (1H, m, *H*-4), 7.16-7.33 (9H, m, Ar*H*), 4.80 (2H, s, CH_2), 1.42 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 154.3, 129.8, 129.5, 129.1, 128.8, 127.1, 126.7, 125.2, 123.1, 121.4, 121.0, 111.5, 51.9, 29.3; *m/z* (C.I.) 307 (100 %, M + H^+); (Found: M^+, 306.1735. $C_{20}H_{22}N_2O$ requires 306.1732).

1-(2,2-Diethylbutyryl)-1*H*-indole-3-carboxylic acid benzyl-*tert*-butylamide 193



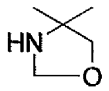
1*H*-Indole-3-carboxylic acid benzyl-*tert*-butylamide **192** (0.20 g, 0.65 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.194 g, 70 %) as a white solid: m.p. 156-157 °C; R_f(5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2928 (CH), 1720, 1604 (C=O); δ_H(300 MHz, $CDCl_3$) 8.44-8.45 (1H, m, Ar*H*), 7.87-7.88 (1H, m, Ar*H*), 7.75 (1H, s, *H*-2), 7.31-7.45 (7H, m, Ar*H*), 4.82 (2H, s, CH_2Ph), 1.62 (6H, q, *J* 7.5, 3 × CH_2CH$_3$), 1.30 (9H, s, *t*Bu), 0.86 (9H, t, *J* 7.5, 3 × CH$_2$CH_3); δ_C(75 MHz, $CDCl_3$) 183.5, 176.6, 140.9, 129.2, 127.4, 125.9, 125.8, 124.3, 122.8, 120.7, 118.5, 117.3, 58.7, 51.4, 50.1, 28.9, 26.2, 8.5; *m/z* (C.I.) 433 (100 %, M + H^+); (Found: M^+, 432.2768. $C_{28}H_{36}N_2O_2$ requires 432.2776).

N-[2-(1-*tert*-Butyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)phenyl]-2,2-dimethylpropionamide 194



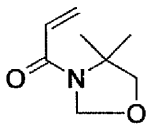
1-(2,2-Diethylbutyryl)-1*H*-indole-3-carboxylic acid benzyl-*tert*-butylamide **193** (0.15 g, 0.35 mmol, 1.0 equiv.) was treated according to **Method G** with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.114 g, 76 %) as a yellow oil: R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 3277 (NH), 2967 (CH), 1662, 1577 (C=O); δ_H(300 MHz, $CDCl_3$) 10.1 (1H, s, N*H*), 7.86 (1H, d, *J* 8.0, Ar*H*), 7.16-7.37 (7H, m, Ar*H*), 7.08 (1H, t, *J* 7.0, Ar*H*), 6.84 (1H, d, *J* 2.0, C*H*CHPh), 5.37 (1H, d, *J* 2.0, CHC*H*Ph), 1.71 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.44 (9H, s, *t*Bu), 0.88 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.5, 172.7, 145.9, 137.6, 137.1, 136.5, 130.5, 129.5, 129.4, 128.5, 126.6, 125.9, 125.3, 124.9, 66.2, 56.7, 50.4, 28.7, 28.4, 26.4, 8.6; *m/z* (C.I.) 433 (100 %, M + H^+); (Found: M^+, 432.2785. $C_{28}H_{36}N_2O_2$ requires 432.2776).

4,4-dimethyloxazolidine 195[190]



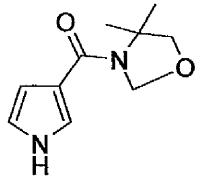
Paraformaldehyde (4.04 g, 0.13 mol, 1.2 equiv.) and 2-amino-2-methyl-1-propanol (10 g, 0.11 mol, 1.0 equiv.) were dissolved in benzene (120 mL). The mixture was heated at reflux (using Dean-Stark apparatus) for 20 h and the solvent removed under reduced pressure. Purification by fractional distillation (120 °C) afforded the *title compound* (8.34 g, 74 %) as a colourless oil: b.p. 123 °C (lit.,[190] 124-125 °C) ; R_f(1:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 3460 (NH); δ_H(300 MHz, $CDCl_3$) 4.45 (2H, s, *H*-2), 3.32 (2H, s, *H*-4), 1.19 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 84.8, 80.7, 60.1, 25.4; *m/z* (C.I.) 102 (100 %, M + H^+); (Found: M^+, 101.0846. $C_5H_{11}NO$ requires 101.0841).

1-(4, 4-Dimethyloxazolidin-3-yl)propenone 196



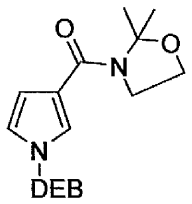
4,4-Dimethyloxazolidine **195** (7.92 mL, 55.5 mmol, 2.2 equiv.) and acryloyl chloride (2.0 mL, 25.2 mmol, 1.0 equiv.) were treated according to **Method A**. Purification by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) afforded the *title compound* (1.62 g, 49 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.30; ν_{max} ($CHCl_3$)/cm^{-1} 2861 (CH), 1656 (C=O); δ_H(300 MHz, $CDCl_3$) 6.32 (1H, d, *J* 17.0, CH_AH$_B$), 6.08 (1H, dd, *J* 17.0 and 10.5, C*H*), 5.65 (1H, d, *J* 10.5, CH$_A$$H_B$), 5.04 (2H, s, OC$H_2$N), 3.75 (2H, s, OC$H_2$C), 1.44 (6H, s, 2 × C$H_3$); δ_C(75 MHz, $CDCl_3$) 164.4 ,129.1, 127.7, 81.5, 80.3, 59.7, 23.1; *m/z* (C.I.) 156 (100 %, M + H^+); (Found: M^+, 155. 0946. $C_8H_{13}NO_2$ requires 155.0946).

(4,4-Dimethyloxazolidin-3-yl)-(1*H*-pyrrol-3-yl)methanone 197



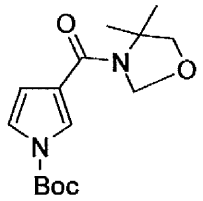
1-(4,4-Dimethyl-oxazolidin-3-yl)propenone **196** (1.0 g, 6.45 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 4:1 Petrol/EtOAc) to afford the *title compound* (2.0 g, 86 %) as an off-white solid: m.p. 107.2-108 °C; R_f(1:1 Petrol:EtOAc) 0.30; ν_{max}($CHCl_3$)/cm^{-1} 3176 (NH), 1621 (C=O); δ_H(300 MHz, $CDCl_3$) 10.18 (1H, brs, N*H*), 7.12 (1H, dd, *J* 5.0 and 2.5, *H*-5), 6.71 (1H, dd, *J* 5.0 and 2.5, *H*-2), 6.38 (1H, dd, *J* 5.0 and 2.5, *H*-4), 5.20 (2H, s, NCH_2O), 3.80 (2H, s, OCH_2C), 1.60 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 140.4, 128.7, 126.9, 125.7, 110.28, 110.25, 58.3, 50.9, 28.4; *m/z* (C.I.) 195 (100 %, M + H^+); (Found: M^+, 194.1053. $C_{10}H_{14}N_2O_2$ requires 194.1055).

1-[3-(2,2-Dimethyloxazolidine-3-carbonyl)-pyrrol-1-yl]-2,2-diethylbutan-1-one 198



(4,4-Dimethyloxazolidin-3-yl)-(1*H*-pyrrol-3-yl)methanone **197** (0.74 g, 3.81 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.94 g, 77 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2969, 2341 (CH), 1710, 1630 (C=O); δ_H(300 MHz, $CDCl_3$) 7.82 (1H, dd, *J* 4.5 and 2.5, *H*-2), 7.43 (1H, dd, *J* 4.5 and 2.5, *H*-5), 6.45 (1H, dd, *J* 4.5 and 2.5, *H*-4), 5.20 (2H, s, CH_2O), 3.84 (2H, s, NCH_2), 1.84 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.62 (6H, s, 2 × CH_3), 0.82 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.4, 161.8, 123.8, 122.2, 120.8, 111.5, 81.3, 80.7, 60.9, 52.9, 27.1, 23.6, 8.6; *m/z* (C.I.) 321 (100 %, M + H^+); (Found: M^+, 320.2103. $C_{18}H_{28}N_2O_3$ requires 320.2099).

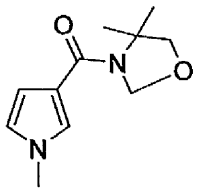
3-(4,4-Dimethyloxazolidine-3-carbonyl)-pyrrole-1-carboxylic acid *tert*-butyl ester 199



DMAP (0.016 g, 0.125 mmol, 0.1 equiv.) and di-*tert*-butyldicarbonate (0.33 g, 1.49 mmol, 1.0 equiv.) were added to a stirred solution of (4,4-dimethyloxazolidin-3-yl)-(1H-pyrrol-3-yl)methanone **197** (0.32 g, 1.65 mmol, 1.1 equiv.) in acetonitrile (4 mL) at room temperature under nitrogen. The mixture was stirred for 24 h and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; Petrol) to afford the *title compound* (0.265 g, 81 %) as a yellow oil: R_f(100 % Petrol) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2978 (CH), 1750 (C=O), 1631 (C=O); δ_H(300 MHz, $CDCl_3$) 7.54 (1H, dd, *J* 1.5 and 1.0, *H*-2), 7.22 (1H, dd, *J* 1.5 and 1.0, *H*-5), 6.46 (1H, dd, *J* 1.5 and 1.0, *H*-4), 5.16 (2H, s, OCH_2N), 3.81 (2H, s, OCH_2C), 1.60 (9H, s, *t*Bu), 1.58 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 123.8, 121.3, 120.0, 111.4,

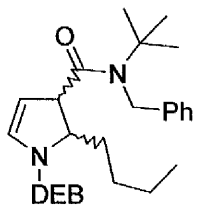
84.7, 80.9, 80.5, 60.4, 27.8, 23.3; *m/z* (C.I.) 295 (100 %, M + H^+); (Found: M^+, 294.1580. $C_{15}H_{22}N_2O_4$ requires 294.1579).

(4,4-Dimethyloxazolidin-3-yl)-(1-methyl-1*H*-pyrrol-3-yl)methanone 200



Attempted cyclisation of 3-(4,4-dimethyloxazolidine-3-carbonyl)-pyrrole-1-carboxylic acid *tert*-butyl ester **199** (0.15 g, 0.51 mmol, 1.0 equiv.) using **Method D** afforded the *title compound* (99.6 mg, 73 %) as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.30; $\nu_{max}(CHCl_3)/cm^{-1}$ 2934, 2859 (CH), 1635 (C=O); δ_H(300 MHz, $CDCl_3$) 7.04 (1H, brs, *H*-2), 6.56 (1H, dd, *J* 5.0 and 2.0, *H*-5), 6.33 (1H, dd, *J* 5.0 and 2.0, *H*-4), 5.20 (2H, s, OCH_2N), 3.81 (2H, s, OCH_2C), 3.64 (3H, s, NCH_3), 1.68 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 162.2, 124.8, 120.7, 108.5, 81.0, 80.5, 60.3, 47.8, 36.3, 23.3, 22.1; *m/z* (C.I.) 209 (100 %, M + H^+); (Found: M^+, 208.1211 $C_{11}H_{16}N_2O_2$ requires 208.1217).

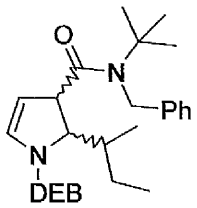
2-Butyl-1-(2,2-diethylbutyryl)-2,3-dihydro-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 201



n-Butyllithium (0.74 mL of a 1.6 M solution in hexane, 1.18 mmol, 3.0 equiv.) was added dropwise to a stirred solution of 1-(2,2-diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **170** (0.15 g, 0.39 mmol, 1.0 equiv.) in THF (5 mL) at –78 °C, under a nitrogen atmosphere. The mixture was stirred at –78 °C for 3 h and quenched by the addition of saturated aqueous ammonium chloride solution (3 mL). After 10 min water (5 mL) was added and the mixture extracted with EtOAC (4 × 5 mL). Combined organic layers were washed with water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) to afford the *title compound* (0.06 g, 40 %) as needles: m.p. 121.8-122.5 °C; R_f(5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2963

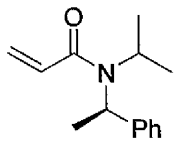
(CH), 1723, 1638 (C=O); δ_H(300 MHz, $CDCl_3$) 7.21-7.41 (5H, m, Ar*H*), 6.87 (1H, dd, *J* 2.5 and 1.5, *H*-4), 5.28 (1H, dd, *J* 2.5 and 1.5, *H*-5), 4.83 (1H, m, *H*-2), 4.60 (2H, s, CH_2Ph), 3.92 (1H, dd, *J* 2.5 and 1.5, *H*-3), 1.60 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.45 (9H, s, *t*Bu), 0.85-0.88 (9H, m, *n*Bu), 0.78 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 200.2, 176.9, 175.7, 172.4, 139.5, 129.1, 129.0, 128.9, 127.4, 126.3, 125.7, 120.3, 112.7, 58.7, 50.5, 49.6, 49.0, 44.1, 40.4, 33.2, 28.9, 26.5, 22.7, 14.2, 8.6; *m/z* (C.I.) 441 (100 %, M + H^+); (Found: M^+, 440.3381. $C_{28}H_{44}N_2O_2$ requires 440.3402).

2-*sec*-Butyl-1-(2,2-diethylbutyryl)-2,3-dihydro-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide 202



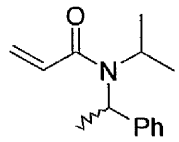
sec-Butyllithium (2.0 mL of a 1.18 M solution in hexane, 2.36 mmol, 3.0 equiv.) was added dropwise to a stirred solution of 1-(2,2-diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-*tert*-butylamide **170** (0.30 g, 0.78 mmol, 1.0 equiv.) in THF (10 mL) at –78 °C, under a nitrogen atmosphere. The mixture was stirred at –78 °C for 3 h and quenched by the addition of saturated aqueous ammonium chloride solution (3 mL). After 10 min water (5 mL) was added and the mixture extracted with EtOAC (4 × 5 mL). Combined organic layers were washed with water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) to afford the *title compound* (0.12 g, 40 %) as needles: m.p. 126.4-127.0 °C; R_f(5:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1645, 1614 (C=O); δ_H(300 MHz, $CDCl_3$) 7.21-7.41 (5H, m, Ar*H*), 6.84 (1H, dd, *J* 2.5 and 1.5, *H*-4), 5.42 (1H, dd, *J* 2.5 and 1.5, *H*-5), 5.05 (1H, dd, *J* 9.5 and 1.5, *H*-3), 4.60 (2H, d, *J* 4.0, CH_2Ph), 4.40-4.41 (1H, m, *H*-2), 1.62 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.45 (9H, s, *t*Bu), 0.98-1.02 (7H, m, *s*Bu), 0.85-0.87 (2H, m, *s*Bu), 0.78 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 174.4, 172.2, 139.0, 129.8, 129.1, 127.5, 125.8, 114.3, 65.5, 58.5, 51.6, 50.9, 49.9, 48.6, 38.9, 29.2, 28.7, 28.5, 26.2, 15.2, 13.0, 8.8; *m/z* (C.I.) 441 (100 %, M + H^+); (Found: M^+, 440.3400. $C_{28}H_{44}N_2O_2$ requires 440.3402).

(*R*)-*N*-Isopropyl-*N*-(1-phenylethyl)acrylamide 206



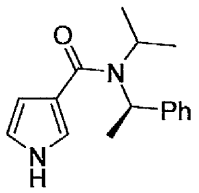
(*R*)-Isopropyl-(1-phenylethyl)amine (3.0 g, 15.1 mmol, 2.2 equiv.) was treated according to **Method A** to afford the *title compound* (1.27 g, 85 %) as a colourless oil: $[\alpha]_D^{22}$ = +392.4 (c = 0.98 in $CHCl_3$), R_f(1:1 Petrol:EtOAc) 0.90; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972 (CH), 1643 (C=O); δ_H(300 MHz, $CDCl_3$) 7.26-7.37 (5H, m, Ar*H*), 6.52 (1H, brs, C*H*), 6.32 (1H, brd, *J* 16.5, C*H*), 5.59 (1H, brs, C*H*CH_3Ph), 5.02 (1H, brs, C*H*), 3.78 (1H, brs, C*H*$(CH_3)_2$), 1.68 (3H, d, *J* 7.0, CH_3), 1.39 (3H, d, *J* 7.0, CH_3), 1.12 (3H, d, *J* 7.0, CH_3); δ_C(75 MHz, $CDCl_3$) 166.6, 141.2, 130.7, 129.5, 128.5, 127.8, 127.3, 126.6, 56.4, 53.5, 47.1; *m/z* (C.I.) 218 (100 %, M + H^+); (Found: M^+, 217.1462. $C_{14}H_{19}NO$ requires 217.1466).

(±)-*N*-Isopropyl-*N*-(1-phenylethyl)acrylamide (±)-206



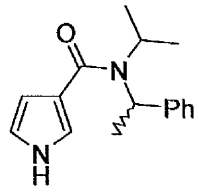
(±)-Isopropyl-(1-phenylethyl)amine (3.50 g, 17.6 mmol, 2.2 equiv.) was treated according to **Method A** to afford the *title compound* (1.16 g, 67 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.90; $\nu_{max}(CHCl_3)/cm^{-1}$ 2973 (CH), 1645 (C=O); δ_H(300 MHz, $CDCl_3$) 7.26-7.37 (5H, m, Ar*H*), 6.52 (1H, brs, C*H*CH_2), 6.32 (1H, brd, *J* 16.5, C$H_A$$H_B$), 5.59 (1H, brs, C*H*$(CH_3)$Ph), 5.02 (1H, brs, C$H_A$$H_B$), 3.88 (1H, brs, C*H*$(CH_3)_2$), 1.68 (3H, d, *J* 7.0, CH_3), 1.39 (3H, d, *J* 7.0, CH_3), 1.12 (3H, d, *J* 7.0, CH_3); δ_C(75 MHz, $CDCl_3$) 166.8, 141.4, 130.9, 129.6, 128.6, 127.9, 127.5, 126.8, 53.7, 47.1, 21.1; *m/z* (C.I.) 218 (100 %, M + H^+); (Found: M^+, 217.1469. $C_{14}H_{19}NO$ requires 217.1466).

(*R*)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl)amide 207



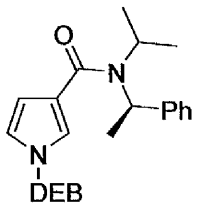
(*R*)-*N*-Isopropyl-*N*-(1-phenylethyl)acrylamide **206** (0.91 g, 4.19 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) to afford the *title compound* (0.80 g, 75 %) as a white solid: $[\alpha]_D^{22}$ = +245.6 (c = 0.62 in $CHCl_3$); m.p. 144.6 °C; R_f (1:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3190 (NH), 2968 (CH), 1592 (C=O); δ_H(300 MHz, $CDCl_3$) 9.45 (1H, brs, N*H*), 7.29-7.44 (5H, m, Ar*H*), 7.09 (1H, dd, *J* 4.5 and 2.5, *H*-5), 6.68 (1H, dd, *J* 4.5 and 2.5, *H*-2), 6.42 (1H, dd, *J* 4.5 and 2.5, *H*-4), 5.42 (1H, brq, C*H*CH_3Ph), 3.63 (1H, brs, C*H*$(CH_3)_2$), 1.76 (3H, d, *J* 7.0, C*H*$_3$), 1.49 (3H, d, *J* 7.0, C*H*$_3$), 1.23 (3H, d, *J* 7.0, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 168.4, 128.5, 127.5, 127.3, 120.8, 120.6, 118.2, 108.2, 48.8, 21. 7, 21.9, 18.4; *m/z* (C.I.) 257 (100 %, M + H^+); (Found: M^+, 256.1576. $C_{16}H_{20}N_2O$ requires 256.1575).

(±)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl)amide (±)-207



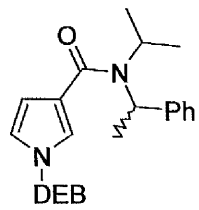
(±)-*N*-Isopropyl-*N*-(1-phenylethyl)acrylamide **206** (1.16 g, 5.35 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) to afford the *title compound* (0.74 g, 54 %) as a white solid: m.p. 144.6-145.2 °C; R_f(1:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3208 (NH), 2969 (CH), 1592 (C=O); δ_H(300 MHz, $CDCl_3$) 9.05 (1H, brs, N*H*), 7.24-7.42 (5H, m, Ar*H*), 7.11 (1H, dd, *J* 4.5 and 2.5, *H*-5), 6.70 (1H, dd, *J* 4.5 and 2.5, *H*-2), 6.40 (1H, dd, *J* 4.5 and 2.5, *H*-4), 5.45 (1H, brs, C*H*(CH_3)Ph), 3.63 (1H, brs, C*H*$(CH_3)_2$), 1.73 (3H, d, *J* 7.0, CH(C*H*$_3$)Ph), 1.46 (3H, d, *J* 7.0, C*H*$_3$), 1.21 (3H, d, *J* 7.0, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 174.6, 144.9, 132.2, 128.6, 128.0, 127.6, 127.1, 126.7, 120.4, 119.9, 70.8, 48.0, 46.6, 21.6, 21.0, 20.4; *m/z* (C.I.) 257 (100 %, M + H^+); (Found: M^+, 256.1575. $C_{16}H_{20}N_2O$ requires 256.1575).

(*R*)-1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl)amide 208



(*R*)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl)amide **207** (0.80 g, 3.13 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.82 g, 69 %) as a colourless oil: $[\alpha]_D^{22}$ = +102.4 (c = 0.26 in $CHCl_3$); R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2970 (CH), 1708, 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.79 (1H, s, *H*-2), 7.46 (1H, dd, *J* 3.5 and 1.5, *H*-5), 7.30-7.40 (5H, m, Ar*H*), 6.46 (1H, dd, *J* 3.5 and 1.5, *H*-4), 5.35 (1H, brs, C*H*CH_3), 3.5 (1H, brs, C*H*$(CH_3)_2$), 1.80 (6H, q, *J* 7.5, 3 × C*H*$_2CH_3$), 1.78 (3H, d, *J* 7.0, C*H*$_3$), 1.49 (3H, d, *J* 7.0, C*H*$_3$), 1.23 (3H, d, *J* 7.0, C*H*$_3$), 0.89 (9H, t, *J* 7.5, 3 × CH_2C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 175.3, 171.4, 166.5, 128.6, 127.5, 127.4, 124.5, 121.0, 120.6, 111.6, 60.6, 52.8, 48.9, 27.1, 21.5, 8.6; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2621. $C_{24}H_{34}N_2O_2$ requires 382.2620).

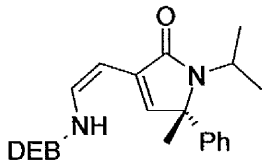
(±)-1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl) amide (±)-208



(±)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl)amide **207** (0.74 g, 2.87 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.82 g, 75 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.60; ν_{max} $(CHCl_3)/cm^{-1}$ 2970 (CH), 1707, 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.79 (1H, s, *H*-2), 7.42 (1H, dd, *J* 3.5 and 1.5, *H*-5), 7.30-7.38 (5H, m, Ar*H*), 6.42 (1H, dd, *J* 3.5 and 1.5, *H*-4), 5.30 (1H, brs, C*H*(CH_3)Ph), 3.53 (1H, brs, C*H*$(CH_3)_2$), 1.82 (6H, q, *J* 7.5, 3 × C*H*$_2CH_3$), 1.73 (3H, d, *J* 7.0, CH(C*H*$_3$)Ph), 1.47 (3H, d, *J* 7.0, C*H*$_3$), 1.21 (3H, d, *J* 7.0, C*H*$_3$), 0.80 (9H, t, *J* 7.5, 3 × CH_2C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 175.3, 171.4, 166.5, 141.1, 128.6, 127.5, 127.4, 124.2,

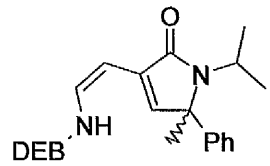
121.0, 120.5, 111.5, 52.8, 48.9, 27.0, 21.5, 8.6; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2623. $C_{24}H_{34}N_2O_2$ requires 382.2620).

(*R*)-2,2-Diethyl-*N*-[2-(1-isopropy-5-methyl-2-oxo-5-phenyl-2,5-dihydo-1*H*-pyrrol-3-yl)-vinyl]butyramide 209



(*R*)-1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl) amide **208** (0.15 g, 0.39 mmol, 1.0 equiv.) was treated according to **Method D** and quenched with saturated aqueous ammonium chloride. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.13 g, 87 %) as a colourless oil: $[\alpha]_D^{22}$ = –229.6 (c = 0.57 in $CHCl_3$); R_f(3:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 3334 (NH), 2969 (CH), 1683, 1641 (C=O); δ_H(300 MHz, $CDCl_3$) 12.25 (1H, d, *J* 10.0, N*H*), 7.24-7.39 (5H, m, Ar*H*), 7.02 (1H, t, *J* 10.0, C*H*NH), 6.54 (1H, s, C*H*C(CH_3)Ph), 5.15 (1H, d, *J* 10.0, C*H*CHNH), 3.32 (1H, qq, *J* 6.5, C*H*C(CH_3)$_2$), 1.80 (3H, s, CH(C*H*$_3$)Ph), 1.72 (6H, q, *J* 7.5, 3 × C*H*$_2$CH$_3$), 1.40 (3H, d, *J* 6.5, C(C*H*$_3$)$_2$), 1.23 (3H, d, *J* 6.5, C(C*H*$_3$)$_2$), 0.83 (9H, t, *J* 7.5, 3 × CH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 176.1, 170.3, 147.1, 138.0, 134.5, 128.8, 128.4, 126.7, 126.1, 98.5, 68.5, 50.2, 46.0, 26.0, 21.3, 8.6; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2618. $C_{24}H_{34}N_2O_2$ requires 382.2620).

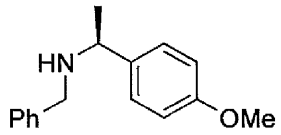
(±)-2,2-Diethyl-*N*-[2-(1-isopropy-5-methyl-2-oxo-5-phenyl-2,5-dihydo-1*H*-pyrrol-3-yl)-vinyl]butyramide (±)-209



(±)-1-(2,2-Diethylbutyryl)1*H*-pyrrole-3-carboxylic acid isopropyl-(1-phenylethyl)amide **208** (0.15 g, 0.39 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride quench. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 73 %) as a colourless oil: R_f(3:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 3191 (NH), 2969 (CH), 1684, 1642 (C=O); δ_H(300 MHz, $CDCl_3$) 12.22 (1H, d, *J* 10.0, N*H*), 7.26-7.36 (5H, m, Ar*H*), 7.01 (1H, t, *J*

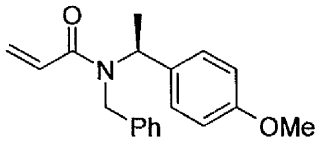
10.0, C*H*NH), 6.51 (1H, s, C*H*C(CH_3)Ph), 5.12 (1H, d, *J* 10.0, C*H*CHNH), 3.30 (1H, qq, *J* 6.5, C*H*C(CH_3)$_2$), 1.78 (3H, s, C(CH_3)Ph), 1.69 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.38 (3H, d, *J* 6.5, CH(CH_3)$_2$), 1.20 (3H, d, *J* 6.5, CH(CH_3)$_2$), 0.81 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.1, 170.3, 147.1, 138.0, 134.5, 128.8, 128.4, 126.8, 126.1, 98.5, 68.5, 50.2, 46.0, 26.0, 21.4, 8.6; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2619. $C_{24}H_{34}N_2O_2$ requires 382.2620).

(*S*)-Benzyl-[1-(4-methoxyphenyl)-ethyl]amine 211[191]



A mixture of (*S*)-(-)-1-(4-methoxyphenyl) ethylamine (0.50 g, 3.31 mmol, 1.0 equiv.) and benzaldehyde (0.34 mL, 3.31 mmol, 1.0 equiv.) in methanol (10 mL) was stirred over 4 Å sieves for 4 h. The sieves were removed by filtration and washed with methanol (5 mL). Sodium borohydride (0.13 g, 3.31 mmol, 1.0 equiv.) was added portion wise and the mixture stirred at room temperature, under a nitrogen atmosphere, for 16 h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL). The organic layer was washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* (0.78 g, 98 %) as a colourless oil: $[\alpha]_D^{20}$ = -64.0 (c = 0.171 in $CHCl_3$); R_f(6:1 Petrol:EtOAc) 0.40; ν_{max} ($CHCl_3$)/cm^{-1} 3289 (NH), 2958 (CH); δ_H(300 MHz, $CDCl_3$) 7.30-7.41 (7H, m, Ar*H*), 6.96 (2H, d, *J* 8.5, Ar*H*), 3.87 (3H, s, OCH_3), 3.84 (1H, q, *J* 6.5, C*H*CH_3), 3.68 (1H, d, *J* 9.5, CH_AH_BPh), 3.66 (1H, d, *J* 9.5, CH_AH_BPh), 1.95 (1H, brs, N*H*), 1.42 (3H, d, *J* 6.5, CHCH_3), δ_C(75 MHz, $CDCl_3$) 158.8, 140.9, 137.8, 128.7, 128.6, 128.4, 128.0, 127.9, 127.7, 127.2, 114.3, 65.2, 57.1, 55.5, 51.8, 24.8; *m/z* (C.I.) 242 (100 %, M + H^+); (Found: M^+, 241.1462. $C_{16}H_{19}NO$ requires 241.1466).

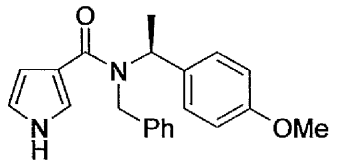
(*S*)-*N*-Benzyl-*N*-[1-(4-methoxyphenyl)-ethyl]acrylamide 212



(*S*)-Benzyl-[1-(4-methoxyphenyl)-ethyl]amine **211** (0.96 g, 3.98 mmol, 2.2 equiv.) was treated according to **Method A** to afford the *title compound* (0.49 g, 94 %) as a white solid: m.p. 84.6-85.0 °C; $[\alpha]_D^{22}$ = +207.0 (c = 0.15 in $CHCl_3$), R_f(5:1 Petrol:EtOAc)

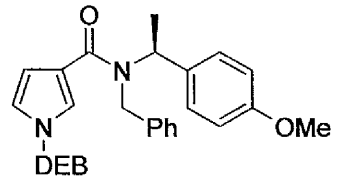
0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2974 (CH), 1647 (C=O); δ_H(300 MHz, $CDCl_3$) 7.10-7.30 (7H, m, Ar*H*), 6.85 (2H, d, *J* 8.5, Ar*H*), 6.44-6.45 (1H, dd, *J* 6.5 and 1.0, C*H*CH_2), 6.20 (1H, d, *J* 6.5, CHCH_AH_B), 5.52 (1H, d, *J* 6.5, CHCH_AH_B), 4.18 (1H, d, *J* 18.0, CH_AH_BPh), 4.17 (1H, d, *J* 18.0, CH_AH_BPh), 3.80 (4H, s, OCH_3 and C*H*CH_3), 1.46 (3H, d, *J* 6.5, CHCH_3); δ_C(75 MHz, $CDCl_3$) 167.4, 159.2, 138.8, 133.1, 129.1, 128.8, 127.7, 127.3, 126.2, 114.0, 55.5, 51.4, 46.9, 31.2, 19.4, 17.4; *m/z* (C.I.) 296 (100 %, M + H^+); (Found: M^+, 295.1575. $C_{19}H_{21}NO_2$ requires 295.1572).

1*H*-Pyrrole-3-carboxylic acid benzyl-[1-(4-methoxyphenyl)-ethyl]amide 213



(*S*)-*N*-Benzyl-*N*-[1-(4-methoxyphenyl)-ethyl]acrylamide **212** (0.49 g, 1.66 mmol, 1.0 equiv.) was treated according to **Method B.** The crude product was purified by flash column chromatography (SiO_2; 6:1 Petrol/EtOAc) to afford the *title compound* (0.39 g, 70 %) as a white solid: m.p. 72.4-72.7 °C; $[\alpha]_D^{22}$ = +78.0 (c = 0.078 in $CHCl_3$), R_f(6:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3237 (NH), 2359 (CH), 1603 (C=O); δ_H(300 MHz, $CDCl_3$) 8.75 (1H, brs, N*H*), 7.20-7.28 (7H, m, Ar*H*), 6.86 (2H, d, *J* 8.5, Ar*H*), 6.70 (1H, brs, *H*-2), 6.48 (1H, brs, *H*-5), 6.0 (1H, brs, *H*-4), 4.80 (1H, d, *J* 15.0, CH_AH_BPh), 4.05 (1H, brs, CH_AH_BPh), 3.80 (4H, brs, CH_3 and C*H*CH_3), 1.50 (3H, d, *J* 7.0, CHCH_3); δ_C(75 MHz, $CDCl_3$) 159.0, 139.8, 133.5, 128.7, 128.5, 127.2, 126.8, 125.9, 121.5, 119.4, 118.3, 114.0, 55.5, 53.7, 47.3, 18.8; *m/z* (C.I.) 335 (100 %, M + H^+); (Found: M^+, 334.1685. $C_{21}H_{22}N_2O_2$ requires 334.1681).

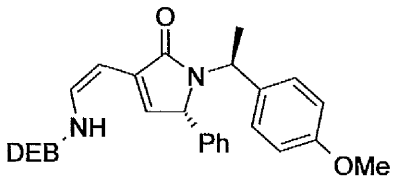
1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-[1-(4-methoxyphenyl)-ethyl]amide 214



1*H*-Pyrrole-3-carboxylic acid benzyl-[1-(4-methoxyphenyl)-ethyl]amide **213** (0.38 g, 1.14 mmol, 1.0 equiv.) was treated according to **Method E.** Purification by column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.29 g, 54 %) as a colourless oil: $[\alpha]_D^{22}$ = +73.2 (c = 0.31 in $CHCl_3$), R_f(5:1 Petrol:EtOAc) 0.60;

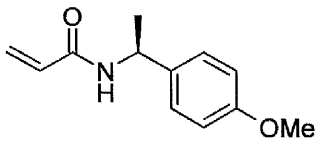
$\nu_{max}(CHCl_3)/cm^{-1}$ 2969 (CH), 1709, 1615 (C=O); δ_H(300 MHz, $CDCl_3$) 7.70 (1H, brs, *H*-2), 7.40 (1H, brs, *H*-5), 7.20-7.30 (7H, m, Ar*H*), 6.88 (2H, d, *J* 8.5, Ar*H*), 6.42 (1H, brs, *H*-4), 6.0 (1H, brs, CH_AH_BPh), 5.82 (1H, brs, CH_AH_BPh), 4.14 (1H, q, *J* 7.0, $CHCH_3$), 3.80 (3H, s, OCH_3), 1.68 (6H, brs, 3 × CH_2CH_3), 1.46 (3H, d, *J* 7.0, $CHCH_3$), 0.73 (9H, brs, 3 × CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 175.2, 171.4, 167.5, 159.2, 139.4, 133.1, 128.7, 127.1, 126.9, 122.5, 121.6, 120.6, 114.1, 112.2, 60.6, 55.5, 52.7, 26.9, 25.3, 21.3, 14.5, 8.6; *m/z* (C.I.) 461 (100 %, M + H^+); (Found: M^+, 460.2800. $C_{29}H_{36}N_2O_3$ requires 460.2726).

2,2-Diethyl-*N*-(2-{1-[1-(4-methoxyphenyl)-ethyl]-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl}-vinyl)butyramide 215



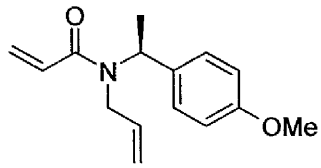
1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid benzyl-[1-(4-methoxyphenyl)-ethyl]amide **214** (0.19 g, 0.41 mmol, 1.0 equiv.) was treated according to **Method D** and **Method G** with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.084 g, 56 %) as a yellow oil: $[\alpha]_D^{22}$ = –34.7 (c = 0.27 in $CHCl_3$), R_f (5:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 3200 (NH), 2966 (CH), 1682, 1642 (C=O); δ_H(300 MHz, $CDCl_3$) 12.05 (1H, d, *J* 10.0, N*H*), 7.27 (3H, m, Ar*H*), 6.96-7.08 (6H, m, Ar*H*), 6.83 (1H, d, *J* 9.0, C*H*NH), 6.44 (1H, d, *J* 3.0, CHC*H*Ph), 5.54 (1H, q, *J* 7.0, $CHCH_3$), 5.12 (1H, d, *J* 10.0, C*H*CHNH), 4.67 (1H, d, *J* 3.0, C*H*CHPh), 3.82 (3H, s, OCH_3), 1.68 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.11 (3H, d, *J* 7.0, $CHCH_3$), 0.80 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.1, 171.6, 159.3, 141.9, 136.1, 134.4, 133.4, 132.5, 129.1, 128.9, 128.8, 128.7, 128.5, 128.1, 127.8, 126.3, 126.1, 114.0, 98.2, 64.3, 55.5, 52.1, 50.9, 50.3, 28.2, 26.1, 18.0, 8.6; *m/z* (C.I.) 461 (100 %, M + H^+); (Found: M^+, 460.2796. $C_{29}H_{36}N_2O_3$ requires 460.2726).

N-[1-(4-methoxyphenyl)-ethyl]acrylamide 219



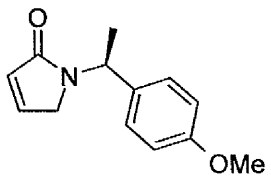
(*S*)-(-)-1-(4-Methoxyphenyl) ethylamine (10.0 g, 66.2 mmol, 2.2 equiv.) was treated according to **Method A** to afford the *title compound* (6.06 g, 98 %) as needles: m.p. 107.5 °C; $[\alpha]_D^{22}$ = –159.7 (c = 0.12 in $CHCl_3$); R_f(5:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3270 (NH), 2971 (CH), 1657 (C=O); δ_H(300 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.5, Ar*H*), 6.83 (2H, d, *J* 8.5, Ar*H*), 6.24 (1H, dd, *J* 17.5 and 1.5, C*H*$_A$H$_B$CH), 6.10 (2H, m, *J* 10.0, N*H* and CH_2CH), 5.60 (1H, dd, *J* 10.0 and 1.5 CH$_A$*H*$_B$CH), 5.15 (1H, q, *J* 7.0, C*H*CH$_3$), 3.78 (3H, s, OC*H*$_3$), 1.50 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 164.5, 158.7, 135.2, 130.9, 127.4, 126.4, 113.9, 109.9, 55.3, 48.2, 21.5; *m/z* (C.I.) 206 (100 %, M + H$^+$); Found: M$^+$, 205.1104. $C_{12}H_{15}NO_2$ requires 205.1103.

N-Allyl-N-[1-(4-methoxyphenyl)-ethyl]acrylamide 220



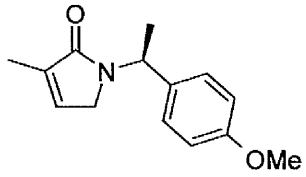
N-[1-(4-Methoxyphenyl)-ethyl]acrylamide **219** (0.25 g, 1.22 mmol, 1.0 equiv.) was treated according to **Method H**. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.142 g, 48 %) as a clear oil: $[\alpha]_D^{22}$ = –86.0 (c = 0.02 in $CHCl_3$); R_f(5:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1676 (C=O); δ_H(300 MHz, DMSO, 100 °C) 7.22 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.65 (1H, dd, *J* 16.5 and 10.5, C*H*CH$_2$), 6.18 (1H, dd, *J* 16.5 and 2.5, CHC*H*$_A$H$_B$), 5.60-5.70 (3H, m, C*H*CH$_3$ and CH$_2$CHC*H*$_2$), 5.0 (2H, m, CHCH$_A$*H*$_B$ and CH$_2$C*H*CH$_2$), 3.75 (3H, s, OC*H*$_3$), 3.60-4.0 (2H, m, C*H*$_2$CHCH$_2$), 1.48 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 158.5, 136.1, 133.0, 129.4, 128.6, 128.2, 115.9, 113.7, 55.1, 50.3, 44.8, 38.7, 16.9; *m/z* (C.I.) 246 (100 %, M + H$^+$); (Found: M$^+$, 245.1420. $C_{15}H_{19}NO_2$ requires 245.1416).

1-[1-(4-Methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one 221



Grubbs catalyst[139] (0.05 g, 0.061 mmol, 0.1 equiv.) was added portion wise to a solution of *N*-Allyl-*N*-[1-(4-methoxyphenyl)-ethyl]acrylamide **220** (0.15 g, 0.61 mmol, 1.0 equiv.) in CH_2Cl_2 (20mL) at room temperature under a nitrogen atmosphere. The solution was heated under reflux for 12 h and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 85 %) as a yellow oil: $[\alpha]_D^{22} = -122.0$ (c = 0.15 in $CHCl_3$); R_f (5:1 Petrol:EtOAc) 0.20; $\nu_{max}(CHCl_3)/cm^{-1}$ 2934 (CH), 1687 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 7.02 (1H, dd, *J* 6.0 and 1.5, CH_2CHCH), 6.85 (2H, d, *J* 8.5, Ar*H*), 6.18 (1H, dd, *J* 6.0 and 1.5, CH_2CHCH), 5.55 (1H, q, *J* 7.0, $CHCH_3$), 3.80 (3H, s, OCH_3), 3.58-4.0 (2H, dd, *J* 18.5 and 1.5, NCH_2), 1.60 (3H, d, *J* 7.5, $CHCH_3$); δ_C(75 MHz, $CDCl_3$) 171.2, 159.1, 143.0, 133.3, 128.4, 128.2, 114.2, 55.5, 48.8, 48.6, 18.4; *m/z* (C.I.) 218 (100 %, M + H^+); (Found: M^+, 217.1102. $C_{13}H_{15}NO_2$ requires 217.1103).

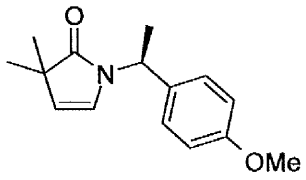
1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one 222



1-[1-(4-Methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one **221** (0.15 g, 0.7 mmol, 1.0 equiv.) and iodomethane (0.10 mL, 1.4 mmol, 2.0 equiv.) were treated according to **Method I**. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 60 %) as a yellow oil: $[\alpha]_D^{22} = -124.2$ (c = 0.15 in $CHCl_3$); R_f(1:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972 (CH), 1658 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.62 (1H, d, *J* 1.0, NCH_2CH), 5.55 (1H, q, *J* 7.0, $CHCH_3$), 3.82 (3H, s, OCH_3), 3.75 (1H, dd, 18.5 and 1.5, NCH_AH_BCH), 3.45 (1H, dd, *J* 18.5 and 1.5, NCH_AH_BCH), 1.95 (3H, s, CH_3), 1.60 (3H, d, *J* 7.0, $CHCH_3$); δ_C(75 MHz, $CDCl_3$) 171.8, 159.1, 135.8, 135.4, 133.6, 129.2, 128.4,

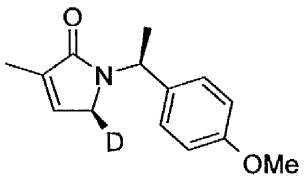
114.1, 55.5, 49.1, 46.6, 18.1, 11.6; *m/z* (C.I.) 232 (100 %, M + H^+); (Found: M^+, 231.1266. $C_{14}H_{17}NO_2$ requires 231.1259).

1-[1-(4-Methoxyphenyl)ethyl]-3,3-dimethyl-1,3-dihydropyrrol-2-one 223



n-Butyllithium (1.04 mL of a 2.0 M solution in hexane, 2.1 mmol, 3.0 equiv.) was added dropwise to a solution of diisopropylamine (0.29 mL, 2.1 mmol, 3.0 equiv.) in THF (2.5 mL) at 0 °C, under a nitrogen atmosphere. The LDA solution was stirred at 0 °C for 20 min and a solution of 1-[1-(4-methoxyphenyl)ethyl]-1,5-dihydropyrrol-2-one **221** (0.15 g, 0.69 mmol, 1.0 equiv.) in THF (2.5 mL) added dropwise. The solution was stirred at 0 °C for 3 h and quenched by the addition of iodomethane (0.26 mL, 4.14 mmol, 6.0 equiv.). The mixture was warmed to room temperature for 30 min and water (5 mL) added. The mixture was extracted with EtOAc (4 × 5 mL) and the combined organic layers washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 66 %) as a yellow oil: $[\alpha]_D^{22}$ = –126.4 (c = 0.15 in $CHCl_3$); R_f(5:1 Petrol:EtOAc) 0.25; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967 (CH), 1695 (C=O); δ_H(300 MHz, $CDCl_3$) 7.18 (2H, d, *J* 8.5, Ar*H*), 6.85 (2H, d, *J* 8.5, Ar*H*), 6.26 (1H, d, *J* 5.5, NC*H*CH), 5.35 (1H, q, *J* 7.0, C*H*CH_3), 5.30 (1H, d, *J* 5.5, NCHC*H*), 3.80 (3H, s, OCH_3), 1.55 (3H, d, *J* 7.0, CHCH_3), 1.20 (3H, s, CH_3), 1.17 (3H, s, CH_3); δ_C(75 MHz, $CDCl_3$) 182.3, 159.1, 133.3, 129.0, 128.7, 127.9, 126.8, 117.9, 114.2, 55.5, 48.7, 46.9, 26.1, 23.4, 18.9; *m/z* (C.I.) 246 (100 %, M + H^+); (Found: M^+, 245.1412. $C_{15}H_{19}NO_2$ requires 245.1416).

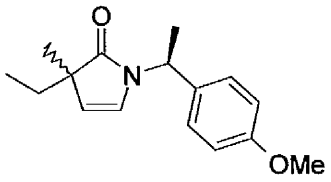
1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-5-deutero-1,5-dihydropyrrol-2-one 224



1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **222** (0.15 g, 0.65 mmol, 1.0 equiv.) and deuterium oxide (0.5 mL) were treated according according to **Method I**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc)

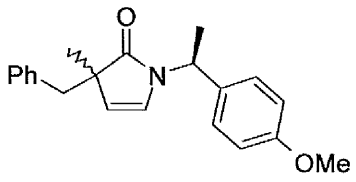
afforded the *title compound* (0.11 g, 85 %) as a colourless oil: $[\alpha]_D^{22} = -95.1$ (c = 0.12 in $CHCl_3$); R_f(3:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2973 (CH), 1668 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.65 (1H, d, *J* 2.0, NCDC*H*), 5.55 (1H, q, *J* 7.0, C*H*CH_3), 3.80 (3H, s, OCH_3), 3.65 (1H, d, *J* 8.5, NC*D*CH), 1.95 (3H, s, CH_3), 1.60 (3H, d, *J* 7.0, CHCH_3); δ_C(75 MHz, $CDCl_3$) 171.9, 159.2, 136.1, 135.5, 135.4, 133.7, 128.5, 114.2, 55.6, 49.2, 18.2, 11.7; *m/z* (C.I.) 233 (100 %, M + H^+); (Found: M^+, 232.1314. $C_{14}H_{16}NO_2D$ requires 232.1317).

3-Ethyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one 225



1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **222** (0.10 g, 0.43 mmol, 1.0 equiv.) and iodoethane (0.05 mL, 0.52 mmol, 1.2 equiv.) were treated according according to **Method I**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.065 g, 58 %) as a yellow oil in a 2:1 ratio of diastereoisomers: R_f(5:1 Petrol:EtOAc) 0.35; ν_{max} $(CHCl_3)/cm^{-1}$ 2935 (CH), 1660 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 6.92 (2H, d, *J* 8.5, Ar*H*), 6.35 (1H, d, *J* 5.0, NC*H*CH), 5.45 (1H, q, *J* 7.0, C*H*CH_3), 5.28 (1H, d, *J* 5.0, NCHC*H*), 3.85 (3H, s, OCH_3), 1.75 (2H, q, *J* 7.5, C$H_2$$CH_3$), 1.62 (3H, d, *J* 7.0, CHCH_3), 1.25 (3H, s, CH_3), 0.82 (3H, t, *J* 7.5, CH_2CH_3), 0.75 (3H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 181.9, 159.3, 133.4, 129.2, 128.9, 128.3, 128.2, 127.8, 115.8, 114.6, 114.3, 114.2, 55.6, 51.7, 48.9, 48.8, 31.6, 30.4, 22.6, 22.4, 19.2, 19.1, 9.5, 9.3; *m/z* (C.I.) 260 (100 %, M + H^+); (Found: M^+, 259.1563. $C_{16}H_{21}NO_2$ requires 259.1567).

