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UNIVERSITY OF SOUTHAMPTON

Faculty of Natural and Environmental Sciences

School of Chemistry

**Towards the Total Syntheses of
Aspidospermidine and Aspidofractinine: The
Curious Chemistry of the Indolinyl Radical**

by

Kerri Joanne Stenning

A Thesis Submitted for the Degree of Doctor of Philosophy

September 2011

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ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

Doctor of Philosophy

TOWARDS THE TOTAL SYNTHESSES OF ASPIDOSPERMIDINE AND
ASPIDOFRACTININE: THE CURIOUS CHEMISTRY OF THE INDOLINYL
RADICAL

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This thesis is concerned with the total syntheses of the natural products aspidospermidine and aspidofractinine. These targets are noteworthy not only for the biological activity displayed within the class but also for their interesting molecular architecture. Herein, two routes towards the natural products are presented. Key features of the first route, a unified approach to both targets *via* the indolinyl radical, include the elegant construction of the core *ABDE* ring system, a mild lactam reduction and synthesis of the key cyclic imine. The second route features a highly efficient Stille coupling and a Wittig olefination. Attempts to effect a critical radical cyclisation reaction are also discussed.

The chemistry of the C2 indolinyl radical is investigated, in particular the influence of the C3 indolinyl substitution upon the radical pathway followed. A discussion of the study and its findings is presented in Chapter 4.

A review of synthetic approaches to these natural products since 2007 is presented in Chapter 1, in addition to details on their isolation, characterisation and biosynthesis, and an overview of their biological activity. Experimental procedures and characterisation data are provided in Chapter 6.

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The research described in this thesis was carried out under the supervision of Prof. D. C. Harrowven at the University of Southampton and at Pfizer, Sandwich between October 2007 and August 2011. No part of this thesis has previously been submitted for a degree.

The work described is entirely my own, except where I have *either* acknowledged help from a named person *or* given a reference to a published source or a thesis. Text taken from another source is enclosed in quotation marks and a reference given. Pictures taken from another source are clearly indicated in the caption. Parts of this work have been published as:

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KJS 2011

Abbreviations

2D	two dimensional	HPLC	high performance liquid chromatography
$[\alpha]_D$	optical rotation	HRMS	high resolution mass spectrometry
Ac	acetyl	HWE	Horner-Wadsworth-Emmons
AIBN	1,1'-azobis(isobutyronitrile)	Hz	hertz
app.	apparent	IC	inhibitory concentration
Ar	aryl	<i>J</i>	coupling constant
aq.	aqueous	JMOD	J-modulated spin-echo
Bn	benzyl	Kg	kilogram(s)
Boc	<i>tert</i> -butyloxycarbonyl	kJ	kilojoule
br.	broad	LCMS	liquid chromatography-mass spectrometry
Bu	butyl	LDA	lithium diisopropylamide
<i>c</i>	concentration	LRMS	low resolution mass spectrometry
°C	degrees centigrade	M	molar
Cbz	carbobenzyloxy	<i>m</i>	medium / multiplet
Cl	chemical ionisation	<i>m</i>	meta
cm^{-1}	wavenumber	MALDI	matrix-assisted laser desorption / ionization
COSY	correlated spectroscopy	Me	methyl
CSA	camphorsulfonic acid	<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid
Cy	cyclohexyl	min	minute(s)
d	doublet	mL	millilitre(s)
DABCO	1,4-diazabicyclo[2.2.2]-octane	mM	millimolar
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene	mmol	millimole(s)
DCC	dicyclohexylcarbodiimide	mol	mole(s)
DCM	dichloromethane	MOM	methoxymethyl ether
DEPT	distortionless enhancement by polarisation transfer	MP	melting point
DIBALH	diisobutylaluminium hydride	Ms	mesyl
DIPE	diisopropyl ether	MS	molecular sieves
DMAP	4-dimethylaminopyridine	MTBE	methyl <i>tert</i> butyl ether
DME	dimethyl ether	<i>m/z</i>	mass / charge ratio
DMF	<i>N,N</i> -dimethylformamide	NBS	<i>N</i> -bromosuccinimide
DMP	Dess-Martin periodinane	NIS	<i>N</i> -iodosuccinimide
DMSO	dimethylsulfoxide	nM	nanomolar
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride	NMM	<i>N</i> -methylmorpholine
EI	electron ionisation	NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
ES+	electrospray ionisation (positive mode)	NMP	<i>N</i> -methylpyrrolidone
ES-	electrospray ionisation (negative mode)	NMR	nuclear magnetic resonance
ESI	electrospray ionisation	<i>o</i>	ortho
Et	ethyl	obsc.	obscured
g	gram(s)	OCD	optical circular dichroism
h	hour(s)	<i>p</i>	<i>para</i>
HMDS	hexamethyldisilazane	PCC	pyridinium chlorochromate
HMBC	heteronuclear multiple bond correlation	PG	protecting group
HMPA	hexamethylphosphor-amide	Ph	phenyl
HMQC	heteronuclear multiple-quantum correlation	ppm	parts per million

PPTS	pyridinium <i>p</i> -toluene-sulfonate	TES	triethylsilyl
pyr.	pyridine	Tf	triflate
q	quartet	TFA	trifluoroacetic acid
<i>rac</i>	racemic	THF	tetrahydrofuran
RCM	ring-closing metathesis	THP	tetrahydropyran
RT	room temperature	TLC	thin layer chromatography
s	singlet / strong	TMS	trimethylsilyl
sd	standard deviation	ToF	time of flight
sat.	saturated	TPAP	tetrapropylammonium perruthenate
t	triplet	Ts	tosyl
<i>t</i>	tertiary	TTMSS	<i>tris</i> -trimethylsilylsilane
<i>tert</i>	tertiary	uv	ultraviolet
TBAB	tetra- <i>n</i> butylammonium bromide	ν_{\max}	absorption maxima
TBAF	tetra- <i>n</i> butylammonium fluoride	VAZO	1,1'-azobis(cyclohexanecarbonitrile)
TBDMS	<i>tert</i> -butyldimethylsilyl	<i>viz.</i>	<i>videlicet</i>
TEA	triethylamine	w	weak
		W	watt

Chapter 1: Introduction

1.1 Background

Alkaloids are organic bases containing one or more nitrogen atoms and are found primarily in plants and to a lesser degree in microorganisms and animals. They are classified according to the nitrogen-containing source: piperidine, indole, quinoline, for example. The nitrogen atoms in alkaloids arise from amino acids and often the amino acid constitutes a large portion of the alkaloid skeleton.

One of the major groups of alkaloids in plants is the terpenoid indole family which contains more than 3000 recognised alkaloids. These alkaloids are found predominantly in eight plant families, of which Apocynaceae, Loganiaceae and Rubiaceae represent the most abundant sources. Almost all structures in this group contain a tryptamine portion, and the remaining nine / ten carbon fragment can be divided into three main structural types; *Corynanthe* (e.g. akuammicine **2**), *Aspidosperma* (e.g. tabersonine **4**) and *Iboga* (e.g. catharanthine **5**, Figure 1).¹

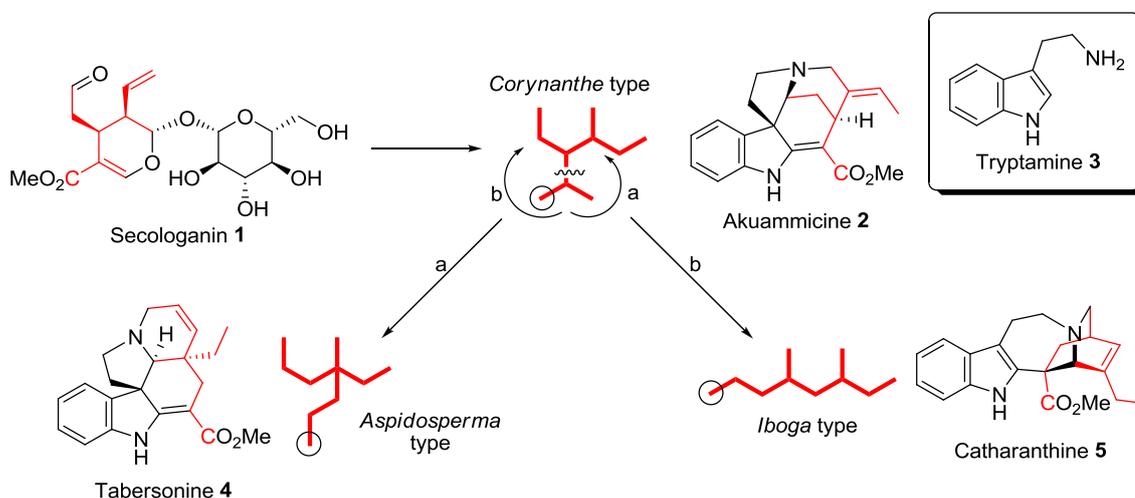


Figure 1: The terpenoid indole alkaloids.

It is the nine / ten carbon fragment that is of terpenoid origin, being derived from the terpene secologanin **1**. When combined with the tryptamine portion all three groups can be accessed through rearrangement of the terpenoid residue, with the *Aspidosperma* and *Iboga* groups arising from removal of a three-carbon unit from the *Corynanthe* framework and reattachment at one of two points (Figure 1).

Where a nine carbon unit is in place, as in akuammicine **2**, it is usually the carbon highlighted with a circle that is lost, which corresponds to the carboxylate group of secologanin **1** with loss through hydrolysis / decarboxylation.

The *Aspidosperma* alkaloids are the largest group of indole alkaloids and are categorised into seven subclasses based on common structural attributes. In each case the subclass is exemplified by the parent member, namely aspidospermidine **6**, aspidofractinine **7**, quebrachamine **8**, vincadiformine **9**, vindolinine **10**, meloscine **11** and kopsine **12** (Figure 2).²

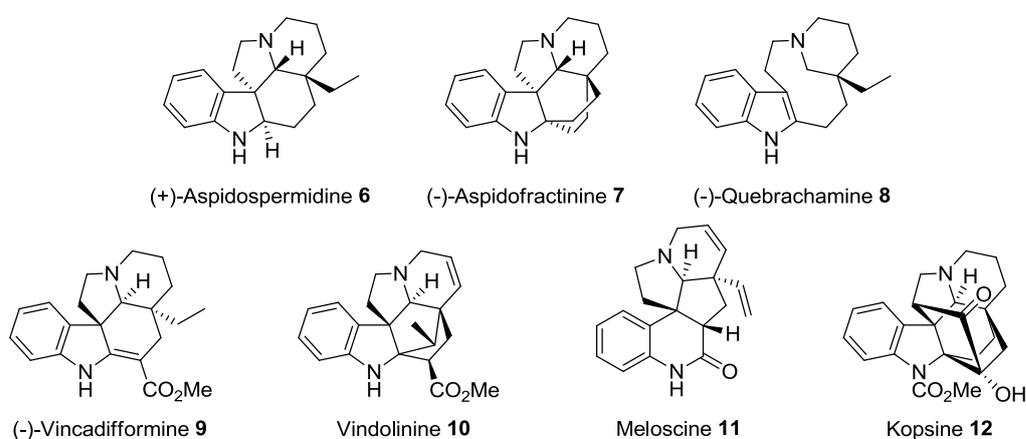


Figure 2: The *Aspidosperma* alkaloid subclasses.

The subjects of this thesis, aspidospermidine **6** and aspidofractinine **7**, are both the parents of their individual subclasses. Whilst both alkaloids bear little substitution on the *Aspidosperma* framework they remain structurally complex targets. Each target contains a pentacyclic fused [6.5.6.5.6] skeleton and aspidospermidine **6** has four contiguous stereocentres. Aspidofractinine **7** has additional complexity, boasting an extra six-membered ring (Figure 3).

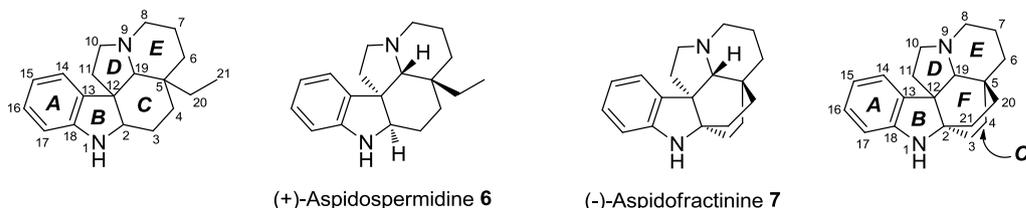


Figure 3: Labelling and numbering of the natural product systems.³

1.2 Isolation and Structural Elucidation

The *Aspidosperma* alkaloids are found predominantly in South America and Mexico and are isolated primarily from plants belonging to Plumerioideae, a subfamily of the Apocynaceae.^{2,4} Aspidospermidine **6** was isolated in 1961 by Biemann *et al.* from the bark of *Aspidosperma quebracho blanco*, a tree native to northern Argentina.⁵ Using a combination of alumina and gas-phase chromatography for separation and mass spectrometry for identification, approximately twenty alkaloids of reasonable purity were isolated from the crude extract. Of these, fifteen were analysed in detail, three of which were already known species, namely yohimbine **13** (Figure 4), aspidospermine **14** and quebrachamine **8**.³

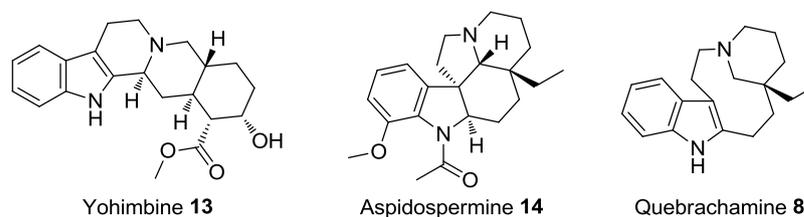
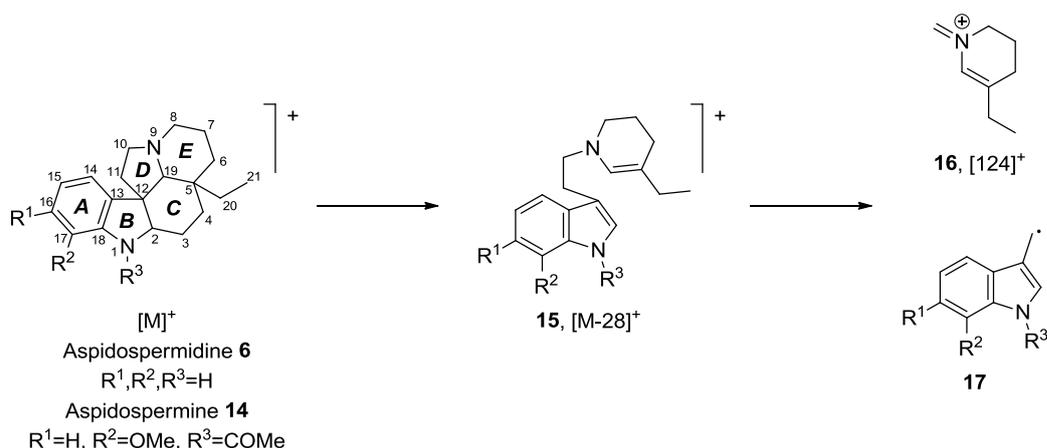


Figure 4

Examining the mass spectra of the twelve remaining alkaloids it was found that they could be divided into two structurally distinct groups. The first group, A, showed characteristic fragmentation patterns, in particular a significant peak of mass 124 that indicated a relationship to aspidospermine **14**, whose spectrum had been previously obtained. The second group, B, showed characteristic fragmentation patterns which all contained a significant peak of mass 136. One alkaloid, with an abundance of 1%, was determined to have a molecular weight of 282 and had a fragmentation pattern which suggested it fell into the first group, and was therefore termed alkaloid 282A. By examining the characteristic fragmentations of alkaloids in group A, Biemann *et al.* were able to deduce a common fragmentation pathway for all six of these alkaloids (Scheme 1).



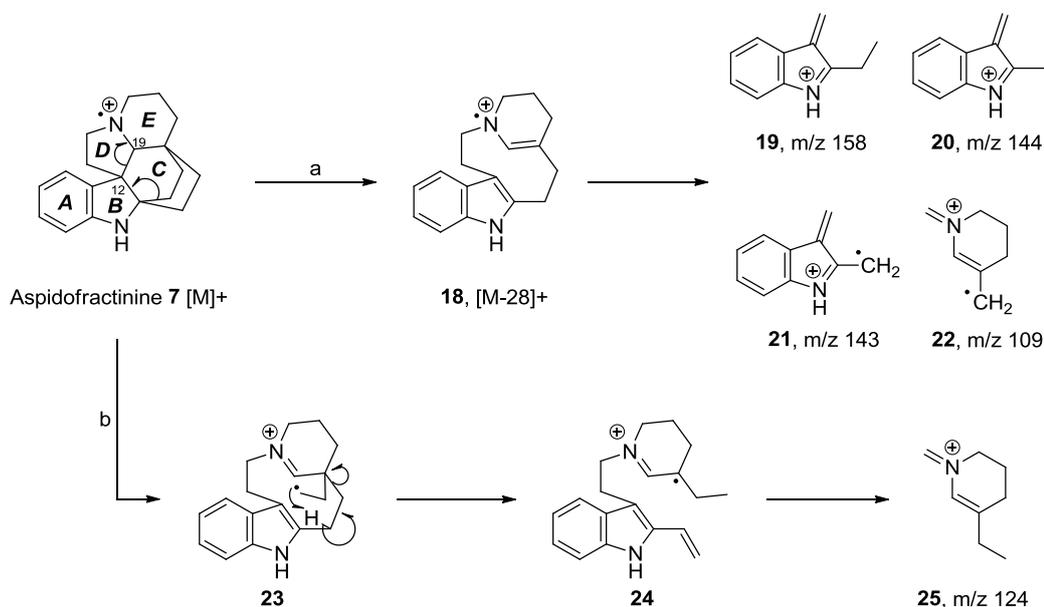
Scheme 1: Generalised fragmentation pattern.

Fragmentation is initiated by cleavage of the C12–C19 bond, which leads to cleavage of the C ring through expulsion of C3–C4 as ethylene. This relieves strain within the fused ring system and, although three bonds are broken, an aromatic ring system is gained in the formation of an indole. The resultant charged fragment **15** then breaks down further, this time across the two-carbon unit tethering the heterocyclic rings. Cleavage of the C10–C11 bond is favoured as the resultant positive charge at C10 can be stabilised by the nitrogen lone pair, affording the characteristic ion **16** of mass 124. The resultant radical intermediate **17** is also stabilised by conjugation to the aromatic ring system. In general terms, this correlates to a characteristic fragmentation pattern of $[M]^+$, $[M-28]^+$ and $[124]^+$. The constant presence of the peak of mass 124 allowed the authors to conclude that the piperidine moiety was unsubstituted in all cases. Furthermore, the fragmentation to ion **15** proved the unsubstituted nature of the C3–C4 two-carbon unit in all alkaloids of this group. It therefore followed that all differing substitution must be confined to the indolyl moiety, on either the nitrogen or aryl component (indicated as R^1 , R^2 and R^3 in Scheme 1).

Alkaloid 282A exhibited a mass spectrum that followed this general fragmentation pattern, showing characteristic peaks at 282, 254 and 124. The molecular weight of 282 indicated that the core aspidospermine skeleton featured no additional substitution, leading them to conclude that the structure was that of **6**, which they named aspidospermidine.³ In 1963 Smith and Wahid reported the specific rotation

of aspidospermidine **6** ($[\alpha]_D +17^\circ$, in ethanol) and proposed the absolute stereochemistry illustrated in Figure 3.⁶

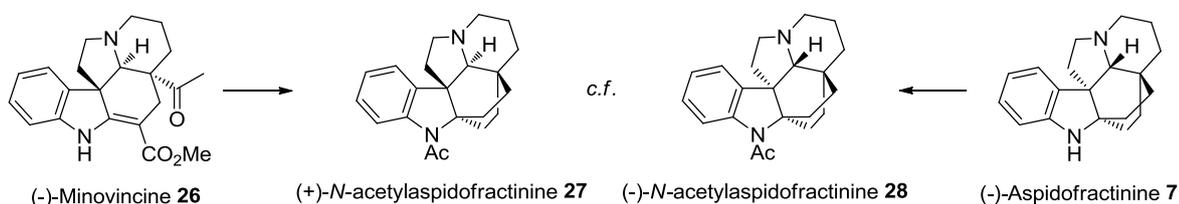
Aspidofractinine **7** was also isolated as a minor alkaloid a few years later in 1963 from the leaves of *Aspidosperma refractum* by Schmid and co-workers.⁷ As with aspidospermidine **6**, the structural elucidation was based predominantly on the mass spectral data and the characteristic fragmentation patterns. The initial fragmentation of aspidofractinine **7** is fission of the C12–C19 bond, again with aromatisation providing the driving force. This affords fragment ion **18**, which undergoes further bond fission at the two benzylic positions to give fragment ions **19–22** (pathway a, Scheme 2). When the fission of the C and D rings occurs without loss of ethylene, in a homolytic fashion (pathway b, Scheme 2), ion **23** is formed, which then fragments to give firstly ion **24** and subsequently **25**. This characteristic peak is also seen in the mass spectrum of aspidospermidine **6**. When this mass spectral data (with key ions at 280, 252, 158, 144, 124 and 109) was combined with the NMR data, which showed an absence of both the methyl signal and the signal corresponding to C2 in the ‘aspidospermine fingerprint’, the structure of aspidofractinine **7** was successfully assigned.²



Scheme 2: Fragmentation pattern for aspidofractinine **7**.

The specific rotation was not reported until a year later ($[\alpha]_D -20^\circ$, $c=0.581$ in chloroform) when the same group isolated aspidofractinine **7** from the leaves of

Pleiocarpa tubicina.⁸ The assignment of the absolute stereochemistry by Schmid *et al.* in 1964 of the natural material, (–)-aspidofractinine **7**, was based on comparison of the OCD (optical circular dichroism) spectra of the acetylated natural material, (–)-*N*-acetylaspidofractinine **28** and that of (+)-*N*-acetyl-aspidofractinine **27**, obtained through degradation of natural (–)-minovincine **26** (Scheme 3). However, the absolute stereochemistry of (–)-minovincine **26** was only assigned based on the similarity of structure between itself and that of (–)-vincadifformine **9**. Whilst (–)-vincadifformine **9** had its absolute stereochemistry confirmed by total synthesis at that time, that of natural (–)-minovincine **26** had not. In fact, both (+)- and (–)-minovincine **26** exist in Nature, thus leading to the absolute stereochemistry of (+)-*N*-acetylaspidofractinine **26** initially being inferred for (–)-aspidofractinine **7**. It was not until 2009 that the correct absolute stereochemistry was confirmed by the total synthesis of (+)-aspidofractinine **7** by Spino and Gagnon (*vide infra* Chapter 1.6).⁹ Synthesis of the unnatural enantiomer of aspidofractinine **7** and subsequent single crystal X-ray analysis, as well as taking into account the expected stereochemistry from the reaction sequence, allowed the authors to assign with certainty the correct absolute stereochemistry.



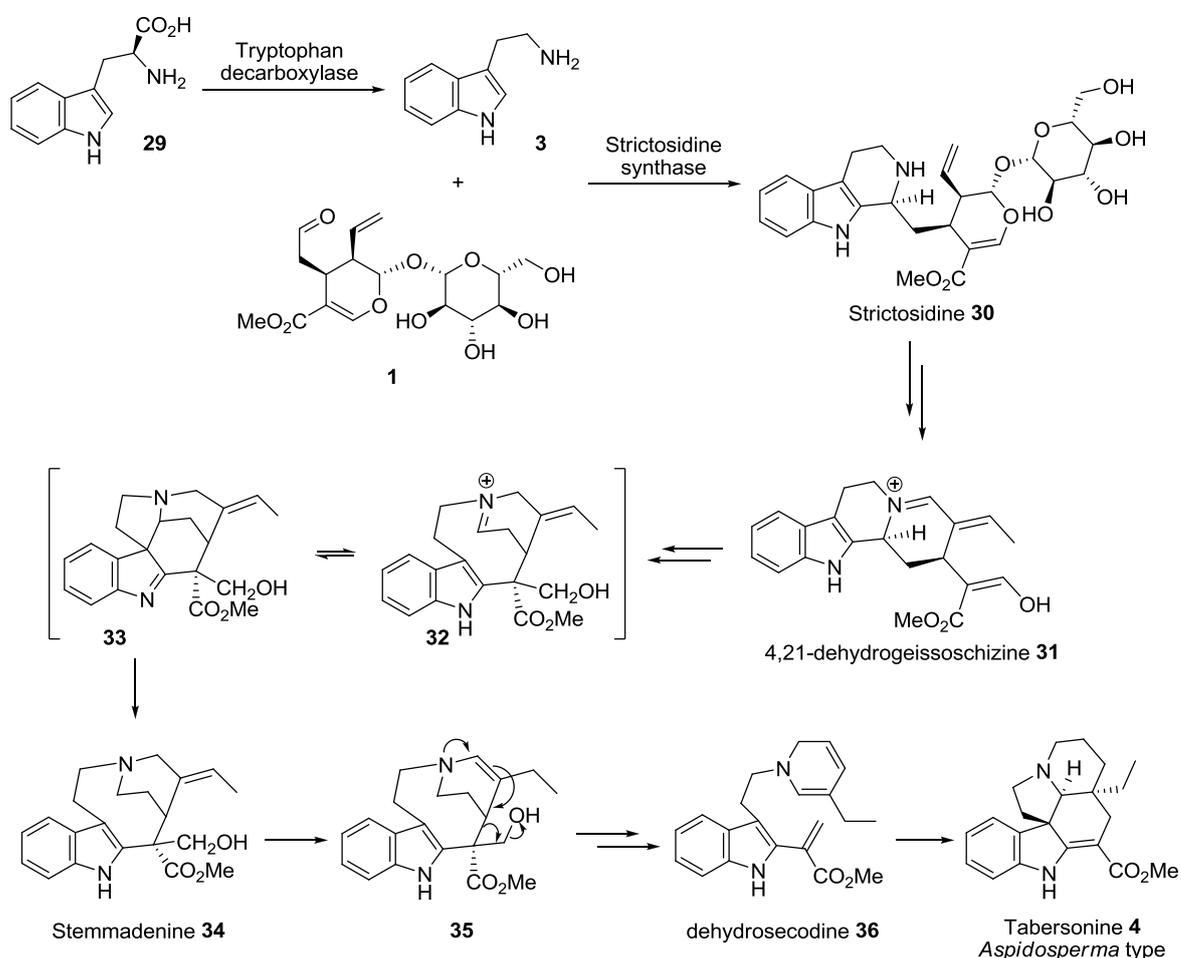
Scheme 3: Schmid and co-workers' determination of absolute stereochemistry.

It is interesting to note that stereochemical consistency amongst the *Aspidosperma* alkaloids at any one stereocentre is not observed. This is in contrast to the *Corynanthe* alkaloids, for whom consistency is observed almost completely throughout the group for at least one stereocentre.² However, when considering the biosynthetic pathways this is perhaps not unexpected – the biosynthetic pathway of the *Corynanthe* alkaloids contains no rearrangement of the terpenoid fragment, secologanin **1** (Figure 1).¹ The biosynthesis of the *Aspidosperma* alkaloids, however, proceeds with a skeletal rearrangement of the

terpene residue. This is highlighted by the achiral intermediates akin to **36** which are implicated in the biosynthetic pathways of the *Aspidosperma* alkaloids.

1.3 Biosynthesis

Studies carried out in the late 1960's and early 1970's by a number of groups have resulted in proposed biosynthetic pathways for the terpenoid indole alkaloids. The biosynthesis for all three major terpenoid indole alkaloid groups (*Corynanthe*, *Aspidosperma* and *Iboga*) begins with the enzymatic conversion of tryptophan **29** to tryptamine **3** with tryptophan decarboxylase (Scheme 4).¹⁰

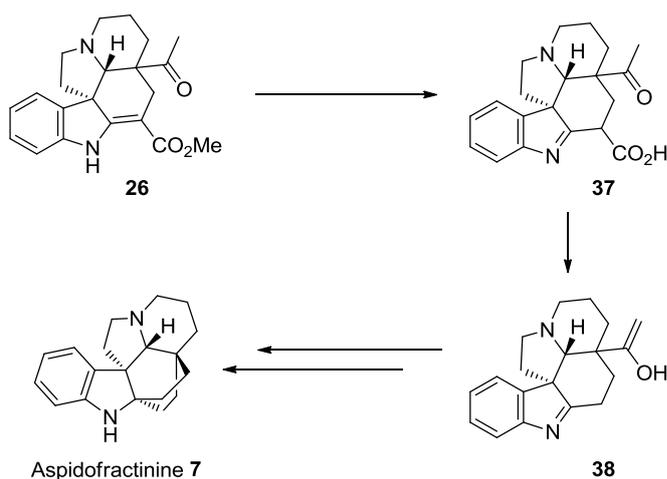


Scheme 4: Biosynthetic pathway for the *Aspidosperma* alkaloids.

Tryptamine **3** then reacts with the aforementioned secologanin **1** in a stereoselective Pictet-Spengler condensation catalysed by the enzyme strictosidine synthase. Strictosidine **30** is then deglycosylated by strictosidine deglycosidase to form a reactive hemiacetal that opens to form a dialdehyde

intermediate. This dialdehyde reacts with the secondary amine of the strictosidine skeleton to afford 4,21-dehydrogeissoschizine **31** after allylic isomerisation. 4,21-Dehydrogeissoschizine **31** is the common intermediate for all three alkaloid groups and it is at this point that the pathways diverge. From here onwards no further enzymes for the construction of the *Aspidosperma* skeleton have been successfully identified. For the *Aspidosperma* alkaloids the next stage is the formation of preakuammicine **33**, though the mechanism still remains unknown despite several proposed pathways. Reduction of preakuammicine **33** gives stemmadenine **34** which rearranges to afford the acrylic ester dehydrosecodine **36**. Cycloaddition of dehydrosecodine **36** is then presumed to install the *Asidosperma* alkaloid framework; however, as yet there is no evidence for this reaction in the plant.

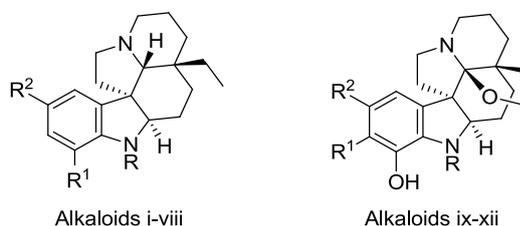
Aspidofractinine-type alkaloids are thought to originate in Nature from intermediates similar to minovincine **26** via hydrolysis of the ester followed by decarboxylation to give intermediates akin to **38**.¹¹ Cyclisation via an intramolecular Mannich reaction to the α -position of the indole then forms the *F* ring of the aspidofractinine-type alkaloids, with a final reduction of the ketone then affording aspidofractinine **7** (Scheme 5). Again, details as to the enzymes involved in these processes are yet to be established.



Scheme 5: Biosynthesis of aspidofractinine **7**.

1.4 Biological Importance and Activity

In 2002 a study into the antimalarial activity of a range of *Aspidosperma*-type alkaloids was published.¹² Twelve alkaloids with the aspidospermine skeleton were tested *in vitro* for their activity against *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria. The alkaloids were tested against two strains of *P. falciparum*, a chloroquine-resistant strain with an IC₅₀ of 445 nM and a chloroquine-sensitive strain with an IC₅₀ of 79 nM. The antiplasmodial activity of the alkaloids against both strains was evaluated after two time periods of incubation of the parasite culture, namely 24 and 72 hours (Table 1).



Alkaloid	R	R ¹	R ²	Chloroquine-resistant (445 nM) IC ₅₀ μM ± sd		Chloroquine-sensitive (79 nM) IC ₅₀ μM ± sd	
				24 h	72 h	24 h	72 h
i *	H	H	H	16.3 ± 2.9	3.8 ± 0.7	11.0 ± 1.7	4.6 ± 0.5
ii	H	H	OMe	19.5 ± 7.2	3.2 ± 0.9	13.1	5.1
iii	CHO	H	H	16.1 ± 3.0	5.6 ± 0.7	22.0 ± 7.1	5.9 ± 1.5
iv	CHO	OMe	H	11.8 ± 0.9	4.1 ± 0.6	9.3 ± 2.4	6.6 ± 1.4
v	C(O)CH ₃	OMe	H	22.3 ± 11.6	5.6 ± 1.3	nd ^a	nd ^a
vi ^b	C(O)CH ₃	OH	H	15.1 ± 1.9	12.2 ± 5.2	21.5 ± 6.5	20.3 ± 6.2
vii	C(O)CH ₃	H	H	7.4	6.2	34.0	15.4
viii	C ₂ H ₅ CO	OMe	H	15.4 ± 4.2	12.7 ± 4.2	27.2	8.7
ix	C ₂ H ₅ CO	H	H	17.7 ± 4.9	28.5 ± 13.0	40.8 ± 3.8	22.6 ± 2.5
x	C ₂ H ₅ CO	OMe	H	52.8 ± 7.1	25.6 ± 2.7	113.1	55.3
xi	C ₂ H ₅ CO	OMe	OMe	90.4 ± 43.7	59.2 ± 5.4	44.4	28.0
xii	C(O)CH ₃	OMe	H	149.7 ± 27.6	49.5 ± 3.7	169.3	57.3

^aNot determined; ^bHemisynthetic alkaloid.

Table 1: Antimalarial activity of some *Aspidosperma* alkaloids.

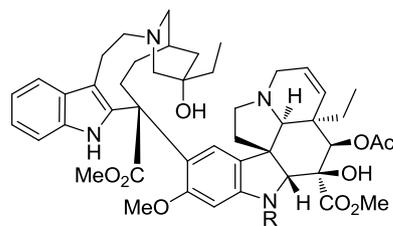
* The authors name both alkaloids **i** and **v** as aspidospermine, however the structural substitutions actually denote **i** as aspidospermidine and **v** as aspidospermine. We have taken the nomenclature to be at error and herein refer to alkaloid **i** as aspidospermidine.

The IC₅₀ data shows two distinct groups, a more active group (alkaloids **i–v**, **vii** and **viii**) with IC₅₀ values in the range of 3.2–15.4 μM for both strains after 72 hours, and a less active group (alkaloids **ix–xii**) with IC₅₀ values in the range of 22.6–59.2 μM after 72 hours. Aspidospermidine **6** is within the more active group (alkaloid **i**), with an IC₅₀ of 3.8±0.7 μM after 72 hours with the chloroquine-resistant strain and an IC₅₀ of 4.6±0.5 μM with the chloroquine-sensitive strain.

There are definite structural similarities within each of the two groups, the more active group all possessing a free ethyl side chain, compared with the less active group all possessing a tetrahydrofuran ring in the same position. The members of the less active group also contain a phenolic moiety. In order to assess whether the tetrahydrofuran ring or the phenol is responsible for the detrimental effect on antimalarial activity the authors synthesised demethylaspidospermine (alkaloid **vi**). This alkaloid features a free ethyl side chain and a phenol and as such exhibited an increased activity, an IC₅₀ of 12.2±5.2 μM. Thus, it was concluded by the authors that the presence of a tetrahydrofuran ring was the likely cause of the decrease in antiplasmodial activity of the alkaloids.

As part of the same study the combinatory antimalarial activities of two alkaloids (alkaloids **iii** and **v**) were determined by the addition of growing sub-inhibitory dilutions of chloroquine to sub-inhibitory dilutions of the alkaloid. After 24 and 72 hours the growth inhibition was then analysed. It was established that the alkaloids had a chloroquine-potentiating effect. Therefore, the authors concluded that *Aspidosperma* alkaloids may represent 'potential agents for reversal of resistance to chloroquine'.¹²

Whilst aspidofractinine **7** is as yet devoid of any reported bioactivity, other *Aspidosperma* alkaloids have found success as therapeutic agents, most notably the dimeric alkaloids vinblastine **39** and vincristine **40** (Figure 5).¹³ They were isolated from a Madagascan periwinkle, *Catharanthus Roseus*, of the Apocynaceae family, a small shrub now common to the tropics.¹ Vinblastine **39** and vincristine **40** are both bisindole alkaloids made up of two monoterpenoid indole alkaloids of the *Aspidosperma* genera and both have been utilised in cancer chemotherapy.



Vinblastine **39**, R = Me
 Vincristine **40**, R = CHO

Figure 5

Whilst these two dimeric alkaloids exhibit little structural difference, the types of cancer that respond to each of them vary significantly. Vinblastine **39** is used to treat Hodgkin's disease, which affects the lymph glands, liver and spleen. By contrast, vincristine **40** can be used against a much wider range of cancers, including breast and cervical cancer, small cell lung cancer and lymphomas. However, it is particularly used against childhood leukaemia, resulting in high rates of remission. It is evident from the differences in these target areas that vincristine **40** boasts enhanced antitumour activity over vinblastine **39**; however, this comes at a price as it is also more neurotoxic. It is interesting to note that the increased importance of vincristine over vinblastine is not reflected in the plant, as *Catharanthus Roseus* actually produces a larger quantity of vinblastine **39**. Both alkaloids are injected into the patient and are usually used in combination with other anticancer drugs. They work by inhibiting cell mitosis by binding to the protein tubulin in the mitotic spindle; this prevents polymerisation into microtubules and stops cell mitosis.¹

However, only very small amounts of vincristine **40** and vinblastine **39** are present in plants, with more than 500 Kg of *Catharanthus Roseus* needed to acquire just 1 g of vincristine **40**, a meagre 0.0002% yield! This is the lowest yield of any medicinally important alkaloid isolated for commercial use. Not only this, but extraction is difficult, expensive and extremely wasteful of the raw material. Synthetic routes to vincristine **40** and vinblastine **39** and their monomer alkaloid units are therefore of great significance.

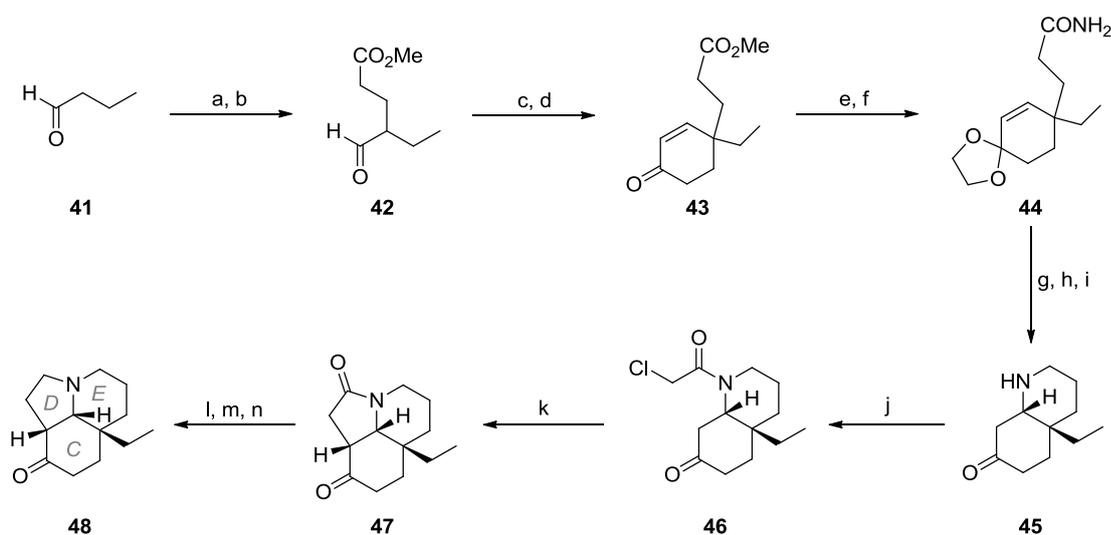
It is clear that not only does aspidospermidine **6** represent a biologically important compound with respect to its antimalarial activity but that, in general, the

development of synthetic routes towards the *Aspidosperma* alkaloids is a challenging and important goal for organic synthesis. Aspidospermidine **6**, being the least functionalised *Aspidosperma* alkaloid, has received the greatest attention from the synthetic community.

1.5 Previous Syntheses of Aspidospermidine

The first synthetic forays within this family were the pioneering syntheses of aspidospermine **14** and quebrachamine **8** by Stork and Dolfini in 1963, whose Fischer indole approach to the pentacyclic core of these alkaloids influenced syntheses of members of the family for many years.¹⁴

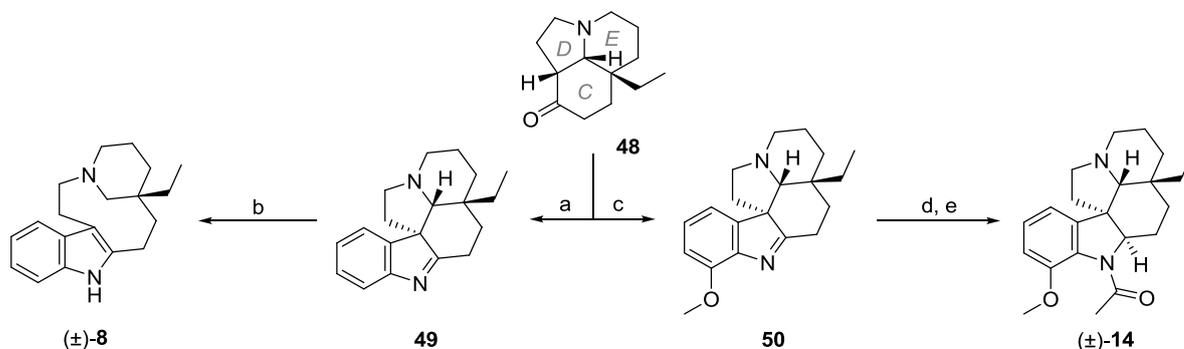
The synthesis of key intermediate **48** began with a sequence of pyrrolidine enamine alkylations of butyraldehyde **41**, firstly with methyl acrylate and then with methyl vinyl ketone. The resultant cyclohexenone **43** was then protected as the acetal and treated with aqueous ammonia to afford amide **44**. Reduction with LiAlH_4 and successive acid and base treatment then installed the *C* and *E* rings to give **45**. Acetylation with chloroacetyl chloride and subsequent cyclisation then installed the *D* ring, with a final ketone protection, reduction and deprotection sequence giving the desired tricyclic ketone **48** (Scheme 6).



a) Pyrrolidine, methyl acrylate; b) aq. AcOH, RT, 67% over two steps; c) pyrrolidine, methyl vinyl ketone; d) aq. AcOH, Δ , 48% over two steps; e) H^+ , $(\text{CH}_2\text{OH})_2$; f) aq. NH_3 , RT; g) LiAlH_4 ; h) H_3O^+ ; i) HO^- ; j) chloroacetyl chloride; k) KOtBu , benzene; l) H^+ , $(\text{CH}_2\text{OH})_2$; m) LiAlH_4 ; n) H_3O^+ .

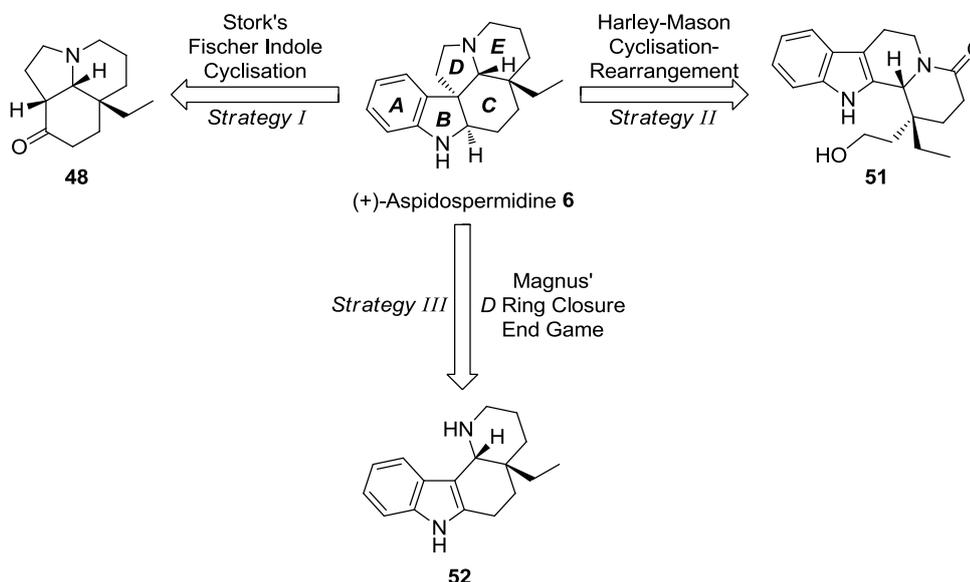
Scheme 6: Stork and Dolfini's key intermediate.

Fischer indole cyclisation of tricyclic ketone **48** with *o*-methoxyphenylhydrazine and phenylhydrazine installed the *ABCDE* ring systems of aspidospermine **14** and quebrachamine **8** respectively. Reduction of indolenines **49** and **50** then afforded the natural products aspidospermine **14** and quebrachamine **8** (Scheme 7).



Scheme 7: Stork and Dolfini's endgame for aspidospermine **14** and quebrachamine **8**.

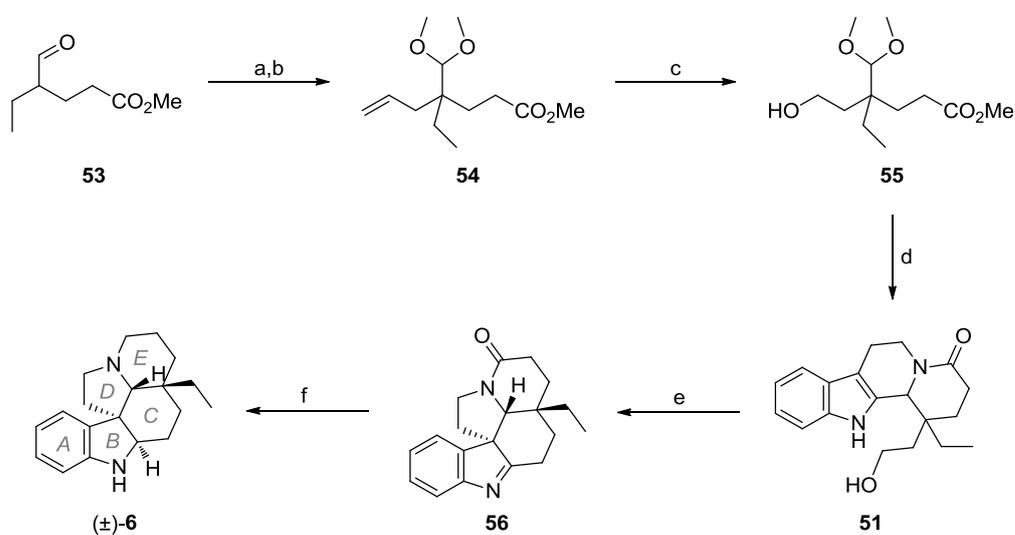
Over the following four decades aspidospermidine **6** has been the focus of over twenty total syntheses which can be classified according to their disconnection approaches. The majority of these syntheses follow one of three synthetic strategies (Scheme 8).



Scheme 8: Approaches to the synthesis of aspidospermidine **XX**.

The strategy based on the Fischer indole cyclisation approach is referred to herein as strategy I (Scheme 8). By contrast, strategy II uses a cyclisation-rearrangement sequence to install the *CDE* rings. This approach was first demonstrated by

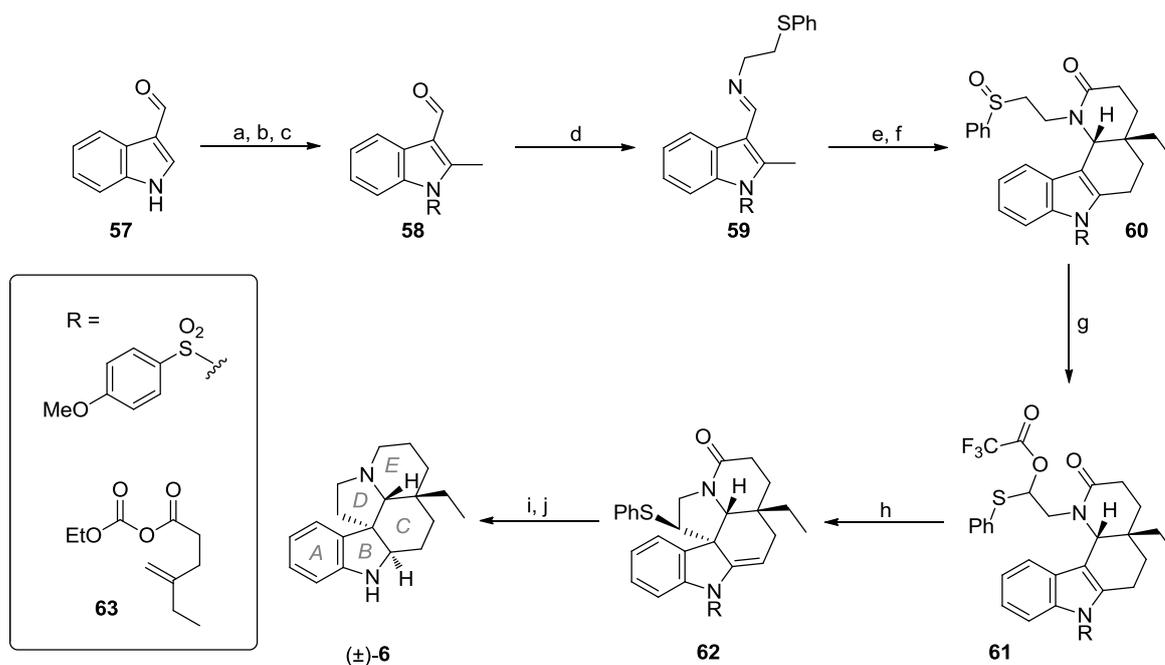
Harley-Mason *et al.* in 1967, whereby dimethyl acetal **55** underwent cyclisation with tryptamine to form tetracycle **51**.¹⁵ Treatment with acid then induced a rearrangement, presumed to proceed *via* the carbocation resulting from loss of the hydroxyl moiety. Reduction with LiAlH_4 then completed the synthesis of aspidospermidine **6** in an overall yield of 20–25% based on tryptamine (Scheme 9). This approach has subsequently been used by a number of groups to complete asymmetric total syntheses of the natural and unnatural enantiomers of aspidospermidine **6**, setting the stereochemistry at the quaternary centre using cyclic analogues akin to **55**.



a) Pyrrolidine, allyl bromide; b) trimethyl orthoformate; c) O_3 then NaBH_4 ; d) tryptamine, boiling AcOH ; e) 40% H_2SO_4 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 100 °C; f) LiAlH_4 .

Scheme 9: Harley-Mason's approach.

The final strategy, strategy III, is based upon the late installation of the *D* ring. Magnus and co-workers were the first to exemplify this approach in 1982, using a Pummerer reaction of sulfoxide **60** followed by heating in chlorobenzene to give the desired pentacycle **62** in 81% over the two steps (Scheme 10).¹⁶ Treatment with Raney[®] nickel and reduction with LiAlH_4 afforded aspidospermidine **6** in 11.7% overall yield from aldehyde **58**.



a) NaH, glyme, imidazole, 4-methoxybenzenesulfonyl chloride, Δ , 2 h, 70%; b) *t*BuNH₂, DCM, Δ , 1 h; c) *n*BuLi, THF, MeI, –78 °C–RT, 16 h, 43% over two steps; d) 2-(thiophenyl)ethylamine, 100%; e) **63**, chlorobenzene, 140 °C, 2.75 h, 33%; f) *m*CPBA, DCM, NaHCO₃, 0 °C, 97%; g) trifluoroacetic anhydride, DCM, 0 °C, 10 min; h) chlorobenzene, 130 °C, 2.5 h, 81% over two steps; i) Raney[®] nickel, EtOH, RT, 1 h, 81%; j) LiAlH₄, THF, RT, 48 h, 54%.

Scheme 10: Magnus' approach to aspidospermidine **6**.