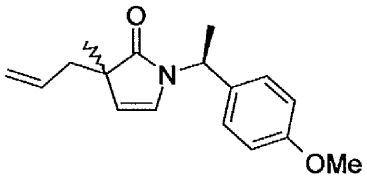
3-Benzyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one 226



1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **222** (0.10 g, 0.43 mmol, 1.0 equiv.) and benzyl bromide (0.06 mL, 0.52 mmol, 1.2 equiv.) were treated according according to **Method I**. Purification by flash column chromatography (SiO_2;

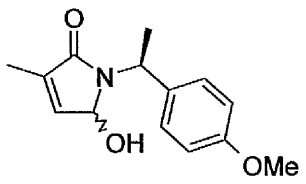
25:1 Petrol/EtOAc) afforded the *title compound* (0.098 g, 71 %) as a yellow oil in a 3:1 ratio of diastereoisomers: R_f(1:1 Petrol:EtOAc) 0.85; ν_{max} ($CHCl_3$)/cm^{-1} 2968 (CH), 1688 (C=O); δ_H(300 MHz, $CDCl_3$) 7.10-7.30 (7H, m, Ar*H*), 6.82 (2H, d, *J* 8.5, Ar*H*), 6.65 (1H, d, *J* 5.0, NC*H*CH_{major}), 6.55 (1H, d, *J* 5.0, NC*H*CH_{minor}), 6.05 (1H, d, *J* 5.0, NCHC*H*$_{major}$) 6.0 (1H, d, *J* 5.0, NCHC*H*$_{minor}$), 5.25 (1H, q, *J* 7.0, C*H*CH_3), 3.80 (3H, s, OCH_3), 3.02 (1H, dd, *J* 13.0 and 3.5, CH_AH_BPh), 2.78 (1H, d, *J* 13.0 and 4.0, CH_AH_BPh), 1.25 (3H, s, CH_3), 1.15 (3H, d, *J* 7.0, CHCH_3); δ_C(75 MHz, $CDCl_3$) 181.0, 159.2, 137.4, 133.2, 130.5, 130.4, 128.2, 128.1, 128.0, 127.8, 127.6, 126.8, 115.3, 114.3, 114.1, 55.6, 52.6, 52.5, 48.6, 48.5, 43.9, 43.6, 23.2, 22.3, 19.2, 18.5; *m/z* (C.I.) 322 (100 %, M + H^+); (Found: M^+, 321.1722. $C_{21}H_{23}NO_2$ requires 321.1723).

3-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one 227



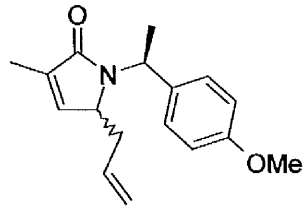
1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **222** (0.15 g, 0.65 mmol, 1.0 equiv.) and allyl bromide (0.08 mL, 0.97 mmol, 1.5 equiv.) were treated according to **Method I**. Purification by flash column chromatography (SiO_2; 30:1 Petrol/EtOAc) afforded the *title compound* (0.065 g, 58 %) as a colourless oil in a 2.5:1 ratio: R_f(5:1 Petrol:EtOAc) 0.65; ν_{max}($CHCl_3$)/cm^{-1} 2968 (CH), 1698 (C=O); δ_H(300 MHz, $CDCl_3$) 7.22 (2H, d, *J* 7.0, Ar*H*), 6.90 (2H, d, *J* 7.0, Ar*H*), 6.30 (1H, d, *J* 4.97, NC*H*CH), 5.65-5.66 (1H, m, CH_2CHCH_2), 5.40 (1H, q, *J* 7.02, C*H*CH_3), 5.28 (1H, d, *J* 5.0, NCHC*H*), 5.03-5.05 (2H, m, CH_2CHCH_2), 3.80 (3H, s, OCH_3), 2.35-2.36 (2H, m, CH_2CHCH_2), 1.58 (3H, d, *J* 7.0, CHCH_3), 1.20 (3H, s, CH_3); δ_C(75 MHz, $CDCl_3$) 181.2, 159.2, 133.7, 133.1, 128.5, 128.4, 127.7, 121.7, 115.4, 55.5, 50.8, 48.7, 41.7, 21.8, 19.1, 18.9; *m/z* (C.I.) 272 (100 %, M + H^+); (Found: M^+, 271.1560. $C_{17}H_{21}NO_2$ requires 271.1572).

5-Hydroxy-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one 228



1-[1-(4-Methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **222** (0.10 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method I** with saturated aqueous ammonium chloride quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 76 %) as a yellow oil in a 1:1 ratio of diastereoisomers: R_f(1:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 3376 (OH), 2935 (CH), 1678 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40 (2H, d, *J* 8.5, ArH_A), 7.32 (2H, d, *J* 8.5, ArH_B), 6.90 (2H, d, *J* 8.5, ArH_A), 6.85 (2H, d, *J* 8.5, ArH_B), 6.48 (1H, t, *J* 2.0, C*H*C(H)OH_A), 6.40 (1H, t, *J* 2.0, C*H*C(H)OH_B), 5.48 (1H, d, *J* 9.0, CHC(*H*)OH_A), 5.40 (1H, q, *J* 7.0, C*H*CH_{3A}), 5.22 (1H, q, *J* 7.0, C*H*CH_{3B}), 5.04 (1H, d, *J* 9.0, CHC(*H*)OH_B), 3.78 (6H, s, 2 × OCH_{3A+B}), 1.88 (6H, s, 2 × CH_{3A+B}), 1.74 (3H, d, *J* 7.0, CHCH_{3A}), 1.68 (3H, d, *J* 7.0, CHCH_{3B}); δ_C(75 MHz, $CDCl_3$) 170.6, 170.5, 159.3, 159.2, 138.5, 138.2, 137.7, 137.2, 134.7, 133.2, 129.2, 128.8, 114.5, 114.2, 81.6, 81.2, 55.7, 50.4, 50.3, 19.3, 18.4, 11.3, 11.2, 0.4; *m/z* (C.I.) 248 (100 %, M + H^+); (Found: M^+, 247.1201. $C_{14}H_{17}NO_3$ requires 247.1203).

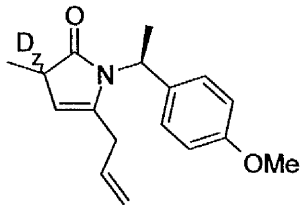
5-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one 229



3-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,3-dihydropyrrol-2-one **227** (0.11 g, 0.41 mmol, 1.0 equiv.) in xylene (7 mL) was heated under reflux for 48 h and the mixture concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.06 g, 60 %) as a colourless oil in a 2:1 mixture of diastereoisomers: $[\alpha]_D^{22}$ = –113.7 (c = 0.15 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.35; ν_{max}($CHCl_3$)/cm^{-1} 2924 (CH), 1680 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.5, Ar*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 6.55 (1H, t, *J* 2.0, C*H*CHCH_2), 5.53-5.55 (1H, m, CH_2C*H*CH_2), 5.45-5.46 (2H, m, CH_2CHCH_2), 5.06-5.08

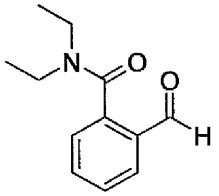
(2H, m, CH_2CHCH_2), 5.02 (1H, d, *J* 2.0, $CHCHCH_2$), 3.80 (3H, s, OCH_3), 1.94 (3H, s, CH_3), 1.70 (3H, d, *J* 7.0, $CHCH_3$); δ_C(75 MHz, $CDCl_3$) 172.6, 159.0, 140.4, 134.9, 132.9, 132.8, 128.6, 118.6, 118.5, 113.9, 59.6, 55.5, 50.7, 36.8, 18.8, 11.5; *m/z* (C.I.) 272 (100 %, $M + H^+$); (Found: M^+, 271.1567. $C_{17}H_{21}NO_2$ requires 271.1572).

5-Allyl-5-deutero-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrolo-2-one 230



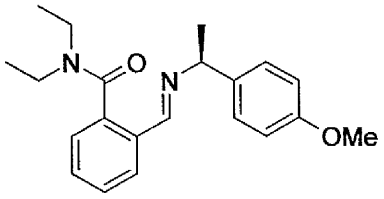
5-Allyl-1-[1-(4-methoxyphenyl)ethyl]-3-methyl-1,5-dihydropyrrol-2-one **229** (0.13 g, 0.48 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise to a suspension of sodium hydride (0.04 g, 0.72 mmol, 1.5 equiv.) in THF (5 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at 0 °C for 3 h and CD_3OD (1 mL) added dropwise. The mixture was allowed to warm to room temperature and extracted EtOAc (4 × 5 mL). The combined organics were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.13 g, 99 %) as a colourless oil in a 2.5:1 ratio of diastereoisomers: R_f(1:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2926 (CH), 1684 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.5, Ar*H*), 7.05 (1H, d, *J* 1.5, C*H*), 6.90 (2H, d, *J* 8.5, Ar*H*), 5.57-5.59 (1H, m, CH_2CHCH_2), 5.39-5.41 (2H, m, CH_2CHCH_2), 5.09-5.10 (2H, m, CH_2CHCH_2), 4.82 (1H, q, *J* 7.0, $CHCH_3$), 3.80 (3H, s, OCH_3), 1.94 (3H, s, CH_3), 1.70 (3H, d, *J* 7.0, $CHCH_3$); δ_C(75 MHz, $CDCl_3$) 169.4, 161.2, 134.8, 132.0, 128.5, 128.1, 115.9, 113.4, 113.1, 105.2, 59.8, 48.5, 39.7, 36.4, 21.3, 19.7; *m/z* (C.I.) 273 (100 %, $M-H^+$); (Found: M^+, 272.1638. $C_{17}H_{20}NO_2D$ requires 272.1635).

_N,N_-Diethyl-2-formylbenzamide 231[141]



_N,N_-Diethyl benzamide (2.0 g, 11.3 mmol, 1.0 equiv.) in THF (25 mL) was added dropwise to a solution of *sec*-butyllithium (12.3 mL of a 1.1 M solution in hexane, 13.6 mmol, 1.2 equiv.) and TMEDA (2.05 mL, 13.6 mmol, 1.2 equiv.) in THF (25 mL) at –78 °C. The solution was stirred at –78 °C for 1 h and DMF (1.74 mL, 22.6 mmol, 2.0 equiv.) added dropwise. The solution was allowed to warm to room temperature over 12 h. Water was added and the mixture extracted with EtOAc (4 × 25 mL). Combined organic layers were washed with water (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (1.41 g, 62 %) as a clear oil: R_f(1:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2947 (CH), 1664, 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 10.07 (1H, s, C*H*O), 7.98 (1H, dd, *J* 9.5 and 1.0, *H*-3), 7.65 (1H, dd, *J* 7.5 and 1.0, *H*-6), 7.55 (1H, dd, *J* 9.5 and 1.0, *H*-4), 7.38 (1H, dd, *J* 7.5 and 1.0, *H*-5), 3.62 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 3.15 (2H, q, *J* 7.0, C*H*$_2$CH$_3$), 1.30 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.05 (3H, t, *J* 7.0, CH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 193.9, 138.6, 137.5, 133.2, 131.1, 130.5, 128.5, 126.9, 43.5, 39.1, 31.2, 13.9, 12.4; *m/z* (C.I.) 206 (100 %, M + H$^+$); (Found: M$^+$, 205.1107. $C_{12}H_{15}NO_2$ requires 205.1103).

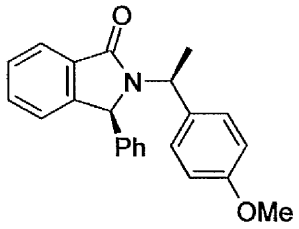
_N,N_-Diethyl-2-{[1-(4-methoxyphenyl)ethylimino]methyl}benzamide 232



A mixture of _N,N_-diethyl-2-formylbenzamide **231** (0.50 g, 2.4 mmol, 1.0 equiv.) and (*S*)-1-(4-methoxyphenyl)ethylamine (0.36 g, 2.4 mmol, 1.0 equiv.) in methanol (15 mL) was stirred at room temperature, under a nitrogen atmosphere, over 4 Å sieves for 12 h. The sieves were removed by filtration and washed with EtOAc (10 mL). Combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.83 g, 100 %) as a clear oil: $[\alpha]_D^{22}$ = +236.0 (c = 0.12 in $CHCl_3$); R_f(1:1

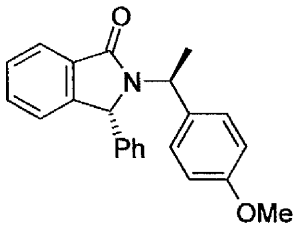
Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1667 (C=O), 1632 (C=N); δ_H(300 MHz, $CDCl_3$) 8.40 (1H, s, *H*C=N), 8.05-8.06 (1H, m, Ar*H*), 7.26-7.42 (5H, m, Ar*H*), 6.88 (2H, d, *J* 6.5, Ar*H*), 4.49 (1H, q, *J* 6.5, C*H*CH_3), 3.82 (3H, s, OCH_3), 3.60 (2H, q, *J* 7.0, CH_2CH_3), 3.08 (2H, q, *J* 7.0, CH_2CH_3), 1.56 (3H, d, *J* 6.5, $CHCH_3$), 1.26 (3H, t, *J* 7.0, CH_2CH_3), 0.98 (3H, t, *J* 7.0, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 170.0, 158.7, 156.8, 138.1, 137.2, 132.8, 130.5, 129.0, 127.9, 126.9, 126.3, 114.0, 69.4, 55.5, 43.3, 39.3, 24.8, 14.1, 13.2; *m/z* (C.I.) 339 (100 %, M + H^+); (Found: M^+, 338.1994. $C_{21}H_{26}N_2O_2$ requires 338.1994).

2-[1-(4-Methoxyphenyl)ethyl]-3-phenyl-2,3-dihydroisoindol-1-one *syn*-233



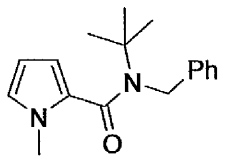
Phenyllithium (0.82 mL of a 2.0 M solution in dibutyl ether, 1.62 mmol, 1.2 equiv.) was added dropwise to a solution of *N,N*-diethyl-2-{[1-(4-methoxyphenyl)ethylimino] methyl}benzamide **232** (0.46 g, 1.35 mmol, 1.0 equiv.) in THF (15 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred at –78 °C for 3 h, quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature over 12 h. Water (5 mL) was added and the mixture extracted with EtOAc (4 × 10 mL). Combined organics were washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.080 g, 30 %) as a yellow oil: $[\alpha]_D^{22}$ = –193.3 (c = 0.10 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2924 (CH), 1687 (C=O); δ_H(300 MHz, $CDCl_3$) 7.88 (1H, dd, *J* 5.5 and 2.5, Ar*H*), 7.40-7.45 (2H, m, Ar*H*), 7.18-7.22 (5H, m, Ar*H*), 7.04 (1H, d, *J* 6.0, Ar*H*), 6.98 (2H, d, *J* 6.0, Ar*H*), 6.68 (2H, d, *J* 8.5, Ar*H*), 5.45 (1H, s, C*H*Ph), 5.05 (1H, q, *J* 7.5, C*H*CH_3), 3.72 (3H, s, OCH_3), 1.85 (3H, d, *J* 7.5, $CHCH_3$); δ_C(75 MHz, $CDCl_3$) 169.5, 158.9, 146.9, 138.0, 134.3, 132.5, 132.1, 129.1, 128.9, 128.6, 128.1, 123.8, 123.3, 113.9, 65.1, 55.6, 52.7, 30.1, 19.0, 0.4; *m/z* (C.I.) 344 (100 %, M + H^+); (Found: M^+, 343.1567. $C_{23}H_{21}NO_2$ requires 343.1572).

2-[1-(4-Methoxyphenyl)ethyl]-3-phenyl-2,3-dihydroisoindol-1-one *anti*-233



Phenyllithium (0.82 mL of a 2.0 M solution in dibutyl ether, 1.62 mmol, 1.2 equiv.) was added dropwise to a solution of *N,N*-diethyl-2-{[1-(4-methoxyphenyl)ethylimino] methyl}benzamide **232** (0.46 g, 1.35 mmol, 1.0 equiv.) in THF (15 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred at –78 °C for 3 h, quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature over 12 h. Water (5 mL) was added and the mixture extracted with EtOAc (4 × 10 mL). Combined organics were washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.070 g, 20 %) as a yellow oil: $[\alpha]_D^{22}$ = +171.9 (c = 0.08 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2932 (CH), 1686 (C=O); δ_H(300 MHz, $CDCl_3$) 7.90 (1H, dd, *J* 6.5 and 1.5, Ar*H*), 7.38-7.44 (3H, m, Ar*H*), 7.28-7.30 (2H, m, Ar*H*), 7.12 (2H, d, *J* 8.5, Ar*H*), 7.0 (2H, dd, *J* 7.5 and 1.5, Ar*H*), 6.95 (1H, d, *J* 7.5, Ar*H*), 6.85 (2H, d, *J* 8.5, ArH), 5.75 (1H, q, *J* 7.5, C*H*CH_3), 5.05 (1H, s, C*H*Ph), 3.85 (3H, s, OCH_3), 1.20 (3H, d, *J* 7.5, CHCH_3); δ_C(75 MHz, $CDCl_3$) 168.2, 158.2, 146.4, 138.1, 131.7, 131.0, 129.5, 128.2, 127.9, 127.7, 127.4, 127.3, 122.8, 122.2, 112.9, 62.4, 54.5, 49.6, 17.3, 0.5; *m/z* (C.I.) 344 (100 %, M + H^+); (Found: M^+, 343.1566. $C_{23}H_{21}NO_2$ requires 343.1572).

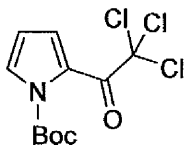
1-methyl-1*H*-pyrrole-2-carboxylic acid benzyl-*tert*-butylamide 235



n-Butyllithium (1.01 mL of a 2.5 M solution in hexane, 2.52 mmol, 2.5 equiv.) was added dropwise at room temperature to a stirred solution of *N*-methyl pyrrole (0.09 mL, 1.01 mmol, 1.0 equiv.) and TMEDA (0.40 mL, 2.52 mmol, 2.5 equiv.) in hexane (6 mL), under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min before the addition of carbamoyl chloride **191** (0.25 g, 1.11 mmol, 1.1 equiv.).

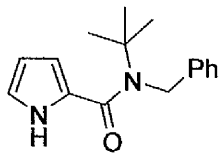
After stirring for 30 min, water (3 mL) was added and the mixture extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) to afford the *title compound* (0.17 g, 66 %) as a yellow oil: R_f(2:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2891 (CH), 1761 (C=O); δ_H(300 MHz, $CDCl_3$) 7.26-7.27 (2H, m, Ar*H*), 7.18-7.20 (3H, m, Ar*H*), 6.53 (1H, dd, *J* 5.0 and 3.5, *H*-5), 6.18 (1H, dd, *J* 5.0 and 3.5, *H*-3), 5.83 (1H, dd, *J* 5.0 and 3.5, *H*-4), 4.75 (2H, s, CH_2), 3.67 (3H, s, NCH_3), 1.40 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 166.6, 140.8, 128.4, 128.1, 126.7, 126.2, 125.6, 110.6, 106.5, 57.9, 51.8, 35.6, 28.7; *m/z* (C.I.) 271 (100 %, M + H^+); (Found: M^+, 270.1733. $C_{17}H_{22}N_2O$ requires 270.1732).

2-Trichloroacetylpyrrole-1-carboxylic acid-*tert*-butyl ester 237[192]



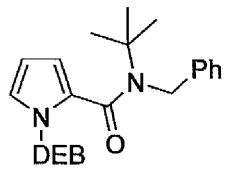
2-(Trichloroacetyl)pyrrole (0.20 g, 0.943 mmol, 1.0 equiv.) dissolved in THF (20 mL) was cooled to –78 °C. Triethylamine (0.18 mL, 1.4 mmol, 1.5 equiv.) was added to the mixture followed by immediate addition of di-*tert*butyl dicarbonate (0.30 g, 1.4 mmol, 1.5 equiv.) in THF (5 mL) and DMAP (10 mg, 0.094 mmol, 0.1 equiv.). The mixture was warmed to room temperature and stirred overnight (14 h). The solvent was removed *in vacuo* and the residue dissolved in EtOAc (50 mL), washed with water (4 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the *title compound* (0.298 g, 99 %) as an orange oil: R_f(5:1 Petrol:EtOAc) 0.80; ν_{max} ($CHCl_3$)/ cm^{-1} 2978 (CH), 1754 (C=O), 1665 (C=O); δ_H(300 MHz, $CDCl_3$) 7.42 (1H, dd, *J* 4.0 and 2.5, *H*-5), 7.30 (1H, dd, *J* 4.0 and 2.5, *H*-4), 6.28 (1H, dd, *J* 4.0 and 2.5, *H*-2), 1.58 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 129.2, 123.3, 110.4, 85.8, 77.4, 76.9, 76.5, 27.4; *m/z* (C.I.) 312 (50 %, M + H^+).

1*H*-pyrrole-2-carboxylic acid benzyl-*tert*-butylamide 240



A solution of diphosgene (0.99 mL, 8.0 mmol, 0.6 equiv.) in toluene (10 mL) was added dropwise to a stirred solution of pyrrole (1.0 mL, 14.4 mmol, 1.0 equiv.) and *N,N*-dimethyl aniline (2.0 mL, 15.9 mmol, 1.1 equiv.) in toluene (10 mL) at 0 °C, under a nitrogen atmosphere. After stirring for 2 h at 0 °C, a solution of *N-tert*-butylbenzylamine (3.2 mL, 17.3 mmol, 1.2 equiv.) and triethylamine (2.2 mL, 15.9 mmol, 1.1 equiv.) in toluene (10 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h and water (10 mL) added. The mixture was extracted with diethyl ether (4 × 15 mL). Combined organics were washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.57 g, 16 %) as a white solid: m.p. 166.2-167 °C; R_f(1:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3254 (NH), 2986 (CH), 1596 (C=O); δ_H(300 MHz, $CDCl_3$) 9.78 (1H, brs, N*H*), 7.26-7.42 (5H, m, Ar*H*), 6.90 (1H, m, *H*-5), 6.22 (1H, m, *H*-3), 6.07 (1H, m, *H*-4), 5.0 (2H, s, CH_2), 1.54 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 164.7, 140.2, 128.6, 126.7, 126.4, 125.9, 111.4, 109.4, 58.4, 50.7, 28.6, 28.4; *m/z* (C.I.) 257 (100 %, M + H^+); (Found: M^+, 256.1575. $C_{16}H_{20}N_2O$ requires 256.1575).

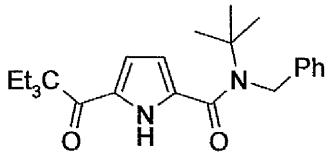
1-(2,2-Diethylbutyryl)-1*H*-pyrrole-2-carboxylic acid benzyl-*tert*-butylamide 241



1*H*-Pyrrole-2-carboxylic acid benzyl-*tert*-butylamide **240** (0.57 g, 2.23 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.43 g, 50 %) as a white solid: m.p. 106-106.7 °C; R_f(1:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2969 (CH), 1803, 1642 (C=O); δ_H(300 MHz, $CDCl_3$) 7.22-7.38 (6H, m, Ar*H* and *H*-5), 6.16 (1H, dd, *J* 3.5 and 2.5, *H*-3), 6.0 (1H, dd, *J* 3.5 and 2.5, *H*-4), 1.65 (6H, q, *J* 7.5, 3 × CH_2), 1.53 (9H, s, *t*Bu), 0.9 (9H, t, *J* 7.5, 3 × CH_3); δ_C (75 MHz, $CDCl_3$) 176.5, 173.4, 167.3, 141.0, 132.4,

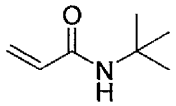
128.6, 126.8, 126.2, 119.9, 110.7, 110.3, 51.7, 28.6, 26.0, 8.4; *m/z* (C.I.) 383 (100 %, M + H^+); (Found: M^+, 382.2623. $C_{24}H_{34}N_2O_2$ requires 382.2620).

5-(2,2-Diethylbutyryl)-1*H*-pyrrole-2-carboxylic acid benzyl-*tert*-butylamide 242



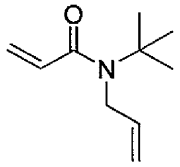
1-(2,2-Diethylbutyryl)-1*H*-pyrrole-2-carboxylic acid benzyl-*tert*-butylamide **241** (0.15 g, 0.39 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride quench. Purification by column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.091 g, 62 %) as a colourless oil: R_f(6:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 3433 (NH), 2964 (CH), 1701, 1641 (C=O); δ_H(300 MHz, $CDCl_3$) 10.18 (1H, brs, N*H*), 7.28-7.41 (5H, m, Ar*H*), 6.69 (1H, d, *J* 3.0, *H*-3), 6.16 (1H, d, 3.0, *H*-4), 4.95 (2H, s, CH_2), 1.76 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.50 (9H, s, *t*Bu), 0.70 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 196.8, 164.3, 140.3, 131.0, 129.6, 129.1, 128.7, 127.3, 126.2, 114.2, 111.9, 92.6, 59.1, 54.1, 51.0, 28.6, 26.5, 8.5; *m/z* (C.I.) 383 (40 %, M + H^+), 327 (100 %, M-56); (Found: M^+, 382.2622. $C_{24}H_{34}N_2O_2$ requires 382.2620).

***N*-*tert*-Butylacrylamide 243**[193]



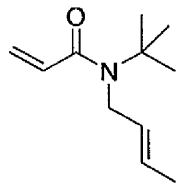
N-*tert*-butylamine (6.18 mL, 58.9 mmol, 2.2 equiv.) was treated according to **Method A** to afford the *title compound* (3.10 g, 91 %) as needles: m.p.126.0-127.9 °C (lit.,[193] 126.2-127.8 °C); R_f(1:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 3253 (NH), 2962 (CH), 1655 (C=O); δ_H(300 MHz, $CDCl_3$) 6.20 (1H, dd, *J* 16.5 and 0.5 $CHCH_AH_B$), 6.05 (1H, dd, *J* 16.5 and 10.0, $CHCH_2$), 5.60 (1H, brs, N*H*), 5.56 (1H, dd, *J* 10.0 and 0.5, $CHCH_AH_B$), 1.40 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 165.1, 132.3, 125.7, 51.5, 28.9; *m/z* (C.I.) 128 (100 %, M + H^+); (Found: M^+, 127.1001. $C_7H_{13}NO$ requires 127.0997).

N-Allyl-N-*tert*-butylacrylamide 244[194]



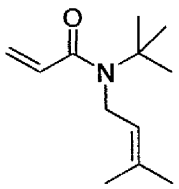
N-*tert*-Butylacrylamide **243** (3.10 g, 24.4 mmol, 1.0 equiv.) was treated according to **Method H**. The crude product was purified by flash column chromatography (SiO_2; 30:1 Petrol/EtOAc) to afford the *title compound* (1.86 g, 46 %) as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1653 (C=O); δ_H(300 MHz, $CDCl_3$) 6.40 (1H, dd, *J* 16.5 and 10.0, C*H*CH_2), 6.18 (1H, dd, *J* 16.5 and 2.0, CHC*H*$_A$H$_B$), 5.84-5.85 (1H, m, CH_2CHCH_2), 5.50 (1H, dd, *J* 10.0 and 2.0, CHCH$_A$*H*$_B$), 5.21 (1H, m, CHC*H*$_A$H$_B$), 5.18 (1H, m, CHCH$_A$*H*$_B$), 3.85 (2H, m, C*H*$_2$CHCH$_2$), 1.42 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.3, 136.2, 131.8, 126.6, 116.3, 57.4, 47.5, 28.7; *m/z* (C.I.) 168 (100 %, M + H$^+$); (Found: M$^+$, 167.1313. $C_{10}H_{17}NO$ requires 167.1310).

N-But-2-enyl-N-*tert*-butylacrylamide 245



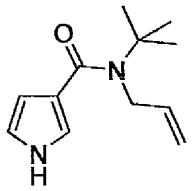
N-*tert*-Butylacrylamide **243** (5.0 g, 39.4 mmol, 1.0 equiv.) and crotyl bromide (5.7 mL, 47.0 mmol, 1.2 equiv.) were treated according to **Method H**. The crude product was purified by flash column chromatography (SiO_2; 30:1 Petrol/EtOAc) to afford the *title compound* (3.95 g, 58 %) as a yellow oil: R_f(5:1 Petrol:EtOAc) 0.80; ν_{max} $(CHCl_3)/cm^{-1}$ 2964 (CH), 1653 (C=O); δ_H(300 MHz, $CDCl_3$) 6.50 (1H, dd, *J* 16.5 and 10.0, C*H*CH_2), 6.25 (1H, dd, *J* 16.5 and 2.0, CHC*H*$_2$), 5.44-5.68 (3H, m, CHC*H*$_2$, C*H*$CHCH_3$ and CHC*H*CH_3), 3.92-3.95 (2H, m, C*H*$_2$CHCHCH$_3$), 1.74 (3H, dd, *J* 6.5 and 1.5, CHCHC*H*$_3$), 1.48 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.3, 131.9, 128.9, 127.2, 126.6, 57.5, 46.9, 28.8, 27.9, 24.2, 17.9; *m/z* (C.I.) 182 (100 %, M + H$^+$); (Found: M$^+$, 181.1470. $C_{11}H_{19}NO$ requires 181.1467).

_N_-*tert*-Butyl-_N_-(3-methylbut-2-enyl)acrylamide 246



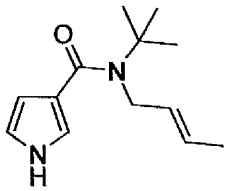
_N_-*tert*-Butylacrylamide **243** (1.0 g, 7.9 mmol, 1.0 equiv.) and prenyl bromide (1.1 mL, 9.5 mmol, 1.2 equiv.) were treated according to **Method H**. The crude product was purified by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) to afford the *title compound* (0.43 g, 30 %) as a yellow oil: R_f(10:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1650 (C=O); δ_H(300 MHz, $CDCl_3$) 6.42 (1H, dd, _J_ 16.5 and 10.5, C*H*CH_2), 6.15 (1H, dd, _J_ 16.5 and 2.0, CHC*H*$_A$H$_B$), 5.48 (1H, dd, _J_ 10.5 and 2.0, CHCH$_A$*H*$_B$), 5.05-5.06 (1H, m, C*H*C$(CH_3)_2$), 3.88 (2H, d, _J_ 5.5, C*H*$_2$CHC$(CH_3)_2$), 1.68 (3H, d, _J_ 1.5, C*H*$_3$), 1.58 (3H, s, C*H*$_3$), 1.40 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.1, 133.0, 132.1, 126.1, 123.9, 57.3, 44.1, 28.9, 25.8, 18.2; *m/z* (C.I.) 196 (100 %, M + H^+); (Found (E.I):M^+, 195.1620. $C_{12}H_{21}NO$ requires 195.1623).

1*H*-Pyrrole-3-carboxylic acid allyl-*tert*-butylamide 247



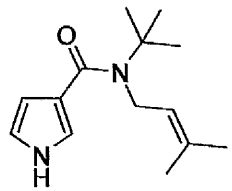
_N_-Allyl-_N_-*tert*-butylacrylamide **244** (1.85 g, 11.1 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 7:1 Petrol/EtOAc) to afford the *title compound* (0.65 g, 30 %) as a yellow oil: R_f(5:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3223 (NH), 2971 (CH), 1596 (C=O); δ_H(300 MHz, $CDCl_3$) 9.95 (1H, brs, N*H*), 7.05 (1H, dd, _J_ 2.5 and 2.0, *H*-2), 6.58 (1H, dd, _J_ 2.5 and 2.0, *H*-5), 6.40 (1H, dd, _J_ 2.5 and 2.0, *H*-4), 5.95 (1H, m, CH_2CHCH_2), 5.25 (1H, m, CHC*H*$_A$H$_B$), 5.22 (1H, m, CHCH$_A$*H*$_B$), 4.22 (2H, m, C*H*$_2$CHCH_2), 1.50 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 170.7, 139.0, 130.4, 128.2, 121.3, 121.0, 118.0, 115.8, 108.6, 57.7, 50.2, 28.9; *m/z* (C.I.) 207 (100 %, M + H^+); (Found (E.I):M^+, 206.1417. $C_{12}H_{18}N_2O$ requires 206.1419).

1*H*-Pyrrole-3-carboxylic acid but-2-enyl-*tert*-butylamide 248



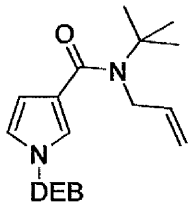
N-But-2-enyl-*N*-*tert*-butylacrylamide **245** (3.94 g, 22.0 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) to afford the *title compound* (1.59 g, 37 %) as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.30; $\nu_{max}(CHCl_3)/cm^{-1}$ 3233 (NH), 2964 (CH), 1599 (C=O); δ_H(300 MHz, $CDCl_3$) 9.40 (1H, brs, N*H*), 7.10 (1H, dd, *J* 5.0 and 2.0, *H*-2), 6.65 (1H, dd, *J* 5.0 and 2.0, *H*-5), 6.42 (1H, dd, *J* 5.0 and 2.5, *H*-4), 5.60-5.63 (2H, m, C*H*CHCH$_3$ and CHC*H*CH$_3$), 4.20 (2H, dd, *J* 3.0 and 1.5, CH_2CHCHCH$_3$), 1.75 (3H, d, *J* 4.5, CHCHCH_3), 1.55 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 174.4, 170.2, 131.5, 126.5, 123.9, 121.2, 117.9, 108.9, 49.3, 46.8, 36.5, 29.1, 18.1; *m/z* (C.I.) 221 (100 %, M + H^+); (Found (E.I):M^+, 220.1574. $C_{13}H_{20}N_2O$ requires 220.1576).

1*H*-Pyrrole-3-carboxylic acid *tert*-butyl-(3-methylbut-2-enyl)amide 249



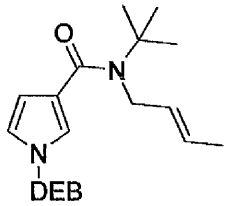
N-*tert*-Butyl-*N*-(3-methylbut-2-enyl)acrylamide **246** (2.86 g, 14.7 mmol, 1.0 equiv.) was treated according to **Method B**. The crude product was purified by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) to afford the *title compound* (1.94 g, 58 %) as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3244 (NH), 2967 (CH), 1610 (C=O); δ_H(300 MHz, $CDCl_3$) 9.42 (1H, brs, N*H*), 7.06 (1H, dd, *J* 4.5 and 2.0, *H*-2), 6.62 (1H, dd, *J* 4.5 and 2.0, *H*-5), 6.40 (1H, dd, *J* 4.5 and 2.0, *H*-4), 5.28-5.29 (1H, m, C*H*C(CH$_3$)$_2$), 4.18 (2H, brs, CH_2CHC(CH$_3$)$_2$), 1.74 (3H, s, CCH_3), 1.54 (3H, s, CCH_3), 1.50 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 170.0, 133.6, 132.6, 131.5, 126.5, 122.1, 121.5, 117.9, 108.9, 57.4, 46.5, 29.2, 25.8, 18.1; *m/z* (C.I.) 235 (100 %, M + H^+); (Found (E.I):M^+, 234.1734. $C_{14}H_{22}N_2O$ requires 234.1732).

1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid allyl-*tert*-butylamide 250



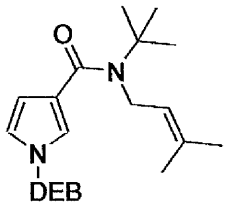
1*H*-Pyrrole-3-carboxylic acid allyl-*tert*-butylamide **247** (0.65 g, 3.16 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 7:1 Petrol/EtOAc) afforded the *title compound* (0.57 g, 53 %) as a white solid: m.p. 94.6-95 °C; R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2970 (CH), 1709, 1628 (C=O); δ_H(300 MHz, $CDCl_3$) 7.78 (1H, dd, *J* 2.5 and 2.0, *H*-2), 7.37 (1H, dd, *J* 2.5 and 2.0, *H*-5), 6.45 (1H, dd, *J* 2.5 and 2.0, *H*-4), 5.95 (1H, m, CH_2CHCH_2), 5.32 (1H, m, $CH_2CHCH_AH_B$), 5.29 (1H, m, $CH_2CHCH_AH_B$), 4.12 (2H, m, CH_2CHCH_2), 1.80 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.52 (9H, s, *t*Bu), 0.77 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 175.3, 168.6, 138.5, 125.1, 120.9, 120.2, 116.3, 112.0, 58.0, 52.7, 49.8, 28.8, 27.0, 8.6; *m/z* (C.I.) 333 (100 %, M + H^+); (Found (E.I):M^+, 332.2466. $C_{20}H_{32}N_2O_2$ requires 332.2464).

1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid but-2-enyl-*tert*-butylamide 251



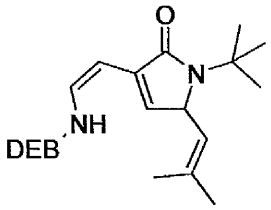
1*H*-Pyrrole-3-carboxylic acid but-2-enyl-*tert*-butylamide **248** (1.59 g, 7.22 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.99 g, 45 %) as a white solid: m.p. 112.4-113 °C; R_f (10:1 Petrol:EtOAc) 0.40; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1708, 1629 (C=O); δ_H(300 MHz, $CDCl_3$) 7.80 (1H, dd, *J* 3.5 and 1.5, *H*-2), 7.42 (1H, dd, *J* 3.5 and 1.5, *H*-5), 6.46 (1H, dd, *J* 3.5 and 1.5, *H*-4), 5.55-5.70 (2H, m, $CHCHCH_3$ and $CHCHCH_3$), 4.10 (2H, dd, *J* 4.0 and 1.5, $CH_2CHCHCH_3$), 1.85 (3H, q, *J* 7.5, CH_2CH_3), 1.78 (3H, dd, *J* 3.0 and 1.5, $CHCHCH_3$), 1.65 (3H, q, *J* 7.5, CH_2CH_3), 1.55 (9H, s, *t*Bu), 0.78-0.9 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.3, 173.4, 168.5, 131.0, 127.0, 125.4, 124.7, 121.3, 120.8, 120.3, 112.1, 57.9, 52.8, 51.7, 49.0, 28.9, 28.8, 27.0, 25.9, 18.1, 8.6, 8.4; *m/z* (C.I.) 347 (100 %, M + H^+); (Found (E.I): M^+, 346.2629. $C_{21}H_{34}N_2O_2$ requires 346.2620).

1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide 252



1*H*-Pyrrole-3-carboxylic acid *tert*-butyl-(3-methylbut-2-enyl)amide **249** (1.94 g, 8.29 mmol, 1.0 equiv.) was treated according to **Method E**. Purification by column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (1.69 g, 58 %) as a yellow oil: R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1707, 1629 (C=O); δ_H(300 MHz, $CDCl_3$) 7.74 (1H, dd, *J* 2.5 and 1.5, *H*-2), 7.40 (1H, dd, *J* 3.5 and 2.5, *H*-5), 6.46 (1H, dd, *J* 3.5 and 1.5, *H*-4), 5.26 (1H, m, C*H*C$(CH_3)_2$), 4.10 (2H, dd, *J* 3.5 and 1.0, CH_2CH$(CH_3)_2$), 1.84 (6H, q, *J* 7.5, 3 × CH_2CH$_3$), 1.77 (3H, d, *J* 1.5, CCH_3), 1.46 (12H, s, *t*Bu and CCH_3), 0.80 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.3, 168.2, 132.5, 125.8, 125.6, 121.1, 120.3, 112.3, 57.8, 52.8, 46.3, 31.2, 28.9, 26.9, 25.8, 18.1, 8.6; *m/z* (C.I.) 361 (100 %, M + H^+); (Found (E.I): M^+, 360.2773. $C_{22}H_{36}N_2O_2$ requires 360.2776).

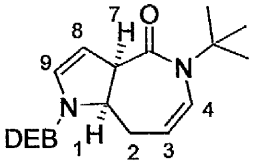
***N*-{2-[1-*tert*-Butyl-5-(2-methylpropenyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]vinyl}-2,2-diethylbutyramide 255**



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl) amide **252** (0.15 g, 4.16 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.5 mL) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.080 g, 56 %) as a colourless oil: R_f (10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3399 (NH), 2966 (CH), 1651, 1613 (C=O); δ_H(300 MHz, $CDCl_3$) 12.40 (1H, d, *J* 10.5, N*H*), 6.95 (1H, t, *J* 10.5, NHC*H*CH), 6.38 (1H, d, *J* 2.5, C*H*), 5.20 (1H, d, *J* 10.5, NHCHC*H*), 4.98 (1H, dd, *J* 8.5 and 2.5, C*H*CHC$(CH_3)_2$), 4.80 (1H, dt, *J* 8.5 and 1.5, CHC*H*C$(CH_3)_2$), 1.77 (6H, dd, *J* 3.5 and 1.0, C$(CH_3)_2$), 1.70 (6H, q, *J* 7.5, 3 × CH_2CH$_3$), 1.50 (9H, s, *t*Bu), 0.82 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.9, 171.4, 139.5, 136.1, 134.8, 130.9, 125.6, 122.7, 111.9, 98.8, 60.7, 57.8, 55.6, 51.0, 50.0, 28.1, 26.4, 18.4, 8.8;

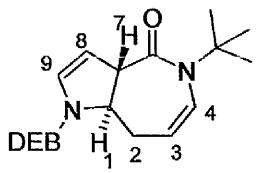
m/z (C.I.) 361 (100 %, M + H^+); (Found (E.I): M^+, 360.2779. $C_{22}H_{36}N_2O_2$ requires 360.2776).

5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one *cis*-257a



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid allyl-*tert*-butylamide **250** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.5 mL) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 70 %) as needles: m.p. 123.2-123.7 °C; R_f(10:1 Petrol:EtOAc) 0.90; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1726, 1649 (C=O); δ_H(300 MHz, DMSO, 120 °C) 7.02 (1H, dd, *J* 4.5 and 2.0, *H*-9), 6.15 (1H, d, *J* 8.0, *H*-4), 5.62 (1H, q, *J* 8.0, *H*-3), 5.05-5.06 (1H, m, *H*-8), 4.75-4.77 (1H, m, *H*-1), 3.88-3.89 (1H, m, *H*-7), 2.58 (1H, m, *H*-2), 2.30 (1H, m, *H*-2), 1.60 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.40 (9H, s, *t*Bu), 0.75 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, DMSO) 173.2, 132.2, 129.8, 119.5, 109.2, 70.7, 58.4, 55.4, 50.3, 31.0, 28.3, 28.1, 27.9, 8.6, 8.3; *m/z* (C.I.) 333 (100 %, M + H^+); (Found (E.I): M^+, 332.2466. $C_{20}H_{32}N_2O_2$ requires 332.2464).

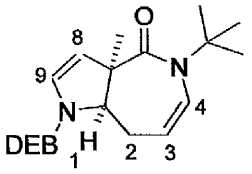
5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one *trans*-257a



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid allyl-*tert*-butylamide **250** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.5 mL) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.02 g, 15 %) as a clear oil: R_f(10:1 Petrol:EtOAc) 0.95; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1723, 1651 (C=O); δ_H(300 MHz, DMSO) 7.05 (1H, dd, *J* 3.5 and 3.0, *H*-9), 6.18 (1H, d, *J* 10.5, *H*-4), 5.15 (1H, m, *H*-3), 5.05 (1H, m, *H*-8), 4.0 (1H, m, *H*-1), 3.52 (1H, m, *H*-7), 3.30 (1H, m, *H*-2), 2.00 (1H, m, *H*-2), 1.54 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.38 (9H, s, *t*Bu), 0.62 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, DMSO) 174.2, 171.8, 131.6, 127.6, 114.2, 107.6, 62.2, 58.3,

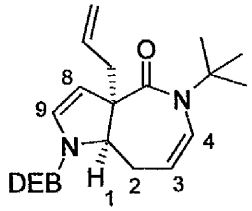
53.7, 50.6, 35.8, 28.9, 26.1, 24.8, 21.7, 18.1, 9.1; *m/z* (C.I.) 333 (100 %, M + H^+); (Found (E.I): M^+, 332.2464. $C_{20}H_{32}N_2O_2$ requires 332.2464).

5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a-methyl-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one 257b



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid allyl-*tert*-butylamide **250** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.17 mL, 2.71 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.156 g, 100 %) as needles: m.p. 106.6 °C; R_f(5:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967 (CH), 1649, 1615 (C=O); δ_H(300 MHz, DMSO, 130 °C) 6.95 (1H, d, *J* 4.5 , *H*-9), 6.18 (1H, d, *J* 4.5, *H*-8), 5.52 (1H, q, *J* 8.0, *H*-3), 5.12 (1H, d, *J* 8.0, *H*-4), 4.23-4.24 (1H, m , *H*-1), 2.44-2.45 (1H, m, *H*-2), 2.22-2.23 (1H, m, *H*-2), 1.60 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.42 (9H, s, *t*Bu), 1.22 (3H, s, CH_3), 0.78 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 175.5, 172.0, 129.8, 116.6, 58.7, 55.2, 50.3, 28.2, 27.4, 26.5, 25.6, 16.5, 8.7; *m/z* (C.I.) 347 (100 %, M + H^+); (Found (E.I): M^+, 346.2621. $C_{21}H_{34}N_2O_2$ requires 346.2620).

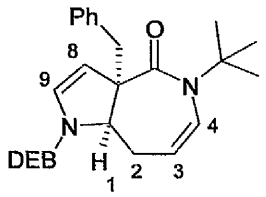
3a-Allyl-5-*tert*-butyl-1-(2,2-diethylbutyryl)-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one 257c



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid allyl-*tert*-butylamide **250** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.23 mL, 2.7 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 65 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1647, 1617 (C=O); δ_H(300 MHz, $CDCl_3$, 60 °C) 6.98 (1H, d, *J* 4.5, *H*-9), 6.10 (1H, d, *J* 7.5, *H*-4), 5.60-5.61 (2H, m, CH_2CHCH_2), 5.55 (1H, q, *J* 7.5, *H*-3), 5.18 (1H, d, *J* 4.5, *H*-8), 5.02 (3H, d, *J* 12.5, CH_2CHCH_2 and CH_2CHCH_2), 4.25 (1H, m, *H*-1), 2.70 (1H, m, *H*-2), 2.55 (1H, m, *H*-2), 1.58 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.40 (9H, s, *t*Bu), 0.70 (9H, t, *J* 7.5, 3 × CH_2CH_3);

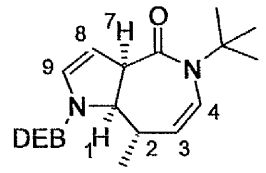
δ_C(75 MHz, $CDCl_3$) 175.9, 173.1, 133.4, 128.5, 118.9, 117.9, 114.1, 59.5, 50.8, 44.9, 28.5, 28.3, 26.4, 26.0, 8.6; *m/z* (C.I.) 373 (100 %, M + H^+); (Found (E.I): M^+, 372.2770. $C_{23}H_{36}N_2O_2$ requires 372.2776).

3a-Benzyl-5-*tert*-butyl-1-(2,2-diethylbutyryl)-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one 257d



1-(2,2-Diethylbutyryl)-1H-pyrrole-3-carboxylic acid allyl-*tert*-butylamide **250** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.32 mL, 2.7 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.16 g, 85 %) as needles: m.p. 110.2-110.9 °C; R_f(10:1 Petrol:EtOAc) 0.90; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1653, 1615 (C=O); δ_H(300 MHz, DMSO, 130 °C) 7.05-7.25 (5H, m, Ar*H*), 6.88 (1H, d, *J* 4.5, *H*-9), 6.22 (1H, d, *J* 8.0, *H*-4), 5.62 (1H, q, *J* 8.0, *H*-3), 5.22 (1H, m, *H*-1), 5.15 (1H, d, *J* 4.5, *H*-8), 4.45 (1H, m, *H*-2), 3.50 (1H, m, *H*-2), 2.80 (2H, m, CH_2Ph), 1.50 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.38 (9H, s, *t*Bu), 0.68 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 176.2, 172.9, 130.9, 130.5, 128.3, 128.1, 127.9, 126.9, 125.4, 118.6, 114.6, 113.5, 63.6, 59.6, 50.7, 28.8, 28.5, 27.9, 26.6, 26.0, 25.3, 8.6; *m/z* (C.I.) 423 (100 %, M + H^+); (Found (E.I): M^+, 422.2990. $C_{27}H_{38}N_2O_2$ requires 422.2933).

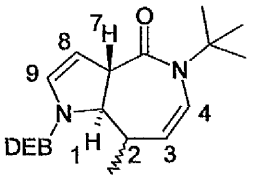
5-*tert*-Butyl-1-(2,2-diethylbutyryl)-8-methyl-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one 257e



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid but-2-enyl-*tert*-butylamide **251** (0.15 g, 4.33 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.5 mL) quench. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.084 g, 56 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1655, 1622 (C=O); δ_H(300 MHz, $CDCl_3$) 6.88 (1H, dd, *J* 2.5 and 1.5, *H*-9), 5.92 (1H, d, *J* 8.5, *H*-4), 5.54 (1H, t, *J* 8.5, *H*-8), 4.96 (1H, dd, *J* 4.5 and 2.0, *H*-3), 4.94 (1H, dd, *J* 10.5 and

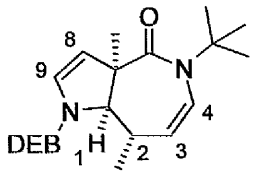
3.0, *H*-1), 3.98 (1H, dt, *J* 10.5 and 2.5, *H*-7), 2.76 (1H, m, *H*-2), 1.60 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.42 (9H, s, *t*Bu), 1.16 (3H, d, *J* 7.5, $CHCH_3$), 0.76 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 200.4, 176.8, 173.9, 172.7, 130.9, 129.7, 127.7, 126.5, 123.7, 109.9, 72.5, 63.1, 59.0, 54.9, 50.7, 28.5, 28.2, 26.6, 26.2, 16.5, 12.6, 8.7; *m/z* (C.I.) 347 (100 %, M + H^+); (Found (E.I): M^+, 346.2629. $C_{21}H_{34}N_2O_2$ requires 346.2620).

5-*tert*-Butyl-1-(2,2-diethylbutyryl)-8-methyl-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one *trans*-257e



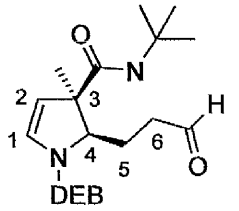
1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid but-2-enyl-*tert*-butylamide **251** (0.15 g, 4.33 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.5 mL) quench. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.012 g, 7 %) as a colourless oil in a 2:1 mixture of diastereoisomers: R_f(10:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1655, 1622 (C=O); δ_H(300 MHz, $CDCl_3$) 7.0 (1H, dd, *J* 4.5 and 2.5, *H*-9_{major}), 6.93 (1H, dd, *J* 4.5 and 2.5, *H*-9_{minor}), 6.05 (1H, d, *J* 1.0, *H*-4_{major}), 6.01(1H, d, *J* 1.0, *H*-4_{minor}), 5.34 (1H, dd, *J* 4.5 and 2.5, *H*-8_{major}), 5.25 (1H, dd, *J* 4.5 and 2.5, *H*-8_{minor}), 5.05 (1H, dd, *J* 10.5 and 5.0, *H*-3_{major}), 4.94 (1H, dd, *J* 10.0 and 2.5, *H*-3_{minor}), 4.40 (1H, dd, *J* 10.0 and 5.5, *H*-1_{major}), 4.32 (1H, t, *J* 10.0, *H*-7_{major}), 3.66 (1H, dt, *J* 10.0 and 2.5, *H*-1_{minor}), 3.52 (1H, dt, *J* 10.0 and 2.5, *H*-7_{minor}), 2.55 (2H, m, *H*-2), 1.62 (12H, q, *J* 7.5, 6 × CH_2CH_3), 1.45 (18H, s, 2 × *t*Bu), 1.28 (6H, d, *J* 7.0, 2 × CCH_3), 0.85 (18H, t, *J* 7.5, 6 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.8, 173.9, 172.7, 130.9, 129.7, 127.7, 126.5, 123.7, 109.9, 72.5, 63.1, 59.0, 54.9, 50.7, 28.5, 28.2, 26.6, 26.2, 16.5, 12.6, 8.7; *m/z* (C.I.) 347 (100 %, M + H^+); (Found (E.I): M^+, 346.2629. $C_{21}H_{34}N_2O_2$ requires 346.2620).

5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a,8-dimethyl-3a,5,8,8a-tetrahydro-1*H*-pyrrolo[3,2-c]azepin-4-one 257f



1-(2,2-Diethylbutyryl)-1*H*-pyrrole-3-carboxylic acid but-2-enyl-*tert*-butylamide **251** (0.15 g, 4.33 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.16 mL, 2.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 62 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.85; ν_{max}($CHCl_3$)/cm^{-1} 2967 (CH), 1620 (C=O); δ_H(300 MHz, $CDCl_3$, 60 °C) 6.85 (1H, d, *J* 4.5, *H*-9), 6.00 (1H, d, *J* 8.5, *H*-4), 5.45 (1H, t, *J* 4.5, *H*-8), 5.18 (1H, m, *H*-1), 4.38 (1H, d, *J* 8.5, *H*-3), 2.65 (1H, q, *J* 7.5, 3 × CH_2CH_3), 1.62 (6H, q, *J* 7.5, 3 × CH_2CH_3), 1.40 (9H, s, *t*Bu), 1.24 (3H, s, CCH_3), 1.08 (3H, d, *J* 8.5, $CHCH_3$), 0.80 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.4, 117.3, 59.2, 50.9, 28.4, 0.80 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.4, 117.3, 59.2, 50.9, 28.4, 27.8, 26.2, 8.7; *m/z* (C.I.) 361 (100 %, M + H^+); (Found (E.I): M^+, 360.2776. $C_{22}H_{36}N_2O_2$ requires 360.2776).

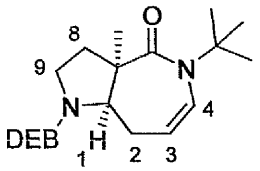
1-(2,2-Diethylbutyryl)-2-(3-oxopropyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylic acid-*tert*-butylamide 258



5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a,5,8,8a-tetrahydro-1H-pyrrolo[3,2-c]azepin-4-one **257b** (0.15 g, 0.45 mmol, 1.0 equiv.) in THF (5 mL) was stirred with 1 M HCl (2 mL) at room temperature under a nitrogen atmosphere for 14 h. Water was added and the mixture extracted with EtOAc (4 × 10 mL). Combined organic layers were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure leaving the *title compound* (0.13 g, 90 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 3362 (NH), 2966 (CH), 1723, 1646, 1514 (C=O); δ_H(300 MHz, $CDCl_3$) 9.70 (1H, s, C*H*O), 6.38 (1H, dd, *J* 7.5 and 2.0, *H*-1), 5.72 (2H, brs and q, *J* 7.5, *H*-2 and N*H*), 4.62-4.63 (1H, m, *H*-3), 3.58 (1H, m, *H*-4), 3.05 (1H, dd, *J* 18.5 and 10.5, *H*-6), 2.48 (1H, m, *H*-6), 2.40 (2H, dd, *J* 18.5 and 3.0, *H*-5), 1.80 (1H, m, *H*-5), 1.58 (6H, q, *J* 7.5, CH_2CH_3), 1.44 (9H, s, *t*Bu), 0.80 (9H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$)

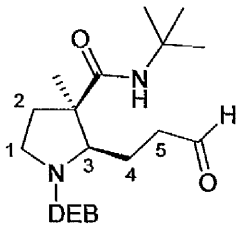
199.3, 174.5, 171.8, 129.8, 117.7, 56.6, 55.5, 47.7, 40.8, 40.6, 28.8, 27.1, 24.5, 7.0; *m/z* (C.I.) 351 (100 %, M + H^+); (Found (E.I): M^+, 350.2564. $C_{20}H_{34}N_2O_3$ requires 350.2569).

5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a-methyl-2,3,3a,5,8,8a-hexahydro-1*H*-pyrrolo[3,2-c]azepin-4-one 259



Palladium on carbon (0.16 g) was added portion wise to a solution of 5-*tert*-butyl-1-(2,2-diethylbutyryl)-3a-methyl-3a,5,8,8a-tetrahydro-1H-pyrrolo[3,2-c]azepin-4-one **257b** (0.16g, 4.62 mmol, 1.0 equiv.) in methanol (7 mL) at room temperature under a nitrogen atmosphere. The flask was flushed with hydrogen and maintained under a hydrogen atmosphere for 2 days. The mixture was filtered through celite, washed with methanol (2 × 5 mL) and evaporated under reduced pressure leaving the *title compound* (0.14 g, 90 %) as needles: mp. 171.4-172.1 °C; R_f(10:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 2965 (CH), 1648, 1619 (C=O); δ_H(300 MHz, $CDCl_3$) 6.20 (1H, dd, *J* 7.5 and 1.0, *H*-4), 5.65 (1H, q, *J* 7.5, *H*-3), 4.28 (1H, dd, *J* 10.5 and 4.0, *H*-1), 3.88-3.89 (1H, m, *H*-9), 3.50-3.52 (1H, m, *H*-8), 2.82-2.83 (1H, m, *H*-9), 2.78 (1H, m, *H*-8), 2.02 (1H, m, *H*-2), 1.70 (1H, m, *H*-2), 1.60 (6H, q, *J* 7.5, CH_2CH_3), 1.44 (9H, s, *t*Bu), 1.38 (3H, s, CH_3), 0.80 (9H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 177.0, 174.2, 130.1, 118.4, 75.1, 59.2, 53.0, 50.4, 46.0, 39.4, 28.6, 27.3, 27.2, 25.7, 8.8; *m/z* (C.I.) 349 (100 %, M + H^+); (Found (E.I): M^+, 348.5321. $C_{21}H_{36}N_2O_2$ requires 348.5320).

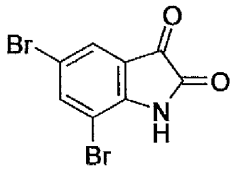
1-(2,2-Diethylbutyryl)-3-methyl-2-(3-oxopropyl)pyrrolidine-3-carboxylic acid-*tert*-butylamine 260



5-*tert*-Butyl-1-(2,2-diethylbutyryl)-3a-methyl-2,3,3a,5,8,8a-hexahydro-1H-pyrrolo[3,2-c]azepin-4-one **259** (0.092 g, 0.264 mmol, 1.0 equiv.) in THF (5 mL) was stirred with 1 M HCl (2 mL) at room temperature under nitrogen for 14 h. Water was added and the mixture extracted with EtOAc (4 × 10 mL). Combined organic layers were washed

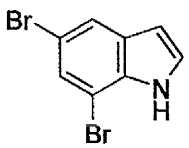
with water, dried ($MgSO_4$) and evaporated under reduced pressure leaving the *title compound* (0.09 g, 93 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 3435 (NH), 2965 (CH), 1720, 1661, 1609 (C=O); δ_H(300 MHz, $CDCl_3$) 9.80 (1H, s, C*H*O), 5.62 (1H, brs, N*H*), 4.36 (1H, dd, *J* 9.0 and 2.5, *H*-3), 3.80 (1H, dd, *J* 9.5 and 2.0, *H*-1), 3.70 (1H, dd, *J* 9.5 and 2.0, *H*-1), 2.82 (1H, m, *H*-5), 2.55-2.50 (2H, m, *H*-5 and *H*-2), 2.05 (1H, m, *H*-2), 1.80 (1H, m, *H*-4), 1.68 (7H, q, *J* 7.5, CH_2CH_3 and *H*-4), 1.42 (9H, s, *t*Bu), 1.30 (3H, s, CH_3), 0.80 (9H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 202.6, 173.4, 64.9, 51.8, 50.8, 44.0, 41.6, 32.3, 29.7, 28.9, 25.3, 25.1, 24.7, 8.7, 1.3; *m/z* (C.I.) 367 (100 %, M + H^+); (Found (E.I): M^+, 366.2564. $C_{21}H_{38}N_2O_3$ requires 366.2569).

5,7-Dibromoisatin 268[146]



Bromine (2.4 mL, 41.7 mmol, 2.1 equiv.) was added dropwise to a stirring solution of isatin (3.0 g, 20.4 mmol, 1.0 equiv.) in ethanol (40 mL) at 90 °C. The solution was stirred under heating for 1 h and allowed to cool to room temperature. The precipitate was filtered and washed with cold ethanol (10 mL) to afford the *title compound* (3.02 g, 50 %) as yellow needles: m.p. 248.9-250 °C (lit.,[146] 248-250 °C); R_f(1:1 Petrol:EtOAc) 0.40; ν_{max}($CHCl_3$)/cm^{-1} 3430 (NH), 2251 (CH), 1659 (C=O); δ_H(300 MHz, DMSO) 11.05 (1H, brs, N*H*), 7.82 (1H, d, *J* 2.0, *H*-4), 7.60 (1H, d, *J* 2.0, *H*-6); δ_C(75 MHz, DMSO) 172.2, 141.1, 135.9, 129.6, 127.5, 114.9, 104.7, 97.3; *m/z* (C.I.) 300 (50 %, M-Br^{79}-Br^{79}), 302 (100 %, M-Br^{79}-Br^{81}), 305 (40 %, M-Br^{81}-Br^{81}); (Found (E.I): M^+, 302.8464. $C_8H_3NO_2Br_2$ requires 302.8447).

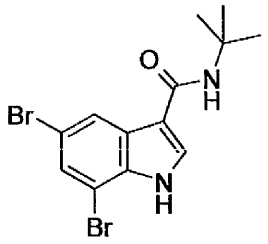
5,7-Dibromoindole 266[146]



Borane (2.0 mL of a 1.0 M solution in THF, 1.64 mmol, 2.0 equiv.) was added dropwise to a stirring solution of 5,7-dibromoisatin **268** (0.25 g, 0.82 mmol, 1.0 equiv.) in THF (5 mL) at –78 °C under a nitrogen atmosphere. The resulting solution was stirred at 0 °C

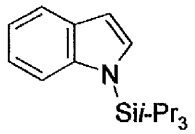
for 24 h, poured into water (10 mL) and made slightly acidic (pH 5). The mixture was extracted with Et_2O (3 × 5 mL). Combined organics were washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 35:1 Petrol/EtOAc) afforded the *title compound* (0.18 g, 75 %) as needles: m.p. 67.7-69.0 °C (lit.,[146] 67-69 °C); R_f(5:1 Petrol:EtOAc) 0.55; ν_{max} ($CHCl_3$)/cm^{-1} 3432 (NH); δ_H (300 MHz, $CDCl_3$) 8.40 (1H, brs, N*H*), 7.75 (1H, dd, *J* 1.5 and 0.5, *H*-4), 7.51 (1H, d, *J* 1.5, *H*-6), 7.30 (1H, dd, *J* 3.0 and 2.5, *H*-2), 6.61 (1H, dd, *J* 3.0 and 0.5, *H*-3); δ_C(75 MHz, $CDCl_3$) 133.8, 130.3, 126.8, 126.2, 122.8, 113.0, 105.3, 103.8; *m/z* (C.I.) 273 (50 %, M-Br^{79}-Br^{79}), 302 (275 %, M-Br^{79}-Br^{81}), 277 (40 %, M-Br^{81}-Br^{81}); (Found (E.I): M^+, 272.8777. $C_8H_5NBr_2$ requires 272.8790).

5,7-Dibromo-1*H*-indole-3-carboxylic acid-*tert*-butylamide 269



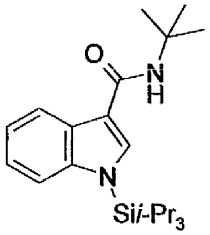
5,7-Dibromoindole **266** (0.2 g, 0.73 mmol, 2.0 equiv.) in benzene (5 mL) was added dropwise to a solution of methylmagnesium iodide (0.24 mL of a 3.0 M solution, 0.73 mmol, 2.0 equiv.) in benzene (2 mL). The solution was stirred for 10 min and a solution of *N-tert*-butylisocyanate (0.05 mL, 0.36 mmol, 1.0 equiv.) in benzene (1 mL) added dropwise. The mixture was heated at reflux for 67 h and then allowed to cool to room temperature and water (5 mL) added. The mixture was extracted with EtOAc (3 × 5 mL). Combined organics were washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 40 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.25; ν_{max}($CHCl_3$)/cm^{-1} 3421 (NH), 2965 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 8.75 (1H, brs, N*H*), 8.20 (1H, dd, *J* 2.0 and 0.5, *H*-4), 7.70 (1H, d, *J* 2.0, *H*-6), 7.57 (1H, d, *J* 0.5, *H*-2), 5.70 (1H, brs, N*H*), 1.52 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 163.9, 134.1, 128.0, 127.7, 122.9, 115.0, 105.7, 51.9, 29.4, 29.3, 14.5; *m/z* (C.I.) 373 (50 %, M-Br^{79}-Br^{79}), 375 (75 %, M-Br^{79}-Br^{81}), 377 (40 %, M-Br^{81}-Br^{81}); (Found (E.I) M^+, 371.9545. $C_{13}H_{14}N_2OBr_2$ requires 371.9546).

1-Triisopropylsilyl indole 270[147]



n-Butyllithium (4.1 mL of a 2.5 M solution in hexane, 10 mmol, 1.2 equiv.) was added dropwise to a stirred solution of indole (1.0 g, 8.55 mmol, 1.0 equiv.) in THF (25 mL) at –20 °C, under a nitrogen atmosphere and the mixture stirred for 1 h. A solution of triisopropylsilyl triflate (2.75 mL, 10 mmol, 1.2 equiv.) in THF (10 mL) was added dropwise and the mixture stirred at -20 °C for 1 h and allowed to warm to room temperature. Water (20 mL) was added and the mixture extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; 100 % Petrol) to afford the *title compound* (1.94 g, 83 %) as a colourless oil: b.p.140 °C/0.2 mmHg (lit.,[147] 140.2-141 °C); R_f(Petrol) 0.25; ν_{max} ($CHCl_3$)/cm^{-1} 2940, 2840 (CH); δ_H(300 MHz, $CDCl_3$) 7.65 (1H, dd, *J* 7.0 and 3.0, *H*-7), 7.58 (1H, dd, *J* 6.0 and 1.0, *H*-6), 7.32 (1H, dd, *J* 3.0 and 1.0, *H*-2), 7.14-7.24 (2H, m, *H*-4 and *H*-5), 6.65 (1H, dd, *J* 3.0 and 1.0, *H*-3), 1.78 (3H, d, *J* 3.0, (C*H*Me$_2$)$_3$), 1.10 (18H, d, *J* 8.0, (CHMe$_2$)$_3$); δ_C(75 MHz, $CDCl_3$) 131.3, 131.0, 121.2, 120.4, 119.6, 113.7, 104.6, 18.8, 18.1, 12.8; *m/z* (C.I.) 273 (100 %, M + H$^+$); (Found (E.I): M$^+$, 273.1916. $C_{17}H_{27}NSi$ requires 273.1913).

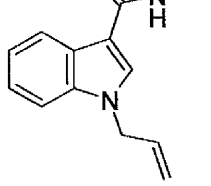
1-Triisopropylsilanyl-1*H*-indole-3-carboxylic acid-*tert*-butylamide 271[195]



t-Butyllithium (7.0 mL of a 1.6 M solution in hexane, 11.0 mmol, 1.5 equiv.) was added dropwise to a stirred solution of 1-triisopropylsilyl indole **270** (2.0 g, 7.33 mmol, 1.0 equiv.) and TMEDA (2.0 mL, 13.0 mmol, 1.8 equiv.) in hexane (50 mL) at 0 °C, under a nitrogen atmosphere and the mixture stirred for 3h. After cooling to –78 °C a solution *tert*-butylisocyanate (2.5 mL, 22.0 mmol, 3.0 equiv.) in diethyl ether (10 mL) was added dropwise and the solution stirred at –78 °C overnight. The mixture was allowed to warm to room temperature, quenched with NH_4Cl (5 mL) and extracted with EtOAc (5 × 15 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$)

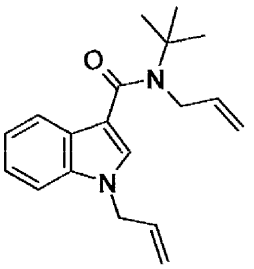
and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) to afford the *title compound* (2.25 g, 83 %) as a white solid: m.p. 114.4 °C; R_f(1:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 3351 (NH), 2960, 2868 (CH), 1628 (C=O); δ_H(300 MHz, $CDCl_3$) 7.82-7.85 (2H, m, *H*-2 and *H*-5), 7.58 (1H, dd, *J* 7.0 and 1.5, *H*-7), 7.26-7.29 (2H, m, *H*-6 and *H*-4), 5.90 (1H, brs, N*H*), 1.75-1.76 (3H, m, 3 × C*H*(CH_3)$_2$), 1.57 (9H, s, *t*Bu), 1.20 (18H, d, *J* 7.5, 6 × CH_3); δ_C(75 MHz, $CDCl_3$) 165.2, 135.4, 121.9, 119.1, 114.6, 51.3, 29.2, 17.9, 12.6; *m/z* (C.I.) 373 (100 %, M + H^+); (Found (E.I): M^+, 372.2597. $C_{22}H_{36}N_2OSi$ requires 372.2596).

1-Allyl-1*H*-indole-3-carboxylic acid-*tert*-butylamide 272



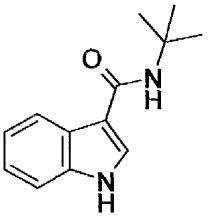
1-Triisopropylsilanyl-1H-indole-3-carboxylic acid-*tert*-butylamide **271** (0.10 g, 0.27 mmol, 1.0 equiv.) in DMF (3 mL) was added dropwise to a suspension of sodium hydride (0.02 g, 0.40 mmol, 1.5 equiv.) in DMF (2 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at room temperature for 1 h and allyl bromide (0.04 mL, 0.46 mmol, 1.7 equiv.) in DMF (1 mL) added dropwise. The mixture was stirred at room temperature for 16 h and water added (5 mL). The mixture was extracted with EtOAc (3 × 5 mL). Combined organics were washed with water (4 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.05 g, 45 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.35; ν_{max}($CHCl_3$)/cm^{-1} 3444 (NH), 2963 (CH), 1620 (C=O); δ_H(300 MHz, $CDCl_3$) 7.93-7.91 (1H, m, Ar*H*), 7.70 (1H, s, *H*-2), 7.41-7.29 (3H, m, Ar*H*), 6.09-5.95 (1H, ddd, *J* 17.0, 10.0 and 5.5, C*H*CH_2), 5.85 (1H, brs, N*H*), 5.30 (1H, ddd, *J* 10.0, 2.5 and 1.5, CHCH_AH_B), 5.16 (1H, ddd, *J* 17.0, 2.5 and 1.5, CHCH_AH_B), 4.78 (2H, dt, *J* 5.5 and 1.5, CH_2CHCH_2); δ_C(75 MHz, $CDCl_3$) 132.6, 131.5, 122.7, 121.6, 120.1, 118.5, 114.2, 110.7, 49.4, 29.5; *m/z* (C.I.) 257 (100 %, M + H^+); (Found (E.I): M^+, 256.1647. $C_{16}H_{20}N_2O$ requires 256.1648).

1-Allyl-1*H*-indole-3-carboxylic acid allyl-*tert*-butylamide 273



1-Triisopropylsilanyl-1H-indole-3-carboxylic acid-*tert*-butylamide **271** (0.10 g, 0.27 mmol, 1.0 equiv.) in DMF (3 mL) was added dropwise to a suspension of sodium hydride (0.02 g, 0.40 mmol, 1.5 equiv.) in DMF (2 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at room temperature for 1 h and allyl bromide (0.04 mL, 0.46 mmol, 1.7 equiv.) in DMF (1 mL) added dropwise. The mixture was stirred at room temperature for 16 h and water added (5 mL). The mixture was extracted with EtOAc (3 × 5 mL). Combined organics were washed with water (4 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.03 g, 27 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2961 (CH), 1624 (C=O); δ_H(300 MHz, $CDCl_3$) 7.82-7.83 (1H, m, Ar*H*), 7.49 (1H, s, *H*-2), 7.36-7.20 (3H, m, Ar*H*), 6.07-5.84 (2H, m, C*H*CH_2), 5.29-5.13 (4H, m, 2 × CHCH_2), 4.73 (2H, dt, *J* 5.5 and 1.5, CH_2CHCH_2), 4.24 (2H, dt, *J* 5.5 and 1.5, CH_2CHCH_2), 1.52 (9H, s, *t*Bu); δ_C (75 MHz, $CDCl_3$) 138.9, 133.0, 129.1, 126.9, 122.6, 121.1, 121.0, 118.2, 116.0, 114.1, 110.1, 57.6, 50.7, 49.3, 29.9, 29.2; *m/z* (C.I.) 297 (100 %, M + H^+); (Found (E.I): M^+, 296.1964. $C_{19}H_{24}N_2O$ requires 296.1961).

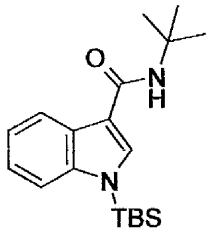
1*H*-Indole-3-carboxylic acid-*tert*-butylamide 274[196]



TBAF (2.96 mL of a 1.0 M solution in THF, 2.96 mmol, 1.1 equiv.) was added dropwise to a solution of 1-triisopropylsilanyl-1H-indole-3-carboxylic acid-*tert*-butylamide **271** (1.0 g, 2.69 mmol, 1.0 equiv.) in THF (25 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 2 h and water (20 mL)

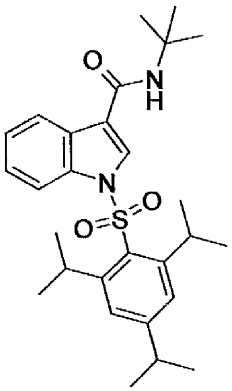
added. The mixture was extracted with EtOAc (3 × 15 mL). Combined organics were washed with water (2 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.41 g, 75 %) as needles: m.p. 188.8-189.1 °C (lit.,[196] 188-189 °C); R_f(1:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (NH), 3218 (NH), 2968 (CH), 1630 (C=O); δ_H(300 MHz, $CDCl_3$) 9.78 (1H, brs, N*H*), 7.88 (1H, dd, *J* 7.5 and 3.5, *H*-4), 7.70 (1H, d, *J* 2.5, *H*-6), 7.49-7.46 (1H, m, *H*-2), 7.30-7.25 (2H, m, *H*-7 and *H*-5), 5.98 (1H, brs, N*H*), 1.58 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 165.6, 136.9, 128.6, 124.6, 122.9, 121.6, 119.4, 113.5, 112.6, 51.8, 29.6; *m/z* (C.I.) 217 (100 %, M + H^+); (Found (E.I): M^+, 216.1258. $C_{13}H_{16}N_2O$ requires 216.1257).

1-(*tert*-Butyldimethylsilanyl)-1*H*-indole-3-carboxylic acid-*tert*-butylamide 275



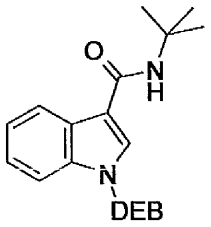
n-Butyllithium (0.23 mL of a 2.0 M solution in hexane, 0.46 mmol, 1.0 equiv.) was added dropwise to a solution of 1*H*-indole-3-carboxylic acid-*tert*-butylamide **274** (0.10 g, 0.46 mmol, 1.0 equiv.) in THF (8 mL) at –20 °C under a nitrogen atmosphere. The solution was stirred at –20 °C for 1 h and a solution of TBSOTf (0.11 mL, 0.46 mmol, 1.0 equiv.) in THF (2 mL) added dropwise. The mixture was maintained at –20 °C for 1 h and allowed to warm to room temperature. Water (10 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). Combined organics were washed with water (2 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.07 g, 45 %) as needles: m.p. 242.3-242.7 °C; R_f(1:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 3366 (NH), 2950 (CH), 1625 (C=O); δ_H(300 MHz, $CDCl_3$) 7.86 (1H, dd, *J* 6.5 and 2.5, *H*-4), 7.79 (1H, s, *H*-2), 7.58 (1H, dd, *J* 6.5 and 2.5, *H*-6), 7.28-7.24 (2H, m, *H*-5 and *H*-7), 5.91 (1H, brs, N*H*), 1.57 (9H, s, *t*Bu), 0.98 (9H, s, *t*Bu), 0.66 (6H, s, 2 × C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.0, 141.9, 135.6, 127.7, 122.3, 121.6, 119.6, 115.9, 115.0, 51.7, 29.5, 26.5, 19.5, 3.6; *m/z* (C.I.) 331 (100 %, M + H^+); (Found (E.I): M^+, 330.2203. $C_{19}H_{30}N_2OSi$ requires 330.2200).

1-(2,4,6-Triisopropylbenzenesulfonyl)-1*H*-indole-3-carboxylic acid-*tert*-butylamide 276



1*H*-Indole-3-carboxylic acid-*tert*-butylamide **274** (0.10 g, 0.46 mmol, 1.0 equiv.) in THF (2.5 mL) was added dropwise to a suspension of sodium hydride (0.02 g, 0.51 mmol, 1.1 equiv.) in THF (2.5 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at room temperature for 1 h and cooled to 0 °C. 2,4,6-Triisopropyl-benzenesulfonylchloride (0.18 g, 0.60 mmol, 1.3 equiv.) in THF (1.0 mL) was added dropwise and the solution stirred at room temperature for 48 h. Water (5 mL) was added and the mixture extracted with EtOAc (3 × 5mL). Combined organics were washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.20 g, 90 %) as needles: m.p. 153.2-153.5 °C; R_f(1:1 Petrol:EtOAc) 0.65; ν_{max} ($CHCl_3$)/cm^{-1} 3343 (NH), 2963 (CH), 1642 (C=O); δ_H(300 MHz, $CDCl_3$) 7.99-8.02 (2H, m, *H*-4 and *H*-2), 7.42 (1H, dd, *J* 7.5 and 1.0, *H*-6), 7.33-7.25 (2H, m, *H*-5 and *H*-7), 5.91 (1H, brs, N*H*), 4.15 (2H, m, 2 × C*H*(CH_3)$_2$), 2.94 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 1.53 (9H, s, *t*Bu), 1.27 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.13 (12H, d, *J* 7.0, 2 × CH(C*H*$_3$)$_2$); δ_C(75 MHz, $CDCl_3$) 163.3, 155.4, 151.8, 135.5, 131.0, 127.2, 125.1, 124.7, 123.8, 121.4, 117.5, 112.9, 52.1, 34.5, 29.9, 29.4, 24.7, 23.7; *m/z* (C.I.) 483 (100 %, M + H^+); (Found (E.I): M^+, 482.2598. $C_{28}H_{38}N_2O_3S$ requires 482.2598).

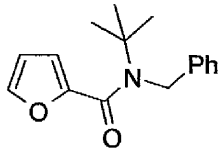
1-(2,2-Diethylbutyryl)-1*H*-indole-3-carboxylic acid-*tert*-butylamide 277



PMDTA (0.52 mL, 2.47 mmol, 3.0 equiv.) was added to a solution of 1-(2,2-diethylbutyryl) indole (0.2 g, 0.82 mmol, 1.0 equiv.) in diethyl ether (7 mL) and the mixture cooled to –78 °C. *s*-Butyllithium (1.4 mL of a 1.2 M solution in hexane, 1.65 mmol, 2.0 equiv.) was added dropwise and the solution stirred at –78 °C for 1h, and *tert*-butyl isocyanate (0.38 mL, 3.29 mmol, 4.0 equiv.) added dropwise. The mixture was stirred for 1 h then quenched by addition of saturated aqueous NH_4Cl solution (5 mL) and warmed to room temperature. The mixture was extracted with EtOAc (4 × 5 mL) and the combined organic layers washed with water (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 100 % Petrol) to afford the *title compound* (0.11 g, 42 %) as an off-white solid: m.p.149.5-149.7 °C; R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 3349 (NH), 2963 (CH), 1703, 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 8.55-8.56 (1H, m, *H*-7), 8.34 (1H, s, *H*-2), 7.75-7.76 (1H, m, *H*-4), 7.41-7.43 (2H, m, *H*-5 and *H*-6), 5.92 (1H, brs, N*H*), 1.95 (6H, q, *J* 7.5, 3 × CH_2CH_3), 0.88 (9H, t, *J* 7.5, 3 × CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 176.6, 137.4, 128.2, 125.4, 125.1, 124.2, 118.6, 117.6, 53.4, 51.8, 50.2, 29.5, 29.0, 27.0, 8.4; *m/z* (C.I.) 343 (100 %, M + H^+); (Found (E.I) (E.I.): M^+, 342.2310. $C_{21}H_{30}N_2O_2$ requires 342.2307).

4.3.2 Experimental Details for Chapter 2.2

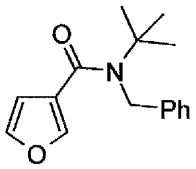
Furan-2-carboxylic acid benzyl-*tert*-butylamide 282



2-Furoic acid (2.0 g, 17.8 mmol, 1.0 equiv.) and N-*tert*-butylbenzylamine (4.94 mL, 26.7 mmol, 1.7 equiv.) were treated according to **Method J**. The crude product was purified by flash column chromatography (SiO_2; 4:1 Petrol/EtOAc) to afford the *title compound* (1.09 g, 24 %) as an off-white solid: m.p. 112.4-113.0 °C; R_f (1:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2925 (CH), 1628 (C=O); δ_H(300 MHz, $CDCl_3$)

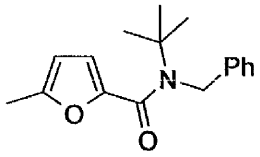
7.33-7.36 (5H, m, Ar*H*), 7.34 (1H, dd, *J* 1.5 and 1.0, *H*-5), 6.80 (1H, dd, *J* 3.5 and 1.0, *H*-3), 6.36 (1H, dd, *J* 3.5 and 1.5, *H*-4), 4.85 (2H, s, CH_2), 1.50 (9H, s, *t*Bu); δ_C (75 MHz, $CDCl_3$) 163.4, 121.5, 120.1, 118.5, 107.9, 81.1, 80.5, 60.3, 23.4; *m/z* (C.I.) 258 (100 %, M + H^+); (Found (E.I): M^+, 257.1412. $C_{16}H_{19}NO_2$ requires 257.1416).

Furan-3-carboxylic acid benzyl-*tert*-butylamide 283



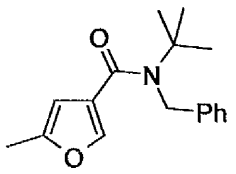
3-Furoic acid (2.0 g, 17.8 mmol, 1.0 equiv.) and N-*tert*-butylbenzylamine (4.94 mL, 26.7 mmol, 1.7 equiv.) were treated according to **Method J**. The crude product was purified by flash column chromatography (SiO_2; 4:1 Petrol/EtOAc) to afford the *title compound* (1.80 g, 40 %) as an off-white solid: m.p. 112.6-113.0 °C; R_f (1:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2920 (CH), 1628 (C=O); δ_H(300 MHz, $CDCl_3$) 7.58 (1H, dd, *J* 1.5 and 1.0, *H*-2), 7.42 (1H, dd, *J* 1.5 and 1.0, *H*-5), 7.29-7.33 (5H, m, Ar*H*), 6.53 (1H, dd, *J* 1.5 and 1.0, *H*-4), 4.80 (2H, s, CH_2), 1.52 (9H, s, *t*Bu); δ_C (75 MHz, $CDCl_3$) 158.4, 151.2, 145.8, 130.4, 128.3, 128.1, 126.8, 108.7, 48.9, 46.2, 39.6, 27.4; *m/z* (C.I.) 258 (100 %, M + H^+); (Found (E.I):M^+, 257.1414. $C_{16}H_{19}NO_2$ requires 257.1416).

5-Methylfuran-2-carboxylic acid benzyl-*tert*-butylamide 284



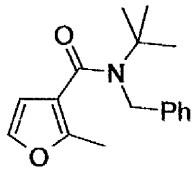
Furan-2-carboxylic acid benzyl-*tert*-butylamide **282** (0.20 g, 0.77 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.85 mL, 4.62 mmol, 6.0 equiv.) quench to afford the *title compound* (0.12 g, 50 %) as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2978, 2962 (CH), 1628 (C=O); δ_H(300 MHz, $CDCl_3$) 7.32-7.19 (5H, m, Ar*H*), 6.53 (1H, d, *J* 3.5, *H*-3), 5.83 (1H, dd, *J* 3.5 and 1.0, *H*-4), 4.78 (2H, s, CH_2), 2.08 (3H, s, CH_3), 1.40 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 154.0, 140.5, 128.3, 126.6, 126.0, 115.4, 107.1, 58.4, 50.5, 28.3, 15.6; *m/z* (C.I.) 272 (100 %, M + H^+); (Found (E.I): M^+, 271.1570. $C_{17}H_{21}N_2O$ requires 271.1572).

5-Methylfuran-3-carboxylic acid benzyl-*tert*-butylamide 285



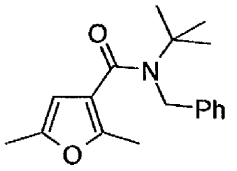
Furan-3-carboxylic acid benzyl-*tert*-butylamide **283** (0.20 g, 0.77 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.85 mL, 4.62 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 100 % Petrol) afforded the *title compound* (0.06 g, 30 %) as an off-white solid: m.p.141.5-142.3 °C; R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1638 (C=O); δ_H(300 MHz, $CDCl_3$) 7.50 (1H, s, *H*-2), 7.21-7.40 (5H, m, Ar*H*), 5.80 (1H, s, *H*-4), 4.78 (2H, s, CH_2Ph), 2.08 (3H, s, CH_3), 1.38 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 165.8, 154.5, 149.6, 137.1, 129.5, 128.3, 128.1, 126.9, 103.2, 48.4, 46.8, 28.7, 15.2; *m/z* (C.I.) 272 (100 %, M + H^+); (Found (E.I):M^+, 271.3625. $C_{17}H_{21}NO_2$ requires 271.3627).

2-Methylfuran-3-carboxylic acid benzyl-*tert*-butylamide 286



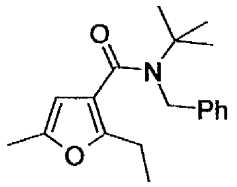
Furan-3-carboxylic acid benzyl-*tert*-butylamide **283** (0.20 g, 0.77 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.85 mL, 4.62 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 100 % Petrol) afforded the *title compound* (0.05 g, 25 %) as an off-white solid: m.p.144.2-145.0 °C; R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1636 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40 (1H, d, *J* 1.5, *H*-5), 7.21-7.37 (5H, m, Ar*H*), 6.48 (1H, d, *J* 1.5, *H*-4), 4.80 (2H, s, CH_2Ph), 2.25 (3H, s, CH_3), 1.36 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 165.4, 156.2, 146.6, 135.4, 129.5, 128.2, 128.1, 126.9, 102.8, 48.7, 47.2, 28.5, 15.2; *m/z* (C.I.) 272 (100 %, M + H^+); (Found (E.I):M^+, 271.3625. $C_{17}H_{21}NO_2$ requires 271.3627).

2,5-Dimethylfuran-3-carboxylic acid benzyl-*tert*-butylamide 288



2,5-Dimethyl-3-furoic acid (2.0 g, 14.3 mmol, 1.0 equiv.) and *N*-*tert*-butylbenzylamine (3.96 mL, 21.4 mmol, 1.5 equiv.) were treated according to **Method J** to afford the *title compound* (2.10 g, 55 %) as a white solid: m.p. 87.2-87.6 °C; R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2925 (CH), 1759 (C=O); δ_H(300 MHz, $CDCl_3$) 7.21-7.37 (5H, m, Ar*H*), 5.83 (1H, s, *H*-4), 4.78 (2H, s, CH_2Ph), 2.38 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.43 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.0, 151.6, 149.7, 140.8, 128.8, 127.2, 126.6, 119.6, 105.6, 58.1, 51.3, 29.0, 13.5, 13.1; *m/z* (C.I.) 286 (100 %, M + H^+); (Found (E.I): M^+, 285.1733. $C_{18}H_{23}NO$ requires 285.1729).

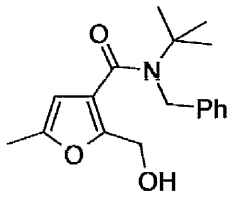
2-Ethyl-5-methylfuran-3-carboxylic acid benzyl-*tert*-butylamide 289



t-Butyllithium (1.25 mL of a 1.05 M solution in hexane, 1.32 mmol, 2.5 equiv.) was added dropwise to a stirred degassed solution of 2,5-dimethylfuran-3-carboxylic acid benzyl-*tert*-butylamide **288** (0.15 g, 0.53 mmol, 1.0 equiv.) and DMPU (0.41 mL, 3.16 mmol, 6.0 equiv.) in THF (5 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred at –78 °C for 12 h and quenched by the addition of iodomethane (0.6 mL). After warming to room temperature for 10 min water (5 mL) was added and the mixture extracted with EtOAc (4 × 5 mL). Combined organics were washed with water (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) to afford the *title compound* (0.087 g, 55 %) as a clear oil: R_f(5:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.21-7.37 (5H, m, Ar*H*), 5.82 (1H, s, C*H*), 4.86 (2H, s, CH_2Ph), 2.75 (2H, q, *J* 7.5, CH_2CH_3), 2.12 (3H, s, CH_3), 1.44 (9H, s, *t*Bu), 1.23 (3H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 168.7, 155.8, 149.2, 140.3, 128.4, 128.3, 126.9, 126.7, 126.3, 126.1, 118.4, 105.0, 57.7, 51.0, 28.6, 28.5, 20.5, 13.1,

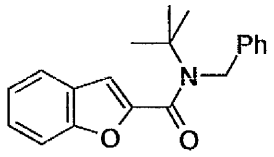
12.4; *m/z* (C.I.) 300 (100 %, M + H^+); (Found (E.I): M^+, 300.1959. $C_{19}H_{25}NO_2$ requires 300.1885).

2-Hydroxymethyl-5-methylfuran-3-carboxylic acid benzyl-*tert*-butylamide 290



t-Butyllithium (0.88 mL of a 1.6 M solution in hexane, 1.32 mmol, 2.5 equiv.) was added dropwise to a stirred solution of 2,5-dimethylfuran-3-carboxylic acid benzyl-*tert*-butylamide **288** (0.15 g, 0.53 mmol, 1.0 equiv.) and DMPU (0.41 mL, 3.16 mmol, 6.0 equiv.) in THF (5 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred at –78 °C for 12 h and quenched with saturated aqueous ammonium chloride (2 mL). After warming to room temperature for 10 min water (5 mL) was added and the mixture extracted with EtOAc (4 × 5 mL). Combined organics were washed with water (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) to afford the *title compound* (0.045 g, 40 %) as a yellow oil: R_f(5:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 3371 (OH), 2965 (CH), 1616 (C=O); δ_H(300 MHz, $CDCl_3$) 7.23-7.41 (5H, m, Ar*H*), 5.81 (1H, s, *H*-4), 4.78 (2H, s, CH_2OH), 4.61 (2H, s, CH_2Ph), 4.30 (1H, brs, O*H*), 2.18 (3H, s, CH_3), 1.24 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 177.2, 169.2, 156.9, 150.4, 140.5, 129.0, 128.9, 128.8, 127.5, 127.3, 126.3, 121.5, 105.5, 58.7, 57.4, 51.4, 28.7, 13.5; *m/z* (C.I.) 302 (100 %, M + H^+); (Found (E.I):M^+, 301.1674. $C_{18}H_{23}NO_3$ requires 301.1678).

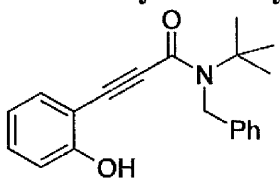
Benzofuran-2-carboxylic acid benzyl-*tert*-butylamide 292



Benzo[b]furan-2-carboxylic acid (2.0 g, 12.3 mmol, 1.0 equiv.) and N-*tert*-butyl benzylamine (3.43 mL, 18.5 mmol, 1.5 equiv.) were treated according to **Method J**. The crude product was purified by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) to afford the *title compound* (4.03 g, 71 %) as an off-white solid: m.p. 120.8-121.4 °C; R_f(1:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2927 (CH), 1728 (C=O); δ_H(300 MHz, $CDCl_3$) 7.61 (1H, dd, *J* 8.5 and 0.5 *H*-7), 7.52 (1H, dd, *J* 9.0 and 1.0, *H*-

4), 7.44 (1H, dd, *J* 9.0 and 1.0, *H*-5), 7.18-7.25 (5H, m, Ar*H*), 7.14 (1H, dd, *J* 8.5 and 0.5, *H*-6), 7.00 (1H, s, *H*-3), 4.80 (2H, s, CH_2), 1.42 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 159.9, 154.2, 140.0, 128.5, 127.0, 126.8, 126.2, 125.9, 123.7, 123.2, 121.9, 113.8, 112.3, 111.6, 109.43, 58.9, 52.3, 50.5, 28.3; *m/z* (C.I.) 308 (100 %, M + H^+); (Found (E.I):M^+, 307.1568. $C_{20}H_{21}NO_2$ requires 307.1571).

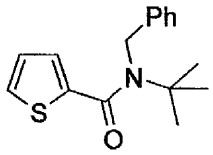
3-(2-Hydroxyphenyl)propynoic acid benzyl-*tert*-butylamide 293



Attempted cyclisation of benzofuran-2-carboxylic acid benzyl-*tert*-butylamide **292** using **Methods C** and **D** afforded the *title compound* (79 mg, 42 %) as a yellow oil: R_f (1:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 3061 (OH), 2967, 2213 (CH), 1602 (C=O), 1448 (CC); δ_H(300 MHz, $CDCl_3$) 7.34-7.12 (6H, m, Ar*H*), 7.02 (1H, d, *J* 8.0, *H*-2), 6.85 (1H, d, *J* 8.0, *H*-3), 6.66 (1H, dd, *J* 14.0 and 7.5, *H*-1), 4.98 (2H, s, CH_2), 1.37 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 160.9, 143.1, 137.2, 133.5, 129.6, 128.3, 128.1, 126.8, 120.7, 115.3, 109.5, 95.8, 88.2, 48.2, 46.4, 28.6; *m/z* (C.I.) 307 (100 %, M + H^+); (Found (E.I): M^+, 308.1573 $C_{20}H_{21}NO_2$ requires 308.1572).

4.3.3 Experimental Details for Chapter 2.3

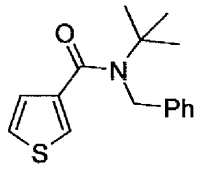
Thiophene-2-carboxylic acid benzyl-*tert*-butylamide 297



Thiophene-2-carboxylic acid (5.0 g, 39 mmol, 1.0 equiv.) and *N*-*tert*-butylbenzylamine (10.8 mL, 58 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (8.89 g, 84 %) as needles: m.p. 141.4-141.8 °C; R_f(10:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1609 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40 (1H, dd, *J* 4.0 and 1.0, *H*-3), 7.28-7.36 (5H, m, Ar*H*), 7.14 (1H, d, *J* 4.0, *H*-5), 6.84 (1H, dd, *J* 4.0 and 1.0, *H*-4), 4.90 (2H, s, CH_2Ph), 1.48 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.9, 141.9,

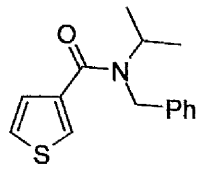
140.7, 129.1, 129.0, 127.6, 127.4, 127.1, 126.5, 59.3, 52.1, 28.9; *m/z* (C.I.) 274 (100 %, $M + H^+$); (Found (E.I):M^+, 273.1180. $C_{16}H_{19}NOS$ requires 273.1187).

Thiophene-3-carboxylic acid benzyl-*tert*-butylamide 298



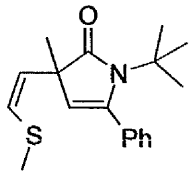
Thiophene-3-carboxylic acid (5.0 g, 39 mmol, 1.0 equiv.) and *N-tert*-butylbenzylamine (10.8 mL, 58 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (5.15 g, 50 %) as needles: m.p. 106.4-106.9 °C; R_f(10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40 (1H, t, *J* 2.5, *H*-5), 7.32-7.38 (3H, m, Ar*H*), 7.25-7.28 (4H, m, Ar*H*), 4.70 (2H, s, CH_2Ph), 1.50 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.9, 140.5, 139.5, 128.7, 127.2, 126.9, 126.0, 125.3, 124.9, 58.3, 51.4, 28.6; *m/z* (C.I.) 274 (100 %, M + H^+); (Found (E.I):M^+, 273.1180. $C_{16}H_{19}NOS$ requires 273.1187).

Thiophene-3-carboxylic acid benzylisopropylamide 299



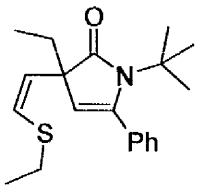
Thiophene-3-carboxylic acid (1.50 g, 11.7 mmol, 1.0 equiv.) and *N*-isopropyl benzylamine (2.94 mL, 17.6 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (2.91 g, 96 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 2973 (CH), 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.54 (1H, brs, *H*-5), 7.20-7.36 (7H, m, Ar*H*, *H*-2 and *H*-4), 4.68 (2H, s, CH_2Ph), 4.40 (1H, brs, $CH(CH_3)_2$), 1.20 (6H, brs, $CH(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 167.9, 139.4, 137.7, 128.8, 128.2, 127.2, 126.1, 125.6, 60.3, 31.2, 21.4, 14.5; *m/z* (C.I.) 260 (100 %, M + H^+); (Found (E.I):M^+, 259.1027. $C_{15}H_{17}NOS$ requires 259.1031).

1-*tert*-Butyl-3-methyl-3-(2-methylsulfanylvinyl)-5-phenyl-1,3-dihydropyrrol-2-one 300a



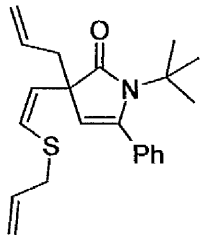
Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.21 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 60 %) as a clear oil: R_f(10:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2970 (CH), 1703 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40-7.45 (2H, m, Ar*H*), 7.33-7.38 (3H, m, Ar*H*), 5.95 (1H, d, *J* 10.0, SC*H*CH), 5.55 (1H, d, *J* 10.0, SCHC*H*), 5.35 (1H, s, C*H*CPh), 2.27 (3H, s, SCH_3), 1.38 (3H, s, CH_3), 1.33 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 182.1, 144.3, 135.9, 128.4, 127.7, 127.0, 126.9, 126.5, 114.3, 56.7, 50.5, 29.1, 23.1, 17.2; *m/z* (C.I.) 302 (100 %, M + H^+); (Found (E.I): M^+, 301.1498. $C_{18}H_{23}NOS$ requires 301.1500).