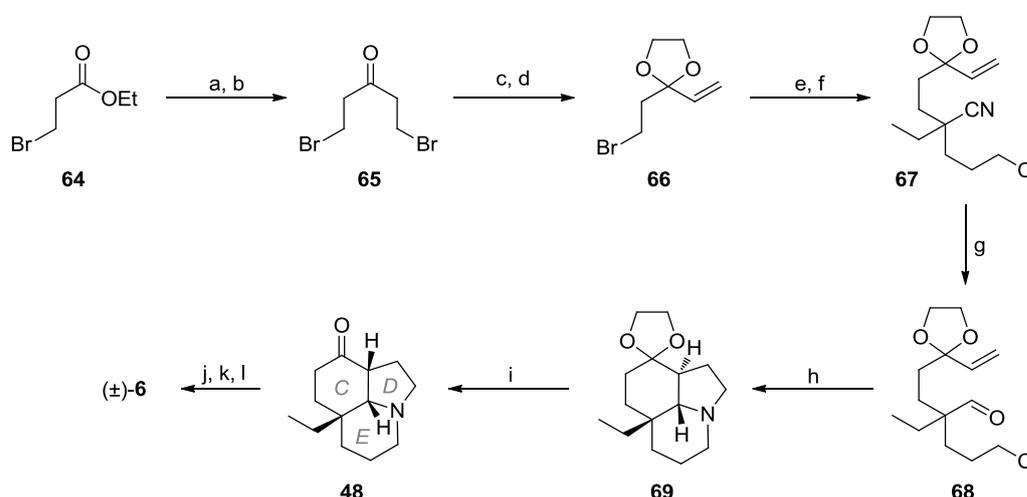
Magnus' approach paved the way for a number of syntheses using the same *D* ring installation strategy, using alternative methods to construct the prerequisite *ABCE* ring system. A number of alternative methods to install the *D* ring have since been published; however common to all is Magnus' original tactic of installing the *ABCE* ring system first, with construction of the *D* ring in the final stages of the syntheses.

A small number of syntheses do not fall into these three strategic groups. For a full review of all syntheses of aspidospermidine **6** from isolation to 2007 see S. Whiting PhD thesis.¹⁷ The following literature review focuses on the total syntheses published post 2007.

There have been 7 total syntheses since 2007, with all save one conforming to one of the disconnection strategies outlined previously. The majority build on Stork and Dolfini's approach, focussing on the synthesis of ketone **48**. In 2007, Coldham *et al.* utilised a cyclisation / cycloaddition cascade to synthesis ketone **48** in just

nine steps from commercially available ethyl 3-bromopropionate **64**, a significant improvement on Stork's original 14 step route (Scheme 11).¹⁸

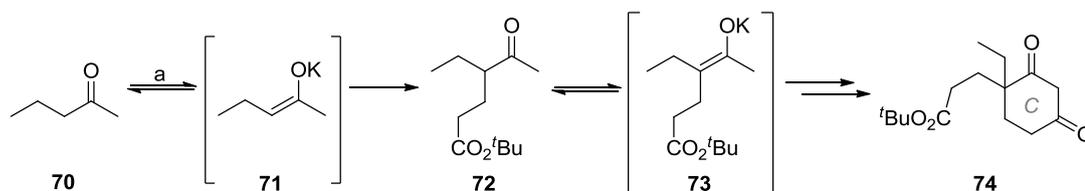
Ethyl 3-bromopropionate **64** was transformed in two steps to dibromoketone **65** via a known procedure, with protection followed by elimination then affording alkene **66**.¹⁹ Two alkylations, firstly with butyronitrile and then with 1-bromo-3-chloropropane proceeded in excellent yields in afford nitrile **67**. Reduction of the nitrile to the aldehyde then gave the precursor to the key step, **68**. The cyclisation / cycloaddition cascade was promoted with CSA in the presence of glycine. Formation of the imine and cyclisation to the tethered alkyl halide gave the required azomethine ylide after decarboxylation. Intramolecular dipolar cycloaddition then completed the sequence to afford the desired tricycle **69** as a single diastereoisomer in excellent yield (79%) when considering that in a single step four bonds, three rings and three new stereocentres have been installed. The synthesis of ketone **48** was then completed by the concomitant acetal deprotection and epimerisation α to the ketone to afford the *cis* / *cis* configuration. The synthesis was concluded following Stork and Dolfini's protocol in 42% yield over three steps (*viz.* **48**→**6**).



a) EtMgBr, Ti(OⁱPr)₄, Et₂O; b) NBS, CCl₄, 82% over two steps; c) (CH₂OH)₂, *p*TSA, PhH, Δ , 6 h, 86%; d) KO^tBu, THF / PhMe (1:1), 0 °C–RT, 1 h, 82%; e) butyronitrile, LDA, THF, then **66**, –78 °C, 1 h, 88%; f) LDA, THF, then 1-bromo-3-chloropropane, –78 °C, 1 h, 96%; g) DIBALH, DCM, –78 °C, oxalic acid, 82%; h) glycine, CSA, PhMe, Δ , 18 h, 79%; i) HCl, THF, Δ , 1 h, 88%; j) PhNHNH₂, PhH, Δ , 2.5 h; k) AcOH, 95 °C, 2.5 h; l) LiAlH₄, THF, Δ , 13 h, 42% over three steps.

Scheme 11: Coldham's total synthesis of aspidospermidine **6**.

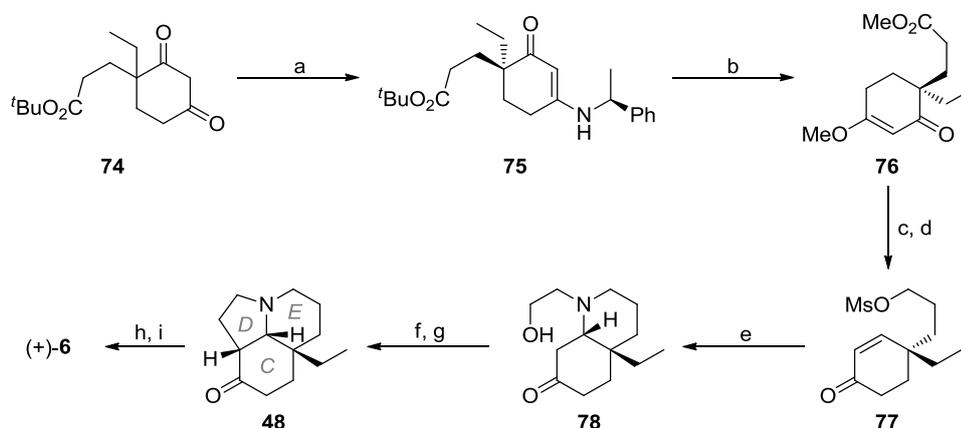
In another example of utilising a cascade process to synthesise ketone **48**, Ishikawa and co-workers used a double Michael-Claisen reaction sequence to install ring *C* and complete the enantioselective synthesis of (+)-aspidospermidine **6**.²⁰ Thus, 2-pentanone **70** was treated with excess *t*butyl acrylate and base to form thermodynamic enolates **71** and **73** which underwent double Michael addition and subsequent Claisen cyclisation to form **74** (Scheme 12).



a) *t*Butyl acrylate (4 equiv.), KO*t*Bu (2 equiv.), *t*BuOH / THF (1:1), 0 °C, 3 h.

Scheme 12: Ishikawa's double Michael-Claisen reaction sequence.

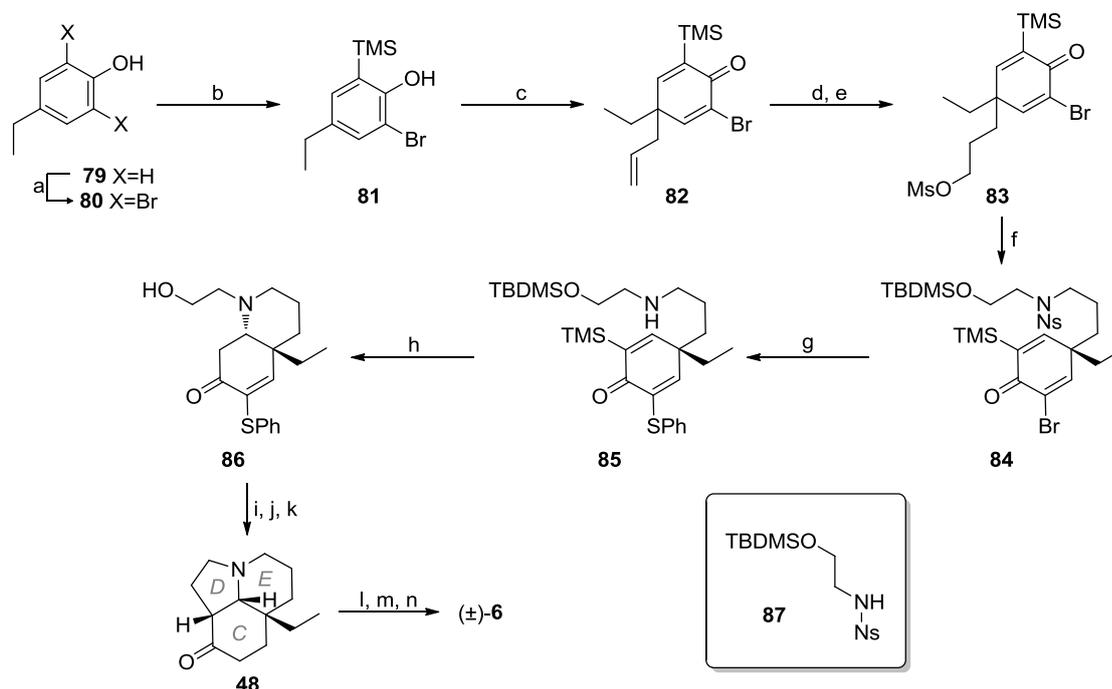
A single step transformed 2-pentanone **70** into dione **74**, forming three new bonds and one new stereocentre. The authors designed an optical resolution of dione **74** via Lewis acid-catalysed enamine formation with (*S*)-1-phenylethylamine. Thus, the desired diastereoisomer was separated and transformed into enol ether **76**, with DIBALH reduction, mesylation and subsequent S_N2 reaction with ethanolamine followed by an intramolecular Michael addition affording the *CE* ring system **78**. Chlorination of **78** then set up an intramolecular alkylation to achieve the enantioselective synthesis of ketone **48**. The transformation to (+)-aspidospermidine **6** was then completed in the usual manner (*viz.* **48**→**6**) in an overall yield of 5.2 % from dione **74** (Scheme 13).



a) Zn(OTf)₂, (*S*)-1-phenylethylamine, MeCN, 50 °C, 99%; b) NaH, ClCO₂Me, THF, then HCl, MeOH, 75%; c) DIBALH, PhMe, -78 °C, 4 h; d) MsCl, Et₃N, THF, RT, 10 h, 59% over two steps; e) ethanolamine, MeOH, RT, 2 h; f) MsCl, Et₃N, THF, RT, 20 h; g) NaH, THF, RT, 3 h, 46% over three steps; h) PhNHNH₂, AcOH; i) NaBH₄, EtOH, 51% over two steps.

Scheme 13: Ishikawa's enantioselective synthesis of (+)-aspidospermidine **6**.

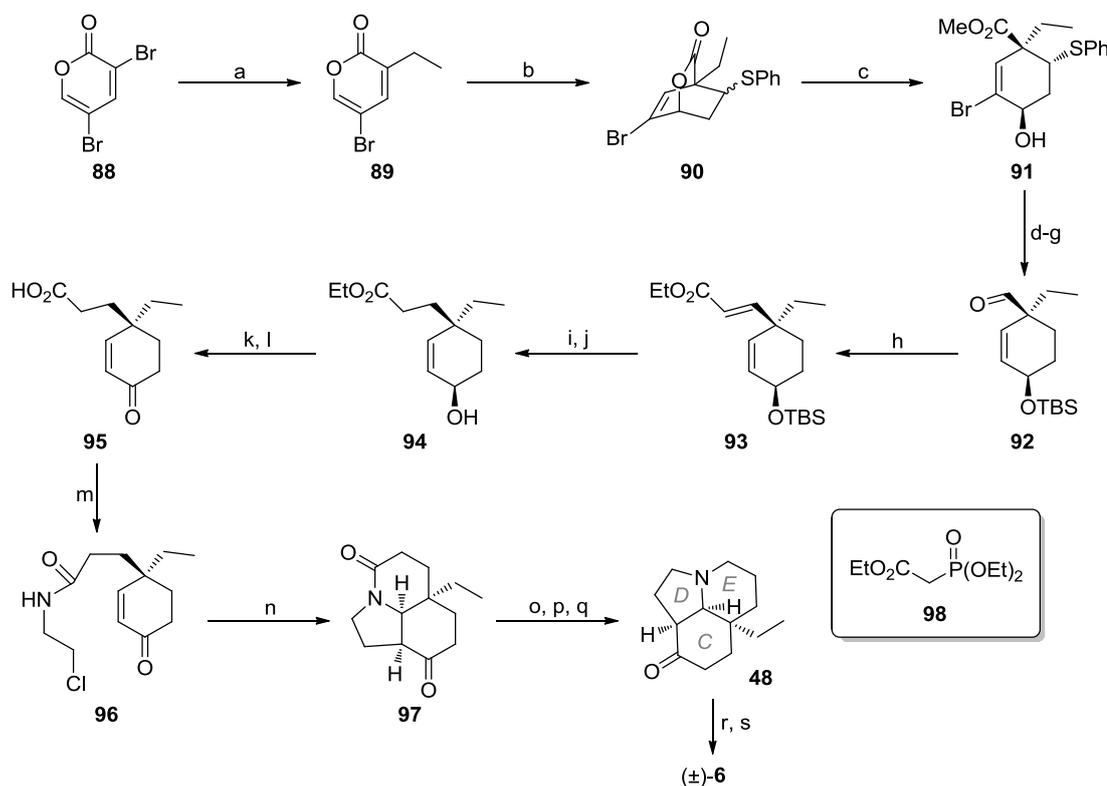
In 2009 Canesi *et al.* reported a total synthesis of aspidospermidine **6** via ketone **48** using an oxidative Hosomi-Sakurai reaction.²¹ Phenol **79** was appropriately substituted to direct the allyl addition in the subsequent key step. Thus, 4-ethylphenol **79** was brominated to afford the *ortho*-dibrominated species **80** which when silylated afforded phenol **81** (Scheme 14). This was then subjected to the oxidative Hosomi-Sakurai conditions to give 4-disubstituted dienone **82** exclusively. Hydroboration followed by mesylation gave dienone **83** which was treated with Fukuyama's sulfonamide **87** in an S_N2 fashion. Deprotection of the nitrogen moiety also led to concomitant addition of thiophenol to afford **85**. Further deprotection of the TBDMS group with TBAF gave the free alcohol as well as cyclisation of the free amine to form the *C* and *E* rings via a Michael addition in a manner akin to Ishikawa's synthesis. The similarity of these approaches then extended to the *D* ring closure, which was achieved by chlorination and base-induced alkylation to afford the desired tricycle, in this case in 84% yield. Desulfurisation with Raney[®] nickel then completed the synthesis of ketone **48**, which was transformed into aspidospermidine **6** in 43% over three steps.



a) Br₂, DCM, 0 °C–RT, 12 h, 99%; b) HMDS, THF, Δ, 45 min, then *n*BuLi, THF, –78 °C–RT, 12 h, 87%; c) PhI(OAc)₂, allyltrimethylsilane, (CF₃)₂CHOH, 0 °C, 15 min, 56%; d) 9-BBN, THF, RT, 2 h, then H₂O₂, K₂CO₃, 0 °C, 5 min, 72%; e) MsCl, lutidine, DCM, RT, 2 h, 97%; f) NaH, **87**, DMF, RT–65 °C, 12 h, 89%; g) K₂CO₃, PhSH, MeCN, RT, 12 h, 85%; h) TBAF, THF, RT, 5 h, 87%; i) MsCl, Et₃N, DCM, RT, 2 h, 79%; j) KO^tBu, PhMe, RT, 12 h, 84%; k) Raney[®] nickel, EtOH, RT, 1 h, 85%; l) PhNHNH₂, PhH, 80 °C, 2 h; m) AcOH, 118 °C, 4 h; n) LiAlH₄, THF, RT, 30 min, 43% over three steps.

Scheme 14: Canesi and co-worker's synthesis of (±)-aspidospermidine **6**.

The most recent example of the synthesis of aspidospermidine **6** via Stork's ketone **48** is that of Cho *et al.*, reported in 2010, in which a tandem conjugate addition-alkylation of cyclohexenone **96** was used to install the *D* and *E* rings in a single step (Scheme 15).²² The pendant ethyl group was first installed on 3,5-dibromo-2-pyrone **88** in a palladium-catalysed coupling to afford diene **89** (Scheme 15). Diels-Alder reaction with phenyl vinyl sulfide afforded bicyclic lactone **90** in good yield and as a mixture of *exo* / *endo* isomers, both of which were progressed as the thiophenyl group is removed later in the synthesis. Lactone opening then gave the appropriately functionalised *C* ring, **91**, in an excellent yield. A series of functional group manipulations afforded aldehyde **92**, which was subjected to Horner-Wadsworth-Emmons olefination with stabilised phosphonate **98** to give (*E*)-**93**. A series of functional group manipulations afforded aldehyde **92**, which was subjected to Horner-Wadsworth-Emmons olefination with stabilised phosphonate **98** to give (*E*)-**93**.

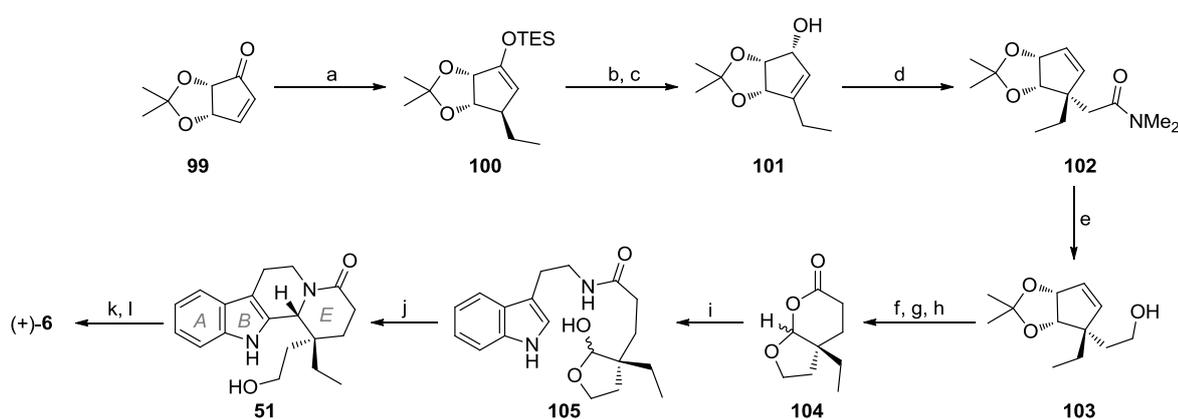


a) $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Et}_3\text{Al-Me}_2\text{N}(\text{CH}_2)_2\text{OH}$, PhMe, 100 °C, 1 h, 55%; b) phenyl vinyl sulfide, PhMe, 100 °C, 68%; c) NaOMe, MeOH, 96%; d) TBSCl, 96%; e) DIBALH, PhMe, -78 °C, 1 h, 88%; f) Raney[®] nickel, EtOH, 30 min, 80%; g) DMP, DCM, 87%; h) NaH, **98**, DME, 85%; i) NiCl_2 , NaBH₄; j) TBAF, Et₃N, 65% over two steps; k) DMP, DCM, 87%; l) LiOH, THF / H₂O, 98%; m) $(\text{COCl})_2$, then $\text{Cl}(\text{CH}_2)_2\text{NH}_2$, Et₃N, DCM, 63%; n) NaH, DMF, 0 °C, 60%; o) $(\text{CH}_2\text{OH})_2$; p) $\text{BH}_3\cdot\text{THF}$, THF; q) aq. HCl, THF, 62% over three steps; r) PhNBocNH₂, pTSA, EtOH; s) LiAlH₄, THF, Δ , 45% over two steps.

Scheme 15: Cho's synthesis of (\pm)-aspidospermidine **6**.

Selective reduction of the eneoate alkene, TBS deprotection, oxidation and ester saponification then gave the required cyclohexenone moiety **95** for the key conjugate addition-alkylation. The amine tether was introduced *via* the acid chloride (*viz.* **95**→**96**). The conjugate addition-alkylation was then promoted by treatment with NaH in DMF to install the *D* and *E* rings in a yield of 60%. The synthesis of ketone **48** was then completed by selective reduction of the amide carbonyl in an acetal protection-amide reduction-deprotection sequence. Fischer indole cyclisation using the Boc-protected hydrazine in the presence of *p*TSA, a deviation from Stork and Dolfini's original protocol, afforded aspidospermidine **6** in 45% yield from ketone **48**.

Another common approach towards aspidospermidine **6** is the cyclisation-rearrangement sequence of Harley-Mason *et al.* Two recent syntheses have used this approach as their basis, those of Iwabuchi *et al.* and Tomioka *et al.*, both reported in 2009.^{23,24} Iwabuchi and co-workers utilised an acetonide moiety as a directing group to induce the enantioselective synthesis of (+)-aspidospermidine **6** from enone **99**, for which they had previously reported a synthesis *via* a chemoenzymatic process.²³ Thus, the necessary pendant ethyl group was installed *via* conjugate addition and *in situ* trapping as silyl enol ether **100**. Oxidation followed by selective 1,2-reduction afforded allylic alcohol **101** as the only product (Scheme 16).

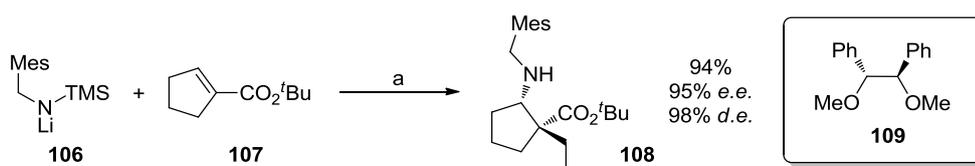


a) EtMgBr, CuI, HMPA, TESCl, THF, $-78\text{ }^{\circ}\text{C}$ – $-40\text{ }^{\circ}\text{C}$; b) Pd(OAc)₂, O₂, DMSO, 50 °C, 9 h, 89% over two steps; c) NaBH₄, CeCl₃·7H₂O, MeOH, $-40\text{ }^{\circ}\text{C}$, 90%; d) Me₂NC(OMe)₂Me, Ph₂O, Δ , 2 h, 86%; e) LiEt₃BH, THF, 0 °C, 100%; f) H₂, 10% Pd / C, EtOAc, 100%; g) HIO₄·2H₂O, dioxane / H₂O (1:1), RT; h) TPAP, NMO, DCM, RT, 94% over two steps; i) tryptamine, PhMe, Δ , 2 h; j) cat. H₂SO₄, PhOH, 50 °C, 1 h, 70% over two steps; k) 40% aq. H₂SO₄, 110 °C, 1.5 h; l) LiAlH₄, THF, Δ , 2 h, 51% over two steps.

Scheme 16: Iwabuchi's synthesis of (+)-aspidospermidine **6**.

Acetamide **102** was then formed using an Eschenmoser rearrangement. When treated with LiEt_3BH this material gave the hydroxyethyl **103** required for a Harley-Mason rearrangement. The directing / protecting acetonide group was then removed *via* hydrolysis, giving a 1,2-diol which, when oxidatively cleaved, formed the resultant dialdehyde which in turn cyclised directly to the lactol. Oxidation then yielded lactone **104**, an intermediate common to both Iwabuchi and Tomioka's syntheses. Amide formation with tryptamine followed by Pictet-Spengler cyclisation afforded tetracycle **51** in good yield over two steps. The synthesis was completed using Harley-Mason's protocol, namely the acid-induced rearrangement of **51** to form the pentacyclic core followed by reduction of the resultant indolenine to give (+)-aspidospermidine **6** in 51% yield.

Tomioka *et al.* published their own enantioselective synthesis of (-)-aspidospermidine **6** within months of Iwabuchi. They also targeted bicyclic lactone intermediate **104** and used the same modified Harley-Mason end game.²⁴ A tandem asymmetric conjugate addition-alkylation strategy was the key transformation of their enantioselective synthesis (Scheme 17). Thus, the conjugate addition of lithium amide **106** to cyclopentene **107** and subsequent *in situ* alkylation with ethyl iodide produced two contiguous stereocentres and new C-N and C-C bonds in one pot in an impressive yield and *e.e.* (94%, 95% *e.e.*; 85%, >99% *e.e.* after recrystallisation of its hydrochloride salt).

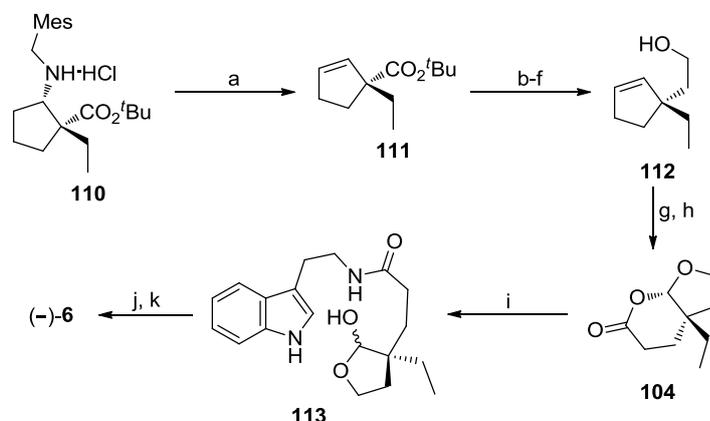


a) **109**, PhMe, -78°C , 1.5 h, then -60°C , 1.5 h, then EtI, HMPA, THF, -40°C , 1 h.

Scheme 17: Tomioka's tandem asymmetric conjugate addition-alkylation protocol.