1-*tert*-Butyl-3-ethyl-3-(2-ethylsulfanylvinyl)-5-phenyl-1,3-dihydropyrrol-2-one 300b



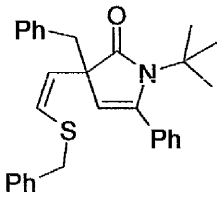
Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.26 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 65 %) as a clear oil: R_f(10:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40-7.45 (2H, m, Ar*H*), 7.33-7.38 (3H, m, Ar*H*), 6.02 (1H, d, *J* 10.0, SC*H*CH), 5.55 (1H, d, *J* 10.0, SCHC*H*), 5.32 (1H, s, C*H*CPh), 2.65 (2H, q, *J* 7.5, SCH_2CH_3), 1.82 (2H, q, *J* 7.5, CH_2CH_3), 1.32 (9H, s, *t*Bu), 1.28 (3H, t, *J* 7.5, SCH_2CH_3), 0.88 (3H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 182.2, 146.2, 137.1, 128.9, 128.8, 128.1, 127.9, 127.7, 127.6, 113.2, 57.9, 56.4, 30.8, 30.2, 28.9, 15.4, 9.6; *m/z* (C.I.) 330 (100 %, M + H^+); (Found (E.I) (E.I): M^+, 329.1808. $C_{20}H_{27}NOS$ requires 329.1808).

3-Allyl-3-(2-allylsulfanylvinyl)-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 300c



Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.28 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 60 %) as a clear oil: R_f(10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2975 (CH), 1703 (C=O); δ_H(300 MHz, $CDCl_3$) 7.35-7.45 (5H, m, Ar*H*), 6.00 (1H, d, *J* 10.0, SC*H*CH), 5.70-5.85 (2H, dd, *J* 7.0 and 3.0, 2 × CH_2CHCH_2), 5.60 (1H, d, *J* 10.0, SCHC*H*), 5.31 (1H, s, C*H*CPh), 5.05-5.18 (4H, m, 2 × CH_2CHCH_2), 3.25 (2H, d, *J* 7.0, SCH_2CHCH_2), 2.55 (2H, dd, *J* 7.5 and 7.0, CH_2CHCH_2), 1.32 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 181.9, 146.7, 137.3, 134.4, 133.3, 129.3, 128.5, 128.3, 127.5, 127.1, 118.7, 118.0, 113.3, 58.3, 55.9, 42.3, 37.8, 30.6; *m/z* (C.I.) 354 (100 %, M + H^+); (Found (E.I): M^+, 353.1811. $C_{22}H_{27}NOS$ requires 353.1808).

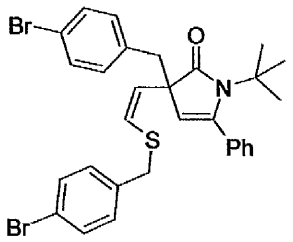
3-Benzyl-3-(2-benzylsulfanylvinyl)-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 300d



Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.39 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 55 %) as a clear oil: R_f(10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967 (CH), 1699 (C=O); δ_H(300 MHz, $CDCl_3$) 7.20-7.35 (15H, m, Ar*H*), 6.08 (1H, d, *J* 10.0, SC*H*CH), 5.70 (1H, d, *J* 10.0, SCHC*H*), 5.35 (1H, s, C*H*CPh), 3.88 (2H, s, SCH_2Ph), 3.10 (2H, d, *J* 12.5, CH_2Ph), 1.10 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 180.9, 145.7, 137.7, 136.7, 136.2, 130.7, 129.0, 128.9, 128.6,

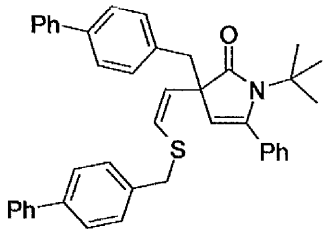
128.1, 127.9, 127.8, 127.6, 127.4, 127.2, 126.8, 126.4, 112.5, 57.7, 57.0, 47.8, 43.4, 38.9, 29.9, 20.8; *m/z* (C.I.) 454 (100 %, M + H^+); (Found (E.I): M^+, 453.2198. $C_{30}H_{31}NOS$ requires 453.2199).

3-(4-Bromobenzyl)-3-[2-(4-bromobenzylsulfanyl)vinyl]-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 300e



Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with 4-bromobenzyl bromide (0.80 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.16 g, 50 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2969 (CH), 1698 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.46 (9H, m, Ar*H*), 7.22 (2H, d, *J* 8.5, Ar*H*), 7.08 (2H, d, *J* 8.5, Ar*H*), 6.05 (1H, d, *J* 10.0, SC*H*CH), 5.72 (1H, d, *J* 10.0, SCHC*H*), 5.34 (1H, s, C*H*CPh), 3.82 (2H, s, SCH_2Ph), 3.10 (1H, d, *J* 12.5, CCH_AH_BPh), 3.00 (1H, d, *J* 12.5, CCH_AH_BPh), 1.08 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 180.9, 146.5, 136.9, 136.7, 135.4, 132.6, 131.9, 130.8, 128.9, 128.6, 128.1, 127.9, 127.8, 127.6, 127.4, 127.2, 126.8, 126.4, 120.7, 112.5, 58.2, 57.0, 42.9, 38.6, 30.1; *m/z* (C.I.) 610 (100 %, M + H^+); (Found (E.I): M^+, 609.0335. $C_{30}H_{29}NOBr_2S$ requires 609.0338).

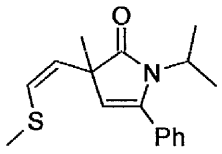
3-Biphenyl-4-ylmethyl-3-[2-(biphenyl-4-ylmethylsulfanyl)vinyl]-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 300f



Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with *p*-bromomethylbiphenyl (0.81 g, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 30:1

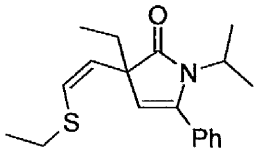
Petrol/EtOAc) afforded the *title compound* (0.13 g, 65 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1696 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25-7.68 (23H, m, Ar*H*), 6.18 (1H, d, *J* 10.0, SC*H*CH), 5.80 (1H, d, *J* 10.0, SCHC*H*), 5.50 (1H, s, C*H*CPh), 3.98 (2H, s, SCH_2Ph), 3.20 (1H, d, *J* 13.0, CCH_AH_BPh), 3.12 (1H, d, *J* 13.0, CCH_AH_BPh), 1.18 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 181.3, 146.1, 141.6, 140.9, 140.6, 139.7, 137.0, 136.9, 135.7, 131.4, 129.6, 129.2, 129.1, 128.9, 128.3, 128.1, 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 126.5, 126.4, 112.9, 58.1, 57.4, 43.4, 38.9, 30.2; *m/z* (C.I.) 606 (100 %, M + H^+); (Found (E.I): M^+, 605.8553. $C_{42}H_{39}NOS$ requires 605.8562).

1-Isopropyl-3-methyl-3-(2-methylsulfanylvinyl)-5-phenyl-1,3-dihydropyrrol-2-one 301a



Thiophene-3-carboxylic acid benzylisopropylamide **299** (0.15 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.22 mL, 3.5 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 65 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1703 (C=O); δ_H(300 MHz, $CDCl_3$) 7.43-7.47 (5H, m, Ar*H*), 6.00 (1H, d, *J* 9.5, SC*H*CH), 5.60 (1H, d, *J* 9.5, SCHC*H*), 5.50 (1H, s, C*H*CPh), 3.85 (1H, q, *J* 6.5, $CH(CH_3)_2$), 2.29 (3H, s, SCH_3), 1.44 (6H, d, *J* 6.5, $CH(CH_3)_2$), 1.40 (3H, s, CCH_3); δ_C(75 MHz, $CDCl_3$) 182.1, 144.6, 132.8, 129.9, 129.0, 128.7, 127.5, 112.9, 51.9, 46.4, 24.3, 20.3, 20.2, 18.4; *m/z* (C.I.) 288 (100 %, M + H^+); (Found (E.I): M^+, 287.1338. $C_{17}H_{21}NOS$ requires 287.1344).

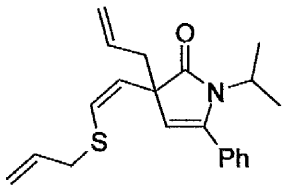
3-Ethyl-3-(2-ethylsulfanylvinyl)-1-isopropyl-5-phenyl-1,3-dihydropyrrol-2-one 301b



Thiophene-3-carboxylic acid benzylisopropylamide **299** (0.15 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.28 mL, 3.5 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 62 %) as a colourless oil: R_f(5:1 Petrol:EtOAc)

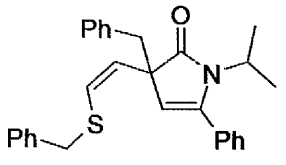
0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965 (CH), 1702 (C=O); δ_H(300 MHz, $CDCl_3$) 7.44-7.47 (5H, m, Ar*H*), 6.05 (1H, d, *J* 10.0, SC*H*CH), 5.62 (1H, d, *J* 10.0, SCHC*H*), 5.48 (1H, s, C*H*CPh), 3.85 (1H, q, *J* 6.5, C*H*$(CH_3)_2$), 2.67 (2H, q, *J* 7.0, SC$H_2$$CH_3$), 1.87 (2H, q, *J* 7.0, CC$H_2$$CH_3$), 1.41 (6H, d, *J* 6.5, CH$(CH_3)_2$), 1.31 (3H, t, *J* 7.0, SCH_2CH_3), 0.90 (3H, t, *J* 7.0, CCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 181.3, 145.4, 133.0, 129.1, 128.9, 128.8, 128.1, 127.6, 110.6, 56.7, 46.5, 31.0, 29.2, 20.3, 20.2, 15.6, 8.9; *m/z* (C.I.) 316 (100 %, $M + H^+$); Found (E.I): M^+, 315.1651. $C_{19}H_{25}NOS$ requires 315.1657.

3-Allyl-3-(2-allylsulfanylvinyl)-1-isopropyl-5-phenyl-1,3-dihydropyrrol-2-one 301c



Thiophene-3-carboxylic acid benzylisopropylamide **299** (0.15 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.29 mL, 3.5 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.12 g, 60 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972 (CH), 1704 (C=O); δ_H(300 MHz, $CDCl_3$) 7.40-7.48 (5H, m, Ar*H*), 6.05 (1H, d, *J* 10.0, SC*H*CH), 5.80-5.82 (2H, m, 2 × CH_2CHCH_2), 5.65 (1H, d, *J* 10.0, SCHC*H*), 5.47 (1H, s, C*H*CPh), 5.10-5.20 (4H, m, 2 × CH_2CHCH_2), 3.84 (1H, q, *J* 6.5, C*H*$(CH_3)_2$), 3.30 (2H, d, *J* 7.0, SCH_2CHCH_2), 2.55 (1H, dd, *J* 13.5 and 7.0, $CCH_AH_BCHCH_2$), 2.48 (1H, dd, *J* 13.5 and 7.0, $CCH_AH_BCHCH_2$), 1.41 (3H, d, *J* 6.5, CH$(CH_3)_2$), 1.38 (3H, d, *J* 6.5, CH$(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 180.6, 145.5, 134.3, 133.1, 132.8, 129.1, 128.8, 128.7, 127.2, 126.9, 118.7, 117.9, 110.5, 55.9, 46.5, 42.1, 37.6, 20.4, 20.3; *m/z* (C.I.) 340 (100 %, $M + H^+$); (Found (E.I): M^+, 339.1651. $C_{21}H_{25}NOS$ requires 339.1657).

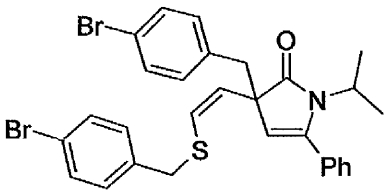
3-Benzyl-3-(2-benzylsulfanylvinyl)-1-isopropyl-5-phenyl-1,3-dihydropyrrol-2-one 301d



Thiophene-3-carboxylic acid benzylisopropylamide **299** (0.15 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.41 mL, 3.5 mmol, 6.0

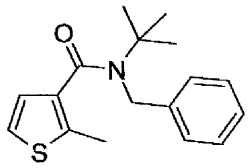
equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.17 g, 67 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1699 (C=O); δ_H(300 MHz, $CDCl_3$) 7.05-7.41 (15H, m, Ar*H*), 6.10 (1H, d, *J* 10.0, SC*H*CH), 5.77 (1H, d, *J* 10.0, SCHC*H*), 5.49 (1H, s, C*H*CPh), 3.91 (2H, s, SCH_2Ph), 3.54 (1H, q, *J* 7.0, C*H*$(CH_3)_2$), 3.16 (1H, d, *J* 12.5, CC$H_A$$H_B$Ph), 3.10 (1H, d, *J* 12.5, CC$H_A$$H_B$Ph), 1.21 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.05 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 180.0, 144.9, 137.9, 136.2, 132.8, 130.9, 129.1, 128.9, 128.8, 127.9, 127.7, 127.5, 127.3, 126.8, 126.6, 110.0, 57.3, 46.1, 43.6, 39.2, 20.2, 19.9; *m/z* (C.I.) 440 (100 %, M + H^+); (Found (E.I): M^+, 439.1651. $C_{29}H_{29}NOS$ requires 439.1657).

3-(4-Bromobenzyl)-3-[2-(4-bromobenzylsulfanyl)vinyl]-1-isopropyl-5-phenyl-1,3-dihydropyrrol-2-one 301e



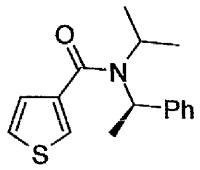
Thiophene-3-carboxylic acid benzylisopropylamide **299** (0.15 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method D** with *p*-bromobenzyl bromide (0.86 g, 3.5 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.19 g, 58 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2969 (CH), 1699 (C=O); δ_H(300 MHz, $CDCl_3$) 7.48 (2H, d, *J* 9.0, Ar*H*), 7.34-7.42 (6H, m, Ar*H*), 7.20 (2H, d, *J* 9.0, Ar*H*), 7.08-7.10 (3H, m, Ar*H*), 6.05 (1H, d, *J* 9.5, SC*H*CH), 5.73 (1H, d, *J* 9.5, SCHC*H*), 5.44 (1H, s, C*H*CPh), 3.83 (2H, s, SCH_2Ph), 3.56 (1H, q, *J* 7.0, C*H*$(CH_3)_2$), 3.10 (1H, d, *J* 12.5, CC$H_A$$H_B$Ph), 3.03 (1H, d, *J* 12.5, CC$H_A$$H_B$Ph), 1.23 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.07 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 179.8, 145.5, 136.9, 135.2, 132.6, 132.5, 131.9, 130.8, 130.7, 129.1, 128.7, 128.6, 127.9, 127.3, 121.4, 120.8, 109.5, 60.7, 57.1, 46.3, 42.9, 38.5, 20.1, 19.9, 14.5; *m/z* (C.I.) 580 (100 %, M + H^+); (Found (E.I): M^+, 597.0173. $C_{29}H_{27}NOBr_2S$ requires 597.0180).

2-Methylthiophene-3-carboxylic acid benzyl-*tert*-butylamide 303



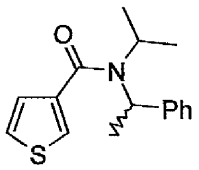
Thiophene-3-carboxylic acid benzyl-*tert*-butylamide **298** (0.15g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** at –78 °C with iodomethane (0.10 mL, 1.65 mmol, 3.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (1.03 g, 48 %) as needles: m.p. 98.3-98.7 °C; R_f(10:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.20-7.45 (5H, m, Ar*H*), 6.95-6.96 (2H, m, Ar*H*), 4.62 (2H, s, CH_2Ph), 2.50 (3H, s, CH_3), 1.75 (9H, s, *t*Bu); δ_C (75 MHz, $CDCl_3$) 169.9, 140.2, 137.9, 136.4, 129.9, 128.8, 127.4, 126.6, 122.8, 121.3, 60.7, 58.5, 51.3, 29.1, 13.9; *m/z* (C.I.) 288 (100 %, M + H^+); (Found (E.I): M^+, 287.1336. $C_{17}H_{21}NOS$ requires 287.1344).

(*R*)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide 309



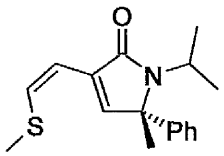
Thiophene-3-carboxylic acid (5.0 g, 39 mmol, 1.0 equiv.) and (*R*)-isopropyl-(1-phenylethyl)amine (11.7 g, 58.5 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (5.61 g, 58 %) as needles: $[\alpha]_D^{22}$ = +74.25 (c = 0.16 in $CHCl_3$); m.p. 89.4-89.7 °C; R_f(10:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2974 (CH), 1710 (C=O); δ_H(300 MHz, $CDCl_3$) 7.55 (1H, dd, *J* 3.0 and 1.0, *H*-5), 7.36-7.42 (5H, m, Ar*H*), 7.29-7.30 (2H, m, Ar*H*), 5.10 (1H, brs, C*H*CH_3), 3.50 (1H, brs, C*H*$(CH_3)_2$), 1.72 (3H, d, *J* 7.0, CHCH_3), 1.50 (3H, d, *J* 7.0, CH$(CH_3)_2$), 1.20 (3H, d, *J* 7.0, CH$(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 167.4, 138.9, 135.8, 134.5, 128.5, 128.4, 127.7, 127.5, 126.7, 124.7, 21.4, 20.7, 18.2; *m/z* (C.I.) 274 (100 %, M + H^+); (Found (E.I): M^+, 273.1182. $C_{13}H_{19}NOS$ requires 273.1187).

(±)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide 309



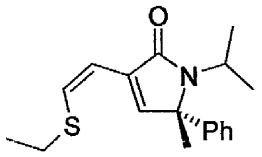
Thiophene-3-carboxylic acid (1.52 g, 11.9 mmol, 1.0 equiv.) and (±)-*N*-isopropyl-(1-phenylethyl)amine (3.55 g, 17.8 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) afforded the *title compound* (2.02 g, 62 %) as needles: m.p. 89.2-89.5 °C; R_f(10:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.55 (1H, dd, *J* 3.0 and 1.0, *H*-5), 7.36-7.42 (5H, m, Ar*H*), 7.30-7.32 (2H, m, Ar*H*), 5.10 (1H, brs, C*H*CH_3), 3.50 (1H, brs, C*H*$(CH_3)_2$), 1.72 (3H, d, *J* 7.0, CHC*H*$_3$), 1.50 (3H, d, *J* 7.0, CH(C*H*$_3)_2$), 1.20 (3H, d, *J* 7.0, CH(C*H*$_3)_2$); δ_C(75 MHz, $CDCl_3$) 167.3, 140.7, 139.1, 134.2, 128.6, 128.5, 127.7, 127.5, 126.7, 124.7, 21.4, 20.7, 18.2; *m/z* (C.I.) 274 (100 %, $M + H^+$); (Found (E.I): M^+, 273.1182. $C_{13}H_{19}NOS$ requires 273.1187).

1-Isopropyl-5-methyl-3-(2-methylsulfanylvinyl)-5-phenyl-1,5-dihydropyrrol-2-one 311a



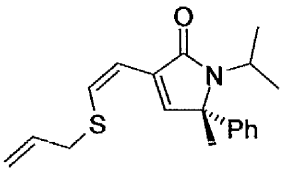
(*R*)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.21 ml, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 50 %) as a colourless oil: $[\alpha]_D^{22}$ = +277.2 (c = 0.10 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.40; $\nu_{max}(CHCl_3)/cm^{-1}$ 2974 (CH), 1680 (C=O); δ_H(300 MHz, $CDCl_3$) 7.32-7.40 (5H, m, Ar*H*), 6.96 (1H, s, C*H*C(CH_3)Ph), 6.53 (1H, d, *J* 10.5, SC*H*CH), 6.40 (1H, d, *J* 10.5, SCHC*H*), 3.35 (1H, q, *J* 6.5, C*H*$(CH_3)_2$), 2.44 (3H, s, SC*H*$_3$), 1.84 (3H, s, CC*H*$_3$Ph), 1.40 (3H, d, *J* 6.5, CH(C*H*$_3)_2$), 1.22 (3H, d, *J* 6.5, CH(C*H*$_3)_2$); δ_C(75 MHz, $CDCl_3$) 170.0, 147.2, 138.8, 135.1, 131.7, 128.9, 128.8, 128.2, 126.9, 113.8, 68.3, 45.5, 21.7, 20.8, 19.7, 18.7; *m/z* (C.I.) 288 (100 %, $M + H^+$); (Found (E.I): M^+, 287.1569. $C_{17}H_{21}NOS$ requires 287.1572).

3-(2-Ethylsulfanylvinyl)-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one 311b



(*R*)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.26 ml, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 60 %) as a colourless oil: $[\alpha]_D^{22}$ = +240.4 (c = 0.10 in $CHCl_3$); R_f(5:1 Petrol:EtOAc) 0.40; ν_{max}($CHCl_3$)/cm^{-1} 2974 (CH), 1683 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.38 (5H, m, Ar*H*), 6.97 (1H, s, C*H*C(CH_3)Ph), 6.58 (1H, d, *J* 10.5, SC*H*CH), 6.42 (1H, d, *J* 10.5, SCHC*H*), 3.30 (1H, q, *J* 6.5, C*H*(CH_3)$_2$), 2.85 (2H, q, *J* 7.5, SCH_2CH_3), 1.84 (3H, s, CCH_3Ph), 1.40 (3H, d, *J* 6.5, CH(CH_3)$_2$), 1.34 (3H, t, *J* 7.5, SCH_2CH_3), 1.22 (3H, d, *J* 6.5, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 170.0, 152.7, 147.2, 138.9, 133.2, 131.8, 128.9, 128.7, 127.9, 126.9, 113.9, 68.3, 45.5, 29.6, 21.7, 20.8, 19.7, 15.7; *m/z* (C.I.) 302 (100 %, M + H^+); (Found (E.I): M^+, 301.1498. $C_{18}H_{23}NOS$ requires 301.1500).

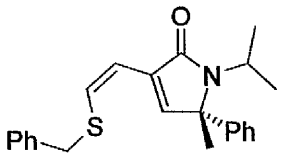
3-(2-Allylsulfanylvinyl)-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one 311c



(*R*)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.28 ml, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 70 %) as a colourless oil: $[\alpha]_D^{22}$ = +167.8 (c = 0.10 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.55; ν_{max} ($CHCl_3$)/cm^{-1} 2973 (CH), 1680 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.38 (5H, m, Ar*H*), 6.98 (1H, s, C*H*C(CH_3)Ph), 6.53 (1H, d, *J* 10.5, SC*H*CH), 6.42 (1H, d, *J* 10.5, SCHC*H*), 5.85-5.86 (1H, m, CH_2CHCH_2), 5.25-5.28 (2H, m, CH_2CHCH_2), 3.43 (2H, d, *J* 7.0, CH_2CHCH_2), 3.33 (1H, q, *J* 6.5, C*H*(CH_3)$_2$), 1.84 (3H, s, CCH_3Ph), 1.41 (3H, d, *J* 6.5, CH(CH_3)$_2$), 1.23 (3H, d, *J* 6.5, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 169.9, 147.3, 138.9, 133.7, 131.8, 131.7,

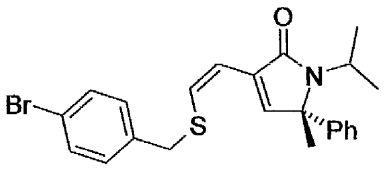
128.8, 128.2, 126.9, 118.6, 114.4, 68.3, 45.5, 37.9, 21.7, 20.8, 19.7; *m/z* (C.I.) 314 (100 %, M + H^+); (Found (E.I): M^+, 313.1495. $C_{19}H_{23}NOS$ requires 313.1500).

3-(2-Benzylsulfanylvinyl)-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one 311d



(*R*)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.39 ml, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 55 %) as a colourless oil: $[\alpha]_D^{22}$ = +133.6 (c = 0.10 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.60; ν_{max} ($CHCl_3$)/cm^{-1} 2973 (CH), 1680 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.38 (10H, m, Ar*H*), 6.97 (1H, s, C*H*C(CH_3)Ph), 6.58 (1H, d, *J* 10.5, SC*H*CH), 6.42 (1H, d, *J* 10.5, SCHC*H*), 4.05 (2H, s, SCH_2Ph), 3.30 (1H, q, *J* 6.5, C*H*(CH_3)$_2$), 1.83 (3H, s, CCH_3Ph), 1.40 (3H, d, *J* 6.5, CH(CH_3)$_2$), 1.22 (3H, d, *J* 6.5, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 169.9, 147.5, 138.9, 137.3, 135.1, 132.1, 129.1, 129.0, 128.8, 128.6, 128.1, 127.8, 127.3, 126.9, 114.3, 68.3, 45.5, 39.5, 21.7, 20.8, 19.7; *m/z* (C.I.) 364 (100 %, M + H^+); (Found (E.I): M^+, 363.5318. $C_{23}H_{25}NOS$ requires 363.5322).

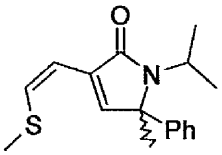
3-[2-(4-Bromobenzylsulfanyl)-vinyl]-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one 311e



(*R*)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with 4-bromobenzyl bromide (0.82 g, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.16 g, 70 %) as a colourless oil: $[\alpha]_D^{22}$ = +204.3 (c = 0.10 in $CHCl_3$); R_f(10:1 Petrol:EtOAc) 0.50; ν_{max}($CHCl_3$)/cm^{-1} 2973 (CH), 1678 (C=O); δ_H(300 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8.5, Ar*H*), 7.30-7.38 (5H, m, Ar*H*), 7.24 (2H, d, *J* 8.5, Ar*H*), 6.95 (1H, s, C*H*C(CH_3)Ph), 6.52 (1H, d, *J* 10.5, SC*H*CH), 6.40 (1H, d, *J* 10.5, SCHC*H*), 3.98 (2H, s, SCH_2Ph), 3.30 (1H, q, *J* 6.5,

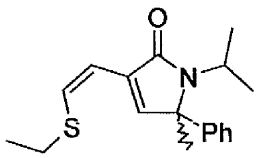
C*H*(CH_3)$_2$), 1.82 (3H, s, CC*H*$_3$Ph), 1.40 (3H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 1.22 (3H, d, *J* 6.5, CH(C*H*$_3$)$_2$); δ_C(75 MHz, $CDCl_3$) 169.8, 147.7, 138.8, 136.4, 132.2, 131.8, 131.6, 131.3, 130.8, 129.8, 128.8, 128.2, 126.9, 121.8, 114.9, 68.3, 45.5, 38.8, 21.7, 20.8, 19.7; *m/z* (C.I.) 442 (100 %, M + H^+); (Found (E.I): M^+, 441.0753. $C_{23}H_{24}NOBrS$ requires 441.0762).

(±)-1-Isopropyl-5-methyl-3-(2-methylsulfanylvinyl)-5-phenyl-1,5-dihydropyrrol-2-one (±)-311a



(±)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.21 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 60 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.40; ν_{max}($CHCl_3$)/cm^{-1} 2971 (CH), 1684 (C=O); δ_H(300 MHz, $CDCl_3$) 7.32-7.40 (5H, m, Ar*H*), 6.96 (1H, s, C*H*C(CH$_3$)Ph), 6.53 (1H, d, *J* 10.5, SC*H*CH), 6.40 (1H, d, *J* 10.5, SCHC*H*), 3.35 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 2.44 (3H, s, SC*H*$_3$), 1.86 (3H, s, CC*H*$_3$Ph), 1.40 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.22 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$); δ_C(75 MHz, $CDCl_3$) 170.0, 147.2, 138.8, 135.1, 131.7, 128.9, 128.8, 128.2, 126.9, 113.8, 68.3, 45.5, 21.7, 20.8, 19.7, 18.7; *m/z* (C.I.) 288 (100 %, M + H^+); Found (E.I): M^+, 287.1332. $C_{17}H_{21}NOS$ requires 287.1344.

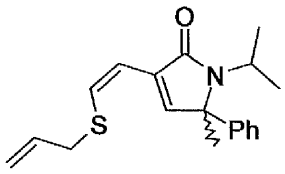
(±)-3-(2-Ethylsulfanylvinyl)-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one (±)-311b



(±)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.26 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 60 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.40; ν_{max}($CHCl_3$)/cm^{-1} 2974 (CH), 1685 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.39 (5H, m, Ar*H*), 6.97 (1H, s, C*H*C(CH$_3$)Ph), 6.58 (1H, d, *J* 10.5, SC*H*CH), 6.40

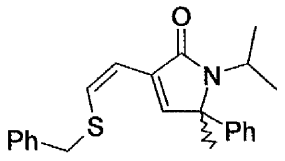
(1H, d, *J* 10.5, SCHC*H*), 3.30 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 2.85 (2H, q, *J* 7.5, S$CH_2$$CH_3$), 1.83 (3H, s, CC$H_3$Ph), 1.40 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.34 (3H, t, *J* 7.5, SCH_2CH_3), 1.22 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 170.0, 152.7, 147.2, 138.9, 133.2, 131.8, 128.9, 128.7, 127.9, 126.9, 113.9, 68.3, 45.5, 29.6, 21.7, 20.8, 19.7, 15.7; *m/z* (C.I.) 302 (100 %, M + H^+); (Found (E.I): M^+, 301.1495. $C_{18}H_{23}NOS$ requires 301.1500).

(±)-3-(2-Allylsulfanylvinyl)-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one (±)-311c



(±)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.28 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 60 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.55; ν_{max}($CHCl_3$)/cm^{-1} 2974 (CH), 1681 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.39 (5H, m, Ar*H*), 6.98 (1H, s, C*H*C(CH$_3$)Ph), 6.54 (1H, d, *J* 10.5, SC*H*CH), 6.42 (1H, d, *J* 10.5, SCHC*H*), 5.85 (1H, m, CH_2C*H*CH_2), 5.25 (2H, m, CH_2CHCH_2), 3.43 (2H, d, *J* 7.0, CH_2CHCH_2), 3.33 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 1.84 (3H, s, CCH_3Ph), 1.41 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.22 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 169.9, 147.3, 138.9, 133.7, 131.8, 131.7, 128.8, 128.2, 126.9, 118.6, 114.4, 68.3, 45.5, 37.9, 21.7, 20.8, 19.7; *m/z* (C.I.) 314 (100 %, M + H^+); (Found (E.I): M^+, 313.1495. $C_{19}H_{23}NOS$ requires 313.1500).

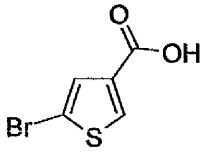
(±)-3-(2-Benzylsulfanylvinyl)-1-isopropyl-5-methyl-5-phenyl-1,5-dihydropyrrol-2-one (±)-311d



(±)-Thiophene-3-carboxylic acid isopropyl-(1-phenylethyl)amide **309** (0.15 g, 0.55 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.39 mL, 3.3 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 55 %) as a colourless oil: R_f(10:1

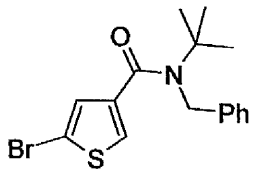
Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2974 (CH), 1679 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.39 (10H, m, Ar*H*), 6.97 (1H, s, C*H*C(CH_3)Ph), 6.58 (1H, d, *J* 10.5, SC*H*CH), 6.42 (1H, d, *J* 10.5, SCHC*H*), 4.05 (2H, s, SCH_2Ph), 3.32 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 1.83 (3H, s, CCH_3Ph), 1.40 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.22 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 169.9, 147.5, 138.9, 137.3, 135.1, 132.1, 129.1, 129.0, 128.8, 128.6, 128.1, 127.8, 127.3, 126.9, 114.3, 68.3, 45.5, 39.5, 21.7, 20.8, 19.7; *m/z* (C.I.) 364 (100 %, M + H^+); (Found (E.I): M^+, 363.1651. $C_{23}H_{25}NOS$ requires 363.1657).

5-Bromothiophene-3-carboxylic acid 312[197]



A solution of bromine (0.60 mL, 11.7 mmol, 1.0 equiv.) in glacial acetic acid (10 mL) was added dropwise to a stirred solution of thiophene-3-carboxylic acid (1.5 g, 11.7 mmol, 1.0 equiv.) in glacial acetic acid (13 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 30 min and poured into cold water. The precipitate was collected by filtration and washed with water (3 × 10 mL) to afford the *title compound* (1.85 g, 75%) as needles: m.p. 117.1-117.9 °C (lit.,[197] 117-118 °C); R_f (1:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3432 (OH), 1690 (C=O); δ_H(300 MHz, $CDCl_3$) 8.16 (1H, d, *J* 1.5, *H*-2), 7.56 (1H, d, *J* 1.5, *H*-4); δ_C(75 MHz, $CDCl_3$) 166.3, 136.0, 133.2, 130.6, 113.6; *m/z* (C.I.) 207 (100 %, M + H^+); (Found (E.I): M^+, 205.9026. $C_5H_3BrSO_2$ requires 205.9032).

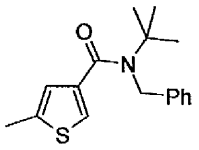
5-Bromothiophene-3-carboxylic acid benzyl-*tert*-butylamide 313



5-Bromothiophene-3-carboxylic acid **312** (1.0 g, 2.4 mmol, 1.0 equiv.) and N-*tert*-butyl benzylamine (1.34 g, 3.6 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.80 g, 95 %) as needles: m.p. 92.2-92.6 °C; R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1631 (C=O); δ_H(300 MHz, $CDCl_3$) 7.27-7.43 (6H, m, Ar*H* and *H*-2), 7.16 (1H, d, *J* 1.5, *H*-4), 4.72 (2H, s, CH_2Ph), 2.20 (9H, s, *t*Bu); δ_C(75

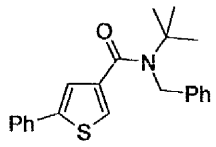
MHz, $CDCl_3$) 167.8, 140.4, 140.2, 130.2, 129.0, 128.9, 127.4, 126.6, 126.3, 126.2, 112.7, 58.7, 51.6, 28.8; *m/z* (C.I.) 352 (100 %, M + H^+-Br^{79}) 354 (100 %, M + H^+-Br^{81}); (Found (E.I): M^+, 351.0364. $C_{16}H_{18}NOBrS$ requires 351.0366).

5-Methylthiophene-3-carboxylic acid benzyl-*tert*-butylamide 314



A solution of sodium hydrogen carbonate (3.42 mL of a 1.0 M solution in water, 3.42 mmol, 6.0 equiv.) was added dropwise to a degassed solution of 5-bromothiophene-3-carboxylic acid benzyl-*tert*-butylamide **313** (0.2 g, 0.57 mmol, 1.0 equiv.), methylboronic acid (0.05 g, 0.79 mmol, 1.4 equiv.) and $PdCl_2$(dppf) (0.023 g, 0.028 mmol, 5 % mol) in acetonitrile (15 mL). The mixture was heated under reflux for 16 h, cooled to room temperature and water added (10 mL). The mixture was extracted with EtOAc (4 × 5 mL) washed with water (2 × 10 mL) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 61 %) as needles: m.p. 89.3-89.6 °C; R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2963 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.25-7.38 (5H, m, Ar*H*), 7.13 (1H, d, *J* 1.5, *H*-4), 6.84 (1H, dd, *J* 1.5 and 1.0, *H*-2), 4.72 (2H, s, CH_2Ph), 2.38 (3H, d, *J* 1.0, CH_3), 1.47 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.4, 140.8, 140.0, 139.5, 129.0, 128.9, 127.2, 126.4, 125.7, 122.7, 58.4, 51.7, 28.8, 15.3; *m/z* (C.I.) 288 (100 %, M + H^+); (Found (E.I): M^+, 287.1417. $C_{17}H_{21}NOS$ requires 287.1344).

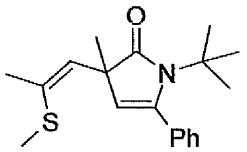
5-Phenylthiophene-3-carboxylic acid benzyl-*tert*-butylamide 315



A solution of sodium hydrogen carbonate (34.2 mL of a 1.0 M solution in water, 34.2 mmol, 6.0 equiv.) was added dropwise to a degassed solution of 5-bromothiophene-3-carboxylic acid benzyl-*tert*-butylamide **313** (2.0 g, 5.7 mmol, 1.0 equiv.), phenylboronic acid (0.97 g, 7.98 mmol, 1.4 equiv.) and $PdCl_2$(dppf) (0.23 g, 0.28 mmol, 5 % mol) in acetonitrile (150 mL). The mixture was heated under reflux for 16 h, cooled to room temperature and water added (25 mL). The mixture was extracted with EtOAc (4 × 50

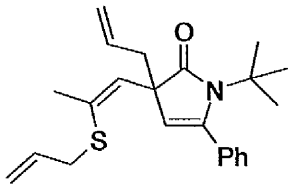
mL) washed with water (2 × 25 mL) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (1.75 g, 88 %) as needles: m.p. 100.2-100.6 °C; R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.48 (2H, d, *J* 7.0, Ar*H*) 7.27-7.42 (10 H, m, Ar*H*), 4.78 (2H, s, CH_2Ph), 1.54 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.1, 144.6, 140.7, 140.6, 133.9, 129.2, 128.9, 128.7, 128.1, 127.3, 126.4, 126.1, 124.2, 123.5, 58.6, 51.7, 28.8, 14.6; *m/z* (C.I.) 350 (100 %, M + H^+); (Found (E.I): M^+, 349.1573. $C_{22}H_{23}NOS$ requires 349.1500).

1-*tert*-Butyl-3-methyl-3-(2-methylsulfanylpropenyl)-5-phenyl-1,3-dihydropyrrol-2-one 316a



5-Methylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **314** (0.124 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.16 mL, 2.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 66 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965, 2923 (CH), 1704 (C=O); δ_H(300 MHz, $CDCl_3$) 7.31-7.39 (5H, m, Ar*H*), 5.54 (1H, d, *J* 1.0, SC(CH_3)C*H*), 5.31 (1H, s, C*H*CPh), 2.20 (3H, s, SCH_3), 2.01 (3H, d, *J* 1.0, SC(CH_3)CH), 1.37 (3H, s, CCH_3), 1.33 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 184.1, 145.1, 137.4, 134.0, 129.7, 129.0, 128.9, 128.3, 128.2, 128.1, 127.7, 116.5, 57.7, 51.3, 30.3, 25.6, 23.8, 14.5; *m/z* (C.I.) 316 (100 %, M + H^+); (Found (E.I): M^+, 315.1657. $C_{19}H_{25}NOS$ requires 315.1651).

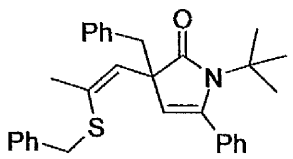
3-Allyl-3-(2-allylsulfanylpropenyl)-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 316b



5-Methylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **314** (0.124 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.22 mL, 2.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1

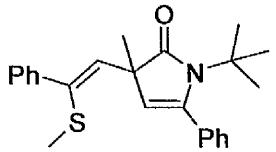
Petrol/EtOAc) afforded the *title compound* (0.12 g, 75 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972, 2920 (CH), 1701 (C=O); δ_H(300 MHz, $CDCl_3$) 7.31-7.41 (5H, m, Ar*H*), 5.76-5.78 (2H, m, 2 × CH_2CHCH_2), 5.71 (1H, d, *J* 1.0, $SC(CH_3)CH$), 5.26 (1H, s, C*H*CPh), 5.06-5.21 (4H, m, 2 × CH_2CHCH_2), 3.33-3.35 (2H, m, SCH_2CHCH_2), 2.55-2.56 (2H, m, CCH_2CHCH_2), 2.01 (3H, d, *J* 1.0, $SC(CH_3)CH$), 1.31 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 182.3, 145.9, 137.3, 134.6, 133.3, 129.2, 129.1, 129.0, 128.7, 128.3, 128.2, 128.1, 127.4, 126.9, 117.3, 114.0, 55.1, 43.3, 34.4, 30.4, 29.1, 24.3; *m/z* (C.I.) 368 (100 %, M + H^+); (Found (E.I): M^+, 367.1961. $C_{23}H_{29}NOS$ requires 367.1964).

3-Benzyl-3-(2-benzylsulfanylpropenyl)-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 316c



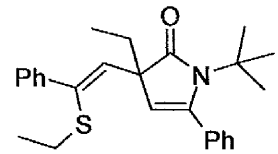
5-Methylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **314** (0.124 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.31 mL, 2.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 56 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968, 2920 (CH), 1698 (C=O); δ_H(300 MHz, $CDCl_3$) 7.18-7.34 (15H, m, Ar*H*), 5.73 (1H, d, *J* 1.5, $SC(CH_3)CH$), 5.40 (1H, s, C*H*CPh), 3.96 (2H, s, SCH_2Ph), 3.04 (2H, s, CCH_2Ph), 2.10 (3H, d, *J* 1.5, $SC(CH_3)CH$), 1.06 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 181.8, 145.3, 138.1, 136.9, 136.5, 133.2, 131.1, 130.9, 130.7, 130.2, 129.4, 129.2, 128.9, 128.7, 128.6, 128.2, 127.9, 127.7, 127.4, 127.2, 127.1, 127.0, 126.6, 113.6, 57.7, 56.8, 44.5, 35.9, 30.1, 24.8; *m/z* (C.I.) 468 (100 %, M + H^+); (Found (E.I): M^+, 467.2353. $C_{31}H_{33}NOS$ requires 467.2356).

3-Methyl-1-(1-methyl-1-phenylethyl)-3-(2-methylsulfanyl-2-phenylvinyl)-5-phenyl-1,3-dihydropyrrol-2-one 317a



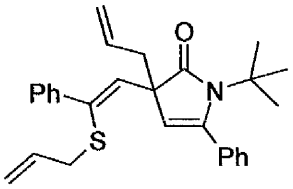
5-Phenylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **315** (0.175 g, 0.50 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.19 mL, 3.0 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 60 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967, 2924 (CH), 1665 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.60 (10H, m, Ar*H*), 5.97 (1H, s, SC(Ph)C*H*), 5.38 (1H, s, C*H*CPh), 1.92 (3H, s, SCH_3), 1.51 (3H, s, CCH_3), 1.38 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 183.9, 145.4, 140.4, 139.8, 137.8, 137.4, 134.9, 129.1, 128.5, 128.3, 128.1, 125.4, 116.6, 57.7, 55.4, 52.0, 30.3, 29.1, 25.8, 15.9; *m/z* (C.I.) 378 (100 %, M + H^+); (Found (E.I): M^+, 377.1886. $C_{24}H_{27}NOS$ requires 377.1813).

1-*tert*-Butyl-3-ethyl-3-(2-ethylsulfanyl-2-phenylvinyl)-5-phenyl-1,3-dihydropyrrol-2-one 317b



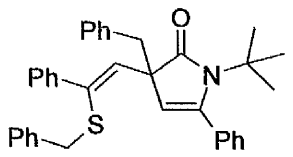
5-Phenylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **315** (0.15 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.21 mL, 2.58 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 61 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966, 2926 (CH), 1701 (C=O); δ_H(300 MHz, $CDCl_3$) 7.30-7.56 (10H, m, Ar*H*), 5.99 (1H, s, SC(Ph)C*H*), 5.38 (1H, s, C*H*CPh), 2.38 (2H, q, *J* 7.5, SCH_2CH$_3$), 1.95 (2H, q, *J* 7.5, CCH_2CH$_3$), 1.39 (9H, s, *t*Bu), 1.07 (3H, t, *J* 7.5, SCH$_2$CH_3), 0.98 (3H, t, *J* 7.5, CCH$_2$CH_3); δ_C(75 MHz, $CDCl_3$) 182.8, 146.1, 140.4, 138.9, 137.5, 135.6, 129.2, 128.4, 128.3, 128.2, 128.1, 127.9, 114.2, 57.9, 56.6, 32.3, 30.4, 29.1, 26.7, 15.0, 8.9; *m/z* (C.I.) 406 (100 %, M + H^+); (Found (E.I): M^+, 405.2194. $C_{26}H_{31}NOS$ requires 405.2197).

3-Allyl-3-(2-allylsulfanyl-2-phenylvinyl)-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 317c



5-Phenylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **315** (0.15 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.22 mL, 2.58 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.13 g, 71 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2973, 2920 (CH), 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 7.28-7.54 (10H, m, Ar*H*), 6.03 (1H, s, SC(Ph)C*H*), 5.63-5.92 (2H, m, 2 × CH_2CHCH_2), 5.38 (1H, s, C*H*CPh), 5.17-5.18 (2H, m, SCH_2CHCH_2), 4.85 (2H, dd, *J* 17.0 and 1.5, CH_2CHCH_2), 3.08 (1H, dd, *J* 13.5 and 7.0, SCH_AH_BCHCH2), 3.04 (1H, dd, *J* 13.5 and 7.0, $SCH_AH_BCHCH_2$), 2.71 (1H, dd, *J* 13.0 and 7.0, CCH_AH_BCHCH2), 2.58 (1H, dd, *J* 13.0 and 7.0, $CCH_AH_BCHCH_2$), 1.37 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 182.2, 146.1, 140.2, 139.1, 137.3, 134.9, 134.2, 133.3, 129.2, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 118.9, 117.2, 114.1, 57.9, 55.8, 43.4, 35.9, 30.4, 28.9; *m/z* (C.I.) 430 (100 %, $M + H^+$); (Found (E.I): M^+, 429.2196. $C_{28}H_{31}NOS$ requires 429.2199).

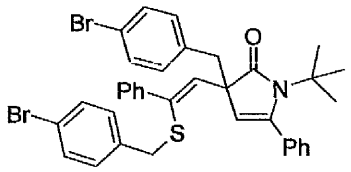
3-Benzyl-3-(2-benzylsulfanyl-2-phenylvinyl)-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 317d



5-Phenylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **315** (0.15 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.31 mL, 2.58 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 50 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2970, 2924 (CH), 1698 (C=O); δ_H(300 MHz, $CDCl_3$) 7.62 (2H, dd, *J* 8.0 and 1.5, Ar*H*), 7.06-7.45 (18H, m, Ar*H*), 6.18 (1H, s, SC(Ph)C*H*), 5.50 (1H, s, C*H*CPh), 3.60 (1H, d, *J* 12.5, SCH_AH_BPh), 3.58 (1H, d, *J* 12.5, SCH_AH_BPh), 3.06 (1H, d, *J* 12.5, CCH_AH_BPh), 3.05 (1H, d, *J* 12.5, CCH_AH_BPh), 1.09

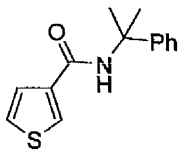
(9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 181.7, 145.3, 140.4, 138.8, 138.4, 136.9, 136.4, 135.6, 131.1, 129.4, 129.1, 128.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 127.1, 126.7, 113.8, 57.8, 57.5, 44.4, 37.5, 30.1; *m/z* (C.I.) 530 (100 %, M + H^+); (Found (E.I): M^+, 529.2515. $C_{36}H_{35}NOS$ requires 529.2512).

3-(4-Bromobenzyl)-3-[2-(4-bromobenzylsulfanyl)-2-phenylvinyl]-1-*tert*-butyl-5-phenyl-1,3-dihydropyrrol-2-one 317e



5-Phenylthiophene-3-carboxylic acid benzyl-*tert*-butylamide **315** (0.15 g, 0.43 mmol, 1.0 equiv.) was treated according to **Method D** with *p*-bromobenzyl bromide (0.64 g, 2.58 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.18 g, 60 %) as needles: m.p. 71.3-71.6 °C; R_f(5:1 Petrol:EtOAc) 0.55; ν_{max}($CHCl_3$)/cm^{-1} 2970, 2922 (CH), 1698 (C=O); δ_H(300 MHz, $CDCl_3$) 7.54 (2H, dd, *J* 8.5 and 1.5, Ar*H*), 7.28-7.43 (12H, m, Ar*H*), 7.10 (2H, d, *J* 8.5, Ar*H*), 6.86 (2H, d, *J* 8.5, Ar*H*), 6.10 (1H, s, SC(Ph)C*H*), 5.43 (1H, s, C*H*CPh), 3.53 (1H, d, *J* 13.0, SCH_AH_BPh), 3.33 (1H, d, *J* 13.0, SCH_AH_BPh), 3.06 (1H, d, *J* 13.0, CCH_AH_BPh), 3.05 (1H, d, *J* 13.0, CCH_AH_BPh), 1.11 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 181.4, 145.9, 139.9, 138.8, 137.4, 136.7, 135.2, 132.8, 131.6, 130.8, 129.1, 128.7, 128.5, 128.4, 128.3, 128.0, 120.9, 120.8, 113.2, 58.0, 57.2, 43.9, 36.7, 30.1; *m/z* (C.I.) 688 (100 %, M + H^+); (Found (E.I): M^+, 687.0750. $C_{36}H_{33}NOBr_2S$ requires 687.0722).

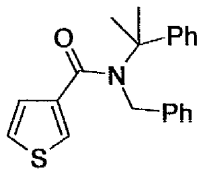
Thiophene-3-carboxylic acid (1-methyl-1-phenylethyl)amide 318



Thiophene-3-carboxylic acid (1.50 g, 11.7 mmol, 1.0 equiv.) and cumylamine (2.37 g, 17.6 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (2.35 g, 82 %) as needles: m.p. 171.8-172.4 °C; R_f(5:1 Petrol:EtOAc) 0.35; ν_{max} ($CHCl_3$)/cm^{-1} 3303 (NH), 2973 (CH), 1629 (C=O); δ_H(300 MHz, $CDCl_3$) 7.86 (1H, dd, *J* 3.0 and 1.5,

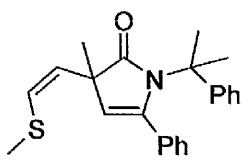
H-5), 7.49-7.52 (2H, m, Ar*H*), 7.30-7.42 (5H, m, Ar*H*), 6.30 (1H, brs, N*H*), 1.86 (6H, s, C(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 162.3, 147.1, 138.8, 128.8, 128.2, 127.1, 126.7, 126.4, 125.0, 56.5, 29.5; *m/z* (C.I.) 246 (100 %, M + H^+); (Found (E.I): M^+, 245.0869. $C_{14}H_{15}NOS$ requires 245.0874).

Thiophene-3-carboxylic acid benzyl-(1-methyl-1-phenylethyl)amide 319



Thiophene-3-carboxylic acid (1-methyl-1-phenylethyl)amide **318** (1.15 g, 4.7 mmol, 1.0 equiv.) in DMF (10 mL) was added dropwise to a suspension of sodium hydride (0.28 g, 7.1 mmol, 1.5 equiv.) at 0 °C under a nitrogen atmosphere and the mixture was stirred at room temperature for 14 h. The mixture was cooled to 0 °C and a solution of benzyl bromide (0.95 mL, 8.0 mmol, 1.7 equiv.) in DMF (5 mL) added dropwise. The mixture was stirred at room temperature for 4 days and quenched with water (10 mL). The mixture was extracted with EtOAc (4 × 15 mL) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.71 g, 50 %) as needles: m.p. 117.8-118.2 °C; R_f(5:1 Petrol:EtOAc) 0.55; ν_{max}($CHCl_3$)/cm^{-1} 2923 (CH), 1633 (C=O); δ_H(300 MHz, $CDCl_3$) 7.21-7.50 (13H, m, Ar*H*), 4.97 (2H, s, CH_2Ph), 1.74 (6H, s, C(CH_3)$_2$Ph); δ_C(75 MHz, $CDCl_3$) 168.4, 148.9, 140.2, 139.1, 129.0, 128.8, 128.2, 127.9, 127.6, 127.1, 126.8, 126.3, 126.1, 125.7, 125.6, 125.0, 124.5, 62.9, 52.2, 29.5, 28.9; *m/z* (C.I.) 336 (100 %, M + H^+); (Found (E.I): M^+, 335.1420. $C_{21}H_{21}NOS$ requires 335.1417).

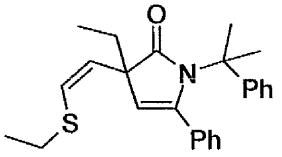
3-Methyl-1-(1-methyl-1-phenylethyl)-3-(2-methylsulfanylvinyl)-5-phenyl-1,3-dihydropyrrol-2-one 320a



Thiophene-3-carboxylic acid benzyl-(1-methyl-1-phenylethyl)amide **319** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.17 mL, 2.68 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 62 %) as a colourless oil: R_f(5:1

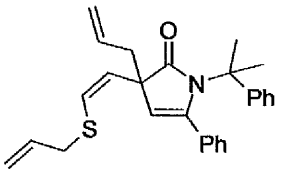
Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2974, 2923 (CH), 1708 (C=O); δ_H(300 MHz, $CDCl_3$) 7.08-7.20 (8H, m, Ar*H*), 6.95 (2H, d, *J* 7.0, Ar*H*), 5.98 (1H, d, *J* 10.0, SC*H*CH), 5.56 (1H, d, *J* 10.0, SCHC*H*), 5.43 (1H, s, C*H*CPh), 2.30 (3H, s, SCH_3), 1.75 (3H, s, $C(CH_3)_2Ph$), 1.68 (3H, s, $C(CH_3)_2Ph$), 1.45 (3H, s, CCH_3); δ_C(75 MHz, $CDCl_3$) 182.7, 148.3, 145.7, 135.5, 129.7, 129.4, 128.5, 128.4, 128.2, 127.9, 127.7, 127.6, 126.6, 126.3, 125.4, 124.7, 115.7, 62.1, 51.9, 31.5, 30.7, 24.5, 18.5; *m/z* (C.I.) 364 (100 %, M + H^+); (Found (E.I): M^+, 363.1728. $C_{23}H_{25}NOS$ requires 363.1657).

3-Ethyl-3-(2-ethylsulfanylvinyl)-1-(1-methyl-1-phenylethyl)-5-phenyl-1,3-dihydropyrrol-2-one 320b



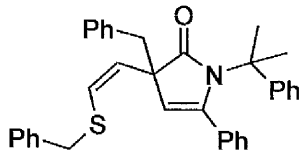
Thiophene-3-carboxylic acid benzyl-(1-methyl-1-phenylethyl)amide **319** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.22 mL, 2.68 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.13 g, 75 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968, 2927 (CH), 1707 (C=O); δ_H(300 MHz, $CDCl_3$) 7.10-7.22 (8H, m, Ar*H*), 6.96 (2H, d, *J* 7.0, Ar*H*), 6.05 (1H, d, *J* 10.5, SC*H*CH), 5.56 (1H, d, *J* 10.5, SCHC*H*), 5.41 (1H, s, C*H*CPh), 2.68 (2H, q, *J* 7.5, SCH_2CH_3), 1.88 (2H, dq, *J* 7.5 and 3.0, CCH_2CH_3), 1.73 (3H, s, $C(CH_3)_2Ph$), 1.69 (3H, s, $C(CH_3)_2Ph$), 1.33 (3H, t, *J* 7.5, SCH_2CH_3), 0.95 (3H, t, *J* 7.5, CCH_2CH_3); δ_C(75 MHz, $CDCl_3$) 181.9, 148.3, 146.5, 135.7, 129.4, 128.3, 127.9, 127.8, 127.7, 127.6, 126.6, 125.5, 113.8, 62.2, 56.9, 31.5, 31.1, 30.7, 29.3, 15.7, 9.2; *m/z* (C.I.) 392 (100 %, M + H^+); (Found (E.I): M^+, 391.2024. $C_{25}H_{29}NOS$ requires 391.1970).

3-Allyl-3-(2-allylsulfanylvinyl)-1-(1-methyl-1-phenylethyl)-5-phenyl-1,3-dihydropyrrol-2-one 320c



Thiophene-3-carboxylic acid benzyl-(1-methyl-1-phenylethyl)amide **319** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.22 mL, 2.68 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.12 g, 66 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2977, 2928 (CH), 1706 (C=O); δ_H(300 MHz, $CDCl_3$) 7.08-7.21 (8H, m, Ar*H*), 6.91 (2H, d, *J* 8.5, Ar*H*), 6.03 (1H, d, *J* 10.0, SC*H*CH), 5.80 (2H, m, 2 × CH_2CHCH_2), 5.60 (1H, d, *J* 10.0, SCHC*H*), 5.40 (1H, s, C*H*CPh), 5.15-5.24 (4H, m, 2 × CH_2CHCH_2), 3.30 (2H, dd, *J* 3.0 and 1.0, SCH_2CHCH_2), 2.64 (1H, dd, *J* 13.5 and 7.0, $CCH_AH_BCHCH_2$), 2.52 (1H, dd, *J* 13.5 and 8.0, $CCH_AH_BCHCH_2$), 1.72 (3H, s, $C(CH_3)_2Ph$), 1.68 (3H, s, $C(CH_3)_2Ph$); δ_C(75 MHz, $CDCl_3$) 181.2, 148.2, 146.7, 135.5, 134.3, 133.4, 129.4, 128.3, 127.9, 127.8, 127.6, 127.2, 127.0, 126.6, 126.0, 125.6, 118.8, 117.9, 113.5, 62.3, 56.1, 42.3, 37.7, 31.5, 30.7; *m/z* (C.I.) 416 (100 %, M + H^+); (Found (E.I): M^+, 415.2042. $C_{27}H_{29}NOS$ requires 415.1970).

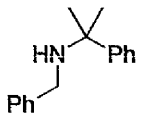
3-Benzyl-3-(2-benzylsulfanylvinyl)-1-(1-methyl-1-phenylethyl)-5-phenyl-1,3-dihydropyrrol-2-one 320d



Thiophene-3-carboxylic acid benzyl-(1-methyl-1-phenylethyl)amide **319** (0.15 g, 0.45 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.32 mL, 2.68 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.14 g, 62 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 3025 (CH), 1704 (C=O); δ_H(300 MHz, $CDCl_3$) 7.27-7.37 (10 H, m, Ar*H*), 6.94-7.10 (6H, m, Ar*H*), 6.68 (2H, d, *J* 6.5, Ar*H*), 6.52 (2H, d, *J* 6.5, Ar*H*), 6.12 (1H, d, *J* 10.0, SC*H*CH), 5.74 (1H, d, *J* 10.0, SCHC*H*), 5.46 (1H, s, C*H*CPh), 3.92 (2H, s, SCH_2Ph), 3.14 (2H, dd, *J* 22.5 and 13.0, CCH_2Ph),

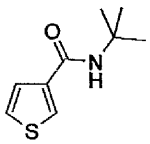
1.65 (3H, s, C(CH_3)$_2$Ph), 1.37 (3H, s, C(CH_3)$_2$Ph); δ_C(75 MHz, $CDCl_3$) 180.4, 147.5, 145.9, 137.6, 136.1, 134.8, 130.8, 129.0, 128.9, 128.8, 128.6, 127.9, 127.7, 127.3, 127.1, 127.0, 126.9, 126.6, 126.1, 125.2, 125.1, 112.5, 61.7, 57.2, 43.2, 38.9, 30.8, 29.8; *m/z* (C.I.) 516 (100 %, M + H^+); (Found (E.I): M^+, 515.2275. $C_{35}H_{33}NOS$ requires 515.2283).

Benzyl-(1-methyl-1-phenylethyl)amine 321[102]



Cumylamine (0.50 g, 3.7 mmol, 1.0 equiv.) and benzaldehyde (0.38 mL, 3.7 mmol, 1.0 equiv.) in methanol (10 mL) were stirred at room temperature over 4 Å molecular sieves under a nitrogen atmosphere for 4 h. The sieves were removed by filtration and washed with methanol (3 mL). Sodium borohydride (0.15 g, 3.7 mmol, 1.0 equiv.) was added portion wise and the mixture stirred at room temperature for 14 h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL), washed with water (2 × 10 mL) and concentrated under reduced pressure to afford the *title compound* (0.45 g, 55 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.35; ν_{max} ($CHCl_3$)/cm^{-1} 3392 (NH), 2966, 2913 (CH); δ_H(300 MHz, $CDCl_3$) 7.60 (2H, d, *J* 7.5, Ar*H*), 7.30-7.46 (8H, m, Ar*H*), 3.60 (2H, s, CH_2Ph), 1.60 (6H, s, C(CH_3)$_2$Ph); δ_C(75 MHz, $CDCl_3$) 148.1, 141.6, 128.7, 128.5, 128.4, 127.0, 126.6, 126.2, 56.4, 47.9, 30.1; *m/z* (C.I.) 226 (100 %, M + H^+); (Found (E.I): M^+, 225.1511. $C_{16}H_{19}N$ requires 225.1517).

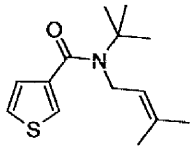
Thiophene-3-carboxylic acid-*tert*-butylamide 322



Thiophene-3-carboxylic acid (5.0 g, 39 mmol, 1.0 equiv.) and *tert*-butylamine (6.15 mL, 58 mmol, 1.5 equiv.) were treated according to **Method J**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (6.79 g, 95 %) as needles: m.p. 165.6-166.1 °C; R_f(10:1 Petrol:EtOAc) 0.50; ν_{max} ($CHCl_3$)/cm^{-1} 3314 (NH), 2969 (CH), 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.78 (1H, dd, *J* 2.5 and 1.5, *H*-2), 7.32-7.34 (2H, m, *H*-4 and *H*-5), 5.80 (1H, brs, *N*H), 1.48 (9H, s, *t*Bu); δ_C(75

MHz, $CDCl_3$) 164.7, 139.2, 127.8, 126.7, 126.4, 51.9, 29.3; *m/z* (C.I.) 184 (100 %, M + H^+); (Found (E.I): M^+, 183.0718. $C_9H_{13}NOS$ requires 183.0712).

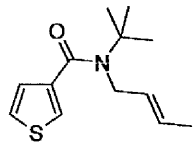
Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide 323



Thiophene-3-carboxylic acid-*tert*-butylamide **322** (2.0 g, 10.9 mmol, 1.0 equiv.) was treated according to **Method H**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (1.52 g, 56 %) as a yellow oil:

R_f(5:1 Petrol:EtOAc) 0.40; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 3.0 and 1.0, *H*-5), 7.25 (1H, dd, *J* 5.0, and 3.0, *H*-2), 7.16 (1H, dd, *J* 5.0 and 1.0, *H*-4), 5.20-5.21 (1H, m, $CH_2CHC(CH_3)_2$), 3.95 (2H, d, *J* 5.5, $CH_2CHC(CH_3)_2$), 1.70 (3H, s, $CH_2CHC(CH_3)_2$), 1.50 (9H, s, *t*Bu), 1.40 (3H, s, $CH_2CHC(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 168.8, 140.3, 132.7, 127.4, 125.4, 125.0, 124.9, 57.7, 46.3, 28.9, 25.9, 17.9; *m/z* (C.I.) 252 (100 %, M + H^+); (Found (E.I): M^+, 251.1338. $C_{14}H_{21}NOS$ requires 251.1344).

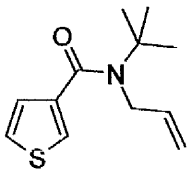
Thiophene-3-carboxylic acid but-2-enyl-*tert*-butylamide 324



Thiophene-3-carboxylic acid-*tert*-butylamide **322** (3.5 g, 19.1 mmol, 1.0 equiv.) was treated according to **Method H.** Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (2.52 g, 60 %) as a yellow oil:

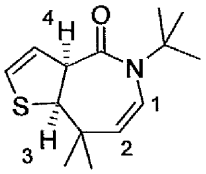
R_f(15:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.46 (1H, dd, *J* 3.0 and 1.0, *H*-2), 7.25 (1H, dd, *J* 5.0 and 3.0, *H*-5), 7.18 (1H, dd, *J* 5.0 and 1.0, *H*-4), 5.40-5.58 (2H, m, $CHCHCH_3$ and $CHCHCH_3$), 3.95-3.96 (2H, m, $CH_2CHCHCH_3$), 1.70 (3H, d, *J* 5.0, $CHCHCH_3$), 1.55 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.9, 140.2, 130.9, 130.4, 127.3, 125.6, 125.1, 124.7, 57.9, 49.3, 28.9, 18.0; *m/z* (C.I.) 238 (100 %, M + H^+); (Found (E.I): M^+, 237.1182. $C_{13}H_{19}NOS$ requires 273.1187).

Thiophene-3-carboxylic acid allyl-*tert*-butylamide 325



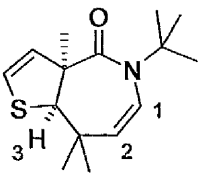
Thiophene-3-carboxylic acid-*tert*-butylamide **322** (6.79 g, 37 mmol, 1.0 equiv.) was treated according to **Method H**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (4.72 g, 60 %) as a colourless oil: R_f(15:1 Petrol:EtOAc) 0.30; $\nu_{max}(CHCl_3)/cm^{-1}$ 2978 (CH), 1620 (C=O); δ_H(300 MHz, $CDCl_3$) 7.50 (1H, dd, *J* 3.0 and 1.0, *H*-2), 7.26 (1H, dd, *J* 5.0 and 3.0, *H*-5), 7.20 (1H, dd, *J* 5.0 and 1.0, *H*-4), 5.86-5.87 (1H, m, CH_2CHCH_2), 5.20-5.23 (2H, m, CH_2CHCH_2), 4.00-4.03 (2H, m, CH_2CHCH_2), 1.50 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.2, 140.1, 138.2, 127.4, 125.6, 124.8, 116.5, 58.1, 50.1, 28.9; *m/z* (C.I.) 224 (100 %, $M + H^+$); (Found (E.I): M^+, 223.1026. $C_{12}H_{17}NOS$ requires 223.1025).

5-*tert*-Butyl-8,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 326a



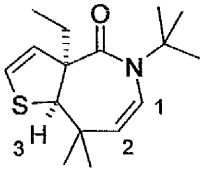
Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide **323** (0.15 g, 0.59 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.19 mL, 3.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 71 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968, 2919 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.48 (1H, dd, *J* 3.0 and 1.0, SC*H*CH), 7.28 (1H, dd, *J* 4.5 and 3.0, SCHC*H*), 7.20 (1H, dd, *J* 4.5 and 1.0, *H*-4), 5.22 (1H, m, *H*-2), 3.98-4.00 (2H, m, *H*-1 and *H*-3), 1.78 (3H, s, $C(CH_3)_2$), 1.58 (9H, s, *t*Bu), 1.42 (3H, s, $C(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 168.9, 140.3, 132.7, 127.4, 125.4, 125.0, 124.9, 57.7, 46.4, 28.9, 25.9, 18.0; *m/z* (C.I.) 252 (100 %, $M + H^+$); (Found (E.I): M^+, 251.1347. $C_{14}H_{21}NOS$ requires 251.1344).

5-*tert*-Butyl-3a,8,8-trimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 326b



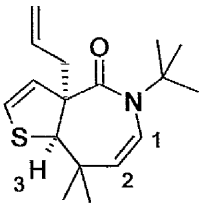
Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide **323** (0.15 g, 0.59 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.22 mL, 3.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 51 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.02 (1H, d, *J* 5.0, SC*H*CH), 6.90 (1H, d, *J* 5.0, SCHC*H*), 5.08 (1H, m, *H*-2), 3.90-3.91 (2H, m, *H*-1 and *H*-3), 2.42 (3H, s, CCH_3), 1.65 (3H, s, $C(CH_3)_2$), 1.55 (9H, s, *t*Bu), 1.38 (3H, s, $C(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 169.4, 137.1, 136.9, 132.9, 126.4, 122.6, 57.5, 45.9, 29.1, 25.9, 17.7, 13.8; *m/z* (C.I.) 266 (100 %, M + H^+); (Found (E.I): M^+, 265.1497. $C_{15}H_{23}NOS$ requires 265.1500).

5-*tert*-Butyl-3a-ethyl-8,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 326c



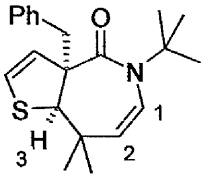
Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide **323** (0.15 g, 0.59 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.29 mL, 3.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) afforded the *title compound* (0.14 g, 60 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.02 (1H, d, *J* 5.0, SC*H*CH), 6.85 (1H, d, *J* 5.0, SCHC*H*), 5.08 (1H, m, *H*-2), 3.90-3.91 (2H, m, *H*-1 and *H*-3), 2.85 (2H, q, *J* 7.5, CH_2CH_3), 1.70 (3H, s, $C(CH_3)_2$), 1.55 (9H, s, *t*Bu), 1.37 (3H, s, $C(CH_3)_2$), 1.26 (3H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 171.4, 144.7, 136.1, 132.8, 126.2, 123.9, 122.4, 60.7, 57.4, 45.9, 29.1, 25.9, 22.1, 17.7, 16.2, 14.5; *m/z* (C.I.) 280 (100 %, M + H^+); (Found (E.I): M^+, 279.1651. $C_{16}H_{25}NOS$ requires 279.1657).

3a-Allyl-5-*tert*-butyl-8,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 326d



Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide **323** (0.15 g, 0.59 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.30 mL, 3.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 55 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968, 2922 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.15 (1H, d, *J* 5.0, SC*H*CH), 6.85 (1H, d, *J* 5.0, SCHC*H*), 5.78-5.98 (2H, m, CH_2CHCH_2), 5.05-5.08 (4H, m, *H*-2, CH_2CHCH_2 and CH_2CHCH_2), 3.90-3.92 (2H, m, *H*-1 and *H*-3), 1.70 (3H, s, $C(CH_3)_2$), 1.58 (9H, s, *t*Bu), 1.40 (3H, s, $C(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 169.1, 145.1, 140.7, 136.2, 132.6, 126.2, 124.3, 123.1, 117.0, 115.5, 57.5, 46.3, 43.6, 41.2, 29.0, 25.9, 17.9; *m/z* (C.I.) 292 (100 %, M + H^+); (Found (E.I): M^+, 291.1652. $C_{17}H_{25}NOS$ requires 291.1657).

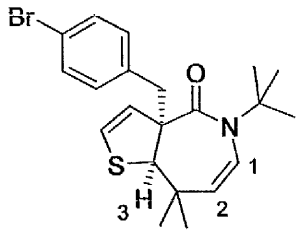
3a-Benzyl-5-*tert*-butyl-8,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 326e



Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide **323** (0.15 g, 0.59 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.43 mL, 3.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 40:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 55 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2962, 2913 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.22-7.38 (5H, m, Ar*H*), 7.10 (1H, d, *J* 5.5, SC*H*CH), 6.92 (1H, d, *J* 5.5, SCHC*H*), 4.99 (1H, m, *H*-2), 4.20 (2H, s, CH_2Ph), 3.75-3.76 (2H, m, *H*-1 and *H*-3), 1.66 (3H, s, $C(CH_3)_2$), 1.54 (9H, s, *t*Bu), 1.36 (3H, s, $C(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 169.2, 141.8, 140.3, 137.0, 132.6, 129.2, 128.6, 128.4, 126.8, 126.4, 124.1, 123.3, 57.5,

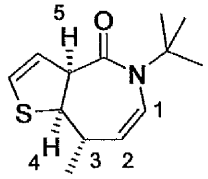
46.0, 34.5, 29.0, 25.9, 17.8; *m/z* (C.I.) 342 (100 %, M + H^+); (Found (E.I): M^+, 341.1800. $C_{21}H_{27}NOS$ requires 341.1813).

3a-(4-Bromobenzyl)-5-*tert*-butyl-8,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 326f



Thiophene-3-carboxylic acid-*tert*-butyl-(3-methylbut-2-enyl)amide **323** (0.15 g, 0.59 mmol, 1.0 equiv.) was treated according to **Method D** with *p*-bromobenzyl bromide (0.89 g, 3.6 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 30:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 50 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2962, 2913 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.5, Ar*H*), 7.20 (2H, d, *J* 8.5, Ar*H*), 7.12 (1H, d, *J* 5.5, SC*H*CH), 6.90 (1H, d, *J* 5.5, SCHC*H*), 4.95 (1H, m, *H*-2), 4.18 (2H, s, CH_2Ph), 3.78-3.79 (2H, m, *H*-1 and *H*-3), 1.68 (3H, s, $C(CH_3)_2$), 1.58 (9H, s, *t*Bu), 1.38 (3H, s, $C(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 168.9, 141.3, 139.3, 137.2, 132.8, 132.7, 131.8, 131.2, 130.4, 127.4, 126.5, 124.8, 123.9, 123.5, 120.7, 57.6, 46.1, 33.9, 29.0, 25.9, 17.8; *m/z* (C.I.) 421 (100 %, M + H^+); (Found (E.I): M^+, 420.4211. $C_{21}H_{26}NOBrS$ requires 420.4219).

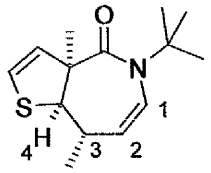
5-*tert*-Butyl-8-methyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 327a



Thiophene-3-carboxylic acid but-2-enyl-*tert*-butylamide **324** (0.15 g, 0.63 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.5 mL) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 65 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1631 (C=O); δ_H(300 MHz, $CDCl_3$) 7.48 (1H, dd, *J* 3.0 and 1.0, SC*H*CH), 7.28 (1H, dd, *J* 5.0 and 3.0, SCHC*H*), 7.20 (1H,

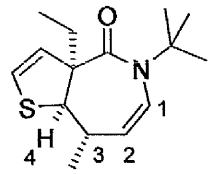
dd, *J* 5.0 and 1.0, *H*-5), 5.42-5.58 (2H, m, *H*-1 and *H*-2), 3.96-3.98 (2H, m, *H*-3 and *H*-4), 1.74 (3H, d, *J* 5.0, CHC*H*$_3$), 1.55 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.1, 140.2, 130.5, 127.3, 125.5, 124.7, 57.9, 49.4, 28.9, 18.1; *m/z* (C.I.) 238 (100 %, M + H^+); (Found (E.I): M^+, 237.1180. $C_{13}H_{19}NOS$ requires 237.1187).

5-*tert*-Butyl-3a,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 327b



Thiophene-3-carboxylic acid but-2-enyl-*tert*-butylamide **324** (0.15 g, 0.63 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.24 mL, 3.79 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 52 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.05 (1H, d, *J* 5.5, SC*H*CH), 6.89 (1H, d, *J* 5.5, SCHC*H*), 5.34-5.38 (2H, m, *H*-1 and *H*-2), 3.87-3.89 (2H, m, *H*-3 and *H*-4), 2.45 (3H, s, CC*H*$_3$), 1.67 (3H, d, *J* 4.5, CHC*H*$_3$), 1.56 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.5, 137.0, 129.7, 127.5, 126.4, 122.5, 57.7, 49.2, 29.1, 17.9, 13.8; *m/z* (C.I.) 252 (100 %, M + H^+); (Found (E.I): M^+, 251.1338. $C_{14}H_{21}NOS$ requires 251.1344).

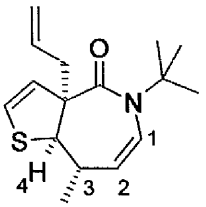
5-*tert*-Butyl-3a-ethyl-8-methyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 327c



Thiophene-3-carboxylic acid but-2-enyl-*tert*-butylamide **324** (0.15 g, 0.63 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.30 mL, 3.79 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.085 g, 55 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.07 (1H, d, *J* 5.5, SC*H*CH), 6.88 (1H, d, *J* 5.5, SCHC*H*), 5.37-5.39 (2H, m, *H*-1 and *H*-2), 3.87-3.89 (2H, m, *H*-3 and *H*-4), 2.86 (2H, q, *J* 7.5, C*H*$_2$CH$_3$), 1.68 (3H, d, *J* 4.5, CHC*H*$_3$), 1.56 (9H, s, *t*Bu), 1.32 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 169.5,

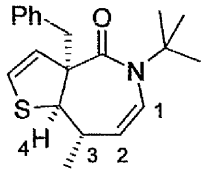
144.7, 135.9, 129.9, 127.4, 126.4, 122.3, 57.7, 49.3, 29.1, 22.1, 17.9, 16.2; *m/z* (C.I.) 266 (100 %, M + H^+); (Found (E.I): M^+, 265.1489. $C_{15}H_{23}NOS$ requires 265.1500).

3a-Allyl-5-*tert*-butyl-8-methyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 327d



Thiophene-3-carboxylic acid but-2-enyl-*tert*-butylamide **324** (0.15 g, 0.63 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.32 mL, 3.79 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 65 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.12 (1H, d, *J* 5.5, SC*H*CH), 6.90 (1H, d, *J* 5.5, SCHC*H*), 6.11-6.12 (1H, m, CH_2CHCH_2), 5.88-5.90 (2H, m, CH_2CHCH_2), 5.40-5.41 (2H, m, CH_2CHCH_2), 3.85-3.86 (2H, m, *H*-1 and *H*-2), 3.36-3.38 (2H, m, *H*-3 and *H*-4), 1.69 (3H, d, *J* 6.5, $CHCH_3$), 1.56 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 169.2, 147.2, 140.7, 136.1, 130.2, 128.3, 125.6, 123.8, 118.2, 117.0, 115.5, 59.5, 30.7, 29.4, 18.7; *m/z* (C.I.) 278 (100 %, M + H^+); (Found (E.I): M^+, 277.1417. $C_{16}H_{23}NOS$ requires 277.1500).

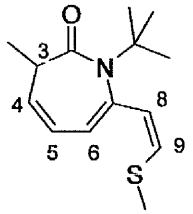
3a-Benzyl-5-*tert*-butyl-8-methyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 327e



Thiophene-3-carboxylic acid but-2-enyl-*tert*-butylamide **324** (0.15 g, 0.63 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.45 mL, 3.79 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 50 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.32-7.37 (5H, m, Ar*H*), 7.09 (1H, d, *J* 5.0, SC*H*CH), 6.92 (1H, d, *J* 5.0, SCHC*H*), 5.37-5.47 (2H, m, *H*-1 and *H*-2), 4.20 (2H, s, CH_2Ph), 3.76-3.78 (2H, m, *J* 1.5, *H*-3 and *H*-4), 1.66 (3H, dd, *J* 6.5 and 1.5, $CHCH_3$), 1.55 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$)

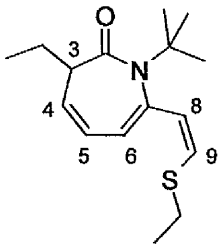
169.2, 147.4, 140.2, 136.8, 129.9, 128.8, 128.6, 128.3, 127.8, 127.5, 126.4, 123.3, 57.8, 49.3, 34.5, 29.0, 21.0, 17.9; *m/z* (C.I.) 328 (100 %, M + H^+); (Found (E.I): M^+, 327.1651. $C_{20}H_{25}NOS$ requires 327.1657).

1-*tert*-Butyl-3-methyl-7-(2-methylsulfanylvinyl)-1,3-dihydroazepin-2-one 330a



Thiophene-3-carboxylic acid allyl-*tert*-butylamide **325** (0.15 g, 0.67 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.25 mL, 4.02 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 61 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972 (CH), 1667 (C=O); δ_H(300 MHz, $CDCl_3$) 6.38 (1H, dd, *J* 4.0 and 1.5, *H*-6), 6.15 (1H, ddd, *J* 9.5, 4.0 and 1.5, *H*-5), 6.06 (1H, d, *J* 10.5, *H*-9), 6.02 (1H, d, *J* 10.5, *H*-8), 5.55 (1H, dd, *J* 9.0 and 4.0, *H*-4), 2.80-2.82 (1H, m, *H*-3), 2.38 (3H, s, SCH_3), 1.47 (9H, s, *t*Bu), 1.35 (3H, d, *J* 7.0, $CHCH_3$); δ_C (75 MHz, $CDCl_3$) 175.3, 139.8, 136.6, 128.9, 125.9, 125.2, 125.1, 60.0, 41.6, 29.3, 18.9, 14.4; *m/z* (C.I.) 252 (100 %, M + H^+); (Found (E.I): M^+, 251.1338. $C_{14}H_{21}NOS$ requires 251.1344).

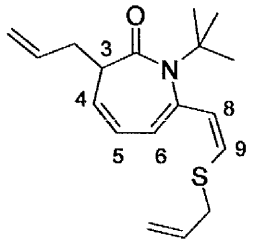
1-*tert*-Butyl-3-ethyl-7-(2-methylsulfanylvinyl)-1,3-dihydroazepin-2-one 330b



Thiophene-3-carboxylic acid allyl-*tert*-butylamide **325** (0.15 g, 0.67 mmol, 1.0 equiv.) was treated according to **Method D** with iodoethane (0.33 mL, 4.02 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.13 g, 70 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2964 (CH), 1666 (C=O); δ_H(300 MHz, $CDCl_3$) 6.40 (1H, dd, *J* 4.0 and 1.5, *H*-6), 6.18 (1H, ddd, *J* 9.5, 4.0 and 2.0, *H*-5), 6.10 (1H, d, *J* 10.5, *H*-9), 6.05 (1H, d, *J* 10.5, *H*-8), 5.58 (1H, dd, *J* 9.5 and 5.0, *H*-4), 2.78 (2H, q, *J* 7.0, SCH_2CH_3), 2.58-2.59 (1H, m, *H*-3), 2.05 (1H, dq, *J* 21.0 and 7.0, $CHCH_AH_BCH_3$), 1.70 (1H, dq, *J*

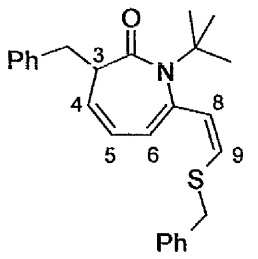
21.0 and 7.0, $CHCH_AH_BCH_3$), 1.47 (9H, s, *t*Bu), 1.35 (3H, t, *J* 7.0, SCH_2CH_3), 1.00 (3H, t, *J* 7.0, $CHCH_2CH_3$); δ_C(75 MHz, $CDCl_3$) 174.2, 139.9, 135.4, 127.0, 126.4, 125.5, 125.1, 60.1, 49.1, 29.7, 29.3, 22.3, 15.8, 12.5; *m/z* (C.I.) 280 (100 %, $M + H^+$); (Found (E.I): M^+, 279.1651. $C_{16}H_{25}NOS$ requires 279.1657).

3-Allyl-7-(2-allylsulfanylvinyl)-1-*tert*-butyl-1,3-dihydroazepin-2-one 330c



Thiophene-3-carboxylic acid allyl-*tert*-butylamide **325** (0.15 g, 0.67 mmol, 1.0 equiv.) was treated according to **Method D** with allyl bromide (0.34 mL, 4.02 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.13 g, 65 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2972 (CH), 1666 (C=O); δ_H(300 MHz, $CDCl_3$) 6.41 (1H, dd, *J* 4.0 and 1.5, *H*-6), 6.18 (1H, ddd, *J* 9.5, 4.0 and 2.0, *H*-5), 6.10 (1H, d, *J* 10.5, *H*-9), 6.05 (1H, d, *J* 10.5, *H*-8), 5.85-5.87 (2H, m, 2 × CH_2CHCH_2), 5.62 (1H, dd, *J* 9.5 and 5.0, *H*-4), 5.10-5.11 (4H, m, 2 × CH_2CHCH_2), 3.37 (2H, d, *J* 6.5, SCH_2CHCH_2), 2.80-2.83 (2H, m, $CHCH_2CHCH_2$), 2.49-2.51 (1H, m, *H*-3), 1.47 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 173.9, 139.9, 136.9, 134.7, 134.1, 126.6, 125.8, 125.5, 125.3, 118.3, 116.4, 60.3, 46.6, 37.9, 33.4, 29.3; *m/z* (C.I.) 304 (100 %, $M + H^+$); (Found (E.I): M^+, 303.1652. $C_{18}H_{25}NOS$ requires 303.1657).

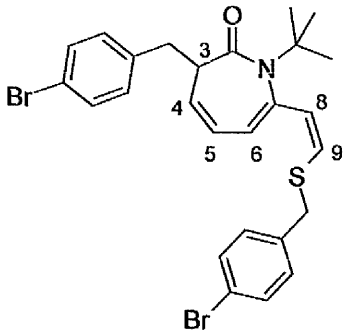
3-Benzyl-7-(2-benzylsulfanylvinyl)-1-*tert*-butyl-1,3-dihydroazepin-2-one 330d



Thiophene-3-carboxylic acid allyl-*tert*-butylamide **325** (0.15 g, 0.67 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.48 mL, 4.02 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 45 %) as a yellow oil: R_f(25:1

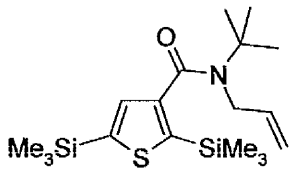
Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1663 (C=O); δ_H(300 MHz, $CDCl_3$) 7.20-7.38 (10H, m, Ar*H*), 6.35 (1H, d, *J* 3.5, *H*-6), 6.14-6.16 (2H, m, *H*-5 and *H*-8), 6.08 (1H, d, *J* 4.5, *H*-9), 5.68 (1H, dd, *J* 9.0 and 4.5, *H*-4), 3.96 (2H, s, SCH_2Ph), 3.44 (1H, dd, *J* 9.0 and 4.5, *H*-3), 3.08 (2H, s, CH_2Ph), 1.48 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 173.8, 140.5, 139.8, 137.8, 134.7, 129.5, 129.2, 128.8, 128.6, 127.7, 127.1, 126.4, 126.2, 125.7, 125.4, 124.7, 113.8, 60.4, 48.6, 39.5, 35.1, 29.3; *m/z* (C.I.) 404 (100 %, M + H^+); (Found (E.I): M^+, 403.1964. $C_{26}H_{29}NOS$ requires 403.1970).

3-(4-Bromobenzyl)-7-[2-(4-bromobenzylsulfanyl)vinyl]-1-*tert*-butyl-1,3-dihydroazepin-2-one 330e



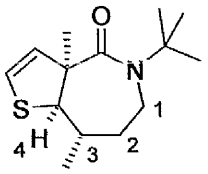
Thiophene-3-carboxylic acid allyl-*tert*-butylamide **325** (0.15 g, 0.67 mmol, 1.0 equiv.) was treated according to **Method D** with *p*-bromobenzyl bromide (1.0 g, 4.02 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.19 g, 50 %) as needles: m.p. 133.5-133.8 °C; R_f(25:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1663 (C=O); δ_H(300 MHz, $CDCl_3$) 7.48 (2H, d, *J* 8.5, Ar*H*), 7.40 (2H, d, *J* 8.5, Ar*H*), 7.20 (2H, d, *J* 8.5, Ar*H*), 7.14 (2H, d, *J* 8.5, Ar*H*), 6.30 (1H, d, *J* 3.5, *H*-6), 6.14 (1H, dd, *J* 4.0 and 1.5, *H*-5), 6.06 (1H, d, *J* 21.0, *H*-8), 6.02 (1H, d, *J* 21.0, *H*-9), 5.62 (1H, dd, *J* 9.0 and 5.0, *H*-4), 3.85 (2H, s, SCH_2Ph), 3.38 (1H, dd, *J* 18.0 and 10.5, *H*-3), 2.98 (2H, s, CCH_2Ph), 1.45 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 173.2, 139.8, 139.6, 136.9, 134.4, 132.1, 131.5, 131.3, 130.8, 127.2, 126.0, 125.7, 125.3, 121.6, 119.9, 60.6, 48.7, 38.7, 34.5, 29.2; *m/z* (C.I.) 560 (100 %, M + H^+); (Found (E.I): M^+, 559.0177. $C_{26}H_{27}NOBr_2S$ requires 559.0181).

2,5-Bistrimethylsilanylthiophene-3-carboxylic acid allyl-*tert*-butylamide 337



Thiophene-3-carboxylic acid allyl-*tert*-butylamide **325** (0.15 g, 0.67 mmol, 1.0 equiv.) was treated according to **Method D** with chlorotrimethylsilane (0.51 mL, 4.04 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.16g, 68 %) as a yellow oil: R_f(5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2957 (CH), 1641 (C=O); δ_H(300 MHz, $CDCl_3$) 7.20 (1H, s, *H*-4), 5.74-5.84 (1H, ddt, *J* 17.0, 10.0 and 5.5, CH_2CHCH_2), 5.13 (1H, ddd, *J* 10.0, 3.0 and 1.0, $CH_2CHCH_AH_B$), 5.05 (1H, ddd, *J* 17.0, 3.0 and 1.0, $CH_2CHCH_AH_B$), 3.91 (2H, dt, *J* 5.5 and 1.0, CH_2CHCH_2), 1.59 (9H, s, *t*Bu), 0.37 (9H, s, 3 × CH_3), 0.32 (9H, s, 3 × CH_3); δ_C(75 MHz, $CDCl_3$) 170.9, 147.9, 145.1, 143.9, 137.8, 134.8, 130.0, 116.2, 57.9, 50.6, 28.9, 0.4; *m/z* (C.I.) 368 (100 %, $M\text{-}H^+$); (Found (E.I): M^+, 367.1894. $C_{18}H_{33}NOSSi_2$ requires 367.1890).

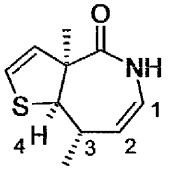
5-*tert*-Butyl-3a,8-dimethyl-3a,5,6,7,8,8a-hexahydrothieno[3,2-c]azepin-4-one 338



Palladium on carbon (0.15 g, 0.59 mmol, 1.0 equiv.) was added portionwise to a solution of 5-*tert*-butyl-3a,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one **327b** (0.15g, 0.59 mmol, 1.0 equiv.) in methanol (7 mL) at room temperature under a nitrogen atmosphere. The flask was flushed with H_2 and maintained under a H_2 atmosphere for 2 days. The mixture was filtered through celite, washed with methanol (2 × 5 mL) and concentrated under reduced pressure leaving the *title compound* (0.12 g, 80 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2961, 2928 (CH), 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 7.03 (1H, d, *J* 5.0, SC*H*CH), 6.87 (1H, d, *J* 5.0, SCHC*H*), 3.23-3.24 (2H, m, *H*-4 and *H*-3), 2.43 (3H, s, CCH_3), 2.36 (1H, d, *J* 11.5, *H*-1), 1.55 (9H, s, *t*Bu), 1.42 (1H, dd, *J* 11.5 and 7.0, *H*-1), 1.06 (2H, dt, *J* 11.5 and 7.0 *H*-2), 0.74 (3H, dd, *J* 14.5 and 7.0, $CHCH_3$); δ_C(75 MHz, $CDCl_3$) 168.9, 136.7, 136.1,

126.3, 126.2, 124.3, 122.4, 122.3, 56.8, 46.7, 34.2, 28.9, 19.7, 13.4; *m/z* (C.I.) 254 (100 %, M + H^+); (Found (E.I): M^+, 253.1573. $C_{14}H_{23}NOS$ requires 253.1500).

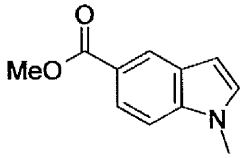
3a,8-Dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one 339



5-*tert*-Butyl-3a,8-dimethyl-3a,5,8,8a-tetrahydrothieno[3,2-c]azepin-4-one **327b** (0.15g, 0.59 mmol, 1.0 equiv.) and 6 M HCl (2 mL) in THF (5 mL) were stirred at room temperature for 3 days. Water (5 mL) was added, the mixture extracted with EtOAc (4 × 5 mL) and the combined organic layers washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 15:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 80 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.40; $\nu_{max}(CHCl_3)/cm^{-1}$ 3314 (NH), 2920 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.07 (1H, d, *J* 5.5, SC*H*CH), 6.98 (1H, d, *J* 5.5, SCHC*H*), 5.82 (1H, brs, N*H*), 5.63-5.64 (1H, m, *H*-1), 5.49-5.50 (1H, m, *H*-2), 3.92.-3.93 (2H, m, *H*-4 and *H*-3), 2.68 (3H, s, CCH_3), 1.68 (3H, dd, *J* 6.0 and 1.0, CHCH_3); δ_C(75 MHz, $CDCl_3$) 164.6, 144.8, 132.1, 128.9, 127.2, 126.5, 124.3, 122.1, 41.8, 18.0; *m/z* (C.I.) 196 (100 %, M + H^+); (Found (E.I): M^+, 195.0712. $C_{10}H_{13}NOS$ requires 195.0711).

4.3.4 Experimental Details for Chapter 2.4

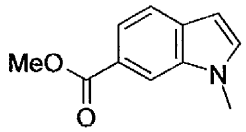
1-Methyl-1*H*-indole-5-carboxylic acid methyl ester 342[158]



Indole-5-carboxylic acid (0.50 g, 3.10 mmol, 1.0 equiv.) in DMF (10 mL) was added dropwise to a suspension of sodium hydride (0.38 g, 9.30 mmol, 3.0 equiv.) in DMF (15 mL) at room temperature under a nitrogen atmosphere. The suspension was stirred for 30 min. and iodomethane (2.0 mL, 31.0 mmol, 10 equiv.) added dropwise. The solution was stirred at room temperature for 16 h and water (10 mL) added. The mixture was extracted with EtOAc (3 × 15mL). Combined organics were washed with water (4 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title*

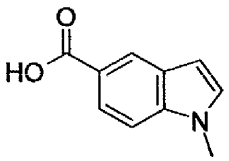
compound (0.60 g, 100 %) as needles: m.p. 104.8-106.4 °C (lit.,[158] 105-106 °C); R_f(1:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2923 (CH), 1706 (C=O); δ_H(300 MHz, $CDCl_3$) 8.38 (1H, dd, *J* 1.5 and 1.0, *H*-4), 7.88 (1H, dd, *J* 8.5 and 1.5, *H*-6), 7.28 (1H, d, *J* 8.5, *H*-7), 7.05 (1H, d, *J* 3.0, *H*-2), 6.52 (1H, dd, *J* 3.0 and 1.0, *H*-3), 3.88 (3H, s, OCH_3), 3.76 (3H, s, NCH_3); δ_C(75 MHz, $CDCl_3$) 168.4, 162.7, 139.3, 130.5, 128.2, 124.0, 121.5, 109.1, 102.8, 51.9, 36.6; *m/z* (C.I.) 190 (100 %, M + H^+); (Found (E.I): M^+, 189.0792. $C_{11}H_{11}NO_2$ requires 189.0790).

1-Methyl-1*H*-indole-6-carboxylic acid methyl ester 343[158]



Indole-6-carboxylic acid (0.50 g, 3.10 mmol, 1.0 equiv.) in DMF (10 mL) was added dropwise to a suspension of sodium hydride (0.38 g, 9.30 mmol, 3.0 equiv.) in DMF (15 mL) at room temperature under a nitrogen atmosphere. The suspension was stirred for 30 min. and iodomethane (2.0 mL, 31.0 mmol, 10 equiv.) added dropwise. The solution was stirred at room temperature for 16 h and water (10 mL) added. The mixture was extracted with EtOAc (3 × 15mL). Combined organics were washed with water (4 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.60 g, 100 %) as needles: m.p. 88.5-89.7 °C (lit.,[158] 89°C); R_f(1:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2924 (CH), 1706 (C=O); δ_H(300 MHz, $CDCl_3$) 8.10 (1H, d, *J* 0.5, *H*-7), 7.80 (1H, ddd, *J* 8.5, 1.5 and 1.0, *H*-4), 7.62 (1H, dd, *J* 8.5 and 0.5, *H*-5), 7.22 (1H, d, *J* 3.0, *H*-2), 6.52 (1H, dd, *J* 3.0 and 1.0, *H*-3), 3.95 (3H, s, OCH_3), 3.85 (3H, s, NCH_3); δ_C(75 MHz, $CDCl_3$) 168.5, 162.8, 136.3, 132.4, 123.3, 120.6, 120.5, 111.9, 101.6, 52.1, 36.7; *m/z* (C.I.) 190 (100 %, M + H^+); (Found (E.I): M^+, 189.0783. $C_{11}H_{11}NO_2$ requires 189.0790).

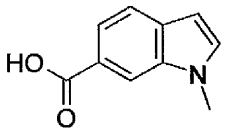
1-Methyl-1*H*-indole-5-carboxylic acid 344[158]



Lithium hydroxide (15 mL of a 1.0 M solution in water) was added to a solution of 1-methyl-1*H*-indole-5-carboxylic acid methyl ester **342** (0.60 g, 3.10 mmol, 1.0 equiv.) in

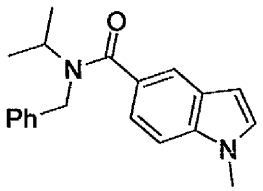
THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at 50 °C for 24 h and diluted with EtOAc (10 mL). The mixture was extracted with saturated sodium hydrogen carbonate solution (2 × 15 mL) and the aqueous layer acidified to pH 1 with 6 M HCl. The acidic layer was extracted with EtOAc (4 × 10 mL). Combined organics were washed with water (4 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.56 g, 100 %) as needles: m.p. 167.9-168.8 °C (lit.,[158] 168°C); R_f(1:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 3472 (OH), 2919 (CH), 1663 (C=O); δ_H(300 MHz, CD_3OD) 8.36 (1H, dd, *J* 2.0 and 0.5, *H*-4), 7.90 (1H, dd, *J* 8.5 and 2.0, *H*-6), 7.38 (1H, d, *J* 8.5, *H*-7), 7.20 (1H, d, *J* 3.0, *H*-2), 6.56 (1H, dd, *J* 3.0 and 0.5, *H*-3), 4.82 (1H, brs, O*H*), 3.84 (3H, s, NCH_3); δ_C(75 MHz, CD_3OD) 170.6, 139.5, 130.6, 124.1, 123.0, 121.3, 108.9, 102.4, 32.5; *m/z* (C.I.) 176 (100 %, M + H^+); (Found (E.I): M^+, 175.0631. $C_{10}H_9NO_2$ requires 175.0628).

1-Methyl-1*H*-indole-6-carboxylic acid 345[158]



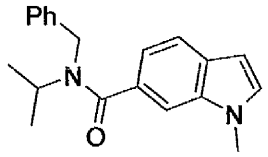
Lithium hydroxide (15 mL of a 1.0 M solution in water) was added to a solution of 1-methyl-1*H*-indole-6-carboxylic acid methyl ester **343** (0.60 g, 3.10 mmol, 1.0 equiv.) in THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at 50 °C for 24 h and diluted with EtOAc (10 mL). The mixture was extracted with saturated sodium hydrogen carbonate solution (2 × 15 mL) and the aqueous layer acidified to pH 1 with 6 M HCl. The acidic layer was extracted with EtOAc (4 × 10 mL). Combined organics were washed with water (4 × 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.56 g, 100 %) as needles: m.p. 190.4-192.0 °C (lit.,[158] 190 °C); R_f(1:1 Petrol:EtOAc) 0.40; ν_{max} $(CHCl_3)/cm^{-1}$ 3445 (OH), 2916 (CH), 1661 (C=O); δ_H(300 MHz, CD_3OD) 8.10 (1H, s, *H*-7), 7.76 (1H, d, *J* 8.0, *H*-5), 7.60 (1H, d, *J* 8.0, *H*-4), 7.35 (1H, d, *J* 3.0, *H*-2), 6.52 (1H, d, *J* 3.0, *H*-3), 4.98 (1H, brs, O*H*), 3.85 (3H, s, NCH_3); δ_C(75 MHz, CD_3OD) 168.6, 139.4, 130.5, 128.2, 124.2, 123.1, 121.6, 109.1, 102.9, 52.1; *m/z* (C.I.) 176 (100 %, M + H^+); (Found (E.I): M^+, 175.0627. $C_{10}H_9NO_2$ requires 175.0628).