The hydrochloride salt of cyclopentane **108** was transformed into alkene **111** *via* a sequence of methylation, *N*-oxidation and Cope elimination (Scheme 18). Ester reduction followed by oxidation to the corresponding aldehyde set up a Wittig reaction to lengthen the carbon chain. Hydrolysis of the resultant enol ether to the aldehyde and subsequent reduction with NaBH_4 afforded alcohol **112**. Oxidative cleavage of the cyclopentene initially gave a lactol which was oxidised to lactone **104** in 85% yield over two steps. Lactone opening with tryptamine then formed

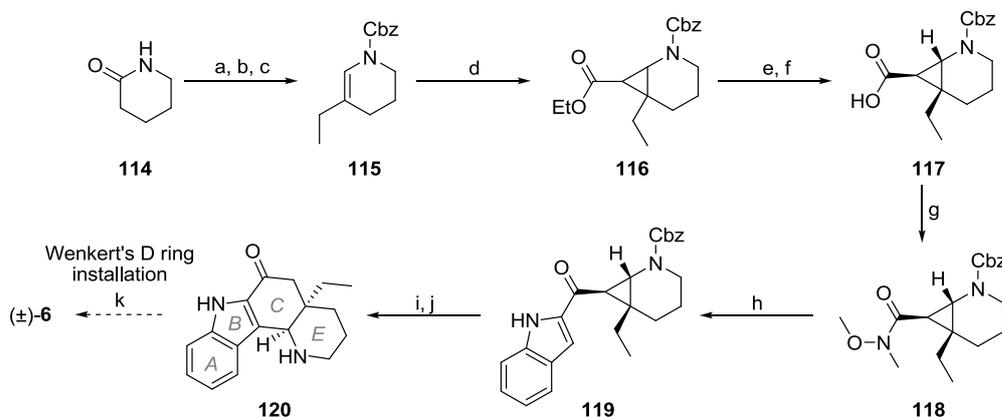
amide **113**, with a modified version of Harley-Mason's strategy completing the enantioselective synthesis of (-)-aspidospermidine **6** in 37% yield for the cyclisation-rearrangement and reduction steps.



a) NaBH_3CN , HCHO , aq. MeCN , then $m\text{CPBA}$, $t\text{BuOH}$, then Al_2O_3 , 65%; b) LiAlH_4 , Et_2O , 97%; c) TPAP, NMO, 4Å MS, DCM; d) $\text{Ph}_3\text{P}=\text{CH}(\text{OMe})$, THF; e) HCl (5 M), Et_2O ; f) NaBH_4 , MeOH , 79% over five steps; g) OsO_4 , NMO, aq. acetone, then NaIO_4 ; h) TPAP, NMO, 4Å MS, DCM, 85% over two steps; i) tryptamine, $n\text{BuOH}$, Δ , 2 h, 75%; j) 40% H_2SO_4 , Δ , 2.5 h; k) LiAlH_4 , THF, Δ , 1.5 h, 37% over two steps.

Scheme 18: Tomioka's synthesis of (-)-aspidospermidine **6**.

The most recent synthesis to be reported is that of Waser *et al.*²⁵ This formal synthesis of (\pm)-aspidospermidine **6** is unique amongst those discussed herein, not falling into any of the classic strategies previously outlined (*vide supra* Scheme 8). The synthesis features a catalytic homo-Nazarov cyclisation of aminocyclopropane **119** as the key step. This gave access to **120**, a late intermediate in Wenkert and Hudlický's 1988 synthesis of aspidospermidine **6** (Scheme 19).²⁶



a) $n\text{BuLi}$, CbzCl , EtI , THF, -78°C , 67%; b) NaBH_4 , MeOH ; c) H_2SO_4 , THF, 93% over two steps; d) $(\text{CuOTf})\cdot\text{PhMe}$, $\text{N}_2\text{CHCO}_2\text{Et}$, DCM, 76% *d.r.* 1:1; e) $\text{BF}_3\cdot\text{Et}_2\text{O}$, DCM; f) NaOH , H_2O / THF / EtOH (1:1:3), 91% over two steps; g) DMTMM, NMM, THF, $\text{MeNHOMe}\cdot\text{HCl}$, 93%; h) indole-1-carboxylic acid, $t\text{BuLi}$, LiCl , THF, 67%; i) $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$, MeCN ; j) H_2 , Pd / C , 100%; k) $(\text{CH}_2\text{Br})_2$, K_2CO_3 , Δ .

Scheme 19: Waser's synthesis of (\pm)-aspidospermidine **6**.

The approach began with δ -valerolactam **114**, which underwent protection as the *N*-Cbz product and the ethyl group installation in a single step (Scheme 19). Reduction with NaBH_4 followed by elimination then afforded dehydropiperidine **115**. Cyclopropanation with ethyl diazoacetate and catalytic copper triflate afforded aminocyclopropane **116** as a 1:1 mixture of diastereoisomers, which were equilibrated to the *exo* isomer when treated with boron trifluoride etherate and saponified to give **117**. Transformation into the Weinreb amide **118** and coupling to indole-1-carboxylic acid in quantitative yield afforded the homo-Nazarov precursor **119**, with deprotection of the *N*-carboxy indole upon work up (no yield was reported). Treatment with catalytic $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ induced the key transformation with removal of the Cbz group then completing the formal total synthesis.

1.6 Previous Syntheses of Aspidofractinine

In stark contrast to the interest in aspidospermidine **6** as a synthetic target, aspidofractinine **7** has been the subject of only six reported total syntheses to date, two of which originated from the same group.^{9,27,28,30,32,33} The syntheses can be broadly categorised into two approaches based on the mode of *F* ring formation, namely a Diels-Alder reaction or acetyl cyclisation (Figure 6).

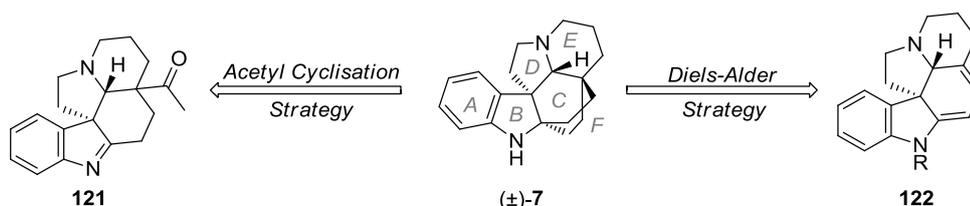
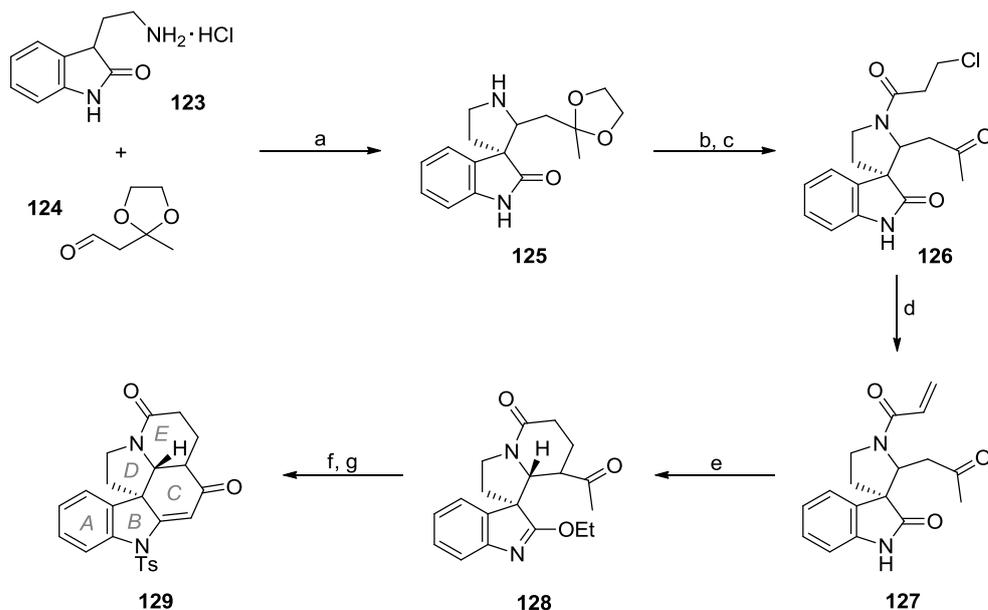


Figure 6: *F* ring installation strategies.

Ban and co-workers were the first to achieve a successful total synthesis in 1976, following this in 1986 with a second route featuring a common intermediate and different end game.^{27,28} Their earlier synthesis utilised a Diels-Alder reaction with nitroethylene to install the *F* ring, whilst the second synthesis, published one decade later, used the acid-promoted cyclisation of an acetyl to an indolenine. Both routes proceed *via* intermediate **129** (Scheme 20).²⁹ Condensation of 2-hydroxytryptamine **123** with acetal **124** afforded oxindole **125**, which was then acylated with β -chloropropionyl chloride to give **126** after acetal hydrolysis.

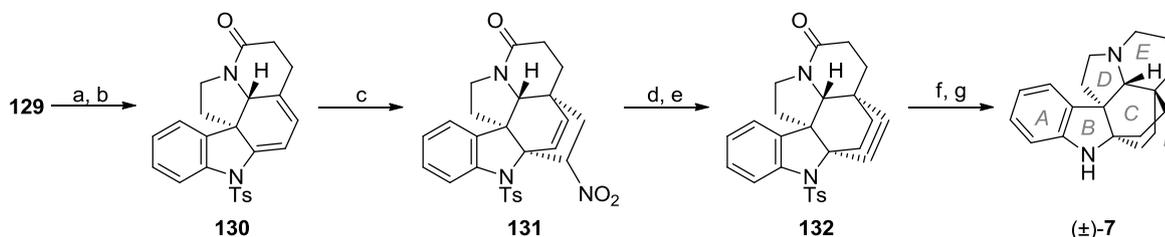


a) Basic aq. EtOH, 63%; b) β -chloropropionyl chloride; c) H_3O^+ ; d) NaOH, EtOH / DCM, RT, 89%; e) $\text{BF}_4^-\text{Et}_3\text{O}^+$, 1,2-dichloroethane, 65 °C, 20 h, 51%; f) NaH, DMSO, Δ , 60 h, 31–50%; g) TsCl, DCM.

Scheme 20: Synthesis of Ban's intermediate.²⁹

Base-induced elimination afforded Michael-acceptor **127**, which underwent addition when exposed to Lewis acid to afford tetracycle **128** in modest yield. Finally, deprotonation with NaH and vigorous heating facilitated C ring closure.

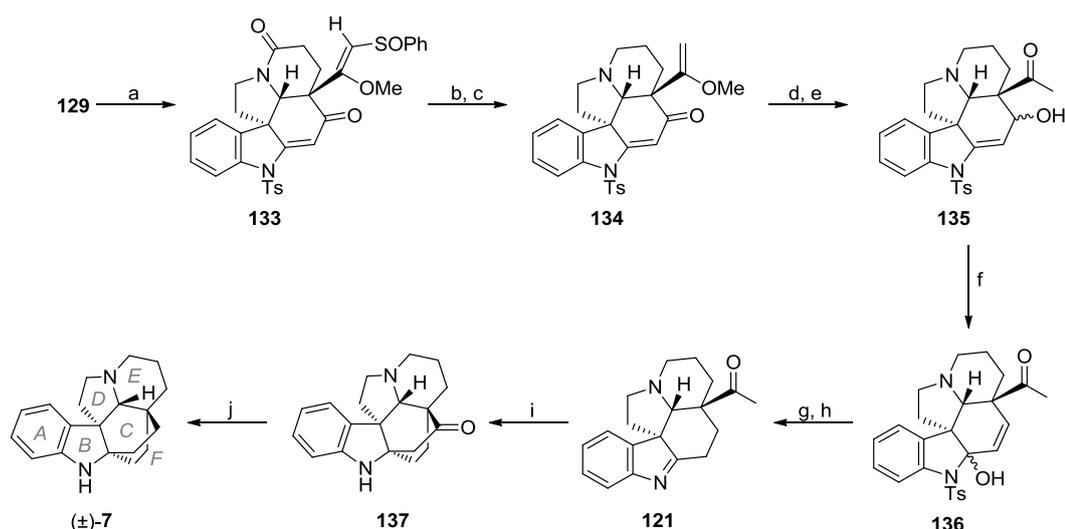
In their first approach Ban and co-workers set the scene for their key Diels-Alder reaction through reduction and dehydration of **129** to form diene **130**.²⁷ This smoothly underwent a Diels-Alder reaction with nitroethylene in DCM at room temperature in 80% yield (Scheme 21). A sequence of functional group manipulations then completed the first total synthesis of aspidofractinine **7** in 14 steps.



a) NaBH_4 , EtOH / THF (1:1), RT, 87%; b) anhydrous pyr., PBr_3 , PhH, RT, 74%; c) nitroethylene, DCM, RT, 12 h, 80%; d) H_2 (5.3 atm), PtO_2 , 90%; e) NaNO_2 , aq. AcOH, 55 °C, 5 h, 43%; f) LiAlH_4 , 1,2-dimethoxyethane, Δ , 3 h; g) H_2 , Pt, EtOAc, 100% over two steps.

Scheme 21: Ban's first total synthesis of aspidofractinine **7**.

The group's second generation approach was based on an acylation and acid-promoted cyclisation strategy to install the *F* ring starting with pentacycle **129** (Scheme 22).²⁸ Acylation was effected *via* Michael condensation with vinyl sulfoxide, which was followed by concomitant reduction to the sulfide and formation of the thiolactam using P_4S_{10} . Desulfurisation with Raney[®] nickel then produced enol ether **134**, reduction of which followed by hydrolysis afforded **135**. Attempted chlorination of alcohol **135** failed, instead giving isomeric alcohol **136**. However, hydrogenation followed by tosyl deprotection and concomitant indolenine formation gave the desired precursor for the *F* ring formation, **121**. Treatment with dilute HCl afforded the hexacycle smoothly in 90% yield, with reduction of the remaining ketone completing the synthesis of (\pm)-aspidofractinine **7** in 17 steps, a longer sequence than the original Diels-Alder approach (Scheme 22).

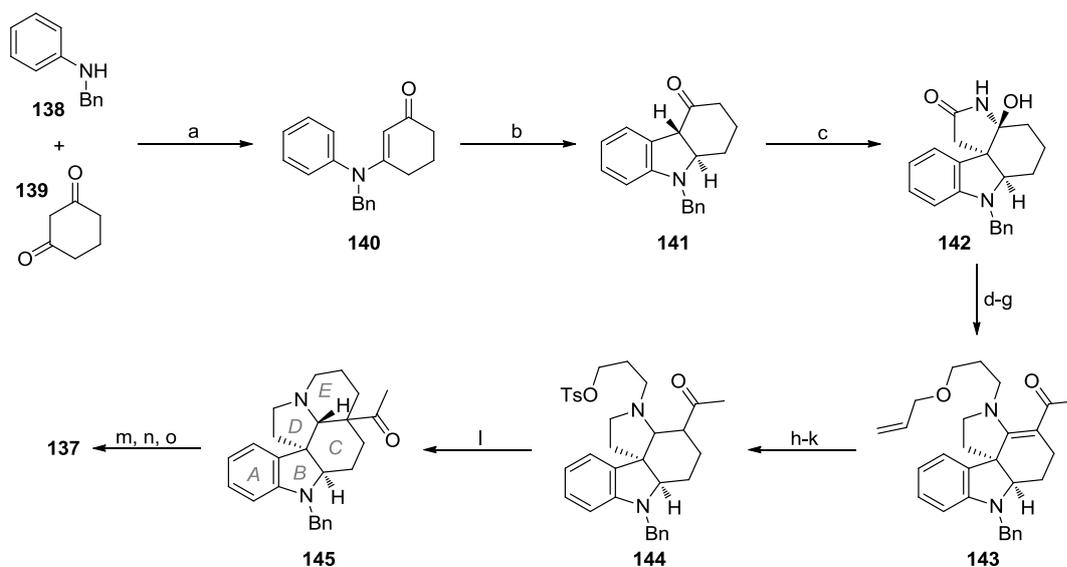


a) $LiN(TMS)_2$, $PhSOCH=C(Cl)OCH_3$, THF, $-50\text{ }^\circ\text{C}$, 60%; b) P_4S_{10} , THF, Δ , 78%; c) Raney[®] nickel, THF, Δ , 67%; d) $LiAlH_4$, THF, $-50\text{ }^\circ\text{C}$; e) aq. H_2SO_4 , THF, 86% over two steps; f) $SOCl_2$, DCM, pyr., $-50\text{ }^\circ\text{C}$, 30 min, then aq. $NaHCO_3$, 53%; g) H_2 , Pt, EtOAc, 100%; h) Na-naphthalene, THF, $-78\text{ }^\circ\text{C}$, 50%; i) dilute HCl, $110\text{ }^\circ\text{C}$, 1.5 h, 90%; j) Huang-Minlon reduction (KOH , $N_2H_4 \cdot H_2O$, $(CH_2OH)_2$, Δ) 74%.

Scheme 22: Ban's second total synthesis of aspidofractinine **7**.

In 1989 Gramain *et al.* reported a route to Ban's key intermediate **137**, thus constituting a formal total synthesis of (\pm)-aspidofractinine **7**.³⁰ The synthesis began with *N*-benzyl aniline **138** which was condensed with 1,3-cyclohexanedione **139** to afford enaminone **140** (Scheme 23). On irradiation in benzene, this gave tricycle **141** in an impressive quantitative yield with excellent stereocontrol. Alkylation of the thermodynamic enolate with iodoacetamide then installed the *D*

ring with contemporaneous aminol formation.³¹ Dehydration, *N*-alkylation and reduction of the amide moiety followed by acylation then gave **143**. LiAlH₄ reduction of **143** gave the 1,4-addition product, the alcohol moiety of which was deprotected with rhodium(III) chloride followed by acidic hydrolysis. Tosylation of the free alcohol then gave **144**. Intramolecular cyclisation was next effected using NaH to afford the core pentacycle **145**. Hydrogenolysis, oxidation and acetyl cyclisation completed the formal total synthesis.

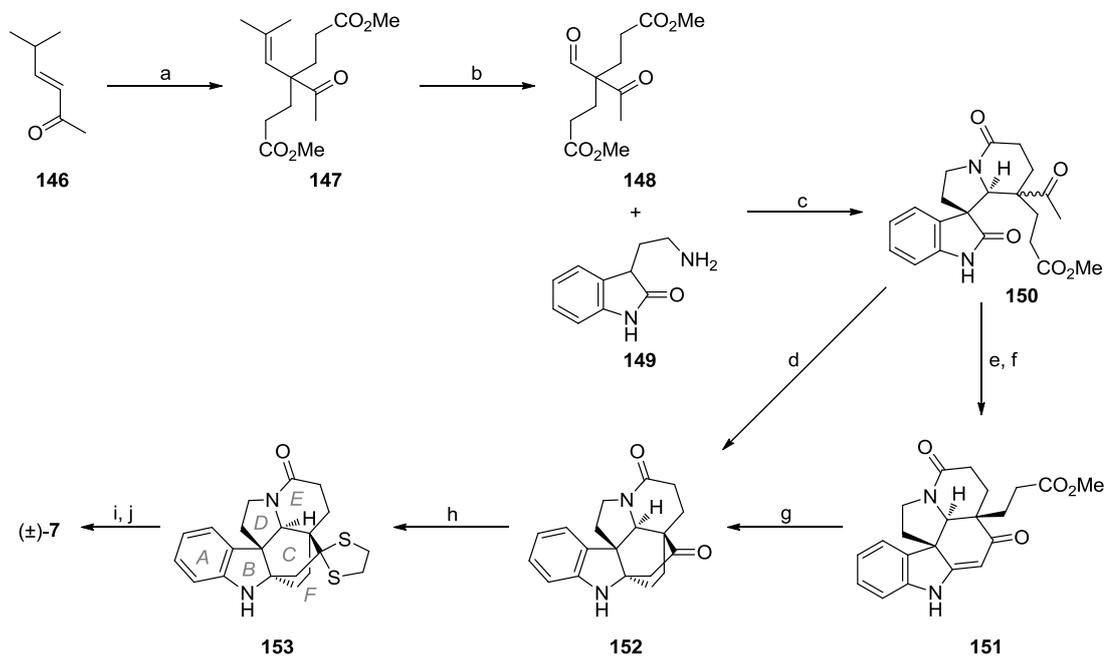


a) *p*TSA, PhH, Dean and Stark, Δ , 20 h, 98%; b) $h\nu$, PhH, 100%; c) KH, ICH₂CONH₂, THF, 93%; d) DCM, Δ , 4Å MS, 100%; e) KH, I(CH₂)₃Oallyl, THF; f) LiAlH₄, THF, Δ ; g) CH₃COCl, Et₃N, DCM, 72% over two steps; h) LiAlH₄, THF, 20 °C, 5 min, 60%; i) DABCO, RhCl₃, EtOH / H₂O; j) H₃O⁺, EtOH / H₂O; k) TsCl, py., 0 °C, 48 h; l) NaH, PhH, Δ , 20% over four steps; m) H₂, Pd / C, EtOH / CHCl₃; n) (COCl)₂, DMSO, Et₃N; o) HCl, MeOH, Δ , 85% over three steps.

Scheme 23: Gramain's formal synthesis of aspidofractinine **7**.

In the same year, Lévy *et al.* reported a double cyclisation strategy to install both the *C* and *F* rings.³² This approach focussed on an oxindolic acetyl cyclisation in a manner akin to Ban's second approach, followed by an acid-promoted cyclisation / decarboxylation sequence. The prerequisite *ABDE* ring system was constructed using 2-hydroxytryptamine **149** and aldehyde **148**, in turn accessed from ketone **146** in two steps (Scheme 24). Tetracycle **150** was then subjected to the double cyclisation sequence to afford ketolactam **152** either directly using *p*TsOH in boiling toluene, or in a more stepwise fashion *via* pentacycle **151**. The stepwise sequence was realised so that the authors could determine in which order the two rings closed. Ketolactam **152** was sequentially reduced by conversion to thioketal **153** and its removal with Raney[®] nickel. Reductive removal

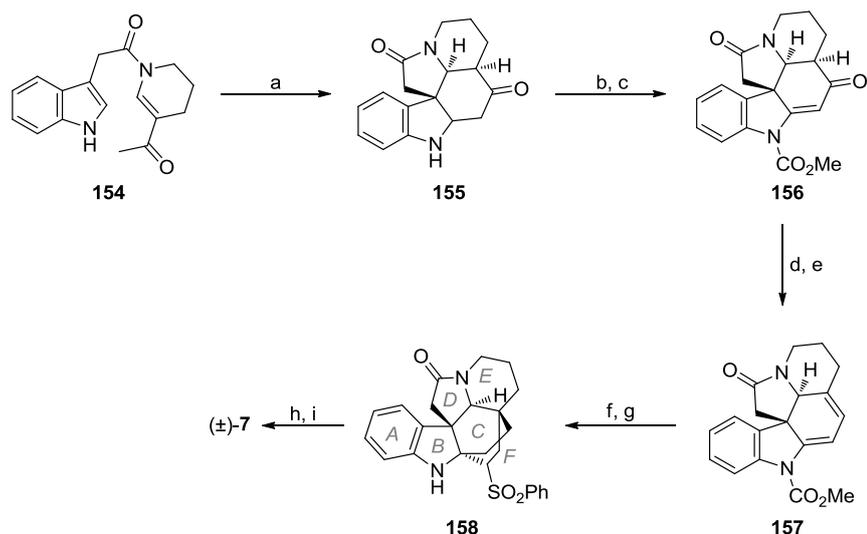
of the remaining carbonyl with LiAlH_4 completed the total synthesis of aspidofractinine **7** in just seven steps and 1.4% overall yield.



a) Methyl acrylate, cat. Triton-B ($\text{PhCH}_2\text{NMe}_3\text{OH}$), K_2CO_3 , PhH, Δ , 20 h, 26%; b) O_3 , Sudan III, 65%; c) PhMe, Dean and Stark, Δ , 2 h then AcOH, Δ , 5 h, 40%; d) *p*TSA, PhMe, Δ , 15 h, 50%; e) Me_3OBF_4 ; f) NaH, DMF, 48 h, 20 °C, 52%; g) *p*TSA, PhMe, 20%; h) $(\text{CH}_2\text{SH})_2$, AcOH, BF_3 , RT, 12 h, 70%; i) Raney[®] nickel, EtOH, 87%; j) LiAlH_4 , 70%.

Scheme 24: Lévy's total synthesis of aspidofractinine **7**.

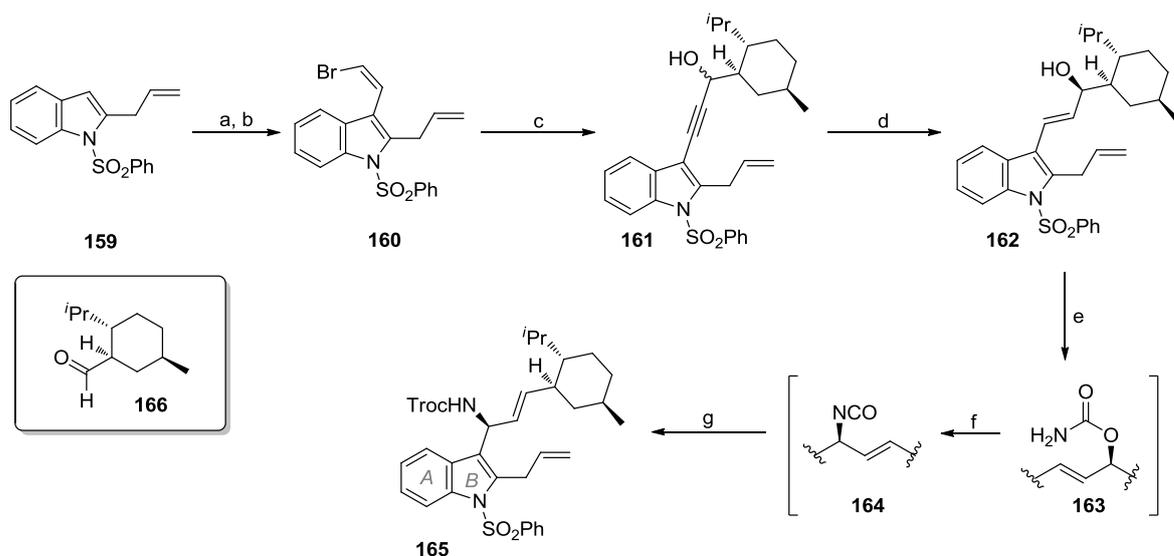
Building on Ban's first approach, Wenkert and Liu used a Diels-Alder reaction in their 1994 synthesis, in this case using phenyl vinyl sulfone as the dienophile (Scheme 25).³³ In contrast to Ban's synthesis their approach featured an early incorporation of the *E* ring, utilising **154** as a key intermediate. Exposure of this to boron trifluoride etherate with heating induced a cascade cyclisation sequence, neatly forming the *C* and *D* rings, albeit in low yield (39%). Subsequent oxidation and *N*-protection afforded α,β -unsaturated ketone **156**, which was selectively reduced and dehydrated in a manner akin to Ban's work to afford diene **157**. Diels-Alder cycloaddition with phenyl vinyl sulfone proceeded slowly, requiring high temperatures and long reaction times, namely 120 °C and four days, compared to the analogous Diels-Alder reaction in Ban's approach. However, the product was obtained in a pleasing 75% yield. *N*-Deprotection with lithium ethanethiolate, desulfurisation with Raney[®] nickel and a final reduction of the amide moiety completed the synthesis.



a) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 85 °C, 10 min, 39%; b) $\text{Pb}(\text{OAc})_4$, CHCl_3 , Δ , 15 min, 85%; c) $n\text{BuLi}$, ClCO_2Me , THF, 96%; d) NaBH_4 , CeCl_3 , MeOH, 75%; e) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 88%; f) phenyl vinyl sulfone, PhH, 120 °C, 4 d, 75%; g) EtSLi , HMPA, THF, 93%; h) Raney[®] nickel, $i\text{PrOH}$, 88%; i) LiAlH_4 , THF, Δ , 1 h, 76%.