1-Methyl-1*H*-indole-5-carboxylic acid benzylisopropylamide 346



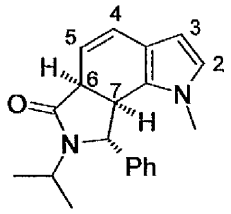
1-Methyl-1*H*-indole-5-carboxylic acid **344** (0.36 g, 2.06 mmol, 1.0 equiv.) and *N*-isopropylbenzylamine (0.51 mL, 3.09 mmol, 1.5 equiv.) were treated according to **Method K**. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.44 g, 70 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1624 (C=O); δ_H(300 MHz, $CDCl_3$) 7.80 (1H, s, *H*-4), 7.39-7.35 (6H, m, Ar*H* and *H*-6), 7.29 (1H, d, *J* 2.5, *H*-7), 7.14 (1H, d, *J* 3.0, *H*-2), 6.57 (1H, d, *J* 3.0, *H*-3), 4.74 (2H, s, C*H*$_2$Ph), 4.42 (1H, brs, C*H*(CH$_3$)$_2$), 3.83 (3H, s, NC*H*$_3$), 1.20 (6H, d, *J* 5.0, CH(C*H*$_3$)$_2$); δ_C(75 MHz, $CDCl_3$) 173.9, 139.9, 137.2, 130.2, 128.7, 128.2, 127.3, 126.9, 120.6, 119.7, 109.5, 101.9, 33.2, 21.6; *m/z* (C.I.) 307 (100 %, M + H$^+$); (Found (E.I): M$^+$, 306.1805. $C_{20}H_{22}N_2O$ requires 306.1804).

1-Methyl-1*H*-indole-6-carboxylic acid benzylisopropylamide 347



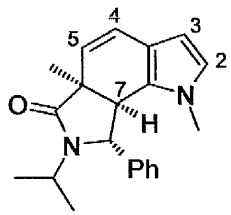
1-Methyl-1*H*-indole-6-carboxylic acid **345** (0.32 g, 1.83 mmol, 1.0 equiv.) and *N*-isopropylbenzylamine (0.46 mL, 2.74 mmol, 1.5 equiv.) were treated according to **Method K**. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.41 g, 73 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 2970 (CH), 1626 (C=O); δ_H(300 MHz, $CDCl_3$) 7.68 (1H, d, *J* 7.5, *H*-5), 7.52 (1H, s, *H*-7), 7.40-7.23 (6H, m, Ar*H* and *H*-4), 7.15 (1H, d, *J* 3.0, *H*-2), 6.55 (1H, s, *H*-3), 4.74 (2H, s, C*H*$_2$Ph), 4.42 (1H, brs, C*H*(CH$_3$)$_2$), 3.80 (3H, s, NC*H*$_3$), 1.22 (6H, brs, CH(C*H*$_3$)$_2$); δ_C(75 MHz, $CDCl_3$) 173.8, 139.9, 136.5, 130.7, 129.5, 128.7, 127.3, 127.0, 120.9, 117.9, 108.4, 101.3, 33.1, 31.2, 21.5; *m/z* (C.I.) 307 (100 %, M + H$^+$); (Found (E.I): M$^+$, 306.1807. $C_{20}H_{22}N_2O$ requires 306.1804).

(5a*R*,8*S*,8a*S*)-8,8a-dihydro-7-isopropyl-1-methyl-8-phenylpyrrolo[3,4-*g*]indol-6(1*H*,5a*H*,7*H*)-one 348a



1-Methyl-1*H*-indole-6-carboxylic acid benzylisopropylamide **347** (0.10 g, 0.33 mmol, 1.0 equiv.) was treated according to **Method D** with saturated aqueous ammonium chloride (0.1 mL, 1.96 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.06 g, 67 %) as needles: $[\alpha]_D^{22}$ = +85.2 (c = 0.75 in $CHCl_3$), m.p. 134.6-135.2 °C; R_f(1:1 Petrol:EtOAc) 0.75; ν_{max} ($CHCl_3$)/cm^{-1} 2970 (CH), 1684 (C=O); δ_H(300 MHz, $CDCl_3$) 7.44-7.33 (5H, m, Ar*H*), 6.52 (1H, dd, *J* 9.5 and 3.0, *H*-4), 6.37 (1H, d, *J* 2.5, *H*-2), 6.03 (1H, d, *J* 2.5, *H*-3), 5.46 (1H, dd, *J* 9.5 and 2.5, *H*-5), 4.45 (1H, d, *J* 8.5, C*H*Ph), 3.80 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 3.70 (1H, ddd, *J* 3.0, 2.5 and 2.0, *H*-6), 3.52 (1H, dd, *J* 8.5 and 2.0, *H*-7), 2.63 (3H, s, NC*H*$_3$), 1.27 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.04 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$); δ_C(75 MHz, $CDCl_3$) 176.5, 141.0, 129.3, 128.9, 128.4, 126.2, 124.1, 122.5, 116.7, 115.4, 105.2, 69.2, 46.9, 46.5, 41.8, 32.9, 20.1, 20.0; *m/z* (C.I.) 307 (100 %, M + H$^+$); (Found (E.I): M$^+$, 306.1805. $C_{20}H_{22}N_2O$ requires 306.1805).

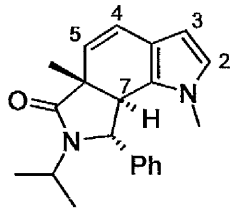
(5a*R*,8*S*,8a*S*)-8,8a-dihydro-7-isopropyl-1,5a-dimethyl-8-phenylpyrrolo[3,4-*g*]indol-6(1*H*,5a*H*,7*H*)-one *cis*-348b



1-Methyl-1*H*-indole-6-carboxylic acid benzylisopropylamide **347** (0.10 g, 0.33 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.13 mL, 1.96 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) afforded the *title compound* (0.06 g, 60 %) as needles: $[\alpha]_D^{22}$ = +104.2 (c = 0.90 in $CHCl_3$), m.p. 122.5-123.1 °C; R_f(1:1 Petrol:EtOAc) 0.70; ν_{max}($CHCl_3$)/cm^{-1} 2923 (CH), 1687 (C=O); δ_H(300 MHz, $CDCl_3$) 7.42-7.31 (5H, m, Ar*H*), 6.48 (1H, d, *J* 9.5, *H*-4), 6.38 (1H, d, *J* 2.5, *H*-2), 6.05 (1H, d, *J* 2.5, *H*-3), 5.34 (1H, dd, *J* 9.5 and 0.5,

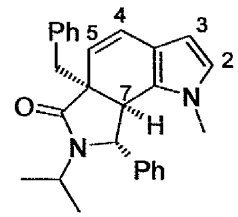
H-5), 4.25 (1H, d, *J* 9.0, C*H*Ph), 3.70 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 3.12 (1H, d, *J* 9.0, *H*-7), 2.60 (3H, s, NCH_3), 1.30 (3H, s, CCH_3), 1.27 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.03 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 178.9, 140.9, 129.3, 129.1, 128.4, 125.9, 122.7, 121.8, 121.3, 116.3, 105.5, 104.9, 67.4, 49.5, 46.8, 32.8, 22.9, 20.0; *m/z* (C.I.) 321 (100 %, M + H^+); (Found (E.I): M^+, 320.1960. $C_{21}H_{24}N_2O$ requires 320.1961).

(5a*S*,8*S*,8a*S*)-8,8a-dihydro-7-isopropyl-1,5a-dimethyl-8-phenylpyrrolo[3,4-*g*]indol-6(1*H*,5a*H*,7*H*)-one *trans*-348b



1-Methyl-1*H*-indole-6-carboxylic acid benzylisopropylamide **347** (0.10 g, 0.33 mmol, 1.0 equiv.) was treated according to **Method D** with iodomethane (0.13 mL, 1.96 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 3:1 Petrol/EtOAc) afforded the *title compound* (0.01 g, 10 %) as a colourless oil: $[\alpha]_D^{22}$ = +99.7 (c = 0.80 in $CHCl_3$), R_f(1:1 Petrol:EtOAc) 0.50; ν_{max}($CHCl_3$)/cm^{-1} 2925 (CH), 1685 (C=O); δ_H(300 MHz, $CDCl_3$) 7.43-7.40 (5H, m, Ar*H*), 6.77 (1H, d, *J* 9.5, *H*-4), 6.40 (1H, d, *J* 3.0, *H*-2), 6.10 (1H, d, *J* 3.0, *H*-3), 5.52 (1H, dd, *J* 9.5 and 1.0, *H*-5), 4.00 (1H, d, *J* 8.5, C*H*Ph), 3.68 (1H, q, *J* 7.0, C*H*(CH_3)$_2$), 3.12 (1H, d, *J* 8.5, *H*-7), 2.61 (3H, s, NCH_3), 1.34 (3H, s, CCH_3), 1.29 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.07 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 176.3, 139.8, 131.3, 129.2, 127.6, 126.0, 123.0, 121.8, 120.7, 116.4, 105.4, 101.3, 66.2, 49.7, 47.4, 32.9, 23.3, 20.1; *m/z* (C.I.) 321 (100 %, M + H^+); (Found (E.I): M^+, 320.1959. $C_{21}H_{24}N_2O$ requires 320.1961).

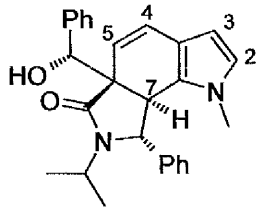
(5a*R*,8*S*,8a*S*)-5a-benzyl-8,8a-dihydro-7-isopropyl-1-methyl-8-phenylpyrrolo[3,4-*g*]indol-6(1*H*,5a*H*,7*H*)-one 348c



1-Methyl-1*H*-indole-6-carboxylic acid benzylisopropylamide **347** (0.10 g, 0.33 mmol, 1.0 equiv.) was treated according to **Method D** with benzyl bromide (0.23 mL, 1.96

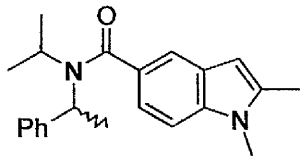
mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 66 %) as needles: $[\alpha]_D^{22} = +113.3$ (c = 0.95 in $CHCl_3$), m.p. 130.8-131.9 °C; R_f(5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2968 (CH), 1686 (C=O); δ_H(300 MHz, $CDCl_3$) 7.37-7.20 (10H, m, Ar*H*), 6.54 (1H, d, *J* 9.5, *H*-4), 6.36 (1H, d, *J* 2.5, *H*-2), 6.04 (1H, d, *J* 2.5, *H*-3), 5.50 (1H, dd, *J* 9.5 and 0.5, *H*-5), 4.15 (1H, d, *J* 8.5, C*H*Ph), 3.70 (1H, q, *J* 7.0, C*H*$(CH_3)_2$), 3.52 (1H, d, *J* 13.5, *H*CH_2Ph), 3.21 (1H, d, *J* 8.5, *H*-7), 2.51 (3H, s, NCH_3), 2.45 (1H, d, *J* 13.5, CH_2Ph), 1.18 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.95 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 176.7, 141.4, 137.5, 130.8, 129.0 128.8, 128.6, 128.5, 128.2, 126.9, 126.1, 123.1, 122.5, 121.2, 116.6, 104.9, 67.2, 54.5, 46.5, 43.2, 40.7, 32.7, 20.3, 19.7; *m/z* (C.I.) 397 (100 %, M + 116.6, 104.9, 67.2, 54.5, 46.5, 43.2, 40.7, 32.7, 20.3, 19.7; *m/z* (C.I.) 397 (100 %, M + H^+); (Found (E.I): M^+, 396.2276. $C_{27}H_{28}N_2O$ requires 396.2274).

(5a*R*,8*S*,8a*S*)-8,8a-dihydro-5a-((*R*)-hydroxy(phenyl)methyl)-7-isopropyl-1-methyl-8-phenylpyrrolo[3,4-*g*]indol-6(1*H*,5a*H*,7*H*)-one 348d



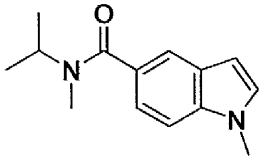
1-Methyl-1*H*-indole-6-carboxylic acid benzylisopropylamide **347** (0.10 g, 0.33 mmol, 1.0 equiv.) was treated according to **Method D** with benzaldehyde (0.20 mL, 1.96 mmol, 6.0 equiv.) quench. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 60 %) as needles: $[\alpha]_D^{22} = +105.4$ (c = 0.90 in $CHCl_3$), m.p. 117.3-118.5 °C; R_f(1:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 3412 (OH), 2930 (CH), 1667 (C=O); δ_H(300 MHz, $CDCl_3$) 7.35-7.19 (10 H, m, Ar*H*), 7.08 (1H, brs, O*H*), 6.54 (1H, d, *J* 9.5, *H*-4), 6.17 (1H, d, *J* 2.5, *H*-2), 5.80 (1H, d, *J* 2.5, *H*-3), 5.62 (1H, dd, *J* 9.5 and 1.0, *H*-5), 4.89 (1H, s, C*H*(OH)Ph), 4.20 (1H, d, *J* 8.5, C*H*Ph), 3.74 (1H, q, *J* 7.0, C*H*$(CH_3)_2$), 3.50 (1H, d, *J* 8.5, *H*-7), 2.48 (3H, s, NCH_3), 1.25 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.03 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 177.5, 140.8, 140.2, 128.8, 127.7, 127.5, 126.8, 126.1, 125.9, 125.8, 121.9, 117.0, 116.4, 104.8, 67.7, 57.2, 46.8, 42.2, 32.5, 20.2, 19.9; *m/z* (C.I.) 413 (100 %, M + H^+); (Found (E.I): M^+, 412.2226. $C_{27}H_{28}N_2O_2$ requires 396.2224).

1,2-Dimethyl-1*H*-indole-5-carboxylic acid isopropyl-(1-phenylethyl)amide 353



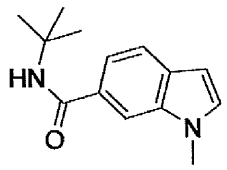
1-Methyl-1*H*-indole-5-carboxylic acid benzylisopropylamide **346** (0.10 g, 0.33 mmol, 1.0 equiv.) and iodomethane (0.06 mL, 0.98 mmol, 3.0 equiv.) were treated according to **Method C**. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.06 g, 50 %) as an off-white solid: m.p. 171.4-172.0 °C; R_f(1:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1624 (C=O); δ_H(300 MHz, $CDCl_3$) 7.65 (1H, d, *J* 2.0, *H*-4), 7.28-7.42 (7H, m, Ar*H*, *H*-6 and *H*-7), 6.33 (1H, s, *H*-3), 5.05 (1H, q, *J* 6.5, C*H*(CH_3)Ph), 3.70 (3H, s, NCH_3), 3.55 (1H, brs, C*H*(CH_3)$_2$), 2.45 (3H, s, CCH_3), 1.70 (3H, d, *J* 6.5, CH(CH_3)Ph), 1.50 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.20 (3H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 173.2, 141.4, 138.2, 137.6, 130.3, 128.4, 127.7, 127.5, 127.3, 120.1, 118.9, 117.7, 109.5, 108.9, 101.8, 100.4, 29.8, 21.5, 21.3, 20.7, 18.0, 13.0; *m/z* (C.I.) 335 (100 %, M-H$^+$); (Found (E.I): M$^+$, 334.2113. $C_{22}H_{26}N_2O$ requires 334.2118).

1-Methyl-1*H*-indole-5-carboxylic acid isopropylmethylamide 354



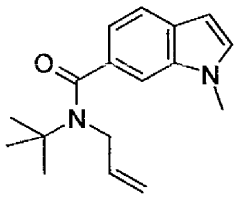
1-Methyl-1*H*-indole-5-carboxylic acid benzylisopropylamide **346** (0.20 g, 0.65 mmol, 1.0 equiv.) and iodomethane (0.12 mL, 1.95 mmol, 3.0 equiv.) were treated according to **Method C** with warming to 0 °C before the quench. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.09 g, 45 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 2971 (CH), 1620 (C=O); δ_H(300 MHz, $CDCl_3$) 7.70 (1H, s, *H*-4), 7.34 (1H, d, *J* 8.5, *H*-6), 7.27 (1H, dd, *J* 8.5 and 1.5, *H*-7), 7.12 (1H, d, *J* 3.0, *H*-2), 6.54 (1H, dd, *J* 3.0 and 0.5, *H*-3), 4.20 (1H, brs, C*H*(CH_3)$_2$), 3.82 (3H, s, NCH_3), 2.95 (3H, s, NCH_3), 1.20 (6H, brd, *J* 6.0, CH(CH_3)$_2$); δ_C(75 MHz, $CDCl_3$) 173.1, 137.2, 130.1, 129.8, 128.5, 128.1, 120.7, 119.8, 109.3, 101.8, 33.2, 20.3; *m/z* (C.I.) 231 (100 %, M-H$^+$); (Found (E.I): M$^+$, 230.1494. $C_{14}H_{18}N_2O$ requires 230.1492).

1-Methyl-1*H*-indole-6-carboxylic acid-*tert*-butylamide 355



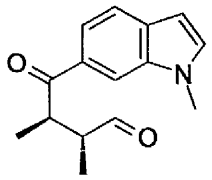
1-Methyl-1*H*-indole-6-carboxylic acid **345** (0.83 g, 4.74 mmol, 1.0 equiv.) and *N-tert*-butylamine (0.75 mL, 7.11 mmol, 1.5 equiv.) were treated according to **Method K**. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.93 g, 85 %) as needles: m.p. 106.8-107.7 °C; R_f(1:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 3351 (NH), 2966 (CH), 1636 (C=O); δ_H(300 MHz, $CDCl_3$) 7.96 (1H, d, *J* 1.5, *H*-7), 7.61 (1H, d, *J* 8.5, *H*-4), 7.38 (1H, dd, *J* 8.5 and 1.5, *H*-5), 7.17 (1H, d, *J* 3.0, *H*-2), 6.52 (1H, d, *J* 3.0, *H*-3), 6.14 (1H, brs, N*H*), 3.85 (3H, s, NCH_3), 1.54 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 168.0, 162.8, 136.7, 131.5, 130.9, 129.2, 120.6, 117.2, 109.7, 101.3, 51.8, 36.7, 33.2, 29.3; *m/z* (C.I.) 231 (100 %, M + H^+); (Found (E.I): M^+, 230.1491. $C_{14}H_{18}N_2O$ requires 230.1492).

1-Methyl-1*H*-indole-6-carboxylic acid allyl-*tert*-butylamide 356



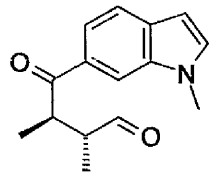
1-Methyl-1*H*-indole-6-carboxylic acid-*tert*-butylamide **355** (0.60 g, 2.60 mmol, 1.0 equiv.) and allyl bromide (0.44 mL, 5.22 mmol, 2.0 equiv.) were treated according to **Method H**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.30 g, 43 %) as a colourless oil: R_f(10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965 (CH), 1632 (C=O); δ_H(300 MHz, $CDCl_3$) 7.60 (1H, dd, *J* 8.0 and 1.0, *H*-4), 7.45 (1H, s, *H*-7), 7.15 (1H, d, *J* 8.0 and 1.0, *H*-5), 7.12 (1H, d, *J* 3.0, *H-2)*, 6.50 (1H, d, *J* 3.0, *H-3)*, 5.80-5.90 (1H, m, CH_2CHCH_2), 5.10-5.16 (2H, m, CH_2CHCH_2), 4.03-4.05 (2H, m, CH_2CHCH_2), 3.82 (3H, s, NCH_3), 1.62 (9H, s, *t*Bu); δ_C(75 MHz, $CDCl_3$) 175.2, 138.3, 136.4, 133.1, 130.4, 129.2, 120.7, 119.7, 118.1, 115.9, 108.1, 101.2, 57.7, 50.7, 33.1, 29.1; *m/z* (C.I.) 271 (100 %, M-H^+); (Found (E.I): M^+, 270.1802. $C_{17}H_{22}N_2O$ requires 270.1805).

2,3-Dimethyl-4-(1-methyl-1*H*-indol-6-yl)-4-oxobutyraldehyde 357



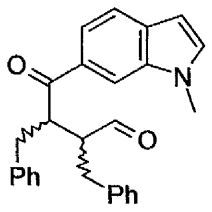
1-Methyl-1*H*-indole-6-carboxylic acid allyl-*tert*-butylamide **356** (0.10 g, 0.37 mmol, 1.0 equiv.) and iodomethane (0.14 mL, 2.2 mmol, 6.0 equiv.) were treated according to **Method D**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.08 g, 73 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2966 (CH), 1718, 1661 (C=O); δ_H(300 MHz, $CDCl_3$) 9.90 (1H, d, *J* 2.0, C*H*O), 8.10 (1H, s, *H*-7), 7.79 (1H, dd, *J* 8.5 and 1.5, *H*-4), 7.72 (1H, d, *J* 8.5, *H*-5), 7.30 (1H, d, *J* 3.0, *H*-2), 6.58 (1H, dd, *J* 3.0 and 1.5, *H*-3), 3.92 (3H, s, NCH_3), 3.83-3.85 (1H, m, C*H*CH_3), 3.00 (1H, dq, *J* 7.0 and 2.0, C*H*(CH_3)CHO), 1.35 (3H, d, *J* 7.0, CHCH_3), 1.18 (3H, d, *J* 7.0, CH(CH_3)CHO); δ_C(75 MHz, $CDCl_3$) 204.7, 202.9, 133.2, 132.8, 130.2, 120.9, 119.9, 110.8, 107.6, 101.7, 48.9, 42.3, 33.4, 16.6, 12.9; *m/z* (C.I.) 244 (100 %, M-H^+); (Found (E.I): M^+, 243.1336. $C_{15}H_{17}NO_2$ requires 243.1332).

2,3-Dimethyl-4-(1-methyl-1*H*-indol-6-yl)-4-oxobutyraldehyde *trans*-357



1-Methyl-1*H*-indole-6-carboxylic acid allyl-*tert*-butylamide **356** (0.10 g, 0.37 mmol, 1.0 equiv.) and iodomethane (0.14 mL, 2.2 mmol, 6.0 equiv.) were treated according to **Method D**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.01 g, 9 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2926 (CH), 1719, 1663 (C=O); δ_H(300 MHz, $CDCl_3$) 9.85 (1H, s, C*H*O), 8.08 (1H, s, *H*-7), 7.79 (1H, dd, *J* 8.5 and 1.5, *H*-4), 7.72 (1H, d, *J* 8.5, *H*-5), 7.27 (1H, d, *J* 3.0, *H*-2), 6.56 (1H, dd, *J* 3.0 and 1.5, *H*-3), 3.97-3.99 (1H, m, C*H*CH_3), 3.90 (3H, s, NCH_3), 2.98 (1H, dq, *J* 7.0 and 2.0, C*H*(CH_3)CHO), 1.32 (3H, d, *J* 7.0, CHCH_3), 1.24 (3H, d, *J* 7.0, CH(CH_3)CHO); δ_C(75 MHz, $CDCl_3$) 204.6, 203.3, 136.7, 133.0, 130.5, 120.9, 119.8, 110.8, 110.3, 101.7, 48.9, 41.9, 33.3, 15.5, 11.1; *m/z* (C.I.) 244 (100 %, M-H^+); (Found (E.I): M^+, 243.1333. $C_{15}H_{17}NO_2$ requires 243.1332).

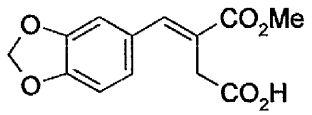
2,3-Dibenzyl-4-(1-methyl-1*H*-indol-6-yl)-4-oxobutyraldehyde 358



1-Methyl-1*H*-indole-6-carboxylic acid allyl-*tert*-butylamide **356** (0.10 g, 0.37 mmol, 1.0 equiv.) and benzyl bromide (0.26 mL, 2.2 mmol, 6.0 equiv.) were treated according to **Method D**. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (0.06 g, 45 %) as a colourless oil in a 1:1 ratio: R_f(5:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH), 1717, 1660 (C=O); δ_H (300 MHz, $CDCl_3$) 10.1 (1H, d, *J* 1.0, C*H*O$_A$), 9.90 (1H, d, *J* 2.0, C*H*O$_B$), 7.89 (1H, d, *J* 0.5, *H*-7$_A$), 7.71 (1H, d, *J* 0.5, *H*-7$_B$), 7.20-7.63 (24H, m, Ar*H*$_{A+B}$, *H*-4$_{A+B}$ and *H*-5$_{A+B}$), 7.00 (1H, d, *J* 3.5, *H*-2$_A$), 6.98 (1H, d, *J* 3.0, *H*-2$_B$), 6.56 (1H, dd, *J* 3.0 and 1.0, *H*-3$_A$), 6.51 (1H, dd, *J* 3.5 and 1.0, *H*-3$_B$), 4.20-4.27 (4H, m, C*H*$_2$Ph$_{A+B}$), 3.84 (3H, s, NC*H*$_{3A}$), 3.77 (3H, s, NC*H*$_{3B}$), 3.26-3.30 (4H, m, C*H*$_2$Ph$_{A+B}$), 3.06-3.14 (2H, m, C*H*CH$_{3A+B}$), 2.89 (1H, dt, *J* 3.5 and 1.0, C*H*$_A$(Bn)CHO), 2.72-2.73 (1H, m, C*H*$_B$(Bn)CHO); δ_C(75 MHz, $CDCl_3$) 204.1, 203.1, 202.1, 201.9, 139.6, 139.1, 136.5, 136.4, 133.4, 133.2, 132.9, 132.7, 130.8, 130.3, 129.9, 129.6, 129.5, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 127.9, 127.3, 126.9, 126.8, 126.7, 120.9, 120.8, 119.9, 119.8, 111.1, 110.9, 101.7, 101.6, 65.7, 55.0, 52.6, 50.2, 49.2, 47.7, 36.9, 35.5, 33.8, 33.3, 31.2, 21.0; *m/z* (C.I.) 396 (100 %, M-H$^+$); (Found (E.I): M$^+$, 395.1960. $C_{27}H_{25}NO_2$ requires 395.1958).

4.3.5 Experimental Details for Chapter 3

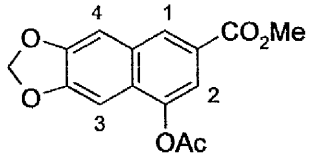
2-Benzo[1,3]dioxol-5-ylmethylene succinic acid methyl ester 419[182]



A solution of piperonal (15 g, 99.0 mmol, 1.0 equiv.) and dimethyl succinamide (17.5 g, 119.8 mmol, 1.2 equiv.) in *tert*-butanol (25 mL) was added dropwise to a refluxing solution of potassium *tert*-butoxide (16.7 g, 149 mmol, 1.5 equiv.) in *tert*-butanol (60 mL) over 15 min. The solution was heated at reflux for 1 h, cooled to room temperature and acidified with 10 M HCl (25 mL). The solvent was removed under reduced pressure and water (50 mL) added. The mixture was extracted with EtOAc (4 × 50 mL).

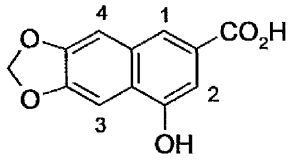
Combined organics were washed with water (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (26.4 g, 100 %) as a yellow oil: R_f (1:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 3075 (OH), 2906 (CH), 1714, 1617 (C=O); δ_H(300 MHz, $CDCl_3$) 7.87 (1H, s, Ar*H*), 7.30 (1H, d, *J* 7.5, Ar*H*), 7.22 (1H, d, *J* 7.5, Ar*H*), 6.90 (1H, s, *H*C=C(CO_2Me)), 6.05 (2H, s, OCH_2O), 3.90 (3H, s, OCH_3), 3.60 (2H, s, CH_2CO_2H); δ_C(75 MHz, $CDCl_3$) 176.4, 168.2, 148.5, 148.0, 142.6, 128.6, 124.1, 123.6, 109.1, 108.7, 101.5, 52.4, 29.7; *m/z* (C.I.) 265 (100 %, M + H^+); (Found (E.I): M^+, 264.2418. $C_{13}H_{12}O_6$ requires 264.2420).

8-Acetoxynaphtho[2,3-d][1,3]dioxole-6-carboxylic acid methyl ester 420[182]



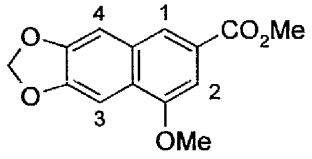
2-Benzo[1,3]dioxol-5-ylmethylene succinic acid methyl ester **419** (26.4 g, 99 mmol, 1.0 equiv.) and sodium acetate (9.0 g, 110 mmol, 1.1 equiv.) in acetic anhydride (170 mL) were heated at reflux for 5 h, cooled to room temperature and water (50 mL) added. The mixture was extracted with EtOAc (4 × 50 mL). Combined organics were washed with water (2 × 50 mL) and saturated aqueous sodium carbonate solution (3 × 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (28.8 g, 100 %) as a yellow oil: R_f(1:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2919 (CH), 1767, 1717 (C=O); δ_H(300 MHz, $CDCl_3$) 8.38 (1H, s, *H*-1), 7.75 (1H, s, *H*-2), 7.22 (1H, s, *H*-3), 7.20 (1H, s, *H*-4), 6.10 (2H, s, OCH_2O), 4.02 (3H, s, OCH_3), 2.50 (3H,s, OAc); δ_C (75 MHz, $CDCl_3$) 169.3, 166.6, 150.3, 148.7, 146.1, 131.1, 127.6, 126.8, 126.0, 116.8, 105.3, 101.8, 97.9, 52.3, 29.7, 20.9; *m/z* (C.I.) 289 (100 %, M + H^+); (Found (E.I): M^+, 288.2704. $C_{15}H_{12}O_6$ requires 288.2710).

1-(8-Hydroxynaphtho[2,3-d][1,3]dioxol-6-yl)ethanone 421[182]



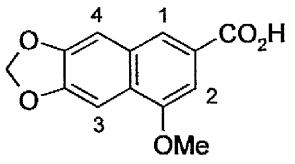
A solution of 8-Acetoxynaphtho[2,3-d][1,3]dioxole-6-carboxylic acid methyl ester **420** (28.8 g, 98.6 mmol, 1.0 equiv.) in 15 % aqueous-methanolic potassium hydroxide (61 g in 185 mL H_2O: 185 mL CH_3OH) was heated at reflux for 3 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The solution was acidified with 10 M HCl (50 mL) and the resulting precipitate filtered off and dried, affording the *title compound* (23.2 g, 100 %) as yellow solid. The product was directly methylated as decomposition was reported.[182]

8-Methoxynaphtho[2,3-d][1,3]dioxole-6-carboxylic acid methyl ester 422[182]



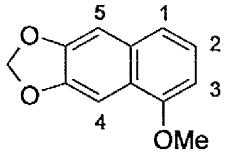
A solution of 1-(8-Hydroxynaphtho[2,3-d][1,3]dioxol-6-yl)ethanone **421** (23.2 g, 100 mmol, 1.0 equiv.), dimethyl sulfate (52.1 mL, 550 mmol, 5.5 equiv.) and potassium carbonate (93.8 g, 680 mmol, 6.8 equiv.) in acetone (600 mL) were heated at reflux for 12 h. The mixture was cooled to room temperature and the volume reduced *in vacuo*. The mixture was extracted with EtOAc (4 × 75 mL) and combined organic layers washed with water (3 × 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (13.6 g, 53 %) as a yellow solid: m.p. 107.6 °C; R_f(10:1 Petrol:EtOAc) 0.75; ν_{max} ($CHCl_3$)/cm^{-1} 2952 (CH), 1714 (C=O); δ_H(300 MHz, $CDCl_3$) 8.02 (1H, s, *H*-1), 7.58 (1H, s, *H*-2), 7.32 (1H, s, *H*-3), 7.18 (1H, s, *H*-4), 6.08 (2H, s, OCH_2O), 4.02 (3H, s, CO_2CH_3), 3.98 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 167.0, 154.4, 148.7, 148.0, 125.7, 124.5, 122.2, 104.4, 102.1, 100.9, 98.7, 55.3, 51.7, 26.4; *m/z* (C.I.) 261 (100 %, M + H^+); (Found (E.I): M^+, 260.2522. $C_{14}H_{12}O_5$ requires 260.2531).

8-Methoxynaphtho[2,3-d][1,3]dioxole-6-carboxylic acid 423[182]



A solution of 8-Methoxynaphtho[2,3-d][1,3]dioxole-6-carboxylic acid methyl ester **422** (13.6 g, 52.0 mmol, 1.0 equiv.) in 15 % aqueous-methanolic potassium hydroxide (31.5 g in 95 mL H_2O: 95 mL CH_3OH) was heated at reflux for 3 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The solution was acidified with 10 M HCl (50 mL) and the resulting precipitate filtered off and dried, to afford the *title compound* (12.9 g, 100 %) as an off-white solid: m.p. 247.7 °C; R_f (10:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 3205 (OH), 2954 (CH), 1707 (C=O); δ_H(300 MHz, $CDCl_3$) 8.02 (1H, s, *H*-1), 7.48 (1H, s, *H*-2), 7.35 (1H, s, *H*-3), 7.22 (1H, s, *H*-4), 6.08 (2H, s, OCH_2O), 4.00 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 172.0, 154.0, 152.1, 151.8, 129.4, 125.3, 123.6, 121.0, 106.9, 100.8, 100.1, 91.7, 56.5; *m/z* (C.I.) 247 (100 %, $M + H^+$); (Found (E.I): M^+, 246.0530. $C_{13}H_{10}O_5$ requires 246.0528).

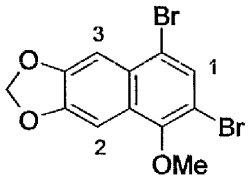
5-Methoxynaphtho[2,3-d][1,3]dioxole 424[182]



A mixture of 8-methoxynaphtho[2,3-d][1,3]dioxole-6-carboxylic acid **423** (24.2 g, 98.4 mmol, 1.0 equiv.) and copper powder (12.5 g, irregular mesh, 196.7 mmol, 2.0 equiv.) in quinoline (400 mL) was heated at reflux for 30 min and copper powder (12.5 g, irregular mesh, 196.7 mmol, 2.0 equiv.) added portionwise over 1.5 h. The mixture was maintained at reflux for 3 h and cooled to room temperatue. The mixture was extracted with EtOAc (4 × 100 mL). Combined organics were washed with water (2 × 100 mL), 2 M HCl (2 × 100 mL), saturated aqueous sodium hydrogen carbonate solution (2 × 100 mL) dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 10:1 Petrol/EtOAc) afforded the *title compound* (14.5 g, 75 %) as a yellow solid: m.p. 183.2 °C; R_f(10:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 2956 (CH); δ_H(300 MHz, $CDCl_3$) 7.58 (1H, s, *H*-4), 7.25-7.27 (2H, m, *H*-2 and *H*-1), 7.12 (1H, s, *H*-5), 6.78 (1H, dd, *J* 6.0 and 2.5, *H*-3), 6.05 (2H, s, OCH_2O), 3.98 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 153.8, 150.9, 149.6, 131.2, 124.8, 122.2, 118.8, 106.4,

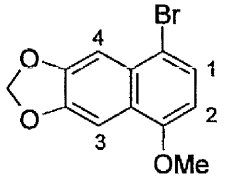
101.9, 101.0, 91.4, 56.4; *m/z* (C.I.) 203 (100 %, M + H^+); (Found (E.I): M^+, 202.0643. $C_{12}H_{10}O_3$ requires 202.0630).

6,8-Dibromo-5-methoxynaphtho[2,3-d][1,3]dioxole 425



Bromine (1.02 mL, 19.8 mmol, 2.0 equiv.) was added dropwise to a solution of 5-methoxynaphtho[2,3-d][1,3]dioxole **424** (2.0 g, 9.9 mmol, 1.0 equiv.) in CH_2Cl_2 (65 mL) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 h. Saturated aqueous sodium metabisulfite solution (25 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 25 mL). Combined organics were washed with water (2 × 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (3.55 g, 100 %) as needles: m.p. 130.5-131.1 °C; R_f(5:1 Petrol:EtOAc) 0.75; ν_{max} ($CHCl_3$)/cm^{-1} 2899 (CH); δ_H(300 MHz, $CDCl_3$) 7.78 (1H, s, *H*-1), 7.50 (1H, s, *H*-2), 7.40 (1H, s, *H*-3), 6.15 (2H, s, OCH_2O), 3.95 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 152.5, 149.7, 149.4, 131.8, 130.0, 127.3, 117.0, 111.0, 104.7, 104.2, 102.1, 99.4, 61.6; *m/z* (C.I.) 358 (100 %, M + H^+); (Found (E.I): M^+, 357.8813. $C_{12}H_8O_3Br_2$ requires 357.8811).

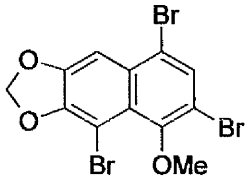
5-Bromo-8-methoxynaphtho[2,3-d][1,3]dioxole 426



Bromine (0.04 mL, 0.74 mmol, 1.0 equiv.) was added dropwise to a solution of 5-methoxynaphtho[2,3-d][1,3]dioxole **424** (0.15 g, 7.4 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 h. Saturated aqueous sodium metabisulfite solution (5 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 5 mL). Combined organics were washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.22 g, 100 %) as needles: m.p. 123.3 °C; R_f(5:1 Petrol:EtOAc) 0.70; ν_{max}($CHCl_3$)/cm^{-1} 2937 (CH); δ_H(300 MHz, $CDCl_3$) 7.55 (1H, s, *H*-4), 7.53 (1H, s, *H*-3),

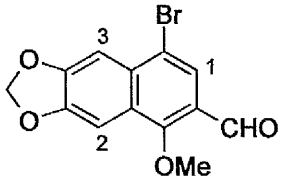
7.50 (1H, d, *J* 8.5, *H*-1), 6.60 (1H, d, *J* 8.5, *H*-2), 6.08 (2H, s, OC*H*$_2$O), 3.95 (3H, s, OC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 154.9, 149.4, 147.9, 130.2, 128.3, 123.5, 112.6, 104.2, 102.1, 101.6, 99.9, 55.9; *m/z* (C.I.) 280 (100 %, M + H^+);(Found (E.I): M^+, 279.9737. $C_{12}H_9O_3Br$ requires 279.9735).

4,6,7-Tribromo-5-methoxynaphtho[2,3-d][1,3]dioxole 427



Bromine (0.12 mL, 2.1 mmol, 3.0 equiv.) was added dropwise to a solution of 5-methoxynaphtho[2,3-d][1,3]dioxole **424** (0.15 g, 7.0 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) and the mixture stirred at room temperature under a nitrogen atmosphere for 2 h. Saturated aqueous sodium metabisulfite solution (7 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 5 mL). Combined organics were washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.23 g, 85 %) as needles: m.p. 204 °C; R_f(5:1 Petrol:EtOAc) 0.75; ν_{max}($CHCl_3$)/cm^{-1} 2937, 2251, 2125 (CH); δ_H(300 MHz, DMSO) 7.98 (1H, s, *H*-3), 7.42 (1H, s, *H*-6), 6.22 (2H, s, OC*H*$_2$O), 3.70 (3H, s, OC*H*$_3$); δ_C(75 MHz, DMSO) 148.6, 132.9, 117.3, 114.1, 104.2, 103.1, 79.0, 62.5; *m/z* (C.I.) 440 (100 %, M + H^+); (Found (E.I): M^+, 439.7939. $C_{12}H_7O_3Br_3$ requires 439.7945).

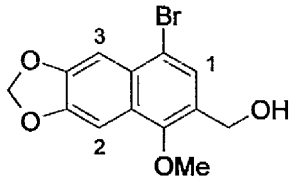
8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxole-6-carbaldehyde 429



n-Butyllithium (0.23 mL of a 2.4 M solution in hexane, 0.56 mmol, 1.0 equiv.) was added dropwise to a solution of 6,8-dibromo-5-methoxynaphtho[2,3-d][1,3]dioxole **425** (0.2 g, 0.56 mmol, 1.0 equiv.) in diethyl ether (7 mL) at –78 °C under a nitrogen atmosphere. The mixture was stirred at –78 °C for 30 min and DMF (0.5 mL) added dropwise. The solution was stirred at room temperature for 2 h and quenched by the addition of saturated aqueous ammonium chloride solution (2 mL). The mixture was extracted with EtOAc (4 × 5 mL) and combined organic layers washed with water

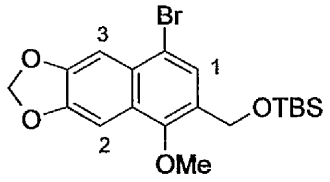
(5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 65 %) as needles: m.p. 184.9-185.2 °C; R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2855 (CH), 1676 (C=O); δ_H(300 MHz, $CDCl_3$) 10.42 (1H, s, C*H*O), 8.05 (1H, s, *H*-2), 7.62 (1H, s, *H*-1), 7.55 (1H, s, *H*-3), 6.18 (2H, s, OCH_2O), 4.08 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 188.5, 161.0, 151.9, 149.4, 134.8, 126.3, 125.8, 124.7, 117.9, 105.5, 102.5, 100.1, 65.8; *m/z* (C.I.) 308 (100 %, M + H^+); (Found (E.I): M^+, 307.9683. $C_{13}H_9O_4Br$ requires 307.9684).

(8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-yl)methanol 430



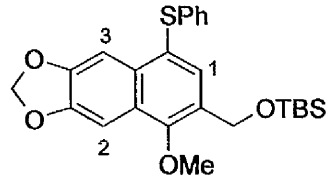
8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxole-6-carbaldehyde **429** (4.57 g, 14.7 mmol, 1.0 equiv.) was dissolved in ethanol (200 mL) and stirred with sodium borohydride (0.61 g, 16.2 mmol, 1.2 equiv.) at room temperature under a nitrogen atmosphere for 14 h. The mixture was quenched by the addition of saturated aqueous ammonium chloride solution (25 mL) and the solvents removed under reduced pressure. Water (50 mL) was added and the mixture extracted with EtOAc (4 × 50 mL). Combined organics were washed with water (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (4.12 g, 90 %) as an off-white solid: m.p. 215.0-215.6 °C; R_f(5:1 Petrol:EtOAc) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 3060 (OH), 2349 (CH); δ_H(300 MHz, $CDCl_3$) 7.68 (1H, s, *H*-2), 7.55 (1H, s, *H*-1), 7.40 (1H, s, *H*-3), 6.10 (2H, s, OCH_2O), 4.85 (2H, s, CH_2OH), 3.95 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 149.5, 130.6, 129.1, 117.0, 104.6, 101.9, 99.2, 62.8, 60.6; *m/z* (C.I.) 310 (100 %, M + H^+); (Found (E.I): M^+, 309.9843. $C_{13}H_{11}O_4Br$ requires 309.9841).

(8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane 431



A solution of *tert*-Butyldimethylsilyl chloride (0.14 g, 0.89 mmol, 1.2 equiv.) in DMF (1 mL) was added dropwise to a stirred solution of (8-bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-yl)methanol **430** (0.23 g, 0.75 mmol, 1.0 equiv.) and imidazole (0.13 g, 1.86 mmol, 2.5 equiv.) in DMF (2 mL). The solution was stirred at room temperature under a nitrogen atmosphere for 18 h and water (2 mL) added. The mixture was extracted with EtOAc (4 × 5 mL) and the combined organic layers washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.21 g, 68 %) as an off-white solid: m.p. 86.8-87.3 °C; R_f(5:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2967 (CH); δ_H(300 MHz, $CDCl_3$) 7.75 (1H, s, *H*-2), 7.55 (1H, s, *H*-1), 7.38 (1H, s, *H*-3), 6.08 (2H, s, OCH_2O), 4.87 (2H, s, CH_2OTBS), 3.90 (3H, s, OCH_3), 0.95 (9H, s, *t*Bu), 0.18 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 152.0, 149.2, 148.7, 130.1, 129.7, 128.7, 126.3, 116.9, 104.6, 101.8, 99.1, 62.4, 59.8, 26.3, 18.7, 4.9; *m/z* (C.I.) 426 (5 %, M + H^+), 354 (50 % M-(*t*Bu + Me)Br^{81}) 352 (50 % M-(*t*Bu + Me)Br^{79}); (Found (E.I): M^+, 424.0708. $C_{19}H_{25}O_4SiBr$ requires 424.0706).

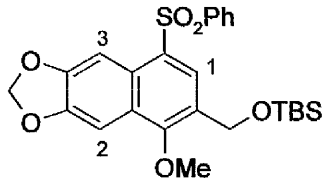
***tert*-Butyl-(5-methoxy-8-phenylsulfanylnaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)dimethylsilane 432**



(8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **431** (0.25 g, 0.58 mmol, 1.0 equiv.) was treated according to **Method L**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.16 g, 62 %) as a clear oil: R_f(10:1 Petrol:EtOAc) 0.65; ν_{max} $(CHCl_3)/cm^{-1}$ 2953 (CH); δ_H(300 MHz, $CDCl_3$) 7.84 (1H, s, *H*-2), 7.78 (1H, s, *H*-1), 7.48 (1H, s, *H*-3), 7.15-7.22 (5H, m, Ar*H*), 6.08 (2H, s, OCH_2O), 4.96 (2H, s, CH_2OTBS), 4.00 (3H, s, OCH_3), 0.98 (9H, s, *t*Bu), 0.20 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 153.9, 149.0, 148.5, 138.1,

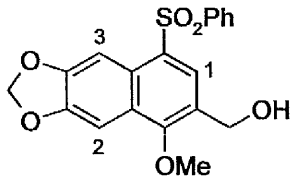
133.5, 132.9, 131.1, 129.2, 129.1, 129.1, 129.0, 128.0, 127.1, 125.0, 104.4, 103.4, 101.6, 99.7, 62.5, 60.4, 26.3, 18.7, 4.89; *m/z* (C.I.) 455 (5 %, M + H^+), 384 (50 % M-(*t*Bu + Me)) 382 (50 % M-(*t*Bu + Me)); (Found (E.I): M^+, 454.1634. $C_{25}H_{30}O_4SiS$ requires 454.1633).

(8-Benzenesulfonyl-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyl-dimethylsilane 433



tert-Butyl-(5-methoxy-8-phenylsulfanylnaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-dimethylsilane **432** (0.20 g, 4.41 mmol, 1.0 equiv.) was treated according to **Method M**. Purification by flash column chromatography (SiO_2; 4:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 50 %) as a white solid: m.p. 130.8-131.3 °C; R_f(1:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2952 (CH); δ_H(300 MHz, $CDCl_3$) 8.50 (1H, s, *H*-2), 8.05 (1H, s, *H*-1), 7.98 (2H, dd, *J* 6.5 and 1.0, Ar*H*), 7.48-7.52 (3H, m, Ar*H*), 7.45 (1H, s, *H*-3), 6.18 (2H, s, OCH_2O), 4.98 (2H, s, CH_2OTBS), 3.95 (3H, s, OCH_3), 1.00 (9H, s, *t*Bu), 0.2 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 157.5, 149.8, 148.6, 142.2, 134.0, 133.2, 130.8, 130.5, 130.1, 129.7, 129.4, 128.5, 128.2, 127.5, 126.4, 102.0, 99.7, 62.6, 59.9, 26.2, 18.6, 4.9; *m/z* (C.I.) 504 (100 %, M + 18); (Found (E.I): M^+, 486.1536. $C_{25}H_{30}O_6SiS$ requires 486.1532).

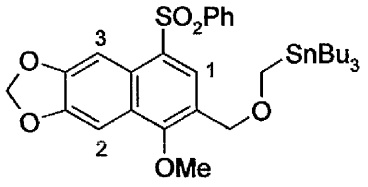
(8-Benzenesulfonyl-5-methoxynaphtho[2,3-d][1,3]dioxol-6-yl)methanol 434



(8-Benzenesulfonyl-5-methoxynaphtho-[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **433** (0.10 g, 0.19 mmol, 1.0 equiv.) was treated according to **Method N**. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.05 g, 75 %) as a white solid: m.p. 197.2-197.8 °C; R_f(1:1 Petrol:EtOAc) 0.25; $\nu_{max}(CHCl_3)/cm^{-1}$ 3502 (OH), 2914 (CH); δ_H(300 MHz, $CDCl_3$) 8.45 (1H, s, *H*-2), 7.98 (3H, dd, *J* 6.5 and 1.0, Ar*H*), 7.58 (1H, s, *H*-1), 7.44-7.52 (2H, m, Ar*H*), 7.38 (1H, s, *H*-3), 6.05 (2H, s, OCH_2O), 4.90 (2H, s, CH_2OH), 3.95 (3H, s,

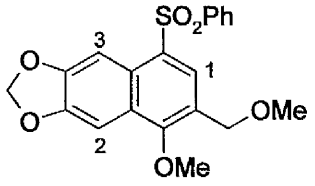
OC*H*$_3$), 2.30 (1H, brs, O*H*); δ_C(75 MHz, $CDCl_3$) 158.6, 149.9, 148.7, 141.9, 133.1, 130.7, 130.0, 129.3, 127.9, 127.5, 127.3, 126.5, 101.9, 101.8, 99.7, 62.9, 60.4, 29.4; *m/z* (C.I.) 390 (100 %, M + 18); (Found (E.I): M^+, 372.0667. $C_{19}H_{16}O_6S$ requires 372.0668).