Scheme 25: Wenkert's total synthesis of aspidofractinine **7**.

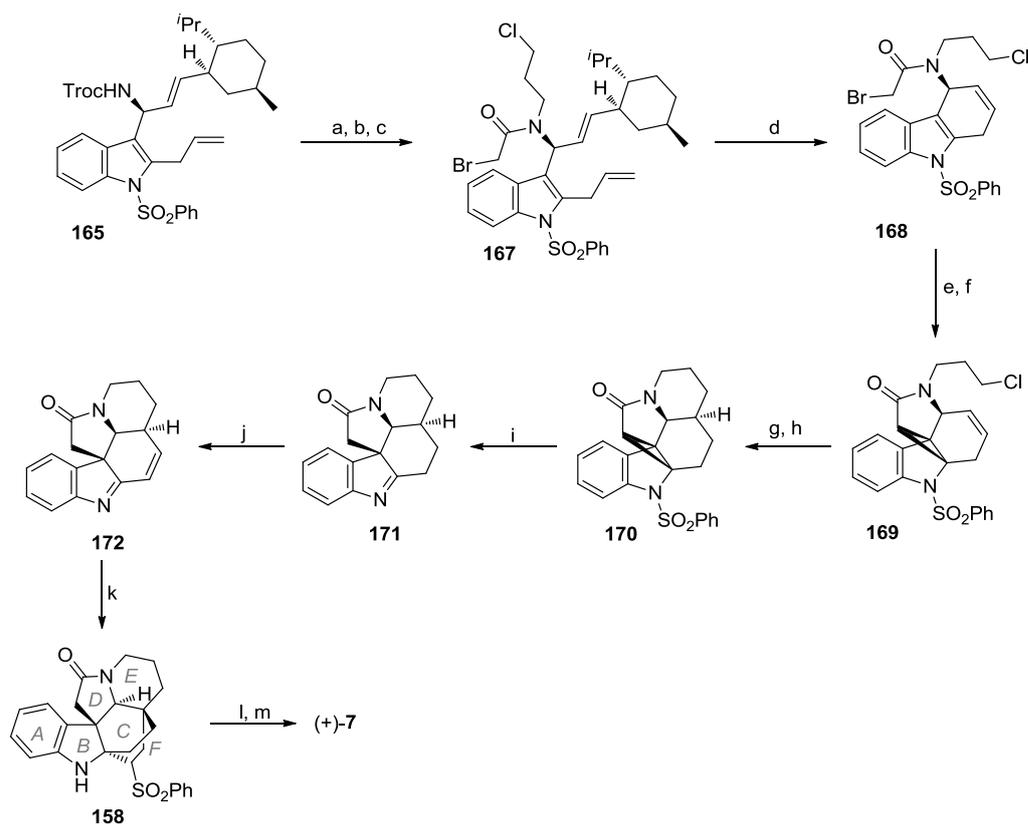
The first asymmetric synthesis of aspidofractinine **7** was reported in 2009 by Spino and Gagnon in a unique approach leading to the unnatural enantiomer (+)-**7**.⁹ The key features included a stereoselective cyclopropanation to introduce the quaternary centre at the *BCD* ring juncture with complete stereocontrol, combined with Wenkert's Diels-Alder reaction with phenyl vinyl sulfone to install the *F* ring. The stereoselectivity is imparted by the addition of chiral auxiliary **166** to the alkynyllithium resulting from vinyl bromide **160** (Scheme 26). The two resulting diastereoisomers were separated after Red-Al[®] reduction to give allylic alcohol **162** in good yield and *d.e.* (>99%). The chiral integrity was then transferred through formation of the carbamate **163**, followed by dehydration to the isocyanate **164** with *in situ* protection as the Troc protected amine **165** with $\text{Cl}_3\text{CCH}_2\text{OH}$ (*viz.* **162**→**165**).



a) MeOCHCl_2 , TiCl_4 , DCM, -78°C , 89%; b) CBr_4 , Et_3N , PPh_3 , DCM, -78°C , 100%; c) NaHMDS , THF, -95°C then $n\text{BuLi}$, THF, **166**; d) Red-Al° , THF, 25°C , 71% over two steps; e) $\text{Cl}_3\text{CC(O)NCO}$, THF, 0°C , 1 h then aq. K_2CO_3 , MeOH, 0°C , 1 h, 96%; f) TFAA, Et_3N , DCM, 0°C ; g) $\text{Cl}_3\text{CCH}_2\text{OH}$, 87% over two steps, *d.r.* 11:1.

Scheme 26

Deprotection was then followed by alkylation, acylation and ring-closing metathesis (RCM) to afford the *ABC* ring system **168**, the latter proceeding at room temperature using Grubbs' second generation catalyst with concomitant removal of the chiral auxiliary (Scheme 27). The key stereoselective cyclopropanation was then accomplished, firstly by formation of the α -diazoketone from α -bromoketone **168** followed by Cu(I) -catalysed cyclopropanation to form the *ABCD* ring system **169** with complete stereoselectivity and in good yield. The *E* ring was then installed through a 6-*exo*-trig radical cyclisation in excellent yield, with subsequent reductive deprotection and ring-opening of the cyclopropane to afford indolenine **171**. Oxidation with phenylseleninic acid gave enimine **172** which under the Diels-Alder conditions tautomerised to the required diene. The Diels-Alder product **158** is an intermediate in Wenkert's 1994 racemic synthesis and the synthesis was completed in two steps using their reduction protocol.



a) Zn, AcOH, THF, RT; b) $I(CH_2)_3Cl$, MeCN, K_2CO_3 , 77% over two steps; c) $BrCH_2COCl$, Et_3N , DCM, 84%; d) Grubbs' II, DCM, RT, 86%; e) $(TsNH)_2$, DBU, THF, 92%; f) $CuOTf$, DCM, 76%; g) NaI , acetone; h) Bu_3SnH , AIBN, PhH, Δ , 92% over two steps; i) Na, anthracene, DME, $-70^\circ C$, 96%; j) $PhSeO_2H$, THF / pyr. 6:1, Δ , 61%; k) phenyl vinyl sulfone, PhH, $90^\circ C$, 5 h, 55%; l) Raney[®] nickel, $nPrOH$, Δ , 67%; m) $LiAlH_4$, THF, Δ , 70%.

Scheme 27: Spino's total synthesis of (+)-aspidofractinine **7**.

It was the completion of this stereoselective synthesis that confirmed the absolute stereochemistry of natural aspidofractinine (–)-**7**. This was the same as that which had been assumed by Schmid *et al.* for natural aspidofractinine **7** in the 1960's.⁸ The stereochemistry of the synthesised unnatural enantiomer (+)-**7** was confirmed by single crystal X-ray analysis, OCD spectra and through logical extrapolation of the synthetic sequence. In addition, all spectral data proved to be identical to that reported in the literature for the natural enantiomer except the $[\alpha]_D$ (*vide supra* Chapter 1.2).⁹

1.7 Conclusions

The *Aspidosperma* alkaloids represent the largest family of terpenoid indole alkaloids with more than 250 members. The family is known to originate in Nature from the terpene secologanin **1** and tryptamine **3**. Whilst a biosynthetic pathway

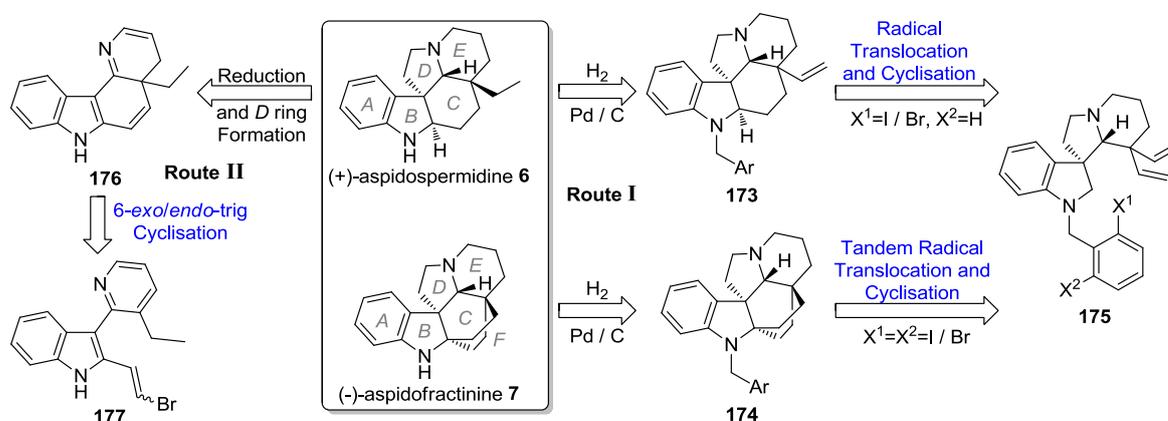
has been elucidated, many of the enzymatic details remain unresolved. The subjects of this thesis, aspidospermidine **6** and aspidofractinine **7**, are the parents of their individual subclasses and were isolated in 1961 and 1963 respectively.

Significant synthetic interest has surrounded the area since their isolation due to their interesting molecular architecture and the biological activity shown within the family. Related natural products have found clinical applications, namely dimeric indole alkaloids vinblastine **39** and vincristine **40**, whose monomeric units are members of the *Aspidosperma* family. Aspidospermidine **6** itself has also been shown to display activity against the parasite *Plasmodium falciparum*. However, aspidofractinine **7** has no reported biological activity to date.

It is evident that the synthetic interest in the *Aspidosperma* alkaloids has led to the discovery and implementation of a diverse range of methodologies and that aspidospermidine **6**, as the least functionalised member, provides a convenient scaffold on which to exemplify these strategies.

Chapter 2: Our Strategies

Our two strategies towards the targets aspidospermidine **6** and aspidofractinine **7** share a common disconnection: radical closure of the *C* ring and, in the case of route I, the *F* ring of aspidofractinine **7** (Scheme 28). This represents a unique approach to the total syntheses of these natural products as the majority of previous syntheses involve the installation of the *C* ring prior to the assembly of the *ABDE* core system. Those that install it at a later stage have used indole and oxindole centres to achieve *C*/*F* ring closure rather than radical pathways.^{27,32,33}



Scheme 28: Our retrosynthetic analysis.

2.1 Radical Translocation

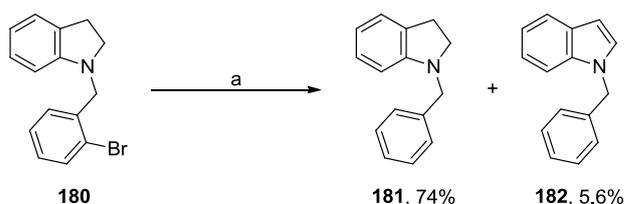
*'The intramolecular abstraction of an atom (usually hydrogen) or group by a radical centre; this results in a repositioning of the site of the unpaired electron.'*³⁴

Direct activation of CH bonds is an attractive goal in synthetic chemistry as it allows targets to be synthesised with little prefunctionalisation and excellent atom economy. Thus, radical translocation is a particularly useful process as it allows the functionalisation of sites that may otherwise be unreactive. Abstraction usually occurs in a 1,5-fashion as this allows reactive conformers to accommodate the stereoelectronic preference for an X--H--C bond angle close to 180° (Figure 7). The translocation step is driven by the formation of a more stable radical intermediate and the formation of a relatively strong bond (i.e. Ar-H) when compared with the bond that is broken (i.e. alkyl-H).



Figure 7: 1,5-*H* atom abstraction.

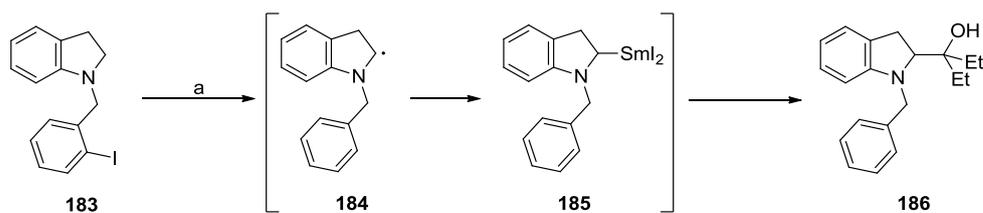
Our initial approach was inspired by reports in the literature of indolines undergoing radical translocation. Whilst investigating the synthesis of phenanthridines using radical cyclisation strategies, Lobo *et al.* reported that the treatment of indoline **180** under radical forming conditions afforded the expected debrominated product **181** and a small amount of indole **182** (Scheme 29).³⁵ Therefore the aryl radical produced by homolysis of the C–Br bond must have undergone radical translocation *via* 1,5-*H* atom abstraction to create a radical intermediate at C2 of the indoline before aromatisation to afford indole product **182**.



a) Bu_3SnH , AIBN, PhH, Δ .

Scheme 29

In 1995 Undheim and co-workers employed radical translocation *en route* to α -substituted amines (Scheme 30).³⁶ Samarium(II) iodide was used to initiate the homolysis of *o*-benzylhalides, subsequent radical translocation, cross-over to the corresponding organosamarium(II) intermediate **185** and finally addition to pentan-3-one, giving **186**. To the best of our knowledge this represents the only example in the literature of a C2 indolinyl radical resulting from radical translocation being used for the elaboration of an indoline motif.

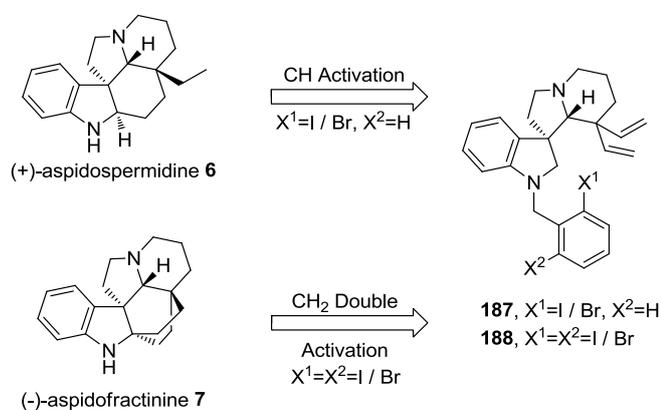


a) SmI_2 , HMPA, THP, Et_2CO , 68%.

Scheme 30: Undheim's radical translocation.

We believed that intramolecular additions of the C2 indoliny radical could offer great scope for the synthesis of new polycyclic heterocyclic ring systems, with good regio- and diastereocontrol. In the context of our synthetic ambitions we envisaged that functionalisation at the C2 position *via* radical translocation followed by radical addition to a proximal alkene would offer a powerful method for the construction of these complex natural ring systems under mild and selective conditions.

Applying this radical translocation / cyclisation approach to a retrosynthetic analysis of our targets gave indolines **187** and **188** as our key intermediates. We believed that the aryl radical formed by homolysis of the aryl-halide bond of indoline **187** would undergo translocation *via* 1,5-*H* atom abstraction to C2 of the indoline. The indoliny radical would then undergo a 6-*endo*-trig cyclisation to the terminal alkene to establish the *C* ring of aspidospermidine **6** (Scheme 31). Moreover, we believed that by subjecting diiodide **188** to the same sequence we could similarly install the *F* ring of aspidofractinine **7** using a double activation / tandem cyclisation approach.



Scheme 31: Our proposed disconnection for aspidospermidine **6** and aspidofractinine **7**.

Taking into account the rigid molecular framework of the tetracyclic intermediates **187** and **188**, we believed that 6-*endo*-trig cyclisation rather than the ubiquitous 5-*exo*-trig pathway was more likely. The terminal carbon of the alkene can approach close to the C2 radical centre whereas addition to the internal carbon of the alkene would need to proceed *via* a more strained reactive conformer (Figure 8).

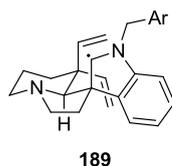
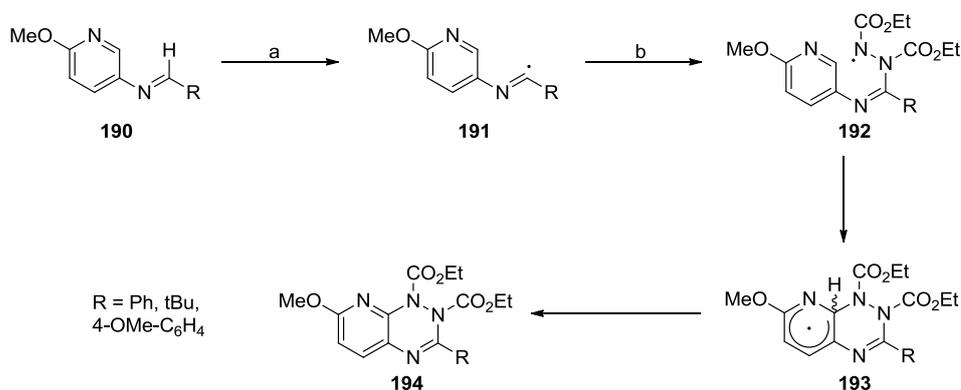


Figure 8

2.2 Radical Cyclisation to Pyridine

Our second strategy was inspired by previous work of the group on the addition of carbon-centred radicals to heteroaromatics and, more specifically for this case, the addition to pyridyl moieties. The first radical addition to a pyridine was reported by Mohlau and Berger in 1893.³⁷ They discovered that thermal decomposition of benzene diazonium chloride in pyridine afforded 2-phenylpyridine (18%) as well as a trace amount of 4-phenylpyridine. Radical additions to pyridines then received little attention for many years, presumably due to their poor yielding and unselective nature. In the 1960's interest was reignited in the area following work by Dou and Minisci, who both showed that under acidic conditions such radical additions gave dramatically improved yields and regioselectivities.^{38,39}

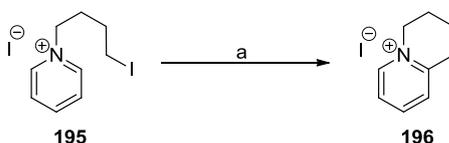
It was not until 1989 that the first example of an intramolecular radical addition to a pyridyl moiety was reported. Nanni and co-workers reported radical addition to an azo group, followed by 6-*exo/endo*-trig cyclisation to the adjacent pyridine in an intramolecular fashion (*viz.* **190**→**194**, Scheme 32).⁴⁰



a) di-isopropyl peroxydicarbonate, PhH, 60 °C; b) diethyl azodicarboxylate.

Scheme 32: Nanni's pioneering work on intramolecular radical additions to pyridine.

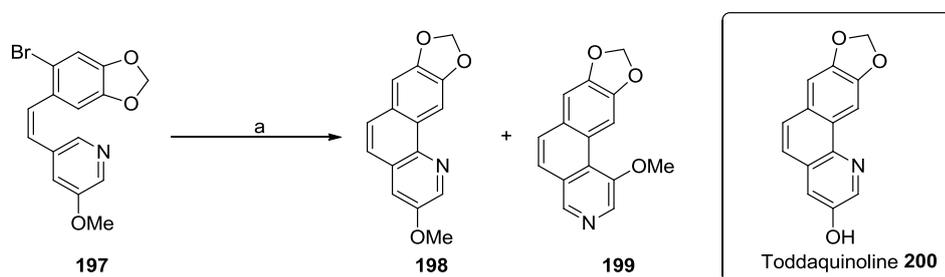
One year later Murphy *et al.* reported further intramolecular radical additions to pyridine ring systems. They extended Minisci's previous work by showing the potential for cyclisation to pyridinium salts such as **195** (Scheme 33).⁴¹



a) Bu_3SnH , AIBN, MeCN/THF, 60%.

Scheme 33: Murphy's intramolecular cyclisation.

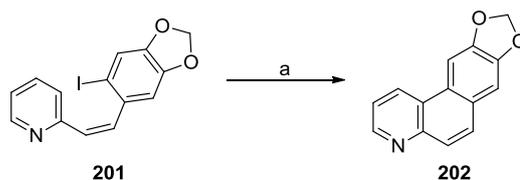
The Harrowven group were the first to apply intramolecular radical additions to pyridine to natural product synthesis when in 1998 they reported the first total synthesis of toddaquinoline **200**.⁴² In their key step arylbromide **197** was subjected to standard radical forming conditions and gave a separable 1:1 mixture of benzoquinolines **198** (toddquinoline methyl ether) and **199**. These products resulted from cyclisation of the intermediate aryl radical to C6 and C4 of the pyridyl moiety respectively (Scheme 34).



a) Bu_3SnH , AIBN, PhMe, 80 °C, 4 h, **198:199** 1:1, 58%.

Scheme 34: Harrowven *et al.*'s key radical cyclisation *en route* to toddaquinoline **200**.

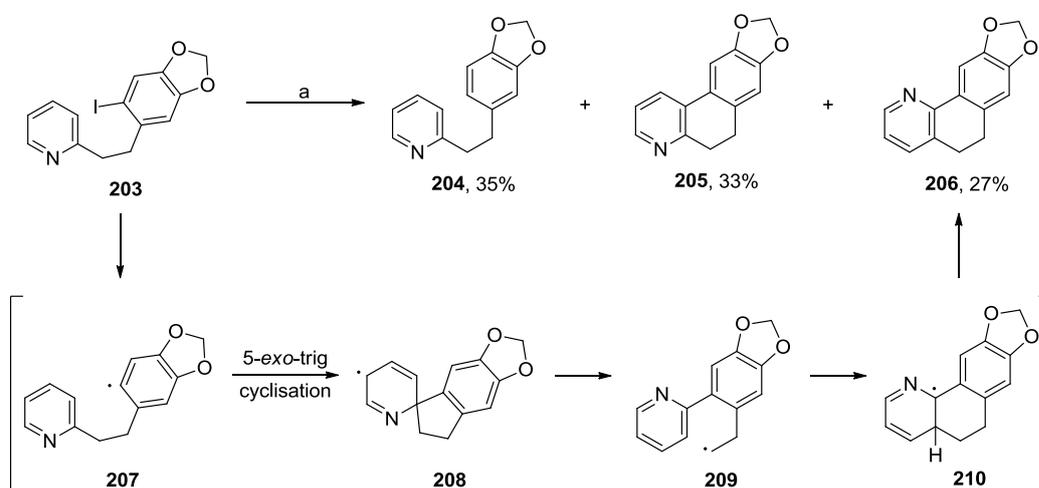
In 2001 Harrowven *et al.* reported further studies on radical cyclisations to pyridines, noting that the intramolecular radical addition to the β -carbon of a pyridine is a '*facile process*' when the aryl radical intermediate and the pyridine are linked by a *cis*-alkene.⁴³ Treatment of azastilbene **201** under radical forming conditions afforded solely the 6-*exo/endo*-trig cyclisation product **202** in 47% yield (Scheme 35).



a) Bu_3SnH , AIBN, PhMe, 80 °C, 47%.

Scheme 35

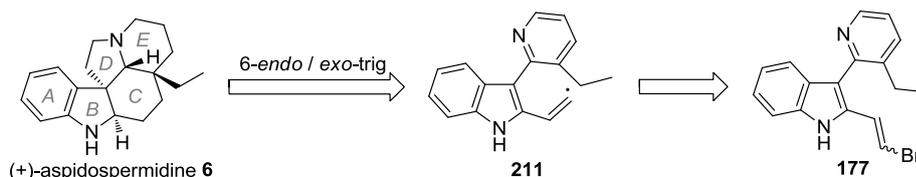
The authors reported no discernible 5-*exo*-trig addition in this system. Indeed, a 5-*exo*-trig cyclisation product was only isolated when conformational rigidity was lost through the reduction of the azastilbene alkene to **203**. This slowed the 6-*exo/endo*-trig cyclisation pathway significantly, with the increased flexibility in the tethering chain allowing *ipso*-substitution to compete (Scheme 36).



a) Bu_3SnH , AIBN, PhMe, 80 °C, 47%.

Scheme 36

The advantages offered by intramolecular radical addition to pyridines over the intermolecular variant appear numerous, with improvements in both yield and selectivity being noted. Tethering of the radical precursor to the pyridine can ensure that a radical intermediate is held in close proximity to the pyridine ring. This reduces the likelihood of potential intermolecular side reactions and limits regiochemical outcomes as the radical is constrained. Consequently, only additions to adjacent carbon centres are available. With this in mind, the key disconnection for our target, aspidospermidine **6**, is detailed in Scheme 37.



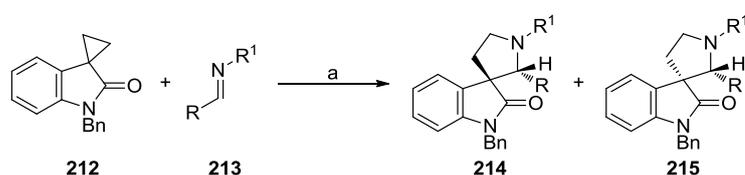
Scheme 37: Our proposed disconnection for aspidospermidine **6**.

It is worth noting that vinyl bromide **177** may be *cis* or *trans* in configuration as the C–Br bond is homolysed, resulting in a vinyl radical intermediate that is configurationally labile. Cyclisation to the proximal pyridine in a 6-*exo/endo*-trig fashion would construct the *ABCE* tetracycle, a common intermediate in many previous syntheses.^{25,26,44} The installation of the *D* ring could then be achieved in a number of different ways. For example, a Pummerer reaction as used by Magnus and co-workers (*vide supra* Scheme 10), the addition of 1,2-dibromoethane as used by Wenkert *et al.* (*vide supra* Scheme 19), or *via* radical ring closure techniques as exemplified by Nicolaou *et al.* in the total synthesis of haplophytine.^{16,26,45}

Chapter 3: Results and Discussion

Unified Approach Towards the Total Syntheses of Aspidospermidine and Aspidofractinine

With our key disconnection proceeding *via* indolines **187** and **188**, an investigation began on efficient means of constructing the core *ABDE* ring system. In 1999 Carreira *et al.* reported the Lewis acid-mediated ring-expansion of cyclopropyloxindoles with imines to form spiro[6.5.5] ring systems (Scheme 38).⁴⁶



a) MgI₂, THF, 125 °C, sealed tube, 19 h.

Scheme 38: Carreira's MgI₂ mediated union.

The mechanism is thought to proceed *via* cyclopropyl ring cleavage followed by ring-closure, using MgI₂ both for the Lewis acidity of the metal centre and the nucleophilicity of the iodide counterion (Figure 9). Three pathways have been postulated, although pathway I has largely been discounted due to the need for a nucleophilic counterion (no reaction was observed with Mg(OTf)₂) indicating a ring-opening step involving the halide counterion as featured in step A, pathway II (*viz.* **212**→**217**→**216**) and III (*viz.* **217**→**218**→**214**).

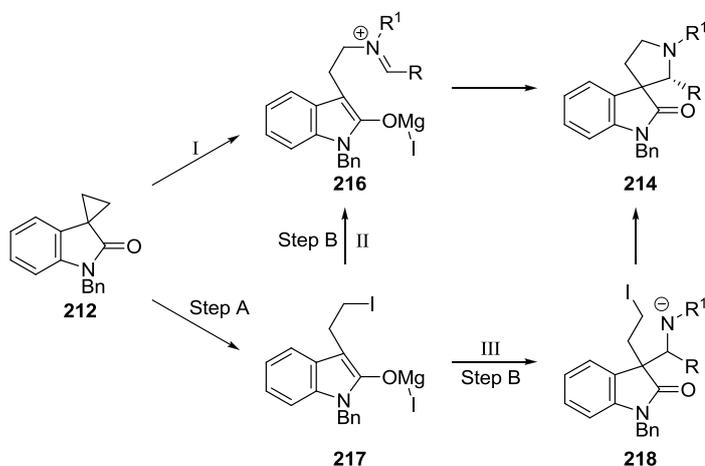
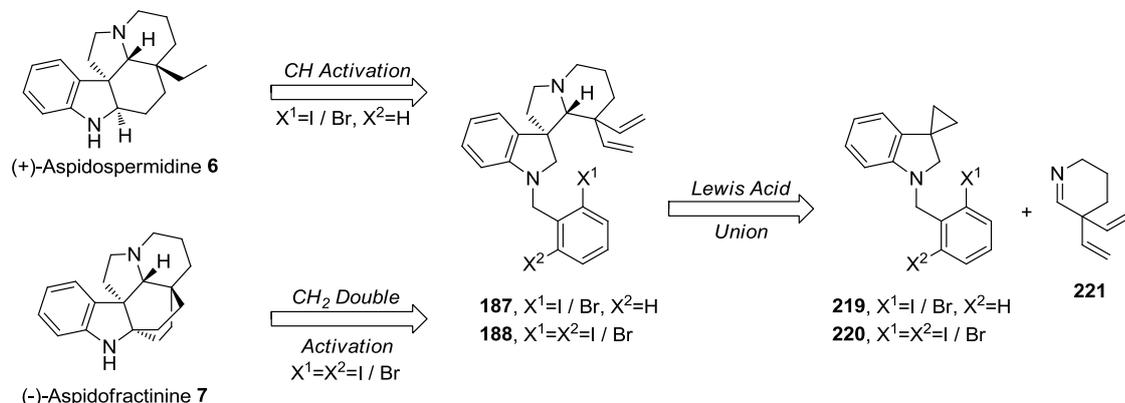


Figure 9: Possible mechanistic pathways.⁴⁶

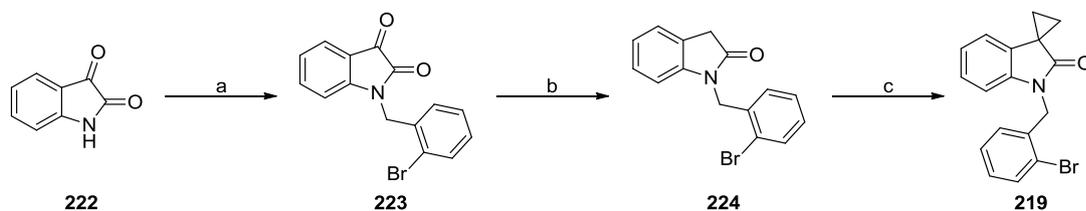
When applied to our key intermediate this elegant chemistry gives us our key synthons, namely cyclopropanes **219** and **220** and imine **221** (Scheme 39).



Scheme 39

3.1 Forming the ABDE Core Structure

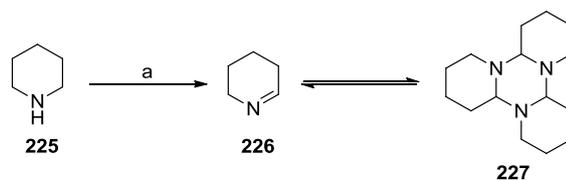
Cyclopropane **219** was synthesised smoothly in three steps from commercially available oxindole **222** in an overall yield of 61%. *N*-Benzylation followed by a modified Wolff-Kishner reduction then gave oxindole **224**. Cyclopropanation by means of a double S_N2 alkylation with dibromoethane completed the sequence (Scheme 40).



a) 2-Bromobenzyl bromide, K₂CO₃, KI, MeCN, RT, 17 h, 98%; b) N₂H₄·H₂O, Δ, 2 h, 90%; c) NaH, 1,2-dibromoethane, 0 °C–RT, 72 h, 69%.

Scheme 40: Cyclopropyl oxindole **219** formation.¹⁷

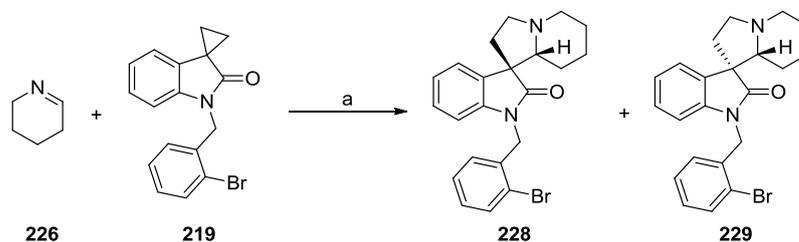
Due to the complexity involved in preparing divinyl imine **221** a model system was sought while an efficient route for its synthesis was developed. The obvious choice was cyclic imine **226**, which exists as the trimer, **227**, and can be prepared in a one pot, two-step process by oxidation of piperidine **225**. In our hands the published procedure gave imine **226** in a disappointing 11% yield.⁴⁷ Nonetheless, the concise nature of the synthesis allowed large quantities to be prepared (Scheme 41).



a) AcOH, Ca(OCl)₂, H₂O, MTBE, -10 °C–RT, 16 h, 11%.

Scheme 41: Model imine formation.

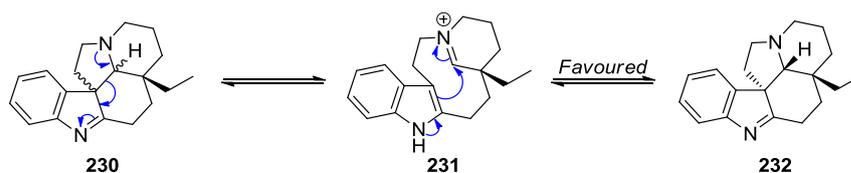
With the two fragments now in hand, attention turned to the application of Carreira's Lewis acid-mediated union to our system. Cyclopropane **219** and imine **226** were heated to 125 °C in THF in a microwave reactor (a slight modification of Carreira's conditions where heating was effected in a sealed tube) in order to reduce the reaction time from nineteen hours to just five (Scheme 42).



a) MgI₂, THF, μW, 125 °C, 5 h, 85% *d.r.* 88:12*.

Scheme 42: Cyclopropyloxindole formation.

As reported by Carreira, a separable mixture of diastereoisomers was isolated with the minor isomer, **229**, having the correct configuration for the natural product system. However, the major isomer was taken on in the synthesis as these systems are known to equilibrate to the more thermodynamically stable arrangement (that of the natural product in the *Aspidosperma* case) *via* a retro-Mannich reaction (Scheme 43).^{2,14} This phenomena was noted as early as 1959 by Wenkert and co-workers. Indeed, many oxindolic alkaloids exist in Nature as pairs of interconvertible isomers as a result (e.g. rychnophylline **233** and isorychnophylline **235**, Figure 10).^{48–50}



Scheme 43: Retro-Mannich interconversion of stereochemistry.

* The diastereomeric ratio was determined using isolated masses; NMR analysis could not be used to determine a representative ratio.

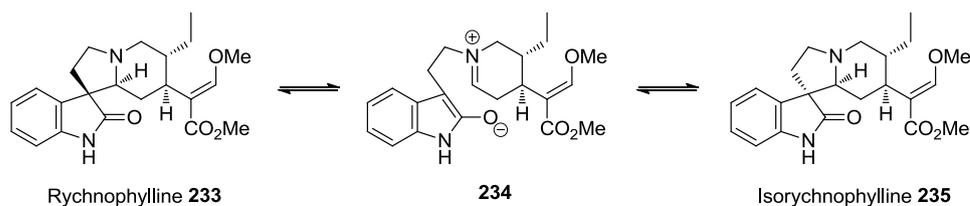


Figure 10: Interconversion on heating with acetic anhydride.

It is interesting to find that this equilibration occurs with our model tetracyclic system. On standing for two years at RT as an oil, pure minor diastereoisomer **229** equilibrated to a diastereomeric mixture of **228** and **229** (*d.r.* 40:60, determined by NMR analysis). The major diastereoisomer **228** remained intact suggesting that it is the more stable of the pair (Figure 11).

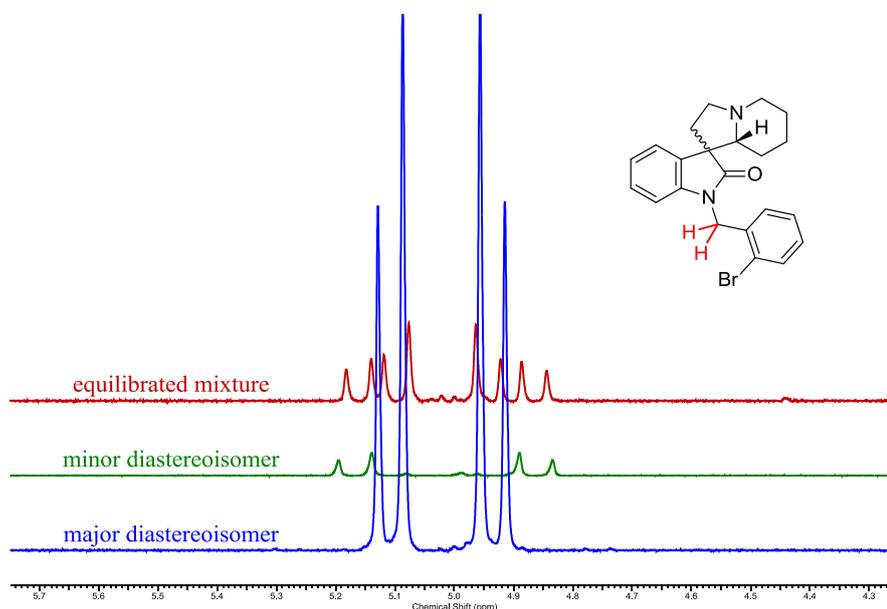
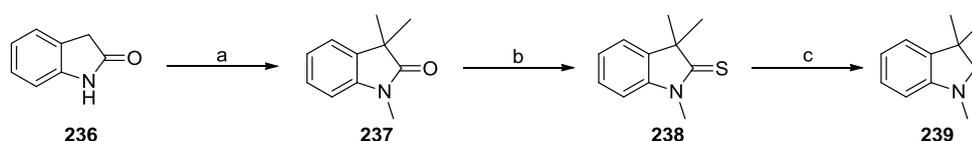


Figure 11: NMR analysis of equilibrated mixture on standing for 2 years in comparison with pure major and minor diastereoisomers **228** and **229**.

3.2 Lactam Reduction

With the key *ABDE* ring system in place, our next task was reduction of the oxindolic carbonyl to give the indoline. However, this proved more troublesome than initially thought. We knew that in the natural product system the intermediate oxindole would contain terminal alkenes, precluding reducing agents such as borane. Furthermore, it would possess a C–Br bond which could be susceptible to reduction using powerful hydride sources such as LiAlH_4 .

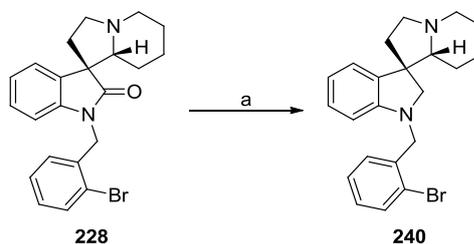
Initial investigations focussed on the reduction of a thiolactam moiety (*viz.* **238**→**239**), as the reduction of the C=S bond can be undertaken using conditions conducive to the preservation of alkenes and a C–Br bond. To model the procedure, oxindole **236** was triply methylated to give oxindole **237** in excellent yield (Scheme 44). Conversion to the thiolactam was then induced using bis(trimethylsilyl)sulfide and phosphorous oxychloride in a modest 43% yield after use of the more standard Lawesson's reagent proved unsuccessful. Reduction was then carried out using Meerwein's salt in conjunction with NaBH₄ to give indoline **239**, albeit in poor yield.



a) NaH, MeI, THF, 0 °C–RT, 18 h, 93%; b) POCl₃, TMS₂S, DCM, Δ, 18 h, 43%; c) Me₃OBF₄, DCM, 0 °C–RT, 18 h, then NaBH₄, MeOH, 0 °C–RT, 4 h, 11%.

Scheme 44: Thiolactam reduction.

In spite of the poor yields we decided to apply the sequence to the *ABDE* tetracycle **228**. However, when attempts to transform this into the corresponding thioamide failed, our attention returned to methods of effecting the direct reduction of the oxindolic carbonyl moiety. Alane (AlH₃) as a complex with *N,N*-dimethylethylamine has been reported to be an effective reagent for the reduction of amides to amines without loss of halide groups.⁵¹ Pleasingly, when tetracycle **228** was treated with alane the desired reduction was observed, giving indoline **240** in 63% yield (Scheme 45).

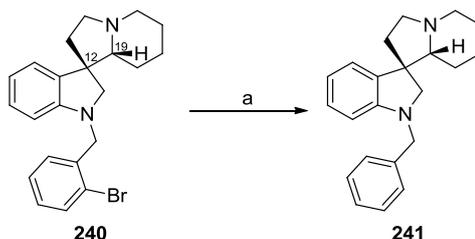


b) AlH₃, PhMe, –78 °C–RT, 4 h, 63%.

Scheme 45: Alane reduction.

Fission of the C12–C19 bond is commonplace in systems such as these and under radical forming conditions fragmentation at this bond can readily occur

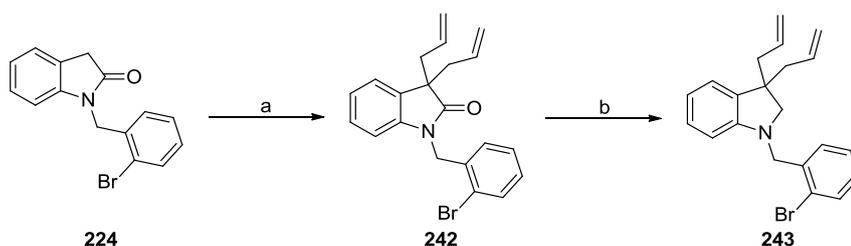
(*vide infra* Chapter 3.1). Thus, our model tetracyclic indoline **240** was subjected to standard radical forming conditions to test the robustness of the system under the key step conditions. Pleasingly, no fragmentation about the C12–C19 bond was observed, with the reduced benzylindoline **241** being the only isolable product. Thus we were confident that our proposed 6-*endo*-trig cyclisation to construct the *ABDE* ring system would not be compromised by fragmentation at C3 of the indoline moiety (Scheme 46).



a) Bu_3SnH , VAZO, PhMe, 18 h, 89%.

Scheme 46

However, the presence of the terminal alkenes in the natural product system must also be considered. Therefore, 3,3-diallyloxindole **242** was synthesised as a representative system on which to test our reduction conditions. This was easy to prepare as a double alkylation of oxindole **224** with allyl bromide first gave 3,3-diallyloxindole **242** which, on treatment with alane underwent reduction in excellent yield with complete alkene preservation (Scheme 47).



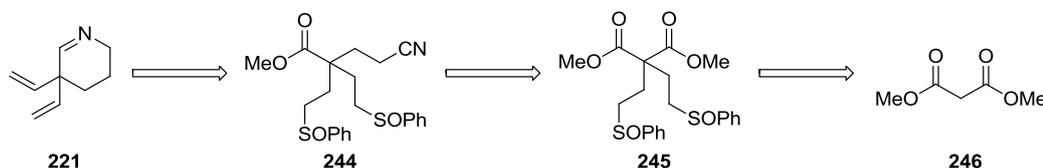
a) NaH, allyl bromide, DMF, RT, 16 h, 73%; b) AlH_3 , PhMe, $-78\text{ }^\circ\text{C}$ –RT, 4 h, 97%.

Scheme 47

3.3 Synthesis of the Key Cyclic Imine

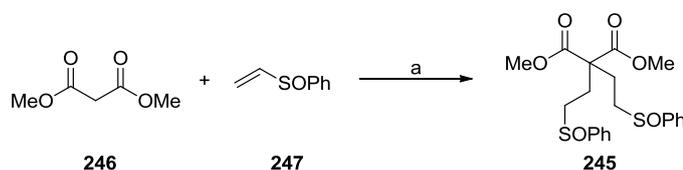
Our work towards *gem*-divinyl imine **221** began with an already established route,¹⁷ utilising a sulfoxide moiety and subsequent elimination to install the two vinyl groups. Double alkylation of dimethyl malonate with phenyl vinyl sulfoxide

followed by decarboxylation and Michael addition with acrylonitrile is used to introduce the carbon backbone of imine **221**. The synthesis is then completed by thermal elimination of the sulfoxide moieties followed by cyclisation (Scheme 48).



Scheme 48

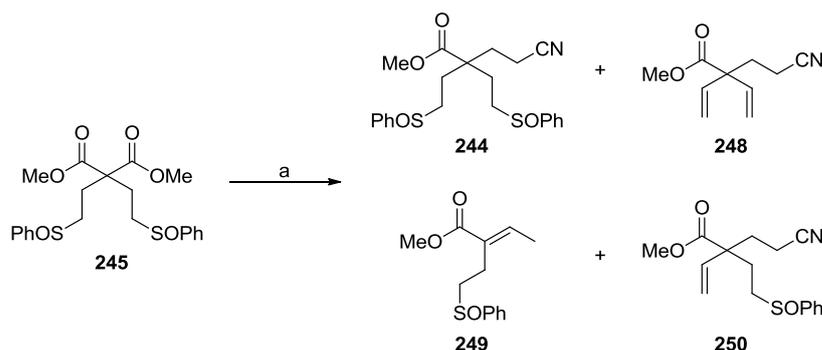
Pleasingly, double Michael addition of dimethyl malonate **246** with phenyl vinyl sulfoxide **247** proceeded smoothly in good yield and on large scale (Scheme 49).



a) NaH, DMF, 0 °C–RT, 4 d., 75%.

Scheme 49

Malonate **245** was then subjected to an elegant one pot Krapcho decarboxylation / Michael addition sequence, installing the required three carbon chain. Treatment with NaI in DMF at 120 °C in the presence of an excess of acrylonitrile afforded the desired nitrile **244** along with a number of both useful and benign side-products (Scheme 50).



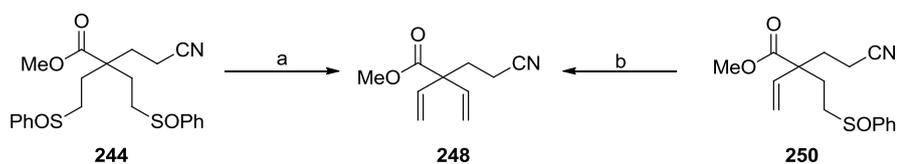
a) NaI, acrylonitrile, DMF, 120 °C, 12 h, 21% **244**, 7% **248**, 5% **249**, 22% **250**.

Scheme 50

The array of different products is a result of the reaction temperature. A high temperature is needed to affect the decarboxylation; however, the following thermal elimination step also occurs at high temperatures, leading to the formation of elimination side-products at this stage. Attempts to optimise the reaction by

prolonging reaction times (>12 h) led to greater formation of elimination side-products **249** and **250**.

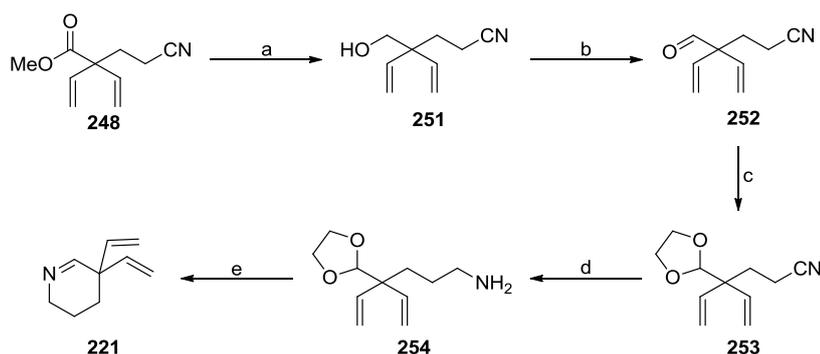
Thermolysis of the bissulfoxide moieties of **244** proceeded in modest yield to give *gem*-divinyl **248**. Pleasingly, when subjected to the thermolysis conditions, side-product **250** also gave *gem*-divinyl **248** (Scheme 51).



a) DMF, 120 °C, 5 h, 40%; b) DMF, 120 °C, 5 h, 76%.

Scheme 51

A sequence of functional group manipulations, namely ester reduction, oxidation, acetal protection and nitrile reduction then afforded the unmasked amine **254** in four steps (Scheme 52). However, the yields for both reduction steps were extremely capricious (*viz.* **248**→**251**, **253**→**254**), presumably due to the number of other functional groups present that may be susceptible to reduction. In addition, the final one pot deprotection / cyclisation sequence proved to be both poor yielding and unreliable. It is also worth drawing attention at this point to our use in the first step of phenyl vinyl sulfoxide. When considering its role is to install a two-carbon vinyl group, it is not only an expensive reagent but also an atom inefficient process.

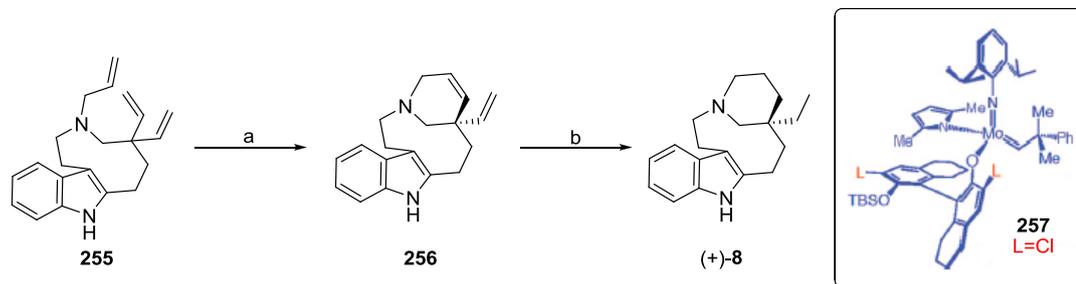


a) LiAlH₄, THF, -78 °C, 6 h, 51–92%; b) DMP, CHCl₃, RT, 4 h, 96%; c) (CH₂OH)₂, *p*TSA, PhMe, Dean and Stark, 6 h, 95%; d) LiAlH₄, THF, 60 °C, 4 h, 58–96%; e) 10% HCl, Et₂O, 2 h, then 10% NaOH, 2.5 h, 12–34%.

Scheme 52

In response to the problems inherent to the sulfoxide route, investigations began into alternative imine formation strategies. Inspiration was taken from Hoveyda and co-workers' enantioselective synthesis of (+)-quebrachamine **8**, reported in

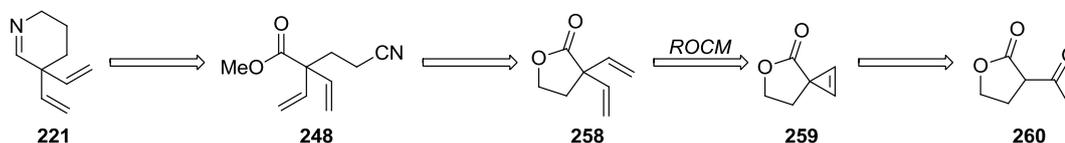
2009.⁵² The key step in their synthesis was a catalytic enantioselective RCM of divinyl **255** (Scheme 53).



a) **257**, PhH, RT, 1 h, 84%, 96% e.e.; b) PtO₂, H₂, EtOH, RT, 1 h, 97%.

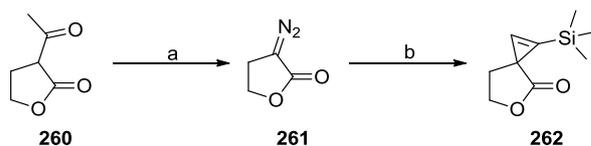
Scheme 53: Hoveyda and co-workers enantioselective RCM.⁵²

It was the divinyl moiety that sparked our interest, the efficient installation of which is nontrivial. Hoveyda and co-workers effected catalytic ring-opening / cross metathesis (ROCM) of spirocyclic lactone **259** in the presence of ethylene to give the required *gem*-divinyl functionality, a protocol we hoped to exploit in our efforts towards imine **221**. By accessing divinyl lactone **258** using Hoveyda's route we hoped to complete the construction of imine **221** *via* the opening of lactone **258** followed by the application of our original end game (Scheme 54).