(8-Benzenesulfonyl-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxymethyl) tributylstannane 412



(8-Benzenesulfonyl-5-methoxynaphtho[2,3-d][1,3]dioxol-6-yl)methanol **434** (0.15 g, 0.40 mmol, 1.0 equiv.) was treated according to **Method O**. Purification by flash column chromatography (SiO_2; 20:1 Petrol/EtOAc) afforded the *title compound* (0.14 g, 56 %) as a yellow oil: R_f (5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 2923 (CH); δ_H(400 MHz, $CDCl_3$) 8.45 (1H, s, *H*-2), 7.92-7.98 (3H, m, *H*-1 and Ar*H*), 7.42-7.55 (4H, m, *H*-3 and Ar*H*), 6.05 (2H, s, OCH_2O), 4.62 (2H, s, CH_2OCH_2Sn), 3.95 (3H, s, OCH_3), 3.85 (2H, apparent t due to Sn coupling, CH_2OCH_2Sn), 1.55 (6H, qt , *J* 8.0 and 7.5, $SnBu_3$), 1.30 (6H, tt, *J* 8.0 and 7.5, $SnBu_3$), 0.95 (6H, t, *J* 8.0, $SnBu_3$), 0.88 (9H, t, *J* 7.5, $SnBu_3$); δ_C(75 MHz, $CDCl_3$) 158.7, 149.6, 148.3, 142.1, 132.8, 130.9, 130.2, 129.0, 127.6, 127.2, 126.4, 125.4, 101.7, 99.8, 62.9, 62.2, 29.1, 29.0, 27.3, 13.7, 9.0; *m/z* (C.I.) 676 (100 %, M + 18); (Found (E.I): M^+, 675.4628. $C_{32}H_{44}O_6SSn$ requires 675.4630).

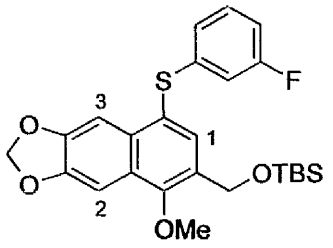
8-Benzenesulfonyl-5-methoxy-6-methoxymethylnaphtho[2,3-d][1,3]dioxole 435



(8-Benzenesulfonyl-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxymethyl)-tributylstannane **412** (0.055 g, 0.081 mmol, 1.0 equiv.) was treated according to **Method P**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.015 g, 50 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.45; $\nu_{max}(CHCl_3)/cm^{-1}$ 2922 (CH); δ_H(300 MHz, $CDCl_3$) 8.50 (1H, s, *H*-2), 7.98-8.01 (4H, m, Ar*H* and *H*-1), 7.50-7.52 (3H, m, Ar*H* and *H*-3), 6.10 (2H, s, OCH_2O), 4.70 (2H, s, CH_2OCH_3), 4.00 (3H, s, OCH_3), 3.55 (3H, s, CH_2OCH_3); δ_C(75 MHz, $CDCl_3$) 157.5, 149.8, 149.5, 138.5, 133.5, 129.5, 127.8, 127.1, 126.5, 124.0, 123.1, 112.2,

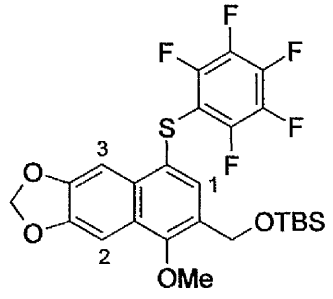
106.1, 100.6, 91.3, 68.4, 56.7, 53.5; *m/z* (C.I.) 387 (100 %, M + H); (Found (E.I): M^+, 386.0819. $C_{20}H_{18}O_6S$ requires 386.0824).

tert-Butyl-[8-(3-fluorophenylsulfanyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxyl]dimethylsilane 436a



(8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **431** (0.20 g, 0.47 mmol, 1.0 equiv.) and bis(3-fluorophenyl)disulfide (0.15 g, 0.59 mmol, 1.25 equiv.) were treated according to **Method L**. Purification by flash column chromatography (SiO_2; 100 % Petrol) afforded the *title compound* (0.17 g, 79 %) as a clear oil: R_f(5:1 Petrol:EtOAc) 0.85; $\nu_{max}(CHCl_3)/cm^{-1}$ 2951 (CH); δ_H(300 MHz, $CDCl_3$) 7.87 (1H, s, *H*-2), 7.68 (1H, s, *H*-1), 7.47 (1H, s, *H*-3), 7.20 (1H, dd, *J* 8.0 and 2.0, Ar*H*), 6.94 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 6.70-6.82 (2H, m, Ar*H*), 6.08 (2H, s, OCH_2O), 4.96 (2H, s, CH_2OTBS), 3.98 (3H, s, OCH_3), 0.97 (9H, s, *t*Bu), 0.17 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 154.4, 149.2, 148.6, 141.0, 134.4, 133.1, 130.4, 129.6, 128.5, 126.3, 114.2, 112.6, 104.4, 103.4, 101.6, 99.7, 62.5, 60.4, 26.3, 18.7, 4.89; *m/z* (C.I.) 473 (100 %, M + H^+); (Found (E.I): M^+, 472.1533. $C_{25}H_{29}O_4SSiF$ requires 472.1534).

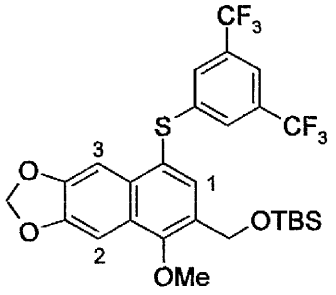
tert-Butyl-(5-methoxy-8-pentafluorophenylsulfanylnaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)dimethylsilane 436b



(8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **431** (0.15 g, 0.35 mmol, 1.0 equiv.) and bis(pentafluorophenyl)disulfide (0.17 g, 0.44 mmol, 1.25 equiv.) were treated according to **Method L**.

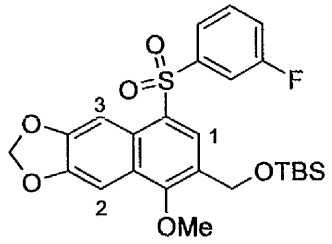
Purification by flash column chromatography (SiO_2; 100 % Petrol) afforded the *title compound* (0.15 g, 78 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH); δ_H(300 MHz, $CDCl_3$) 7.49 (1H, s, *H*-2), 7.42 (1H, s, *H*-1), 7.15 (1H, s, *H*-3),), 6.07 (2H, s, OCH_2O), 4.97 (2H, s, CH_2OTBS), 3.94 (3H, s, OCH_3), 1.02 (9H, s, *t*Bu), 0.19 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 154.9, 149.1, 148.2, 147.1, 132.4, 131.9, 131.7, 129.3, 128.7, 125.6, 120.6, 111.9, 104.4, 102.6, 101.3, 99.6, 98.8, 62.3, 60.3, 26.3, 18.7, 4.93; *m/z* (C.I.) 545 (100 %, M + H^+); (Found (E.I): M^+, 544.1165. $C_{25}H_{25}O_4SSiF_5$ requires 544.1163).

[8-(3,5-Bistrifluoromethylphenylsulfanyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy]-*tert*-butyldimethylsilane 436c



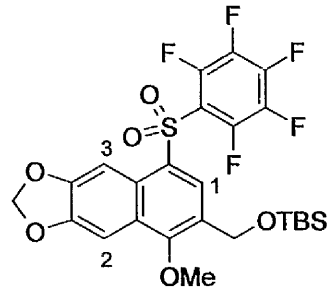
(8-Bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **431** (0.60g, 1.40 mmol, 1.0 equiv.) and bis(trifluoromethylphenyl)disulfide (0.86 g, 1.76 mmol, 1.25 equiv.) were treated according to **Method L**. Purification by flash column chromatography (SiO_2; 100 % Petrol) afforded the *title compound* (0.71 g, 86 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.80; $\nu_{max}(CHCl_3)/cm^{-1}$ 2953 (CH); δ_H (300 MHz, $CDCl_3$) 7.90 (1H, s, Ar*H*), 7.62 (1H, s, *H*-2), 7.60 (1H, s, *H*-1), 7.48 (2H, s, Ar*H*), 7.13 (1H, s, *H*-3), 6.05 (2H, s, OCH_2O), 4.96 (2H, s, CH_2OTBS), 3.93 (3H, s, OCH_3), 1.00 (9H, s, *t*Bu), 0.18 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 171.4, 154.9, 152.5, 151.6, 149.5, 148.2, 142.8, 141.2, 134.9, 123.6, 131.7, 129.7, 129.2, 128.6, 125.7, 124.9, 119.5, 119.1, 105.7, 104.4, 102.6, 101.9, 99.5, 60.7, 26.2, 14.4, 4.9; *m/z* (C.I.) 591 (100 %, M-NH_4^+); (Found (E.I): M^+, 590.1389. $C_{27}H_{28}F_6O_4SSi$ requires 590.1382).

tert-Butyl-[8-(3-fluorobenzesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy]dimethylsilane 437a



tert-Butyl-[8-(3-fluorophenylsulfanyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxyl]dimethylsilane **436a** (0.16 g, 0.34 mmol, 1.0 equiv.) was treated according to **Method M**. Purification by flash column chromatography (SiO_2; 25:1 Petrol/EtOAc) afforded the *title compound* (0.12 g, 65 %) as a white solid: m.p. 122.6-123.4 °C; R_f(5:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH); δ_H(300 MHz, $CDCl_3$) 8.52 (1H, s, *H*-2), 8.00 (1H, s, *H*-1), 7.78 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.64 (1H, dd, *J* 8.0 and 0.5, Ar*H*), 7.46 (1H, s, *H*-3), 7.28-7.20 (2H, m, Ar*H*), 6.10 (2H, s, OCH_2O), 4.97 (2H, s, CH_2OTBS), 3.95 (3H, s, OCH_3), 1.00 (9H, s, *t*Bu), 0.2 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 170.6, 164.3, 157.7, 149.9, 148.7, 144.4, 134.1, 133.2, 130.8, 130.5, 130.1, 129.7, 129.4, 128.5, 128.2, 126.4, 102.0, 99.8, 62.6, 59.9, 26.2, 18.6, 4.9; *m/z* (C.I.) 373 (100 %, M - OTBS); (Found (E.I): M^+, 504.1778. $C_{25}H_{29}O_6SiSF$ requires 504.1776).

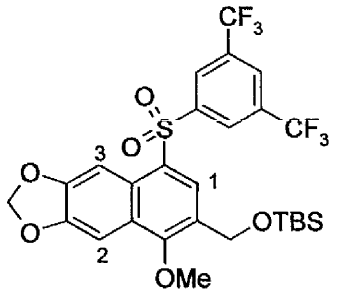
tert-Butyl-(5-methoxy-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)dimethylsilane 437b



tert-Butyl-(5-methoxy-8-pentafluorophenylsulfanylnaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)dimethylsilane **436b** (0.15 g, 0.27 mmol, 1.0 equiv.) was treated according to **Method M**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.14 g, 86 %) as a white solid:. m.p. 142.6-143.9 °C; R_f(5:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH); δ_H(300 MHz, $CDCl_3$) 7.48 (1H, s, *H*-2), 7.30 (1H, s, *H*-1), 7.15 (1H, s, *H*-3), 6.08 (2H, s, OCH_2O), 4.96 (2H, s, CH_2OTBS), 3.93 (3H, s, OCH_3), 0.99 (9H, s, *t*Bu), 0.17 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$)

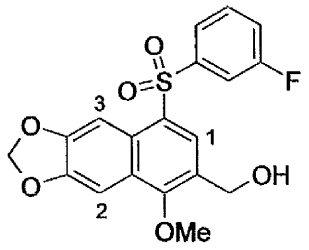
170.7, 163.4, 150.3, 148.9, 144.2, 134.9, 134.1, 130.5, 128.6, 126.6, 123.2, 120.7, 114.9, 102.2, 100.3, 99.9, 26.2, 5.03; *m/z* (C.I.) 577 (100 %, M + H^+); (Found (E.I): M^+, 576.1059. $C_{25}H_{25}O_6SSiF_5$ requires 576.1061).

[8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy]-*tert*-butyldimethylsilane 437c



[8-(3,5-Bistrifluoromethylphenylsulfanyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy]-*tert*-butyldimethylsilane **436c** (0.71 g, 1.2 mmol, 1.0 equiv.) was treated according to **Method M**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.22 g, 40 %) as a colourless oil: R_f (5:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 2931 (CH); δ_H(300 MHz, $CDCl_3$) 8.55 (1H, s, Ar*H*), 8.38 (2H, s, Ar*H*), 8.05 (1H, s, *H*-2), 7.96 (1H, s, *H*-1), 7.13 (1H, s, *H*-3), 6.11 (2H, s, OCH_2O), 4.96 (2H, s, CH_2OTBS), 3.94 (3H, s, OCH_3), 0.99 (9H, s, *t*Bu), 0.17 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 158.3, 150.5, 148.9, 145.2, 133.4, 132.9, 130.4, 128.7, 127.7, 127.5, 126.8, 126.6, 102.3, 101.1, 100.0, 62.6, 59.7, 26.0, 18.5, 5.0; *m/z* (C.I.) 623 (100 %, M-NH_4^+); (Found (E.I): M^+, 622.1284. $C_{27}H_{28}F_6O_6SSi$ requires 622.1280).

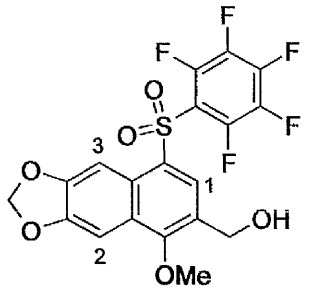
[8-(3-Fluorobenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxo-6-yl]methanol 438a



tert-Butyl-[8-(3-fluorobenzesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy]dimethylsilane **437a** (0.12 g, 0.23 mmol, 1.0 equiv.) was treated according to **Method N**. Purification by flash column chromatography (SiO_2; 5:1 Petrol/EtOAc)

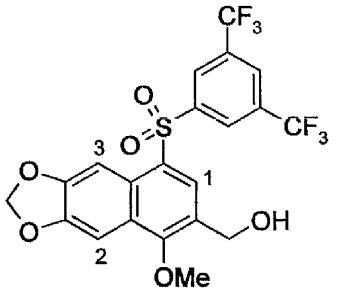
afforded the *title compound* (0.06 g, 65 %) as a white solid: m.p. 184.6-185.9 °C; R_f(1:1 Petrol:EtOAc) 0.25; $\nu_{max}(CHCl_3)/cm^{-1}$ 3503 (OH), 2920 (CH); δ_H(300 MHz, $CDCl_3$) 8.48 (1H, s, *H*-2), 7.94 (1H, s, *H*-1), 7.98 (1H, dd, *J* 8.0 and 1.5, Ar*H*), 7.62 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.28-7.20 (2H, m, Ar*H*), 7.44 (1H, s, *H*-3), 6.11 (2H, s, OCH_2O), 4.95 (2H, s, CH_2OH), 3.99 (3H, s, OCH_3), 2.40 (1H, brs, O*H*); δ_C(75 MHz, $CDCl_3$) 164.3, 158.9, 150.3, 148.9, 144.2, 131.3, 130.4, 127.8, 126.6, 123.2, 120.7, 114.9, 102.2, 101.8, 99.9, 63.0, 60.5; *m/z* (C.I.) 391 (100 %, M + H^+); (Found (E.I): M^+, 390.0569. $C_{19}H_{15}O_6SF$ requires 390.0573).

(5-Methoxy-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxol-6-yl)methanol 438b



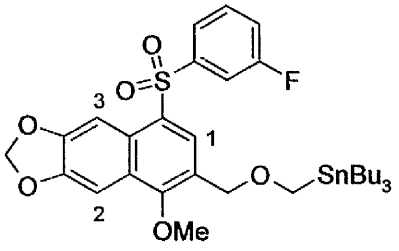
tert-Butyl-(5-methoxy-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)dimethylsilane **437b** (0.15 g, 0.25 mmol, 1.0 equiv.) was treated according to **Method N**. Purification by flash column chromatography (SiO_2; 100 % EtOAc) afforded the *title compound* (0.07 g, 60 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.25; $\nu_{max}(CHCl_3)/cm^{-1}$ 3328 (OH), 2923 (CH); δ_H(300 MHz, $CDCl_3$) 8.47 (1H, s, *H*-2), 7.95 (1H, s, *H*-1), 7.43 (1H, s, *H*-3), 6.08 (2H, s, OCH_2O), 4.95 (2H, s, CH_2OH), 3.99 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 170.7, 163.4, 150.3, 148.9, 144.2, 133.9, 134.7, 130.1, 128.6, 126.6, 123.2, 120.7, 114.9, 102.2, 100.4, 97.9, 67.2, 61.9, 48.6; *m/z* (C.I.) 463 (100 %, M + H^+); (Found (E.I): M^+, 462.0190. $C_{19}H_{11}O_6SiF_5$ requires 462.0196).

[8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-yl]methanol 438c



[8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy]-*tert*-butyldimethylsilane **437c** (0.22 g, 0.35 mmol, 1.0 equiv.) was treated according to **Method N**. Purification by flash column chromatography (SiO_2; 2:1 Petrol/EtOAc) afforded the *title compound* (0.12 g, 68 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 3499 (OH), 2928 (CH); δ_H(300 MHz, $CDCl_3$) 8.53 (1H, s, Ar*H*), 8.40 (2H, s, Ar*H*), 8.06 (1H, s, *H*-2), 7.89 (1H, s, *H*-1), 7.43 (1H, s, *H*-3), 6.13 (2H, s, OCH_2O), 4.97 (2H, s, CH_2OH), 4.00 (3H, s, OCH_3), 2.58 (1H, brs, O*H*); δ_C(75 MHz, $CDCl_3$) 171.6, 159.4, 150.7, 149.1, 145.0, 133.4, 132.9, 130.9, 128.4, 128.1, 128.0, 127.8, 127.0, 127.6, 126.8, 126.5, 124.4, 122.2, 63.0, 60.7, 60.2; *m/z* (C.I.) 509 (100 %, $M\text{-}H^+$); (Found (E.I): M^+, 508.0450. $C_{21}H_{14}F_6O_6S$ requires 508.0451).

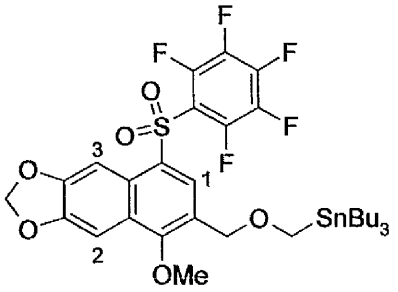
Tributyl-[8-(3-fluorobenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxymethyl]stannane 439a



[8-(3-Fluorobenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxo-6-yl]methanol **438a** (0.06 g, 0.15 mmol, 1.0 equiv.) was treated according to **Method O**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.07 g, 68 %) as a white solid: m.p. 162.8-163.5 °C; R_f(5:1 Petrol:EtOAc) 0.75; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH); δ_H(300 MHz, $CDCl_3$) 8.47 (1H, s, *H*-2), 7.96 (1H, s, *H*-1), 7.79 (1H, dd, *J* 8.5 and 1.0, Ar*H*), 7.64 (1H, dd, *J* 8.0 and 2.5, Ar*H*), 7.49-7.38 (2H, m, ArH), 7.28 (1H, s, *H*-3), 6.11 (2H, s, OCH_2O), 4.66 (2H, s, CH_2OTBS), 3.99 (3H, s, OCH_3), 3.87 (2H, apparent t due to Sn coupling, CH_2OCH_2Sn), 1.63 (6H, qt , *J* 8.0 and

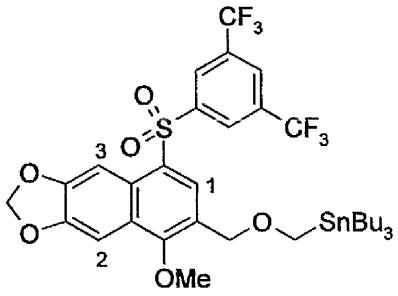
7.5, $SnBu_3$), 1.36 (6H, tt, *J* 8.0 and 7.5, $SnBu_3$), 0.93 (6H, t, *J* 8.0, $SnBu_3$), 0.89 (9H, t, *J* 7.5, $SnBu_3$); δ_C(75 MHz, $CDCl_3$) 158.7, 149.2, 148.0, 142.7, 132.4, 130.7, 130.5, 129.1, 127.6, 127.2, 126.4, 125.4, 101.7, 99.8, 62.9, 62.4, 29.4, 29.0, 27.6, 13.9, 9.3; *m/z* (C.I.) 694 (100 %, $M + H^+$); (Found (E.I): M^+, 693.4521. $C_{32}H_{43}O_6SSnF$ requires 693.4519).

Tributyl-(5-methoxy-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxol-6-ylmethyoxymethyl)stannane 439b



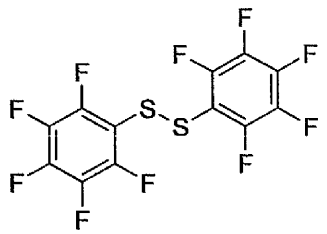
(5-Methoxy-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxol-6-yl)methanol **438b** (0.07 g, 0.15 mmol, 1.0 equiv.) was treated according to **Method O**. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.07 g, 59 %) as a colouriess oil: R_f(1:1 Petrol:EtOAc) 0.45; ν_{max} ($CHCl_3$)/cm^{-1} 2650, 2558 (CH); δ_H(300 MHz, $CDCl_3$) 9.10 (1H, s, *H*-2), 8.46 (1H, s, *H*-1), 7.95 (1H, s, *H*-3), 6.08 (2H, s, OCH_2O), 4.95 (2H, s, CH_2OCH_2Sn), 4.00 (3H, s, OCH_3), 3.12 (2H, apparent t due to Sn coupling, OCH_2Sn), 1.68 (6H, qt , *J* 8.0 and 7.5, $SnBu_3$), 1.40 (6H, tt, *J* 8.0 and 7.5, $SnBu_3$), 1.30 (6H, t, *J* 8.0, $SnBu_3$), 0.93 (9H, t, *J* 7.5, $SnBu_3$); δ_C(75 MHz, $CDCl_3$) 158.5, 148.6, 148.3, 142.1, 140.1, 138.6, 132.8, 130.9, 130.2, 129.0, 128.7, 128.5, 127.6, 127.2, 126.4, 125.4, 101.7, 99.8, 62.9, 62.2, 29.1, 29.0, 27.3, 13.7, 9.0; *m/z* (C.I.) 766 (100 %, $M-H^+$); (Found (E.I): M^+, 765.1412. $C_{32}H_{39}F_5O_6SSn$ requires 765.1408).

[8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxymethyl]tributylstannane 439c



[8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-yl]methanol **438c** (0.12 g, 0.24 mmol, 1.0 equiv.) was treated according to **Method O**. Purification by flash column chromatography (SiO_2; 50:1 Petrol/EtOAc) afforded the *title compound* (0.11 g, 60 %) as a colourless oil: R_f(5:1 Petrol:EtOAc) 0.75; ν_{max} ($CHCl_3$)/cm^{-1} 2923 (CH); δ_H(300 MHz, $CDCl_3$) 8.50 (1H, s, Ar*H*), 8.36 (2H, s, Ar*H*), 8.04 (1H, s, *H*-2), 7.85 (1H, s, *H*-1), 7.43 (1H, s, *H*-3), 6.10 (2H, s, OCH_2O), 4.90 (2H, s, CH_2OCH_2Sn), 3.98 (3H, s, OCH_3), 3.87 (2H, apparent t due to Sn coupling, CH_2OCH_2Sn), 1.65 (6H, qt , *J* 8.0 and 7.5, $SnBu_3$), 1.33 (6H, tt, *J* 8.0 and 7.5, $SnBu_3$), 0.89 (6H, t, *J* 8.0, $SnBu_3$), 0.84 (9H, t, *J* 7.5, $SnBu_3$); δ_C(75 MHz, $CDCl_3$) 158.4, 149.7, 148.2, 141.5, 138.7, 136.4, 132.4, 131.8, 130.7, 130.5, 129.4, 129.1, 127.6, 127.2, 127.0, 126.8, 126.4, 125.4, 101.7, 99.8, 65.7, 62.9, 62.4, 40.8, 29.4, 29.0, 27.6, 13.9, 10.7, 9.3; *m/z* (C.I.) 811 (100 %, $M + H^+$); (Found (E.I): M^+, 812.1630. $C_{34}H_{42}F_6O_6SSn$ requires 810.1627).

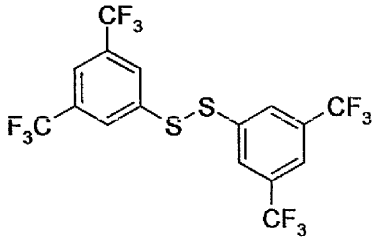
Bis(pentafluorophenyl)disulfide 441[186]



Sodium perborate (3.08 g, 20 mmol, 2.0 equiv.) was added portion wise to a solution of pentafluorothiophenol (2.0 g, 10 mmol, 1.0 equiv.) in acetic acid (40 mL) and water (16 mL) at room temperature. The solution was stirred for 2 h and CH_2Cl_2 (15 mL) added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL). Combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (2 × 10 mL), water (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title*

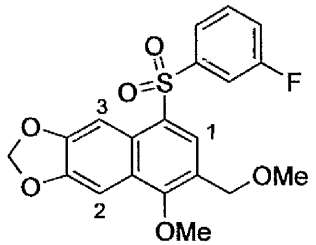
compound (1.66 g, 50 %) as a wax: m.p. 48.8-50 °C (lit.,[186] 49.5 °C); R_f(5:1 Petrol:EtOAc) 0.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 1637, 1514, 1487, 1093; δ_C(75 MHz, $CDCl_3$) 149.4, 146.0, 142.5, 139.7, 137.3; *m/z* (C.I.) 399 (100 %, M + H^+); (Found (E.I): M^+, 398.9276. $C_{12}F_{10}S_2$ requires 398.9282).

Bis(3,5-trifluoromethlphenyl)disulfide 443[198]



Sodium perborate (1.25 g, 8.1 mmol, 2.0 equiv.) was added portion wise to a solution of 3,5-trifluoromethyl thiophenol (1.0 g, 4.05 mmol, 1.0 equiv.) in acetic acid (20 mL) and water (8.0 mL) at room temperature. The solution was stirred for 2 h and CH_2Cl_2 (15 mL) added. The mixture was extracted with CH_2Cl_2 (4 x 10 mL). Combined organic layers were washed with saturated sodium hydrogen carbonate solution (2 x 10 mL), water (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *title compound* (0.86 g, 43 %) as a wax: m.p. 74.2-75.5 °C (lit.,[198] 74-75 °C); R_f(5:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 1355, 1281, 1134, 1100, 890; δ_H(300 MHz, $CDCl_3$) 7.96 (2H, s, *H*-2 and *H*-6), 7.81 (1H, s, *H*-4); δ_C(75 MHz, $CDCl_3$) 139.2, 133.4, 132.9, 127.7, 124.8, 122.0, 121.1; *m/z* (C.I.) 491 (100 %, M-H^+); (Found (E.I): M^+, 490.9720. $C_{16}H_6F_{12}S_2$ requires 490.9714).

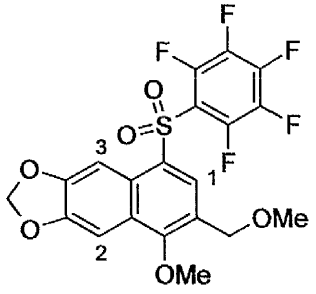
8-(3-Fluorobenzenesulfonyl)-5-methoxy-6-methoxymethylnaphtho[2,3-d][1,3]dioxol 444a



Tributyl-[8-(3-fluorobenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxymethyl]stannane **439a** (0.07 g, 0.10 mmol, 1.0 equiv.) was treated according to **Method P**. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.04 g, 55 %) as a colourless oil: R_f(1:1 Petrol:EtOAc)

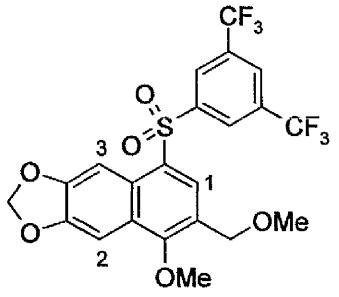
0.60; $\nu_{max}(CHCl_3)/cm^{-1}$ 2923 (CH); δ_H(300 MHz, $CDCl_3$) 8.48 (1H, s, *H*-2), 7.95 (1H, s, *H*-1), 7.78 (1H, dd, *J* 8.0 and 1.0, Ar*H*), 7.65 (1H, dd, *J* 8.0 and 2.5, Ar*H*), 7.52 (1H, m, Ar*H*), 7.48 (1H, s, *H*-3), 7.26 (1H, ddd, *J* 8.0, 2.5 and 1.0, Ar*H*), 6.12 (2H, s, OCH_2O), 4.70 (2H, s, CH_2OCH_3), 4.00 (3H, s, OCH_3), 3.54 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 164.3, 160.9, 159.3, 148.8, 144.3, 131.3, 130.9, 129.8, 126.7, 125.3, 123.2, 120.6, 119.4, 114.9, 114.6, 102.2, 100.9, 69.3, 63.2, 58.9; *m/z* (C.I.) 422 (100 %, M-NH_4^+); (Found (E.I): M^+, 422.1068. $C_{20}H_{17}FO_6S$-NH_4 requires 422.1068).

5-Methoxy-6-methoxymethyl-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxole 444b



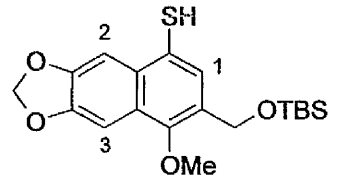
Tributyl-(5-methoxy-8-pentafluorobenzenesulfonylnaphtho[2,3-d][1,3]dioxol-6-ylmethyoxymethyl)stannane **439b** (0.07 g, 0.10 mmol, 1.0 equiv.) was treated according to **Method P**. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.04 g, 45 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.55; $\nu_{max}(CHCl_3)/cm^{-1}$ 2930 (CH); δ_H(300 MHz, $CDCl_3$) 8.55 (1H, s, *H*-2), 7.93 (1H, s, *H*-1), 7.45 (1H, s, *H*-3), 6.06 (2H, s, OCH_2O), 4.75 (2H, s, CH_2OCH_3), 3.97 (3H, s, OCH_3), 3.47 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 154.5, 148.6, 148.3, 142.1, 140.1, 138.6, 132.8, 130.9, 129.7, 129.2, 128.7, 128.5, 127.6, 127.2, 101.7, 99.8, 67.7, 62.8, 59.4; *m/z* (C.I.) 477 (100 %, M-NH_4^+); (Found (E.I): M^+, 476.0358. $C_{20}H_{13}F_5O_6S$ requires 476.0353).

8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxy-6-methoxymethyl-naphtho[2,3-d][1,3]dioxole 444c



[8-(3,5-Bistrifluoromethylbenzenesulfonyl)-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxymethyl]tributylstannane **439c** (0.11g, 0.14 mmol, 1.0 equiv.) was treated according to **Method P**. Purification by flash column chromatography (SiO_2; 1:1 Petrol/EtOAc) afforded the *title compound* (0.03 g, 38 %) as a colourless oil: R_f(1:1 Petrol:EtOAc) 0.50; $\nu_{max}(CHCl_3)/cm^{-1}$ 2923 (CH); δ_H(300 MHz, $CDCl_3$) 8.57 (1H, s, Ar*H*), 8.47 (2H, s, Ar*H*), 8.08 (1H, s, *H*-2), 7.88 (1H, s, *H*-1), 7.40 (1H, s, *H*-3), 6.08 (2H, s, OCH_2O), 4.86 (2H, s, CH_2OCH_3), 3.97 (3H, s, OCH_3), 3.84 (3H, s, OCH_3); δ_C(75 MHz, $CDCl_3$) 170.4, 158.2, 150.5, 149.3, 144.6, 133.7, 132.3, 131.1, 128.4, 128.2, 127.9, 127.7, 127.0, 127.6, 126.8, 126.5, 124.4, 122.2, 69.2, 63.0, 60.7, 58.3; *m/z* (C.I.) 523 (100 %, $M\text{-}H^+$); (Found (E.I): M^+, 522.0369. $C_{22}H_{16}F_6O_6S$ requires 522.0372).

7-(*tert*-Butyldimethylsilanyloxymethyl)-8-methoxy-naphtho[2,3-d][1,3]dioxole-5-thiol 445



n-Butyllithium (0.16 mL of a 2.4 M solution in hexane, 0.38 mmol, 1.1 equiv.) was added dropwise to a solution of (8-bromo-5-methoxynaphtho[2,3-d][1,3]dioxol-6-ylmethoxy)-*tert*-butyldimethylsilane **431** (0.15 g, 0.35 mmol, 1.0 equiv.) in THF (3 mL) at –78 °C under a nitrogen atmosphere. The solution was maintained at –78 °C for 1 h and added dropwise to a suspension of sublimated sulfur (0.02 g, 0.35 mmol, 1.0 equiv.) in THF (3 mL) at –78 °C. The mixture was stirred at –78 °C for 3 h and 2 M HCl (0.2 mL, 0.38 mmol, 1.1 equiv.) added. The mixture was allowed to warm to room temperature and extracted with EtOAc (4 × 5 mL). Combined organics were washed

with water (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2; 30:1 Petrol/EtOAc) afforded the *title compound* (0.10 g, 70 %) as needles: m.p. 116.9-118.2 °C; R_f(5:1 Petrol:EtOAc) 0.70; $\nu_{max}(CHCl_3)/cm^{-1}$ 3297 (SH), 2930 (CH); δ_H(300 MHz, $CDCl_3$) 7.48 (1H, s, *H*-3), 7.41 (1H, s, *H*-2), 7.15 (1H, s, *H*-1), 6.08 (2H, s, OCH_2O), 4.96 (2H, s, CH_2OTBS), 3.93 (3H, s, OCH_3), 0.99 (9H, s, *t*Bu), 0.18 (6H, s, 2 × CH_3); δ_C(75 MHz, $CDCl_3$) 152.5, 148.2, 147.8, 131.7, 128.7, 124.9, 123.4, 104.4, 103.1, 98.8, 62.3, 60.3, 26.3, 18.7, 4.9; *m/z* (C.I.) 379 (100 %, $M + H^+$); (Found (E.I): M^+, 378.1304. $C_{19}H_{26}O_4SSi$ requires 378.1321).

References

1. Bragg, R. A.; Clayden, J. *Tetrahedron Lett.*, **1999**, *40*, 8323.
2. Michael, J. P. *Nat. Prod. Reports*, **1997**, *14*, 619.
3. Rewcastle, G. W.; Katrisky, A. R. *Adv. Heterocycl. Chem.*, **1993**, *56*, 155.
4. a) Furukawa, N.; Shibutani, T.; Matsumura, K.; Fujihara, H.; Oae, S. *Tetrahedron Lett.*, **1986**, *27*, 3899. b) Turner, R. M.; Ley, S. D.; Lindell, S. V. *Synlett*, **1993**, 748.
5. a) Bell, A. S.; Roberts, D. A.; Ruddock, K. S. *Synthesis*, **1987**, 843. b) Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Heterocycles*, **1993**, *36*, 941. c) Browder, C. C.; Mitchell, M. O.; Smith, R. L. *Tetrahedron Lett.*, **1993**, 34, 6245.
6. Florentin, D.; Roques, B. P.; Fournie-Zalaski, M. C. *Bull. Soc. Chim. Fr.*, **1976**, 1999.
7. Haebich, D.; Effenberger, F. *Synthesis*, **1979**, 841.
8. a) Fleming, I.; Taddei, M. *Synthesis*, **1985**, 898. b) Kondo, Y.; Uchiyama, D.; Sakamoto, T.; Yamanaka, H. *Tetrahedron Lett.*, **1989**, *30*, 4249.
9. a) Kalinin, V. N. *Synthesis*, **1992**, 413. b) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.*, **1998**, *27*, 1113. c) Sakamoto, T.; Kondo, Y.; Yamanka, H. *Heterocycles*, **1988**, *27*, 2225.
10. von Rague Schleyer, P.; Chandrasekhar, J.; Kos, A. J.; Clark, T.; Spitznagel, G. W. *J. Chem. Soc., Chem. Commun.*, **1981**, 882.
11. Elvidge, J. A.; Jones, J. R.; O'Brien, C.; Evans, E. A.; Sheppard, H. C. *Adv. Heterocycl. Chem.*, **1974**, *16*, 1.
12. Zoltewicz, J. A.; Grahe, G.; Smith, C. L. *J. Am. Chem. Soc.*, **1969**, *91*, 5501.
13. a) Gschwend, H. W.; Rodriguez, H. R. *Org. Reactions*, **1979**, *26*, 1. b) Undheim, K.; Benneche, T. *Heterocycles*, **1990**, *30*, 1155.
14. Mallet, M. *J. Organomet. Chem.*, **1991**, *406*, 49.
15. Collum, D. B. *Acc. Chem. Res.*, **1992**, *25*, 448.
16. Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.*, **1985**, *107*, 4101.
17. Still, W. C. *J. Am. Chem. Soc.*, **1978**, *100*, 1481.
18. Meyer, N.; Seebach, D. *Chem. Ber.*, **1980**, *113*, 1290.
19. Reich, H. J.; Phillips, N. H. *J. Am. Chem. Soc.*, **1986**, *108*, 2102.

20. von Rague Schleyer, P.; Clark, T.; Kos, A.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.*, **1984**, *106*, 6467.
21. a) Brittain, J. M.; Jones, R. A.; Arques, J. S.; Saliente, T. A. *Synth. Commun.*, **1982**, 231. b) Chadwick, D. J.; Cliffe, I. A. *J. Chem. Soc., Perkin Trans I*, **1979**, *11*, 2845.
22. Hasan, I.; Marineli, E. R.; Lin, L. C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.*, **1981**, *46*, 157.
23. Katritsky, A. R.; Akutagawa, K. *Org. Prep. Proc. Int.*, **1988**, *20*, 585.
24. Edwards, M. P.; Doherty, A. M.; Ley, S. V. *Tetrahedron*, **1986**, *42*, 3723.
25. Gharpure, M.; Stoller, A.; Bellamy, F.; Firnau, G.; Snieckus, V. *Synthesis*, **1991**, 1079.
26. Sotoyama, T.; Hara, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1865.
27. Minato, K.; Tamao, T.; Hayashi, K.; Suzuki, A.; Kumuda, M. *Tetrahedron Lett.*, **1981**, *22*, 5319.
28. Muchowski, J. M.; Naef, R. *Helv. Chim. Acta.*, **1984**, *67*, 1168.
29. Shirley, D. A.; Roussel, P. A. *J. Am. Chem. Soc.*, **1953**, *75*, 375.
30. Sundberg, R. J.; Russel, H. F. *J. Org. Chem.*, **1973**, *38*, 3324.
31. Katritsky, A. R.; Akutagawa, K. *Tetrahedron Lett.*, **1985**, *26*, 5935.
32. Hlasta, D. J.; Bell, M. R. *Heterocycles*, **1989**, *29*, 849.
33. Somei, M.; Kobayashi, T. *Heterocycles*, **1992**, *34*, 1295.
34. Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.*, **1982**, *47*, 757.
35. Johnson, D. A.; Gribble, G. W. *Heterocycles*, **1986**, *24*, 2127.
36. Yokoyama, Y.; Uchida, M.; Murakami, Y. *Heterocycles*, **1989**, *29*, 1661.
37. a) Iwao, M. *Heterocycles*, **1993**, *36*, 29. b) Griffen, E. J.; Roe, D. G.; Snieckus, V. J. *J. Org. Chem.*, **1995**, *60*, 1484.
38. Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron*, **2001**, *57*, 975.
39. Fukuda, T.; Maeda, R.; Iwao, M. *Tetrahedron*, **1999**, *55*, 9151.
40. Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. J. *J. Am. Chem. Soc.*, **1988**, *110*, 8145.
41. Gilman, H.; Breur, F. *J. Am. Chem. Soc.*, **1934**, *56*, 1123.
42. Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron*, **1990**, *46*, 1199.
43. Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1*, **1981**, *4*, 1125.
44. Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.*, **1985**, *26*, 1777.
45. Nasman, J. H.; Koppla, N.; Pensar, G. *Tetrahedron Lett.*, **1986**, *27*, 1391.

46. Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. *J. Chem. Soc., Perkin Trans. 1,* **1982**, *6*, 1343.
47. Bures, E. J.; Keay, A. B. *Tetrahedron Lett.,* **1988**, *29*, 1247.
48. Sornay, R.; Meunier, J. M.; Fournari, P. *Bull. Soc. Chim. Fr.,* **1971**, 990.
49. Gronowitz, S.; Sorlin, G. *Acta Chem. Scand.,* **1961**, *15*, 1419.
50. Bohlmann, F.; Stohr, F.; Staffeldt, J. *Chem. Ber.,* **1978**, *111*, 3146.
51. Florentin, D.; Roques, B. P.; Fournie-Zaluski, M. C. *Bull. Soc. Chim. Fr.,* **1976**, 1999.
52. Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.,* **1948**, *70*, 1655.
53. Shirley, D. A.; Cameron, M. D. *J. Am. Chem. Soc.,* **1950**, *72*, 2788.
54. Reichstein, T.; Baud, J. *Helv. Chim. Acta.,* **1937**, *20*, 892.
55. Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.,* **2002**, *646*, 59.
56. Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.,* **1985**, *50*, 1999.
57. a) Bailey, W. F.; Ovaska, T. V. Advances in detailed reaction mechanisms, in: J.M. Coxon (Ed.), *Mechanisms of Importance in Synthesis*, vol. 3, JA1 Press, Greenwich, CT, **1994**, pp 251-273. b) Afarinkia, K. *J. Chem. Soc., Perkin Trans. 1,* **1999**, *15*, 2025. c) Coldham, I. *J. Chem. Soc., Perkin Trans. 1,* **1993**, *12*, 1275.
58. Klumpp, G. W.; Schmitz, R. F. *Tetrahedron Lett.,* **1974**, *15*, 2911.
59. Lansbury, P. T.; Caridi, F. J. *J. Chem. Soc. Chem. Commun.,* **1970**, 714.
60. Baldwin, J. E.; Dupont, W. A.; Ming, M. F. *J. Chem. Soc. Chem. Commun.,* **1980**, 1042.
61. Bailey, W. F.; Punzalan, E. R. *Tetrahedron Lett.,* **1996**, *37*, 5435.
62. Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.,* **1988**, *53*, 1336.
63. Broka, C. A.; Shen, T. *J. Am. Chem. Soc.,* **1989**, *111*, 2981.
64. a) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.,* **1991**, *113*, 5720. b) Roelle, T.; Hoffmann, R. W. *J. Chem. Soc. Perkin Trans. 2.,* **1995**, *11*, 1953.
65. Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.,* **1995**, *117*, 1954.
66. Nishiyama, H.; Sakata, N.; Motoyama, Y.; Wakita, H.; Nagase, H. *Synlett,* **1997**, 1147.
67. Nishiyama, H.; Sakata, N.; Sugimoto, H.; Motoyama, Y.; Wakita, H.; Nagase, H. *Synlett,* **1998**, 930.

68. Woltering, M. J.; Frolich, R.; Hoppe, D. *Angew. Chem. Int. Ed. Eng.*, **1997**, *36*, 1764.
69. Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.*, **1997**, *38*, 8939.
70. Komine, N.; Tomooka, K.; Nakai, T. *Heterocycles*, **2000**, *52*, 1071.
71. Coldham, I.; Hufton, R. *Tetrahedron Lett.*, **1995**, *36*, 2157.
72. Coldham, I.; Hufton, R. *Tetrahedron*, **1996**, *52*, 12541.
73. Coldham, I.; Hufton, R.; Rathmell, R. E. *Tetrahedron Lett.*, **1997**, *38*, 7617.
74. Coldham, I.; Lang-Anderson, M. M. S.; Rathmell, R. E.; Snowden, D. J. *Tetrahedron Lett.*, **1997**, *38*, 7621.
75. Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomolec. Chem.*, **2003**, *1*, 2111.
76. Barluenga, J.; Sanz, R.; Fananas, F. J. *Tetrahedron Lett.*, **1997**, *38*, 2763.
77. Barluenga, J.; Sanz, R.; Fananas, F. J. *Tetrahedron Lett.*, **1997**, *38*, 6103.
78. Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.*, **1988**, *110*, 4788.
79. Coldham, I.; Fernandez, J. C.; Snowden, D. J. *Tetrahedron Lett.*, **1999**, *40*, 1819.
80. Coldham, I.; Fernandez, J. C.; Price, K. N.; Snowden, D. J. *J. Org. Chem.*, **2000**, *65*, 3788.
81. Bailey, W. F.; Khanolkar, A. D. *Organometallics*, **1993**, *12*, 239.
82. Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.*, **1990**, *55*, 5404.
83. Zhang, D.; Liebeskind, L. S. *J. Org. Chem.*, **1996**, *61*, 2594.
84. Yokum, T. S.; Tungaturthi, P. K.; McLaughlin, M. L. *Tetrahedron Lett.*, **1997**, *38*, 5111.
85. Bailey, W. F.; Carson, M. W. *Tetrahedron Lett.*, **1997**, *38*, 1329.
86. Barluenga, J.; Fananas, F. J.; Sanz, R.; Fernandez, Y. *Tetrahedron Lett.*, **1999**, *40*, 1049.
87. Barluenga, J.; Sanz, R.; Granados, A.; Fananas, F. J. *J. Am. Chem. Soc.*, **1998**, *120*, 4865
88. Fananas, F. J.; Granados, A.; Sanz, R.; Ignacio, J. M. *Chem. Eur. J.*, **2001**, *7*, 2896.
89. Bailey, W. F.; Carson, M. W. *J. Org. Chem.*, **1998**, *63*, 361.
90. Bailey, W. F.; Carson, M. W. *J. Org. Chem.*, **1998**, *63*, 9960.
91. Bailey, W. F.; Carson, M. W. *Tetrahedron Lett.*, **1999**, *40*, 5433.
92. Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.*, **1996**, *118*, 5322.
93. Woltering, M. J.; Frohlich, R.; Wibbeling, B.; Hoppe, D. *Synlett*, **1998**, 797.

94. Deiters, A.; Wibbeling, B.; Hoppe, D. *Adv. Synth. Catal.*, **2001**, *343*, 181.

95. Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.*, **2000**, *122*, 6787.

96. Sanz Gil, G.; Groth, U. M. *J. Am. Chem. Soc.*, **2000**, *122*, 6789.

97. Crandall, J. K.; Ayers, A. *J. Org. Chem.*, **1992**, *57*, 2993.

98. Breternitz, H-J.; Schauman, E.; Adiwidjaja, G. *Tetrahedron Lett.*, **1991**, *32*, 1299.

99. a) Aggarwal, V. K.; Ferrara, M. *Org. Lett.*, **2000**, *2*, 4107. b) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.*, **2002**, *67*, 2335.

100. Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.*, **1998**, 297.

101. Ahmed, A.; Clayden, J.; Yasin, S. *Chem. Commun.*, **1999**, 231.

102. Clayden, J.; Menet, C. J.; Mansfield, D. J. *J. Org. Lett.*, **2000**, *2*, 4229.

103. Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.*, **1998**, *39*, 6103.

104. Fernandez, I.; Ortiz, F. L.; Tejerina, B.; Granda, S. G. *Org. Lett.*, **2001**, *3*, 1339.

105. Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. *Synlett.*, **2001**, 302.

106. Ahmed, A.; Clayden, J.; Rowley, M. *Synlett.*, **1999**, 1954.

107. Ishibashi, H.; Harada, S.; Okada, M.; Somekawa, M.; Kido, M.; Ikeda, M. *Chem. Pharm. Bull.*, **1989**, *37*, 939.

108. Comins, D. L.; Zhang, Y. M. *J. Am. Chem. Soc.*, **1996**, *118*, 12248.

109. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

110. Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. J. *Angew. Chem., Int. Ed. Engl.*, **2002**, *41*, 1049.

111. Woodward, R. B.; Hoffmann, R. In: *The conservation of orbital symmetry,* Academic Press, New York, **1970**.

112. Bragg, R. A.; Clayden, J. *Tetrahedron Lett.*, **1999**, *40*, 8327.

113. Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.*, **2001**, *42*, 3411.