Scheme 54: Our revised retrosynthetic analysis of imine **221**.

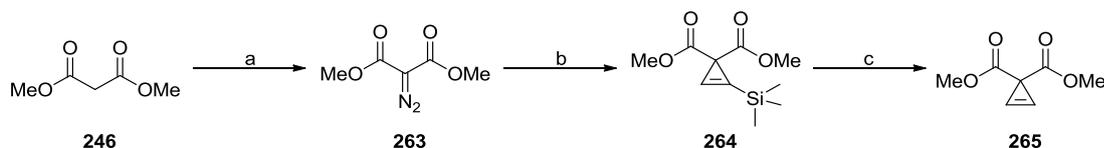
Thus, α -acetylbutyrolactone **260**, was treated with sodium azide and triflic anhydride to form the triflyl azide *in situ*, which in turn gave diazo lactone **261** in 37% yield (Scheme 55). Cyclopropenation to **262** was then investigated using trimethylsilylacetylene as described by Hoveyda *et al.* Alas, this too proved to be poor yielding in comparison to that reported by Hoveyda *et al.* (*viz.* **260**→**261** 66%, **261**→**262** 64%) giving just 12% yield. We believe that the poor yield of the cyclopropenation reaction was due to poor solubility of diazo **261** in the reaction medium, trimethylsilylacetylene, an observation not noted by Hoveyda and co-workers. No success was found optimising the cyclopropenation reaction by the addition of co-solvents. Given that it was to be the starting point of our synthetic sequence, an alternative tactic was sought.



a) NaN₃, TBAB, NaOH, Tf₂O, hexanes:MeCN (~1:1), 0 °C, 30 min, 37%; b) Rh₂(OAc)₄, trimethylsilyl acetylene, Δ, 16 h, 12%.

Scheme 55

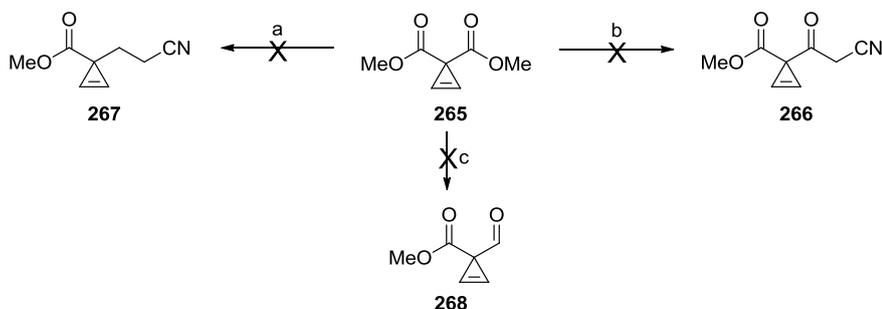
In an approach more akin to our original strategy we decided to attempt the cyclopropenation with diazo malonate **263** (formed in modest yield from dimethyl malonate **246** using an established literature procedure (Scheme 56)). Pleasingly, in this case the cyclopropenation reaction proceeded smoothly to give cyclopropene **264** in 78% yield, a significant improvement on the previous route. It is worth noting that the solubility of diazo **263** in trimethylsilyl acetylene was not an issue for this transformation, confirming our belief that the poor solubility of diazo lactone **261** was responsible for its poor conversion. Finally, desilylation furnished the desired cyclopropene **265** in 58% yield.



a) *p*-toluenesulfonyl azide, Et₂NH, Et₂O, 0 °C–RT, 60 h, 53%; b) Rh₂(OAc)₄, trimethylsilyl acetylene, Δ, 1.5 h, 78%; c) KOH, EtOH, 0 °C, 5 min, 58%.

Scheme 56

Despite the successful installation of the cyclopropene moiety, attempts to progress intermediate **265** towards imine **221** using our original Krapcho decarboxylation / Michael addition sequence failed. Alternative strategies to install the three-carbon chain on intermediate **265** were also attempted but all proved to be unsuccessful (Scheme 57).

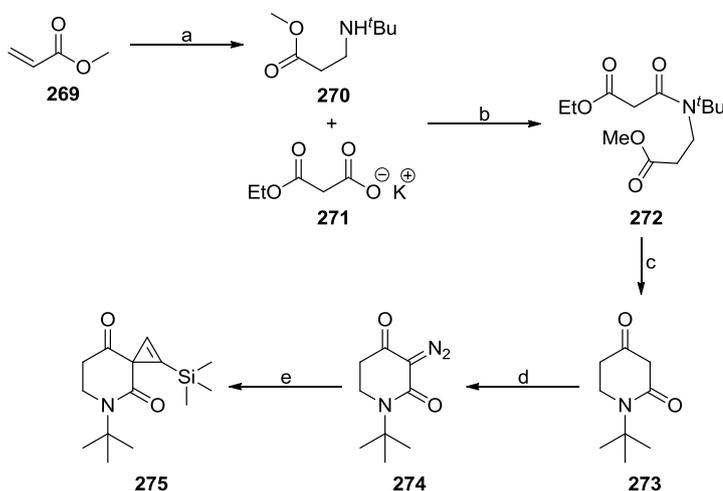


a) NaI, acrylonitrile, DMF, 120 °C, 12 h; b) NaOMe, MeCN, CIPh, Δ, 62 h; c) DIBALH, -78 °C–RT, DCM, 12 h.

Scheme 57

Reduction of the ester functionality to aldehyde **268** afforded a variety of unidentifiable products, none of which contained the desired aldehyde moiety, whereas attempts to install the nitrile group to give **266** returned only unreacted starting material.

As an alternative strategy we proposed the application of ROCM chemistry to the already formed six-membered ring of piperidine-2,4-dione **273**. Thus, *t*-butyl-protected piperidine-2,4-dione **273** was synthesised in three steps from methyl acrylate **269** in an overall yield of 11% (Scheme 58). Diazotisation proceeded smoothly to afford **274** in 75% yield, which was then subjected to the cyclopropenation conditions. However, we were again thwarted by solubility issues, obtaining cyclopropene **275** in a disappointing 9% yield.



a) t BuNH₂, MeOH, RT, 60 h, 67%; b) pivaloyl chloride, Et₂O, 0 °C, 4 h, then Et₃N, dimethylaminopyridine, 0 °C–RT, 40 h, 25%; c) NaH, cyclohexane:PhMe (4:1), Δ, 45 min then AcOH, Δ, 3 h, 64%; d) *p*-toluenesulfonyl azide, Et₂NH, Et₂O, 0 °C–RT, 60 h, 75%; e) Rh₂(OAc)₄, trimethylsilyl acetylene, Δ, 2 h, 9%.

Scheme 58

3.4 Conclusions

A method for construction of the *ABDE* ring system was identified and validated on a model system. An efficient route to the prerequisite *AB* cyclopropane **219** has been established as well as for the model imine **226**, albeit in poor yield. In addition, a reducing agent for the transformation of the oxindole into the required indoline moiety has been identified, this being tolerant to the presence of both alkenes and aryl-halide bonds.

Attempts at improving an already identified route towards imine **221** met with little success, with a more concise and atom economical route proving elusive. A synthesis of imine **221** was undertaken using our established route, wherein the *gem*-divinyl moiety was installed *via* sulfoxide elimination. However, time and a limited quantity of material prevented its application in a Lewis acid-mediated union with cyclopropane **219**, and its further elaboration to the natural product ring systems.

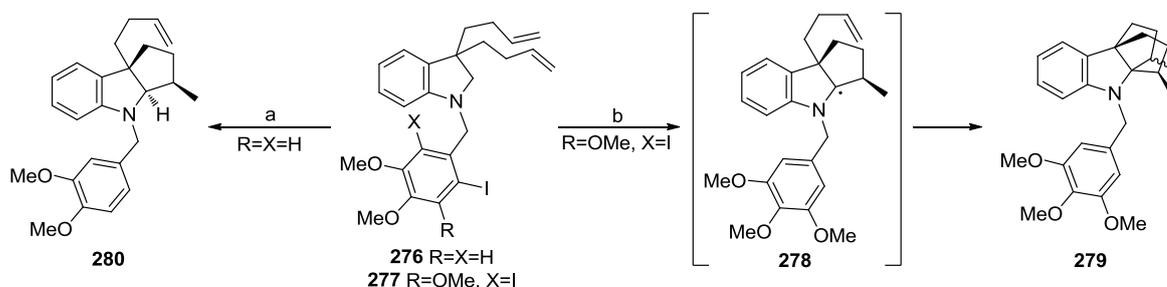
Chapter 4: Results and Discussion

Probing the Chemistry of the Indolinyl Radical

CH activation leading to selective C–C bond formation with no prefunctionalisation is an attractive goal for the synthetic chemist. It is particularly attractive in heterocyclic chemistry owing to their ubiquitous presence in natural and pharmaceutical products. To that end the functionalisation of indoles and indolines has been a significant focus for organic chemistry, and CH activation is a logical extension of this. CH activation protocols as well as transition metal-catalysed coupling reactions have been reported to install aryl, alkyl, alkynyl and vinyl substituents directly onto indoles.^{53–55} Intramolecular radical additions to C2 and C3 of the indole moiety have also been reported.^{56–62} By contrast, the direct functionalisation of indolines has received less attention, with limited examples of transition metal-catalysed processes and only one example *via* radical translocation to C2 of an indoline (*vide supra* Chapter 2.1).^{36,63–65}

4.1 Prior Art

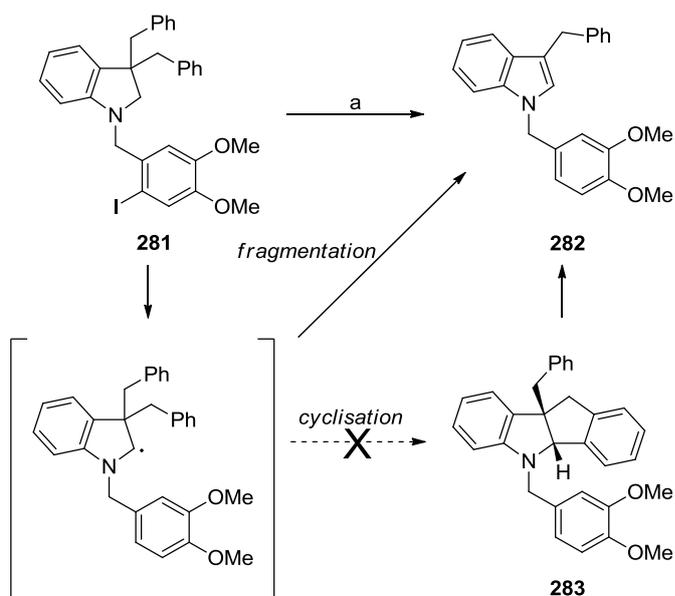
In order to demonstrate the utility of the indolinyl radical as a means of indoline C2 functionalisation, initial studies had been undertaken.¹⁷ Notably, when indoline **276** was treated under standard radical forming conditions tricycle **280** was formed in good yield following the desired translocation / cyclisation sequence. Even more interesting was that under the same conditions indoline **277** underwent a double activation / tandem cyclisation sequence to afford azapropellane **279** in excellent yield (Scheme 59).



a) Bu_3SnH , VAZO, PhMe, Δ , 76% *d.r.* 6:1; b) Bu_3SnH , VAZO, PhMe, Δ , 90% *d.r.* 1:1.

Scheme 59: Prior investigations into functionalisation *via* the indolinyl radical.¹⁷

Intriguingly, when 3,3-dibenzylindoline **281** was exposed to the same conditions, the anticipated cyclisation of the indolinyl radical to the proximal aryl group to give **283** was outpaced by fragmentation of a benzyl substituent to give indole **282** (Scheme 60). This curious result led us to propose that the fate of the indolinyl radical was dependent upon its C3 substitution pattern. As such, a study into the influence of substitution on the indoline on the radical pathway was carried out.

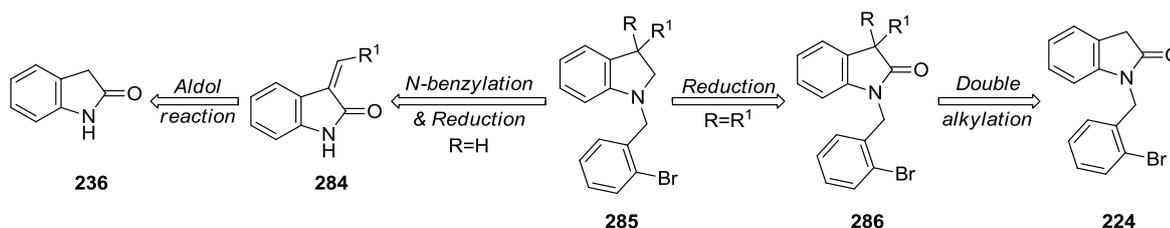


a) Bu_3SnH , VAZO, PhMe, 90 °C, 95%.

Scheme 60: Alternative pathway for the indolinyl radical.¹⁷

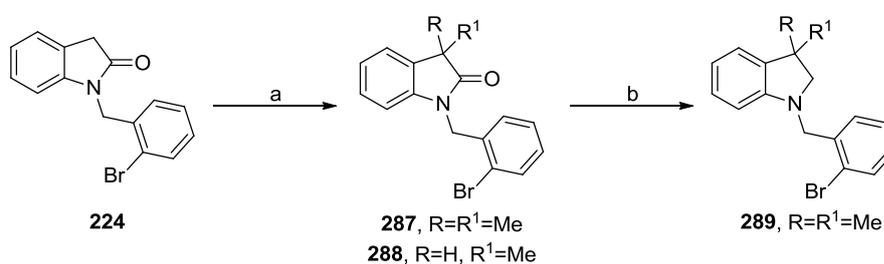
4.2 Synthesis of the Indolinyl Precursors

To initiate that study, an array of methyl, alkyl and benzyl substituted indolines were synthesised. Our plan was to access 3,3-disubstituted indolines by means of a double alkylation of *N*-benzylated oxindole **224**, previously synthesised in two steps from isatin (*vide supra* Chapter 3.1). Monosubstituted analogues would be accessed using Aldol reaction of oxindole **236** followed by alkene and oxindole reduction (Scheme 61).



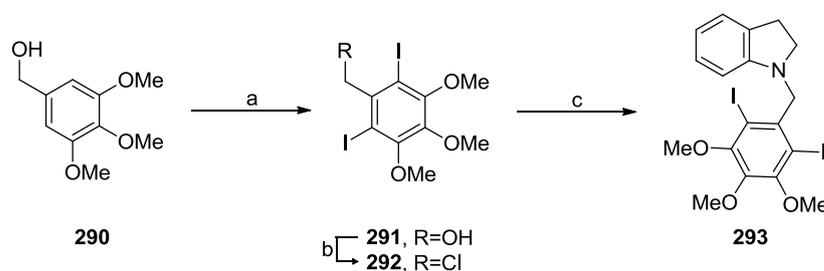
Scheme 61: Retrosynthetic analysis for indoline substitution.

Dimethylated indoline **289** was synthesised in two steps from oxindole **224** via double alkylation with methyl iodide followed by reduction with alane in good yield (74%). A small quantity of monomethylated product **288** was also isolated from the alkylation step (Scheme 62). As the method gave sufficient material for our purposes, optimisation was not deemed necessary. The C3 unsubstituted variant was also synthesised in two steps from benzyl alcohol **290**. Thus, iodination to diiodide **291** proceeded in near quantitative yield followed by transformation of the benzyl alcohol to the benzyl chloride using thionyl chloride (*viz.* **291**→**292**), again in excellent yield. Coupling with indoline then gave the desired radical precursor **293** in modest yield (Scheme 63).



a) NaH, MeI, DMF, RT, 16 h, 40% **287**, 11% **288**; b) AlH₃, PhMe, RT, 3 h, 74%.

Scheme 62

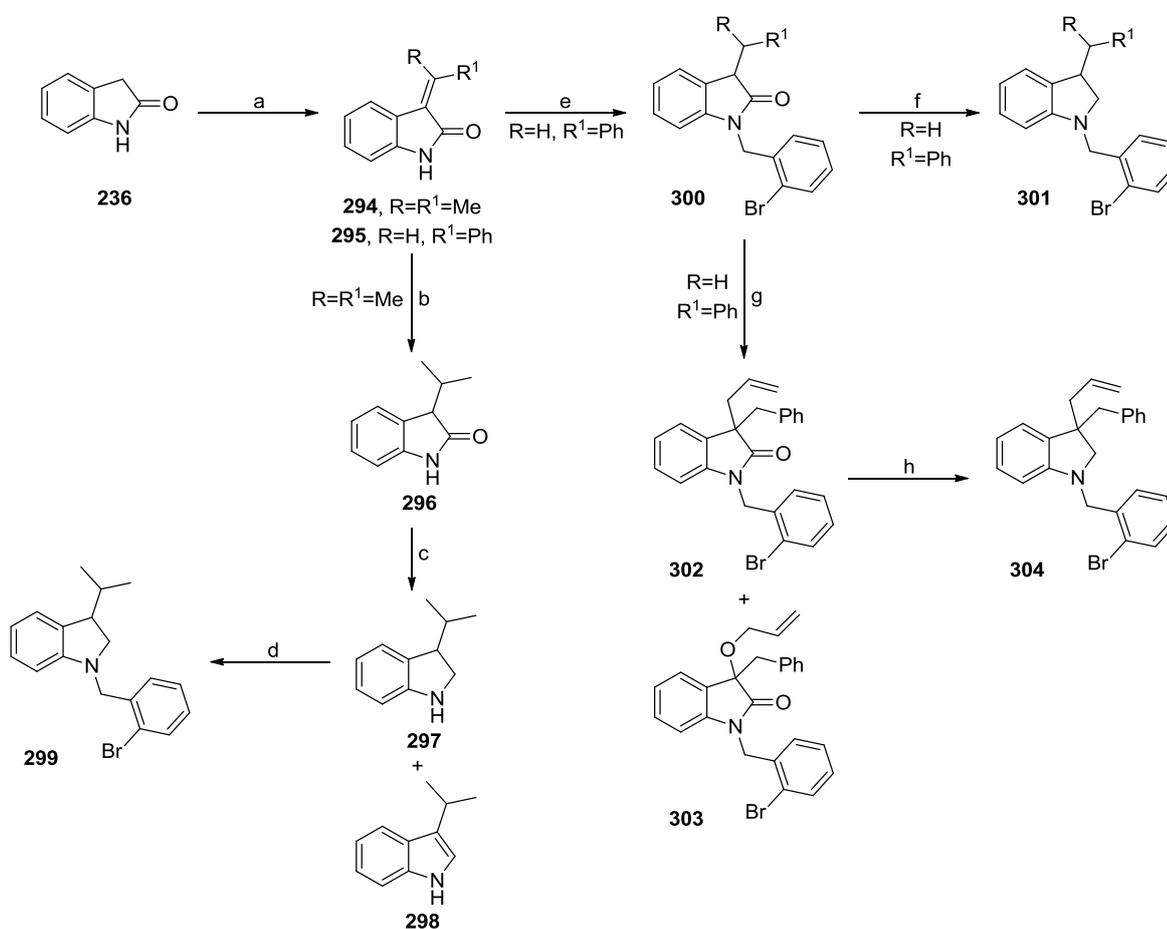


a) I₂, CF₃CO₂Ag, CHCl₃, 0 °C–RT, 16 h, 99%; b) SOCl₂, DCM, 0 °C–RT, 16 h, 100%; c) indoline, K₂CO₃, KI, acetone, Δ, 16 h, 41%.

Scheme 63

Synthesis of the monosubstituted indolines began with oxindole **236**. For these examples the *N*-bromobenzyl moiety was installed at a later stage in the synthesis, after alkene reduction had taken place, to avoid possible problems associated with aryl bromide reduction. Thus, oxindole was subjected to Aldol reaction with acetone and benzaldehyde to afford α,β-unsaturated oxindoles **294** and **295** respectively (Scheme 64). Reduction of alkene **294** by hydrogenation was then achieved in excellent yield to give **296**. Further reduction of the oxindolic carbonyl

then afforded the desired indoline **297** (33%) and indole **298** (27%). Indoline **297** was *N*-benzylated with 2-bromobenzyl bromide to afford the desired precursor **299**. Similarly, after *N*-benzylation and reduction of **296** in a one pot, two-step process, C3-benzylated oxindole **300** was synthesised in good yield. Alane reduction, again in poor yield (30%), gave the desired indolinyl radical precursor **301**. It is interesting to note that the reduction of these oxindoles to the corresponding indolines proved low yielding when monosubstituted at C3. This being in stark contrast to the good to excellent yields obtained for those substrates with C3 disubstitution. Presumably this is a consequence of elimination of the intermediate aluminium alkoxide.



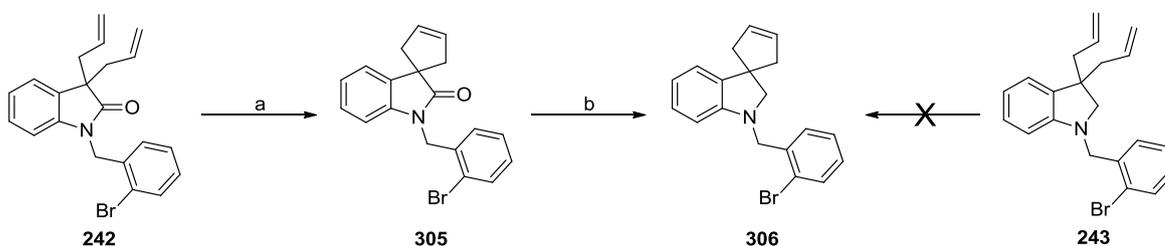
a) RR^1CO , piperidine, EtOH, Δ , 4 h, 67% $R=R^1=Me$ and 86% $R=H, R^1=Ph$; b) H_2 , 10% Pd / C, MeOH:DCM (1:1), RT, 4 h, 100%; c) $BH_3 \cdot DMS$, THF, 0 $^{\circ}C$ -RT, 16 h, 33% **297** and 27% **298**; d) 2-bromobenzyl bromide, K_2CO_3 , KI, MeCN, RT, 12 h, 62%; e) 2-bromobenzyl bromide, K_2CO_3 , KI, MeCN, RT, 12 h, then Zn dust, conc. HCl, RT, 16 h, 64%; f) AlH_3 , PhMe, $-78^{\circ}C$ -RT, 4 h, 30%; g) NaH, allyl bromide, DMF, 0 $^{\circ}C$ -RT, 16 h, 29% **302** and 21% **303**; h) AlH_3 , PhMe, $-78^{\circ}C$ -RT, 4 h, 71%.

Scheme 64

Monobenzylated oxindole **300** was subjected to a second alkylation using NaH and allyl bromide to give disubstituted oxindole **302**. *O*-allyl oxindole **303** was also

isolated in 21% yield as a result of aerial oxidation (Scheme 64). Reduction of **302** then gave indoline **304**, synthesised with the view to carrying out a competition experiment under the indolinyl radical forming conditions.

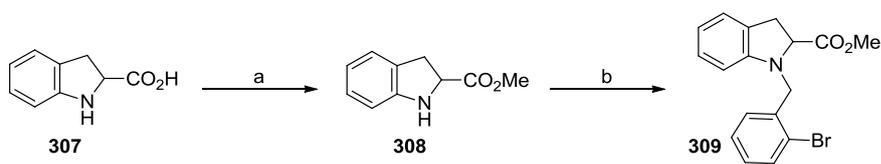
With 3,3-diallylindoline **243** already in hand (*vide supra* Chapter 3.2) synthesis of spiro-analogue **306** was investigated. Treating 3,3-diallylindoline **243** with Hoveyda-Grubbs' II catalyst failed to produce any of the desired spirocyclopentene **306** (Scheme 65). Therefore 3,3-diallyloxindole **242** was instead treated with Hoveyda-Grubbs' II catalyst at reflux and pleasingly oxindole **305** was isolated in 88% yield. Reduction of the carbonyl with alane completed the synthesis of indoline **306** in excellent yield (98%).



a) cat. Hoveyda-Grubbs' II, PhMe, Δ , 22 h, 88%; b) AlH_3 , PhMe, -78°C –RT, 4 h, 98%.

Scheme 65

The final indolinyl radical precursor, methyl ester **309**, was synthesised to investigate the effect of C2 radical stabilisation through conjugation. Commercially available carboxylic acid **307** was esterified and then *N*-benzylated to give the desired indoline **309** in good yield (Scheme 66).



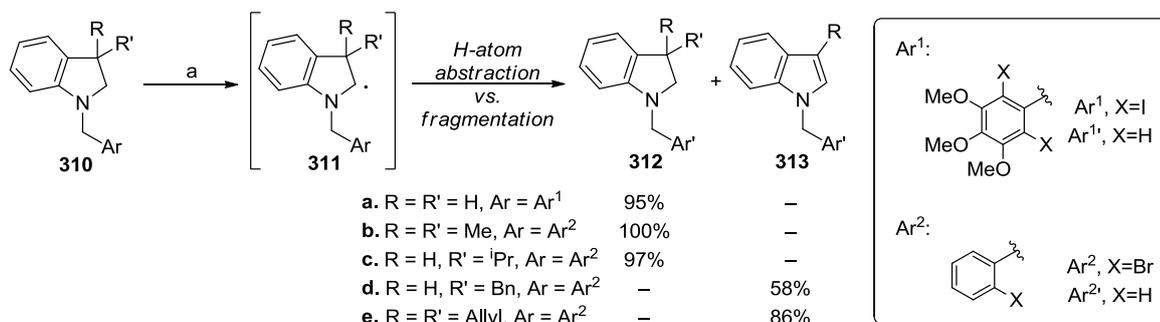
a) SOCl_2 , MeOH, Δ , 2 h, 84%; b) 2-bromobenzyl bromide, K_2CO_3 , KI, MeCN, RT, 12 h, 61%.

Scheme 66

4.3 Indolinyl Radical Reactions

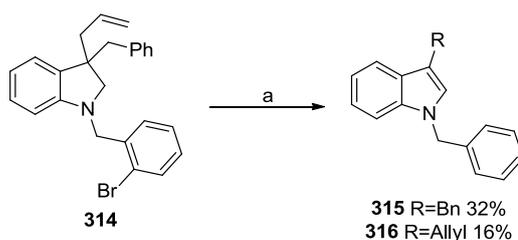
With all the desired indolinyl radical precursors in hand, each one was subjected to the standard radical forming conditions, namely heating a toluene solution of the compound at reflux with tributyltin hydride and VAZO as the initiator (Scheme 67).