114. Bragg, R. A. *Ph.D. Thesis*, University of Manchester, **2001**.

115. Clayden, J.; Menet, C. J; Mansfield, D. J. *Chem. Commun.*, **2002**, 38.

116. Hoppe, D.; Paetzow, M.; Hintze, F. *Agnew. Chem. Int. Ed. Engl.*, **1993**, *32*, 394.

117. a) Clayden, J.; Tchabanenko, K. *J. Chem. Soc., Chem. Commun.*, **2000**, 317. b) Ahmed, A.; Bragg, R. A.; Clayden, J. *Tetrahedron Lett.*, **2001**, *42*, 3407.

118. Shinozaki, H. In: *Excitatory Amino Acid Receptors. Design of Agonists and Antagonists,* Krogsgaard-Larsen, P.; Hansen, J. T. Eds.; Ellis Harwood, New York, **1992**, pp 261.

119. Parsons, A. F. *Tetrahedron,* **1996**, *52*, 4149.

120. Hamilton, S. D. Unpublished results.

121. Oldenziel, O. H.; van Leusen, A. M. *Synth. Commun.,* **1972**, 281.

122. van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett.,* **1972**, *52*, 5337.

123. Donohoe, T. J.; Guyo, P. M.; Harji, R. R.; Helliwell, M. *Tetrahedron Lett.,* **1998**, *39*, 3075.

124. Shea, K. J. *Tetrahedron*, **1980**, *36*, 1683.

125. Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.,* **1984**, *106*, 1010.

126. Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.,* **2003**, *6*, 609.

127. Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Hetero. Chem.,* **1981**, *29*, 141.

128. Boulton, A. J.; Katritzky, A. R.; Majid Hamid, A. *J. Chem. Soc. C.,* **1967**, *20*, 2005.

129. Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.,* **2002**, *4*, 1611.

130. a) Brooks, B. L.; Gunnoe, T. B.; Harman, W. D. *Coord. Chem. Rev.,* **2000**, *206*, 3. b) Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron: Asymmetry,* **1996**, *7*, 317. c) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.,* **2003**, *5*, 999.

131. Mander, L. N. *Synlett.,* **1991**, 134.

132. Rabideau, P. W.; Marcinow, Z. *Org. React.,* **1992**, *42*, 1.

133. Schultz, A. G. *Chem. Commun.,* **1999**, 1263.

134. Clayden, J.; Foricher, Y. J. Y.; Lam, H. K. *Chem. Commun.,* **2002**, 2138.

135. a) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.,* **2003**, *44*, 3397. b) Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett.,* **2003**, 1701.

136. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.,* **1996**, *29*, 552.

137. a) Baussanne, I.; Travers, C.; Royer, J. *Tetrahedron: Asymmetry,* **1998**, *9*, 797. b) Poli, G.; Baffoni, S. C.; Giambastiani, G.; Reginato, G. *Tetrahedron,* **1998**, *54*, 10403.

138. Ma, S.; Ni, B. *Org. Lett.,* **2002**, *4*, 639.

139. Trnka, T. M.; Grubbs, R. H. *Accts. Chem. Res.,* **2001**, *34*, 18.

140. a) Seebach, D.; Boes, M.; Naef, R.; Schweizer. W. B. *J. Am. Chem. Soc.,* **1983**, *103*, 5390. b) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.,* **1995**, *117*, 891.

c) Fehr, C. *Agnew. Chem. Int. Ed.,* **1996**, *35*, 2566. d) Kawabata, T.; Ozturk, O.; Chen, J.; Fuji, K. *Chem. Commun.,* **2003**, 162.

141. Beak, P.; Chen, C. W. *J. Org. Chem.,* **1986**, *51*, 3325.

142. Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.,* **1999**, *40*, 3329.

143. Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin. Trans. 1,* **1998**, *4*, 667.

144. Matsuki, S.; Mizuno, A.; Annoura, H.; Tatsuka, T. *J. Heterocyclic Chem.,* **1997**, *34*, 87.

145. Liu, Y.; McWhorter, W. W. *J. Am. Chem. Soc.,* **2003**, *125*, 4240.

146. a) Lindwall, H. G.; Bandes, J.; Weinberg, I. *J. Am. Chem. Soc.,* **1931**, *53*, 317. b) Sirowej, H.; Khan, S. A.; Plieninger, H. *Synthesis*, **1971**, 84.

147. Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron,* **1988**, *44*, 7334.

148. Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1,* **1977**, *8*, 887.

149. Clayden, J.; Turnbull, R.; Pinto, I.; Helliwell, M. *Chem. Commun.,* **2004**, *21*, 2430.

150. Brandao, M. A. F.; de Oliveira, A. B.; Snieckus, V. *Tetrahedron Lett.,* **1993**, *34*, 2437.

151. Barluenga, J.; Fananas, F. J.; Sanz, R.; Marcos, C.; Trabada, M. *Org. Lett.,* **2002**, *4*, 1587.

152. Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.,* **1997**, *119*, 11561.

153. Bessodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.,* **1986**, *27*, 579.

154. a) Field, D. J.; Jones, D. W.; Kneen, G. *J. Chem. Soc., Chem. Commun.,* **1976**, 873. b) Anderson, C. D.; Sharp, J. T.; Strathdee, R. S. *J. Chem. Soc., Perkin Trans. 1,* **1979**, *11*, 2730. c) Anderson, C. D.; Sharp, J. T.; Stefaniuk, E.; Strathdee, R. S. *Tetrahedron Lett.,* **1976**, *17*, 305.

155. Paquette, L. A. *J. Org. Chem.,* **1963**, *28*, 3590.

156. a) Schwyzer, R.; Costopanagiotis, A.; Sieber, P. *Helv. Chim. Acta.,* **1963**, *46*, 870. b) Lenz, G. R.; Lessor, R. A. *Org. Synth. Coll.,* **1998**, *9*, 268.

157. a) Narasimha Rao, P.; Gollberg, H. R. *Tetrahedron,* **1962**, *18*, 1251. b) Gassman, P. G.; Gruetzmacher, G. *J. Am. Chem. Soc.,* **1973**, *95*, 588. c) Gronowitz, S.; Moses, P.; Hornfeldt, A-B.; Hakansson, R. *Arkiv. Kemi.,* **1961**, *17*, 165.

158. Szczepankiewicz, B. G.; Liu, G.; Jae, H. S.; Tasker, A. S.; Gunawardana, I. W.; von Geldern, T. W.; Gwaltney, S. L.; Wu-Wong, J. R.; Gehrke, L.; Chiou, W. J.; Credo, R. B.; Rosenberg, S. H. *J. Med. Chem.*, **2001**, *44*, 4416.

159. Grant, T. G.; Meyers, A. I. *Tetrahedron,* **1994**, *50*, 2297.

160. Dixon, J. A.; Fishman, D. H.; Dudinyak, R. S. *Tetrahedron Lett.*, **1964**, *5*, 613.

161. Stoyanovich, F. M.; Karpenko, R. G.; Gol'dfarb, Y. L. *Tetrahedron,* **1971**, *27*, 433.

162. Reuman, M.; Meyers, A. I. *Tetrahedron,* **1985**, *41*, 837.

163. Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.*, **1988**, *110*, 4611.

164. Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.*, **1988**, *110*, 7854.

165. Clayden, J.; Kenworthy, M. N. *Org. Lett.*, **2002**, *4*, 787.

166. Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.*, **2003**, *6*, 831.

167. Cast, J.; Stevens, T. S.; Holmes, J. *J. Chem. Soc.*, **1960**, 3521.

168. Tomooka, K.; Harada, M.; Hanji, T.; Nakai, T. *Chem. Lett.*, **2000**, 1394.

169. Garbi, A.; Allain, L.; Chorki, F.; Ourevitch, M.; Crousse, B.; Bonnet-Delpon, D.; Nakai, T.; Begue, J-P. *Org. Lett.*, **2001**, *3*, 2529.

170. Cazes, B.; Julia, S. *Synthetic Commun.*, **1977**, 133.

171. Tsubuki, M.; Okita, H.; Honda, T. *J. Chem. Soc., Chem. Commun.*, **1995**, 2135.

172. Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.*, **2000**, *41*, 8199.

173. Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: Oxford, 1993.

174. Ayres, D. C.; Loike, J. D. *Lignans; Chemical, Biological and Clinical Properties*; Cambridge University Press, 1990.

175. Berkowitz, D. B.; Choi, S.; Maeng, J-H. *J. Org. Chem.*, **2000**, *65*, 847.

176. Leander, K.; Rosen, B.; US Patent 4,788,216, **1988**.

177. Canel, C.; Dayan, F. E.; Ganzera, M.; Rimando, A.; Burandt, C.; Khan, I.; Moraes, R. M. *Planta Medica,* **2001**, *67*, 1.

178. Berowitz, D. B.; Maeng, J-H.; Dantzig, A. H.; Shepard, R. L.; Norman, B. H. *J. Am. Chem. Soc.*, **1996**, *118*, 9426.

179. Macdonald, D. I.; Durst, T. *J. Org. Chem.*, **1988**, *53*, 3663.

180. Engelhardt, U.; Sarkar, A.; Linker, T. *Agnew. Chem. Int. Ed.*, **2003**, *42*, 2487.

181. a) Bols, M.; Skrydstrup, T. *Chem. Rev.*, **1995**, *95*, 1253. b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis,* **1997**, 813.

182. a) El-Abbady, A. M.; El-Assal, L. S. *J. Chem. Soc.,* **1959**, 1024. b) El-Assal, L. S.; El-Wahhab, S. A. M. *J. Chem. Soc.,* **1960**, 849.

183. Green, K. *J. Org. Chem.,* **1991**, *56*, 4325.

184. Seitz, D. E.; Carroll, J. J.; Cartaya, C. P.; Lee, S-H.; Zapata, A. *Synthetic Commun.,* **1983**, 129.

185. Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.,* **1975**, *97*, 649.

186. McKillop, A.; Koyuncu, D. *Tetrahedron Lett.,* **1990**, *31*, 5007.

187. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd Edition, Pergamon: Oxford, 1980.

188. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.,* **1978**, *43*, 2923.

189. Tilley, J. N.; Sayigh, A. R. *J. Org. Chem.,* **1963**, *28*, 2076.

190. Habermehl, G. *Chem. Ber.,* **1963**, *96*, 2029.

191. Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin 1,* **2001**, *23*, 3106.

192. Grehn, L.; Ragnarsson, U. *Agnew. Chem.,* **1984**, *96*, 921.

193. Kashino, S.; Iwamoto, T.; Yamamoto, E.; Shiraga, T. *Bull. Chem. Soc. Japan,* **1994**, *67*, 1226.

194. De Riggi, I.; Gastaldi, S.; Surzur, J. M.; Bertrand, M. P.; Virgili, A. *J. Org. Chem.,* **1992**, *57*, 6118.

195. Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.,* **2001**, *42*, 7621.

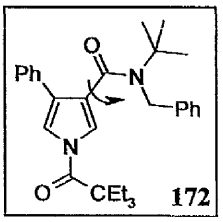
196. Hassinger, H. L.; Soll, R. M.; Gribble, G. W. *Tetrahedron Lett.,* **1998**, *39*, 3095.

197. Campaigne E, E.; Bourgeois, R. C. *J. Am. Chem. Soc.,* **1954**, *76*, 2445.

198. Pilgrim, K.; Korte, F. *Tetrahedron*, **1965**, *21*, 1999.

199. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L.W.; McCarthy, C.; Pink, J, H.; Westlund, N.; Yasin, S. A. *Tetrahedron,* **1998**, *54*, 13277.

A.1 Calculation of the Rates of Rotation of Tertiary Amides



172

Previous work in the Clayden group has shown that tertiary amides have restricted rotation about the Ar-CO bond, which was evident from ^{1}H NMR studies.[199] Here, the rates of rotation of tertiary amides bearing heteroaromatic constituents were investigated. Variable temperature ^{1}H NMR experiments for **172** were carried out in d_8-THF from –80 °C to room temperature in 10 °C increments (Figure A1).

At room temperature coalesence of the diastereotopic benzylic protons was observed. At lower temperatures (–70 °C and below) resolution of the diastereotopic protons was achieved, with the appearance of two doublets in the spectra ($\delta_H \approx 4.5$ ppm, J 18.0 Hz).

Comparison of the dynamic ^{1}H NMR spectra of **172** with the spectra simulated by g NMR (Figure A2) allows the determination of a barrier to rotation. This comparison enables the maximum and minimum values of k to be calculated at each temperature. Using the Eyring equation (Equation 1) it is possible to determine the activation enthalpy ($\Delta H^{\neq}$) in Kcal/mol by plotting ln(k/T) versus 1/T from the values of k obtained from g NMR (Table 1, Figure A3).

$$k = (k_B.T/h).e^{-(\Delta H/RT)}.e^{-(\Delta S/R)} \qquad \text{(Eq. 1)}$$

T (°K)	k	$\ln(k/T)_{average}$
203	10 25	-2.45108
213	26 54	-1.6729
223	55 110	-0.9945
253	550 780	0.9663
263	800 1400	1.4309
293	1500 10000	2.9767

Table 1

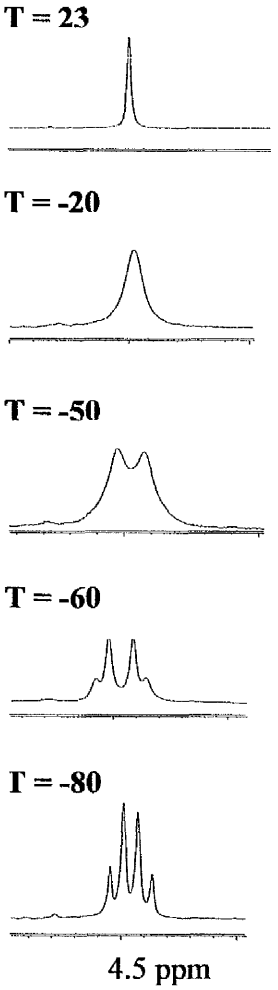


Figure A1
Dynamic ^{1}H NMR spectra of **172**

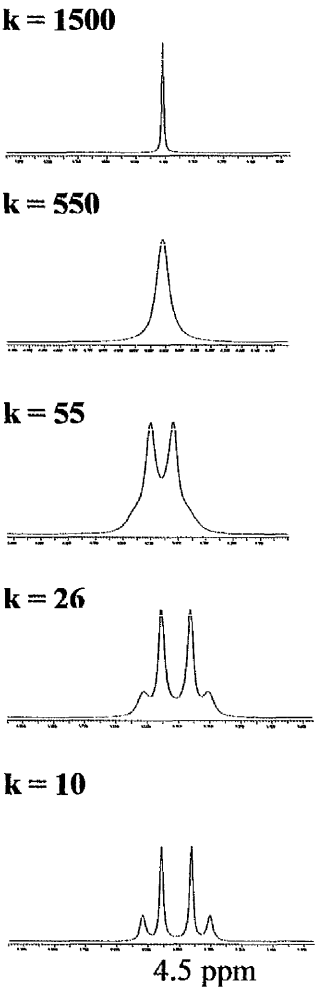


Figure A2
Simulated spectra for **172** using gNMR

$\Delta H^{\neq}$ can be calculated from the gradient (y = -mx + b, where m = $-\Delta H^{\neq}/R$ and x = 1/T) of the graph (Figure A3). Using the y-intercept (b = y(x = 0)), $\Delta S^{\neq}$ can be calculated from Equation 2.

$$y(x = 0) = \ln(k_B/h) + (\Delta S^{\neq}/R) \qquad \text{(Eq. 2)}$$

Thus the calculation of $\Delta G^{\neq}$ for the appropriate temperature is enabled (Equation 3). The racemization half-life can be established at each temperature since $k = \ln 2/t_{1/2}$ for a first order process (Table 2).

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \quad \text{thus} \quad \Delta G^{\neq} = 29.854 + 0.0723.T \qquad \text{(Eq. 3)}$$

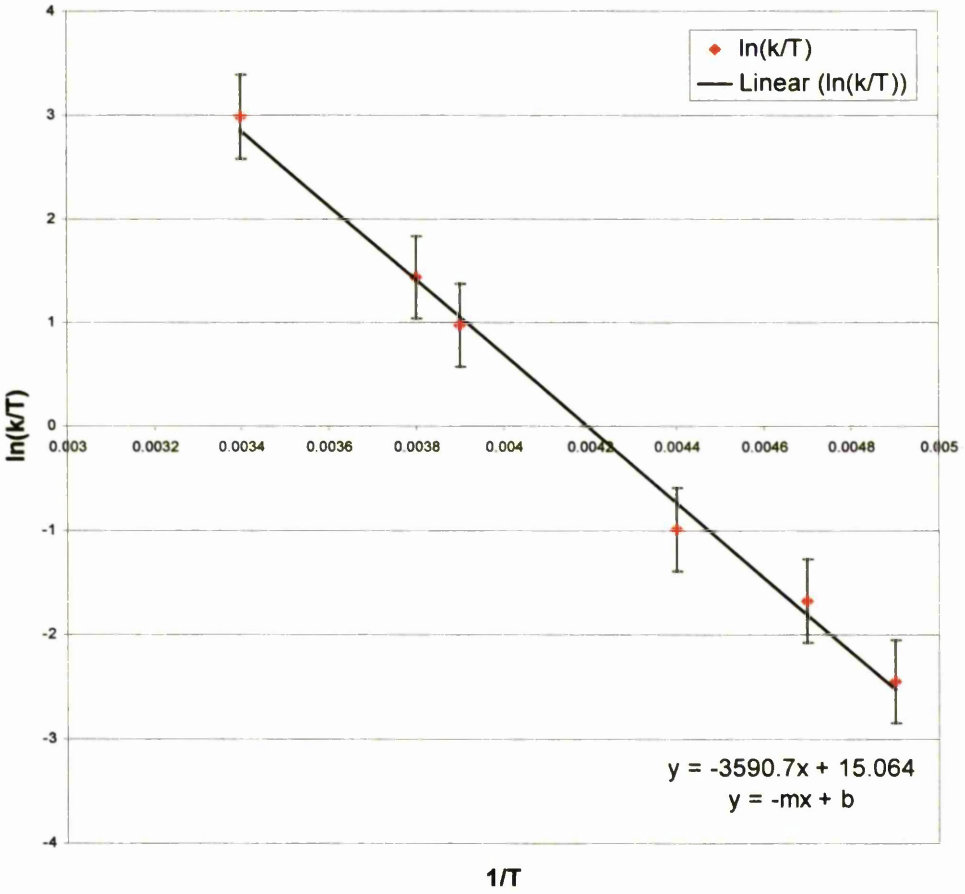


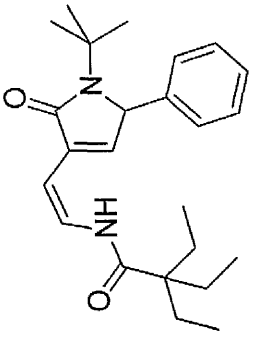
Figure A3 Determination of $\Delta H^{\neq}$

T (°C)	k	$\Delta G^{\neq}$ (Kcal/mol)	$t_{1/2}$ (s)
-70	15.8113	44.532	0.0438
-20	654.9734	48.147	0.00106
RT	9999.9999	51.039	6.95×10^{-5}

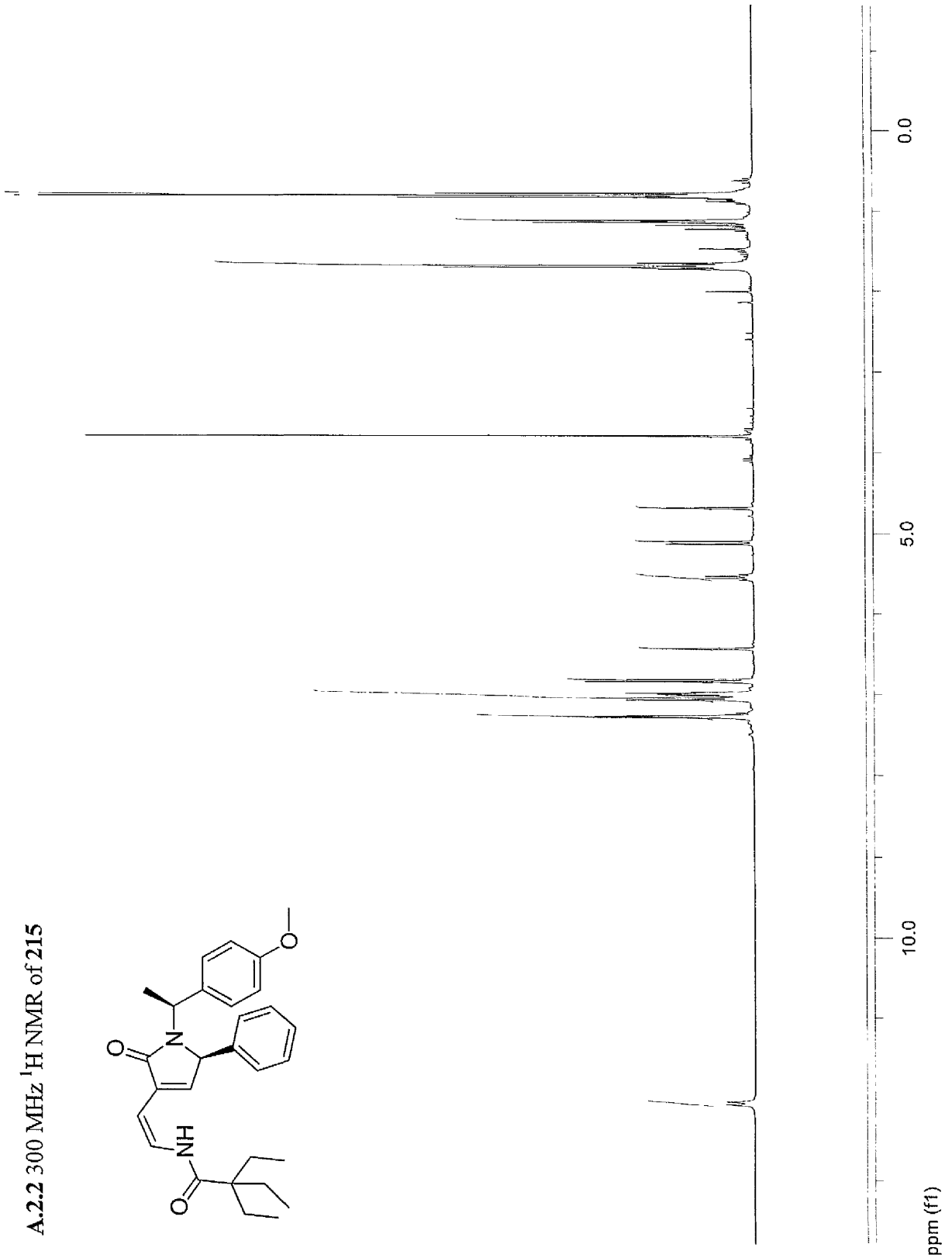
Table 2

As shown, **172** has a rotation barrier of $\Delta G^{\neq}$ = 51.039 Kcal/mol and a half-life of 6.95×10^{-5}, hence the coalesence of the diastereotopic protons at room temperature. At –70 °C and below, the half-life is sufficient to allow resolution of the diastereotopic protons within the NMR timescale.

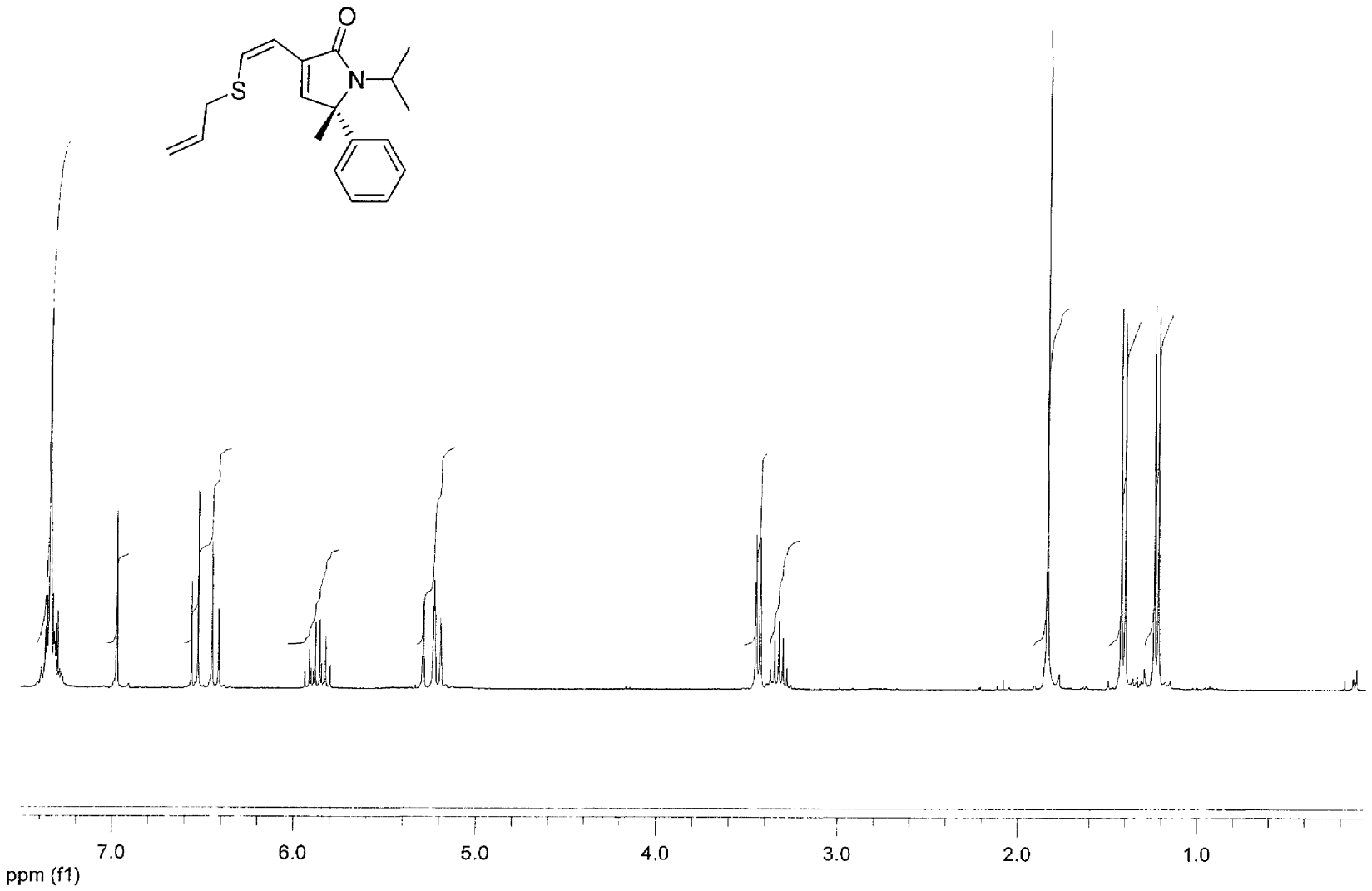
A.2.1 300 MHz ^{1}H NMR of **182**



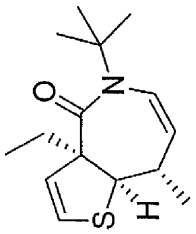
A.2.2 300 MHz ^{1}H NMR of **215**



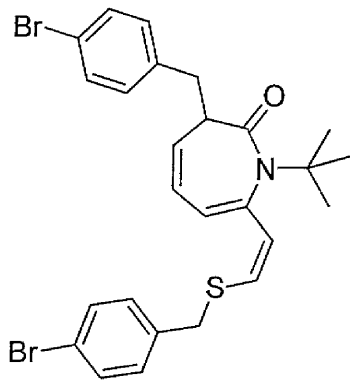
A.2.3 300 MHz ^{1}H NMR of **311c**



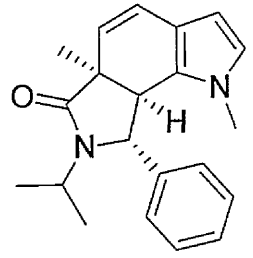
A.2.4 300 MHz ^{1}H NMR of **327c**



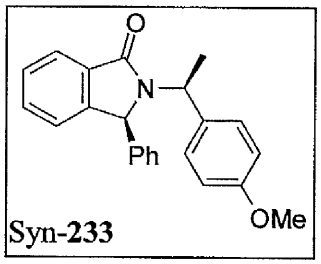
A.2.5 300 MHz ^{1}H NMR of **330e**



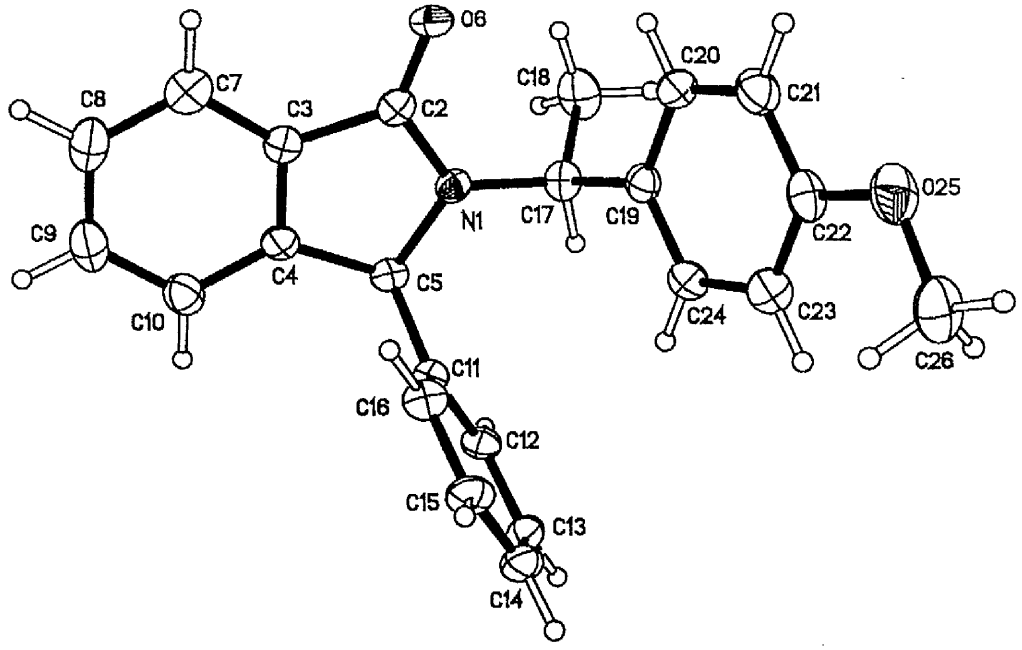
A.2.6 300 MHz ^{1}H NMR of **348b**



A.3.1 X-ray data for ***syn*-233**



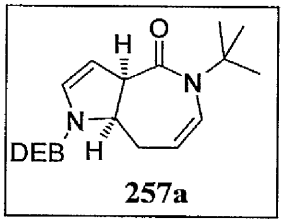
Syn-**233**



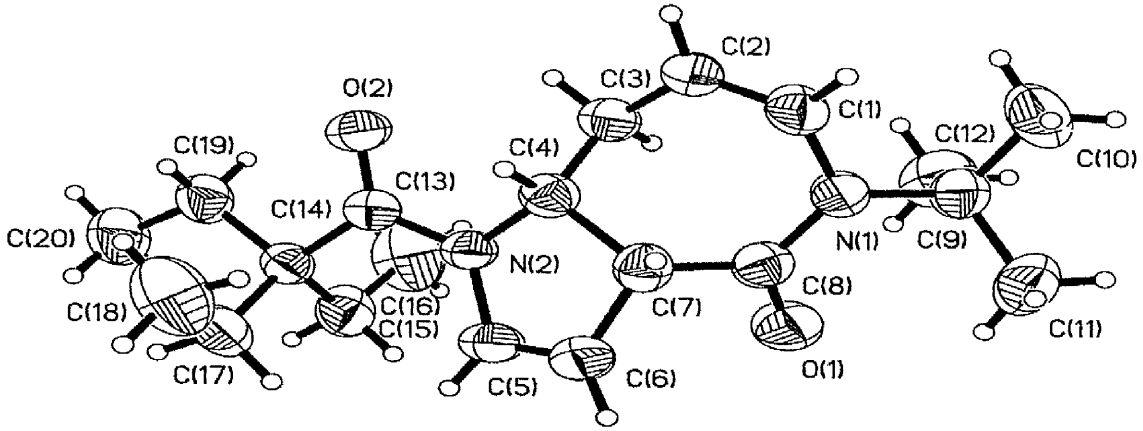
Crystal data and structure refinement for ***syn*-233**

Crystallization solvents	Cyclohexane and dichloromethane
Crystallization method	Vapour diffusion
Empirical formula	$C_{23}H_{21}NO_2$
Formula weight	343.41
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal size	0.60 x 0.20 x 0.20 mm
Crystal habit	Colourless needle
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.903(2) Å α= 90°
	b = 8.243(7) Å β= 91.81(3)°
	c = 18.462(13) Å γ = 90°
Volume	897.9(10) $Å^3$
Z	2
Density (calculated)	1.270 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	364
Theta range for data collection	4.04 to 25.40°
Index ranges	$-7 \leq h \leq 7, -9 \leq k \leq 9, -21 \leq l \leq 21$
Reflections collected	1671
Independent reflections	1671 [R(int) = 0.0000]
Coverage of independent reflections	94.2 %
Max. and min. transmission	0.984 and 0.953
Refinement technique	Full-matrix least-squares on F^2
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	1671 / 1 / 241
Goodness-of-fit on F^2	1.148
Δ/σ_{max}	0.000
Final R indices	
1522 data; I>2σ(I)	R1 = 0.0498, wR2 = 0.1537
all data	R1 = 0.0559, wR2 = 0.1589
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1197P)^2 + 0.0294P]$ where $P = [MAX(F_o^2, 0) + 2F_c^2]/3$
Absolute structure parameter	-3(3)
Extinction coefficient	0.053(18)
Largest diff. peak and hole	0.198 and -0.219 $eÅ^{-3}$

A.3.2 X-ray data for **257a**



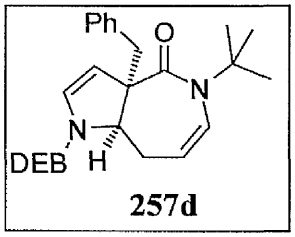
257a



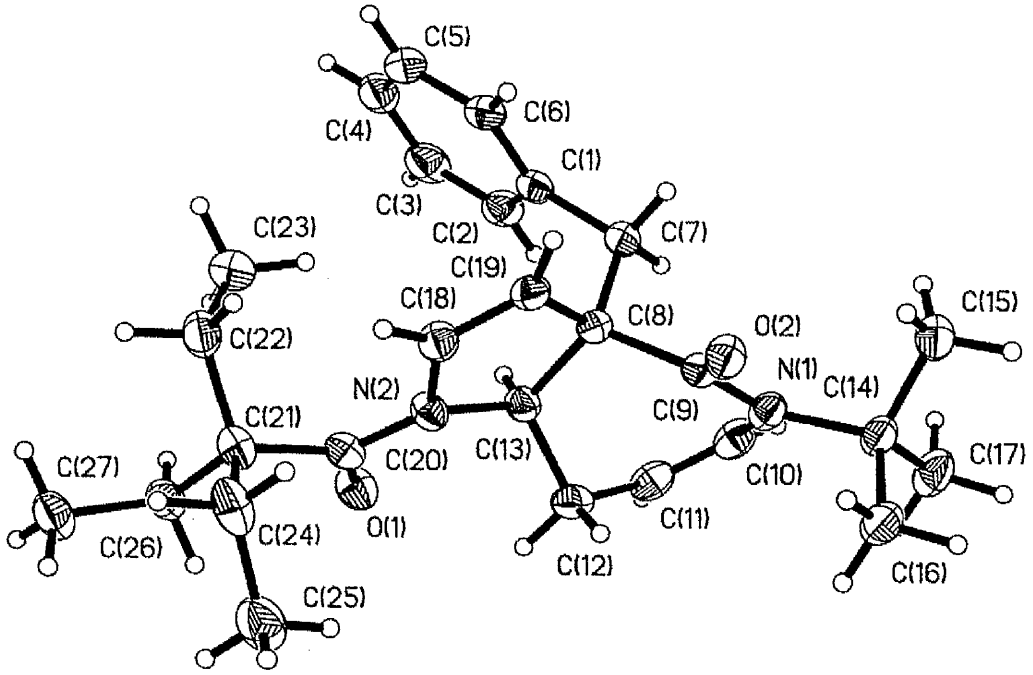
Crystal data and structure refinement for **257a**

Identification code	s1642m
Emirical formula	C20 H32 N2 O2
Formula weight	332.48
Temperature	300(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 12.379(2) A alpha = 90 deg.
	b = 13.856(2) A beta = 115.508(3) deg.
	c = 12.601(2) A gamma = 90 deg.
Volume	1950.7(5) A^3
Z, Calculated density	4 ,1.132 g/m^3
Absorption coefficient	0.073 mm^-1
F(000)	728
Crystal size	0.20 x 0.20 x 0.20 mm
Theta range for data collection	1.82 to 26.37 deg.
Limiting indices	-15<=h<=15, -17<=k<=17, -15<=l<=15
Reflections collected / unique	15332 / 3989 [R(int) = 0.0875]
Completeness to theta	= 26.37 99.9 %
Absorption correction	None
Max. and min. transmission	0.9856 and 0.9856
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3989 / 0 / 223
Goodness-of-fit on F^2	0.760
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.0895
R indices (all data)	R1 = 0.1221, wR2 = 0.1040
Largest diff. peak and hole	0.310 and -0.129 e.A^-3

A.3.3 X-ray details for **257d**



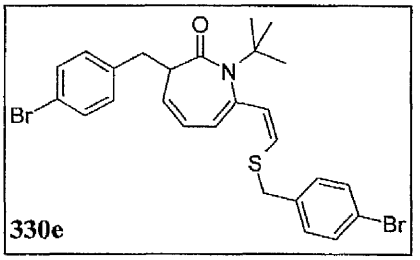
257d

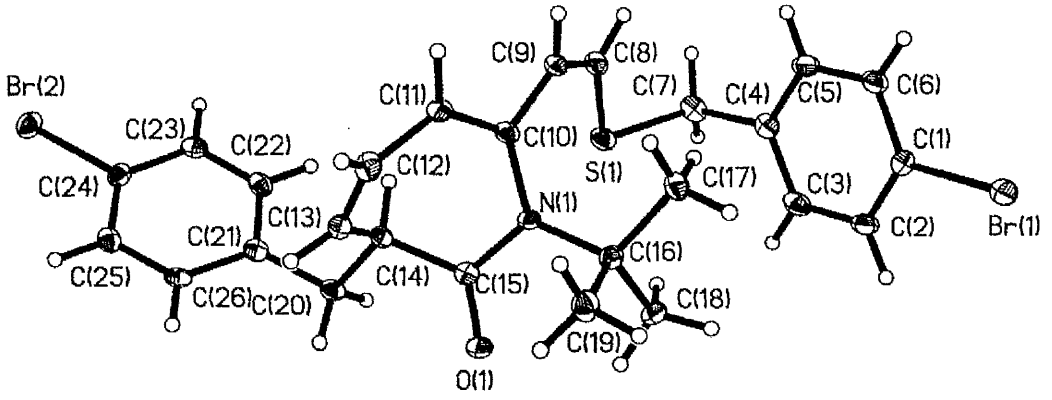


Crystal data and structure refinement for **257d**

Identification code	s1695n
Empirical formula	C27 H38 N2 O2
Formula weight	422.59
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 15.492(5) A alpha = 90 deg. b = 11.134(4) A beta = 105.084(5) deg. c = 14.335(5) A gamma = 90 deg.
Volume	2387.5(13) A^3
Z, Calculated density	4, 1.176 Mg/m^3
Absorption coefficient	0.073 mm^-1
F(000)	920
Crystal size	0.50 x 0.50 x 0.20 mm
Theta range for data collection	1.36 to 28.64 deg.
Limiting indices	-20<=h<=19, -14<=k<=14, -19<=l<=18
Reflections collected / unique	18927 / 5615 [R(int) = 0.0674]
Completeness to theta =	28.64 91.5 %
Absorption correction	None
Max. and min. transmission	0.9855 and 0.9642
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5615 / 0 / 286
Goodness-of-fit on F^2	0.919
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.1095
R indices (all data)	R1 = 0.0700, wR2 = 0.1247
Largest diff. peak and hole	0.315 and -0.179 e.A^-3

A.3.4 X-ray details for **330e**

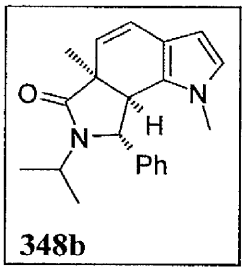




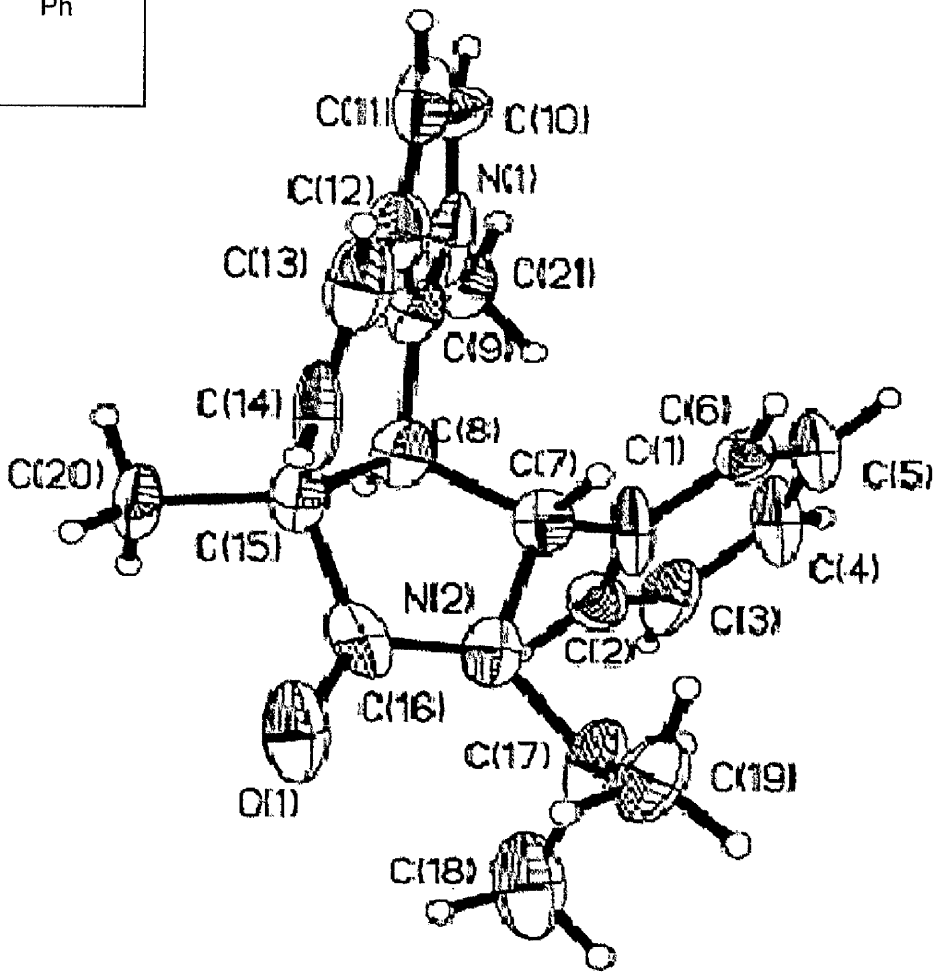
Crystal data and structure refinement for **330e**

Identification code	h:\s1898\work\s1898abs
Empirical formula	C26 H27 Br2 N O S
Formula weight	561.37
Temperature	100(2)K
Wavelength	0.71073A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.608(2)A alpha =102.633(5) deg.
	b =11.932(4)A beta =96.003(5) deg.
	c =13.936(4)A gamma =103.180(5) deg.
Volume	1186.0(6)A^3
Z, calculated density	2, 1.572mg/m^3
Absorption coefficient	3.524mm^-1
F(000)	568
Crystal size	0.20 x 0.20 x 0.20 mm
Theta range for data collection	1.81 to 26.48 deg.
Limiting indices	-9<=h<=9, -14<=k<=14, -17<=j<=10
Reflections collected/unique	6744/4701 [R(int) = 0.220
Completeness of theta =	26.48, 95.7 %
Absorption correction	None
Max. and min. transmission	0.5391 and 0.5391
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4701/0/283
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 =0.0331, wR2 =0.838
R indices (all data)	R1 =0.0418, wR2 =0.875
Largest diff. peak and hole	0.955 and-0.443 e.A^-3

A.3.5 X-ray data for **348b**



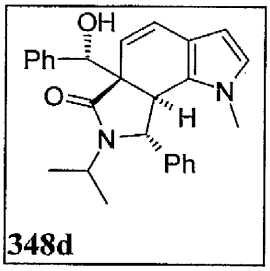
348b



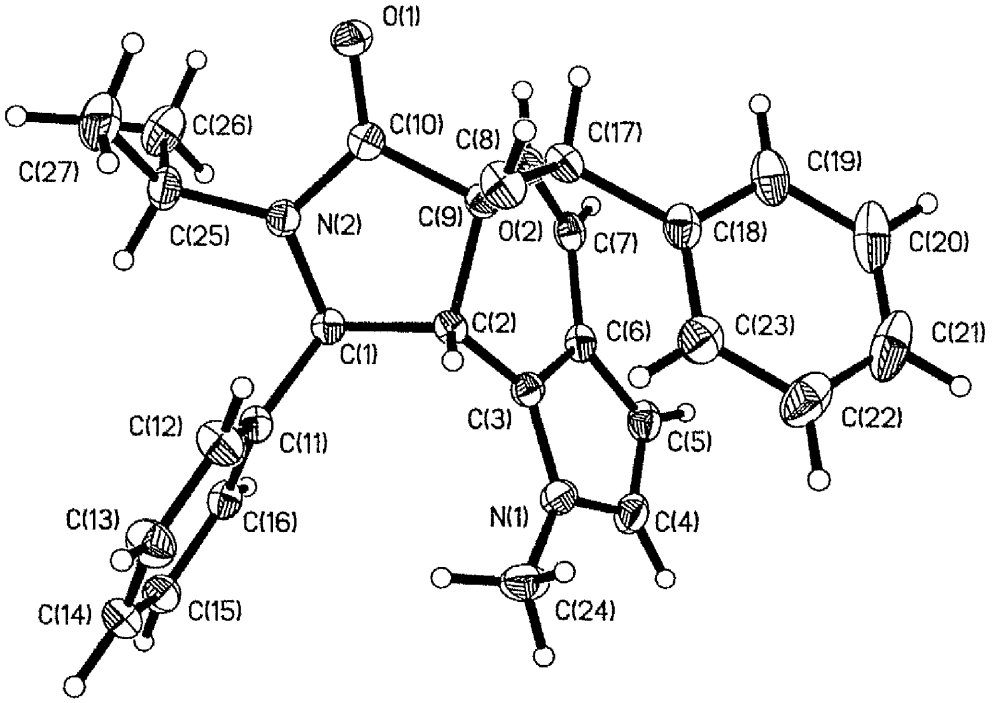
Crystal data and structure refinement for **348b**

Identification code	2033m
Empirical formula	C27 H28 N2 O2
Formula weight	412.51
Temperature	00(2) K
Wavelength	.71073 A
Crystal system, space group	triclinic, P-1
Unit cell dimensions	a = 9.06 (9) A alpha = 67.281(2) deg.
	b = 11.69(12) A beta = 80.755(2) deg.
	c = 11.83(12) A gamma = 76.17(2)deg.
Volume	1126.2(2) A^3
Z, Calculated density	1.216 Mg/m^3
Absorption coefficient	.077 mm^-1
F(000)	440
Crystal size	0.50 x 0.35 x 0.30 mm
Theta range for data collection	0.86 to 28.35 deg.
Limiting indices	-11<=h<=11, -15<=k<=15, -15<=l<=15
Reflections collected / unique	742 / 5086 [R(int) = 0.0300]
Completeness to theta =	8.35 90.2 %
Absorption correction	None
Max. and min. transmission	.9773 and 0.9626
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5086 / 0 / 284
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.1121
R indices (all data)	R1 = 0.0484, wR2 = 0.1157
Largest diff. peak and hole	0.341 and -0.218 e.A^-3

A.3.6 X-ray details for **348d**



348d



Crystal data and structure refinement for **348d**

Identification code	s2034m
Empirical formula	C21 H24 N2 O
Formula weight	320.42
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.075(19) A alpha = 93.09(4) deg.
	b = 10.17(2) A beta = 90.44(4) deg.
	c= 20.15(4) A gamma = 114.86(4) deg.
Volume	1684(6) A^3
Z, Calculated density	4,1.264 Mg/m^3
Absorption coefficient	0.078 mm^-1
F(000)	688
Crystal size	0.45 x 0.20 x 0.15 mm
Theta range for data collection	2.03 to 28.80 deg.
Limiting indices	-12<=h<=10, -8<=k<=13, -27<=l<=26
Reflections collected / unique	10642 / 7668 [R(int) = 0.3028]
Completeness to theta =	28.80 87.4 %
Absorption correction	None
Max. and min. transmission	0.9884 and 0.9658
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7668 / 0 / 441
Goodness-of-fit on F^2	0.931
Final R indices [I>2sigma(I)]	R1 = 0.1751, wR2 = 0.4185
R indices (all data)	R1 = 0.4296, wR2 = 0.5139
Largest diff. peak and hole	0.557 and -0.576 e.A^-3