The outcome was clear: fragmentation of C3 benzyl and allyl substituents was facile (see entries d and e, Scheme 67), outpacing fragmentation of alkyl substituents and hydrogen atoms. Allyl fragmentation proved more facile than benzyl fragmentation in the competition experiment (*viz.* **314**→**315**+**316**, Scheme 68).⁶⁶



a) Bu₃SnH, VAZO, PhMe, Δ, 18 h.

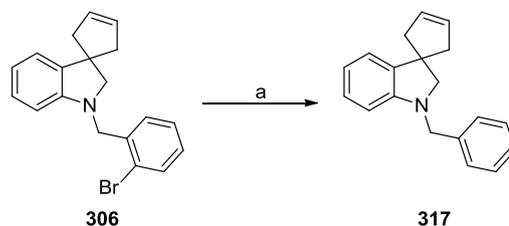
Scheme 67: C2 indolinyl radical investigations.



a) Bu₃SnH, VAZO, PhMe, Δ, 18 h.

Scheme 68

Interestingly, when spirocyclopentene **306** was subjected to radical forming conditions no fragmentation was observed (Scheme 69). Reduced product **317** is presumed to have formed *via* radical translocation followed by H-atom abstraction from tributyltin hydride.



a) Bu₃SnH, VAZO, PhMe, Δ, 18 h, 58%.

Scheme 69

We believe that the increased rigidity inherent to the spirocyclic systems restricts the orbital overlap, therefore favouring the reductive pathway. It can be seen from

Figure 12 that in the spirocyclic system, whilst good $n \rightarrow \sigma_{C-C}$ overlap can be attained, the $\sigma_{C-C} \rightarrow \pi_{C-C}$ overlap is poor causing fragmentation to be a disfavoured process, being more akin to reaction of an alkyl substituent. By way of a comparison, the fragmentation of 3,3-diallylindoline **243** does occur rapidly (*viz.* **243**→**313e**) due to the good overlap that can be attained throughout the allylic system as a result of rotational freedom about the σ -bonds (Figure 12).

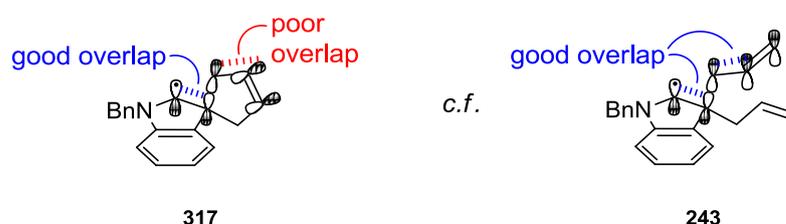
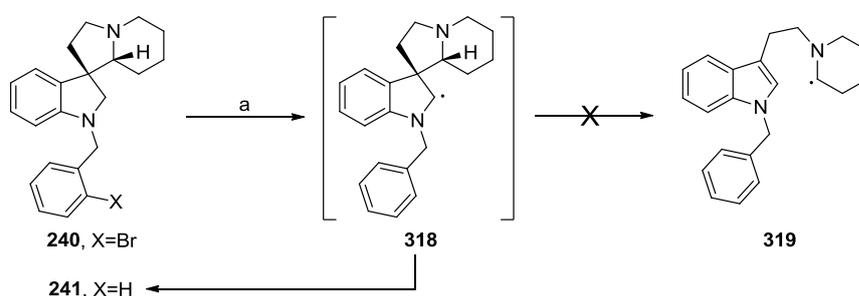


Figure 12: Illustration of orbital overlap in the spirocyclic and allylic systems.

The same effect was seen previously on the *ABDE* tetracyclic system (*vide supra* Chapter 3.2). In addition to the orbital overlap effect seen above, we believe that the poorer stabilisation that would be given by the adjacent nitrogen to the radical product favours the reductive pathway in this case (Scheme 70).

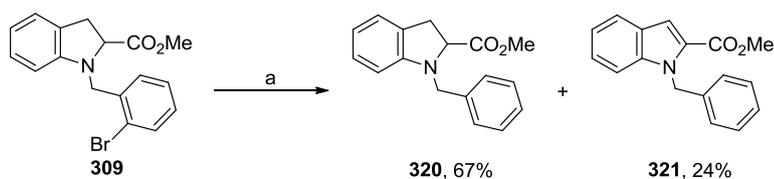


a) Bu_3SnH , VAZO, PhMe, 18 h, 89%.

Scheme 70

Interestingly when the indolinyl radical was stabilised by conjugation, loss of a hydrogen atom from C3 did compete with H-atom abstraction from tributyltin hydride. Indeed, both the reduced and oxidised products **320** and **321** were formed in a ~3:1 ratio (Scheme 71). This is a significant result when compared with the near exclusive formation of the reduced product **312a** in the analogous reduction of the unstabilised indoline **310a*** (Scheme 67).

* When subjected to radical forming conditions indoline **310a** gave reduced product **312a** in excellent yield (95%). In addition, a trace of the tetracyclic product arising from cyclisation of the aryl radical to the C2 position was also formed (5%). It can be therefore be inferred that trace amounts of the oxidised indole product **313a** were formed, despite none being isolated.



a) Bu₃SnH, VAZO, PhMe, Δ.

Scheme 71

4.4 Conclusions

A variety of indolinyl radical precursors were successfully synthesised using alkylation and Aldol reactions. All indolines were subjected to standard radical forming conditions to access the C2 indolinyl radical *via* aryl radical formation and translocation. We conclude that the fate of the indolinyl radical is indeed determined by the substitution at C3 of the indoline, with hydrogen, methyl, primary and secondary alkyl substituents resisting fragmentation. However, when C3 bears a substituent capable of stabilising a radical leaving group we instead see cleavage and formation of the indole product (e.g. benzyl, allyl). This is also true of indolines unsubstituted at C3 but stabilised at the C2 position through conjugation. In such cases fragmentation at C3 appears more facile, perhaps as a result of a slowing of the rate of H-atom abstraction from tributyltin hydride.

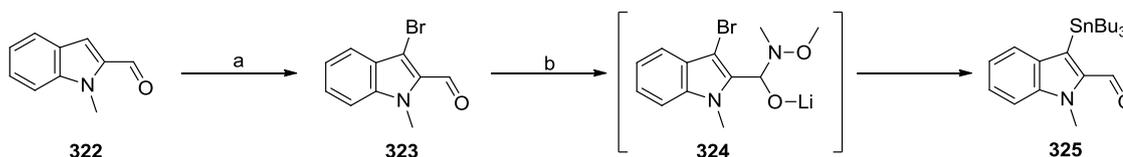
Chapter 5: Results and Discussion

Radical Cyclisation to Pyridine

Having chosen to install the *C* ring *via* radical cyclisation to a pyridyl moiety, work began on the development of a synthetic route to the key radical precursor, vinyl bromide **177**. It was envisaged that a Stille coupling between the indole and pyridyl fragments would provide the most efficient access to this system.

5.1 Synthesis of the Stille Coupling Partners

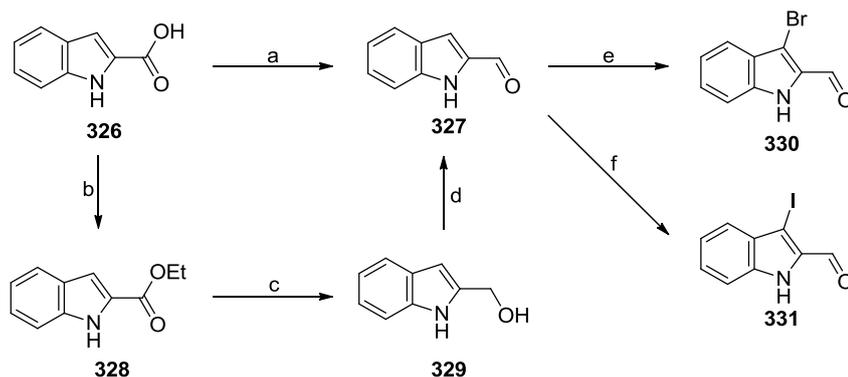
Initial investigations into the synthesis of suitable Stille coupling partners were carried out on *N*-methylindole **322** while an efficient route to the *1H*-indole analogue was sought. Thus, *N*-methylindolecarbaldehyde **322** was brominated with NBS to afford **323** in excellent yield. Stannylation with *in situ* aldehyde protection as the α -amino lithium alkoxide afforded stannane **325**, albeit in low yield (Scheme 72).⁶⁷ It is worth noting that all synthesised stannanes and reactions containing tin residues were purified using our K_2CO_3 / silica chromatographic purification technique.⁶⁸



a) NBS, DMF, RT, 20 h, 94%; b) *N,O*-dimethylhydroxylamine, *n*BuLi, $-78\text{ }^{\circ}\text{C}$ -- $-40\text{ }^{\circ}\text{C}$, 3 h, then *n*Bu₃SnCl, RT, 16 h, 44%.

Scheme 72

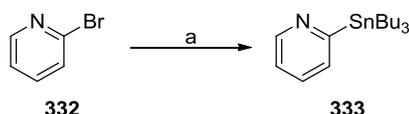
With the stannylated indole **325** in hand, attention then turned to the synthesis of the complimentary coupling partners, that is the halide moiety on the indole fragment and the stannane moiety on the pyridyl fragment. Commercially available indole-2-carboxylic acid **326** was transformed in a two-step, one pot process to aldehyde **327** *via* the acid chloride. However, as this yielded only 19% over the two steps, alternative procedures were investigated. To that end, a three-step procedure involving esterification to **328**, reduction to alcohol **329** and allylic oxidation to aldehyde **327** was developed giving a more reasonable 62% overall yield (Scheme 73).



a) SOCl_2 , THF, 0 °C–50 °C, 4 h, then 10 mol% $\text{Pd}(\text{PPh}_3)_4$, Bu_3SnH , THF, RT, 1 h, 19% over two steps; b) H_2SO_4 , EtOH, Δ , 20 h, 92%; c) LiAlH_4 , THF, -78 °C–0 °C, 1 h, 99%; d) MnO_2 , BaMnO_4 , DCM, RT, 5 d., 68%; e) NBS, DMF, RT, 20 h, 96%; f) I_2 , KOH, DMF, RT, 1.5 h, 99%.

Scheme 73

Halogenation of aldehyde **327** then proceeded smoothly and in excellent yield to afford bromoindole **330** and iodoindole **331** in 96% yield and near quantitative yield respectively (Scheme 73). The stannyl coupling partner for the model system, pyridine **333**, was synthesised in one step from commercially available 2-bromopyridine **332** *via* halogen-lithium exchange and quenching with tributyltin chloride (Scheme 74).



a) $n\text{BuLi}$, Bu_3SnCl , THF, -78 °C–RT, 3 h, 85%.

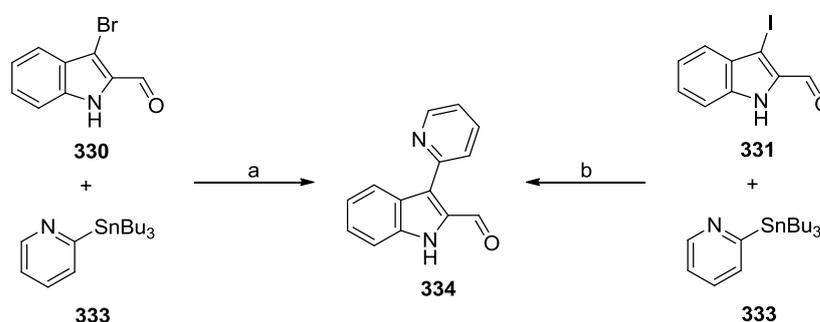
Scheme 74

5.2 Stille Coupling

The Stille reaction is the palladium-catalysed C–C bond forming reaction between an organostannane and an organic electrophile.⁶⁹ It is one of the most general transformations in organic synthesis, displaying high selectivity and broad functional group tolerance, making it particularly appealing to the field of natural product synthesis.⁷⁰

Attempts to effect the coupling of bromopyridine **332** with the stannylated indole **325** failed to afford any product. This is perhaps not unsurprising when the electronics of the Stille reaction are considered. The oxidative insertion step is

most efficient when the halogenated fragment is electron-poor in nature. Similarly, in the transmetallation step it is preferable for the stannane to be electron-rich. This ideal is more akin to the coupling of haloindoles **330** and **331** with pyridyl stannane **333** so we hoped this would offer an improvement. Indeed, upon treatment of bromoindole **330** and stannane **333** with 10 mol% Pd(PPh₃)₄ in the presence of stoichiometric copper(II) oxide desired biaryl **334** was isolated, though in a disappointing 38% yield. Fortunately, iodoindole **331** had also been synthesised and its coupling with pyridyl stannane **333** was realised in an excellent 98% yield (Scheme 75).



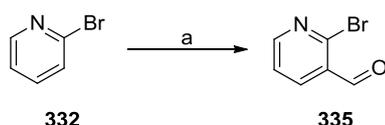
a) Pd(PPh₃)₄, CuO, DMF, Δ , 16 h, 38%; b) Pd(PPh₃)₄, CuI, DMF, RT, 2 d., 98%.

Scheme 75

Copper(I) additives have been shown to dramatically affect the rate of Stille coupling reactions. The first foray into the 'copper effect' was by Liebeskind and Farina, who concluded that the effect of copper(I) salts was dependent upon reaction solvent.⁷¹ In ethereal solvents the copper(I) salt acts as a scavenger for the neutral ligand (in this case PPh₃) released prior to the oxidative insertion step, preventing the retardation effect these free ligands would otherwise have on the rate-determining transmetallation step. In polar solvents, e.g. DMF, it is thought that a second transmetallation pathway comes into play. Thus, the organostannane first reacts with, in this case copper iodide, to afford an iodostannane by-product and a reactive organocuprate that then undergoes transmetallation in the usual fashion.⁷²

5.3 Ethyl Group Installation

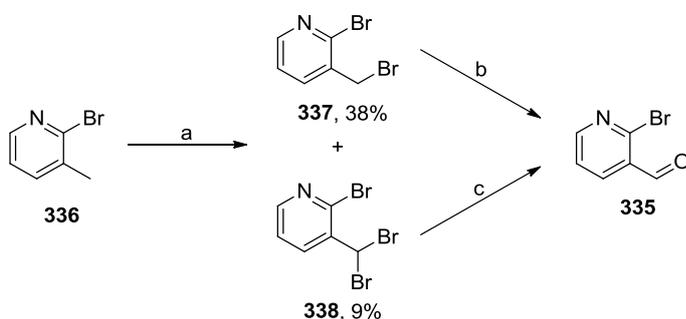
With Stille coupling partners **331** and **333** now in hand and conditions for the coupling identified, attention turned to the incorporation of the ethyl group necessary for the natural product synthesis. It was envisaged that the ethyl group could be accessed from aldehyde **335** using a Wittig olefination followed by reduction of the resultant alkene. Thus, aldehyde **335** was prepared by direct formylation of 2-bromopyridine **332** with DMF (Scheme 76).



a) LDA, DMF, $-78\text{ }^{\circ}\text{C}$ –RT, 16 h, 33%.

Scheme 76

Despite the literature precedent for this step and even with extremely careful temperature control this reaction proved to be capricious, with yields ranging from 0–33%.⁷³ Whilst aldehyde **335** is commercially available, its cost is prohibitive in this case so an alternative strategy was sought. Radical bromination of 3-methyl-2-bromopyridine **336** with NBS in the presence of substoichiometric VAZO and bromine afforded the monobrominated and dibrominated substrates, **337** and **338** respectively, as a 1:4 mixture. Although the minor product was only isolated in 9% yield, on large scales this constitutes an appreciable quantity of material. Therefore oxidation and hydrolysis conditions for the conversion of both bromination products **337** and **338** to aldehyde **335** were identified (Scheme 77).

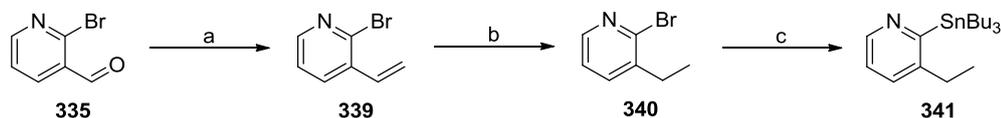


a) NBS, VAZO, Br₂, PhCF₃, Δ , 3 h; b) NMO, MeCN, RT, 3 h, 61%; c) CaCO₃, H₂O, Δ , 15 h, 53%.

Scheme 77

A Wittig reaction between aldehyde **335** and methyltriphenylphosphonium bromide proceeded smoothly under standard conditions to afford alkene **339** in good yield.

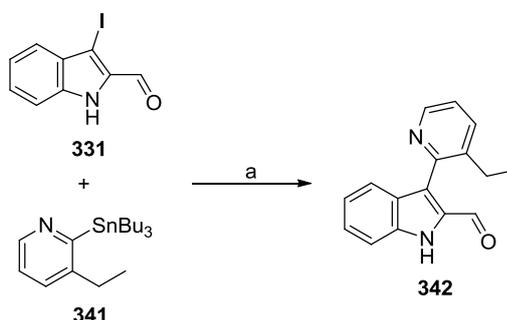
Treatment with *p*-tosylhydrazide and NaOAc in refluxing THF / water formed diimide *in situ* and this smoothly reduced the pendant alkene to afford the desired ethyl substituted pyridine **340** in 75% yield after 7 days. 3-Ethyl-2-bromopyridine **340** was then subjected to the stannylation conditions identified for the model system and, pleasingly, stannane **341** was produced in good yield (Scheme 78).



a) *n*BuLi, MePPh₃Br, THF, 0 °C–RT, 18 h, 88%; b) *p*tosyl hydrazine, NaOAc, THF / H₂O (1:1), Δ, 7 d., 75%; c) *n*BuLi, Bu₃SnCl, THF, –78 °C–RT, 3 h, 87%.

Scheme 78

Iodoindole **331** and stannane **341** were then subjected to the Stille conditions established in the model system. To our delight, the conditions proved to be successful providing the desired biaryl **342** in 82% yield after 18 h at RT (Scheme 79).



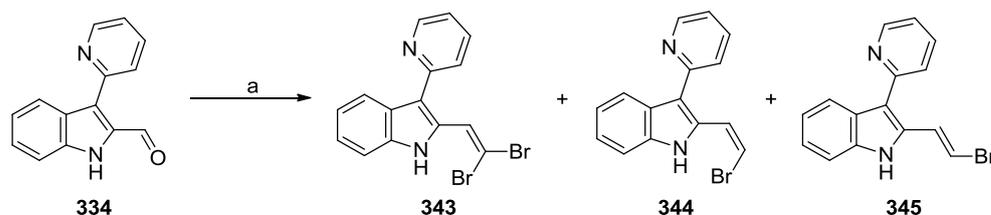
a) Pd(PPh₃)₄, CuI, DMF, RT, 18 h, 82%.

Scheme 79: Stille coupling.

5.4 Wittig Olefination

Owing to the commercial availability of bromomethyltriphenylphosphonium bromide, a Wittig reaction was examined to install the important vinyl bromide moiety.⁷⁴ Thus, aldehyde **334** was treated with bromomethyltriphenylphosphonium bromide in the presence of potassium *t*butoxide to afford the desired vinyl bromide as a *cis* / *trans* inseparable mixture along with side-product dibromoalkene **343** (Scheme 80). Despite the modest yield, no unreacted aldehyde **334** was recovered. As we had observed significant starting material by TLC analysis we

postulated that aldehyde **334** was unstable towards silica. Indeed, the purification procedure used in the preparation of aldehyde **334** was our K_2CO_3 / silica technique used to remove the organotin residues from the Stille reaction, implying an acid-sensitivity. Consequently when subsequent Wittig reactions were purified with this basified stationary phase (10% w/w anhydrous K_2CO_3 -silica), aldehyde **334** was recovered, completing the mass balance.



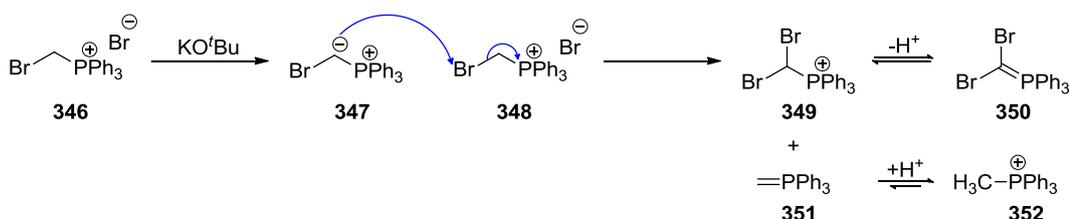
a) $BrCH_2PPh_3^+Br^-$ (2.2 eq), $KOtBu$ (2.2 eq), THF, $-78\text{ }^\circ\text{C}$ -RT, 16 h, 3% **343**, 24% **343:344:345** (1:1.8:0.2), 6% **344:345** (1:0.4), or $BrCH_2PPh_3^+Br^-$ (1.5 eq), NaHMDS (1.3 eq), THF, RT, 16 h, 20% **343**, 31% **343:344:345** (1:1.5:1), 22% **334**.

Scheme 80

Optimisation of reaction conditions met with limited success, with most attempts resulting in little or no improvement. Our best conditions utilised a different base, namely NaHMDS, reaction stoichiometry and addition sequence, namely preformed ylide was added to aldehyde **334**. In addition to an increased yield of *cis*- and *trans*-alkenes **344** and **345**, we also observed an increase in the formation of dibromoalkene **343**. This is perhaps unsurprising considering our proposed mechanism, as a slight excess of phosphonium salt is now present.

We believe that dibromoalkene **343** is formed from reaction of ylide **347** with another molecule of its unreacted self to form dibrominated phosphonium salt **349** (Scheme 81). In turn, this can undergo the Wittig reaction with aldehyde **334**. This mechanism is supported by Chapleur *et al.* who reported the first preparative use of this reaction in 2001.⁷⁵ Indeed, until their investigations there had only been a few reports in the literature for the formation of such a side-product.^{76,77} Using phosphorous NMR to follow the course of the reaction, Chapleur *et al.* were able to identify five phosphorylated species after phosphonium salt **346** had been treated with $KOtBu$ in THF for 2 h. The identified species were ylide **347** (12.5 ppm), phosphonium salt **346** (14 ppm), triphenylphosphine oxide (21.6 ppm), phosphonium salt **352** (22.5 ppm) and dibrominated phosphonium salt **349** (26.7 ppm). The authors noted that no traces of phosphorane **351** were detected

in any studies concluding a 'rapid ylide exchange' between **351** and **349**, favouring the formation of phosphorane **350** and methyltriphenylphosphonium salt **352**. This provided strong evidence for the postulated mechanism above, rather than the alternative method for formation initially suggested by Chapleur, namely electrophilic bromination of the monobromoalkene followed by elimination to give the dibromoalkene.



Scheme 81: Postulated mechanism for the formation of dibromoalkene **343**.

Using our optimised Wittig conditions a similar study was carried out, analysing the reaction of phosphonium salt **346** with NaHMDS at RT by ^{31}P NMR at various time intervals (Figure 13).

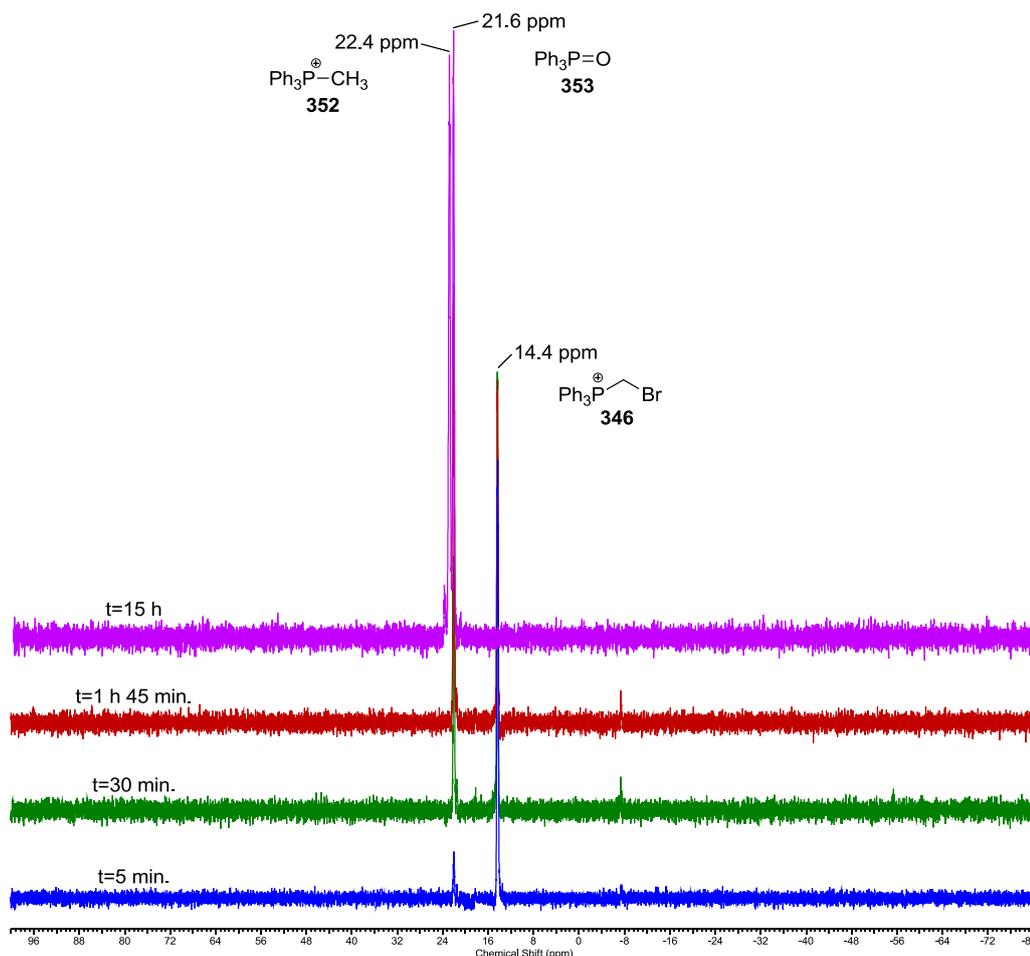
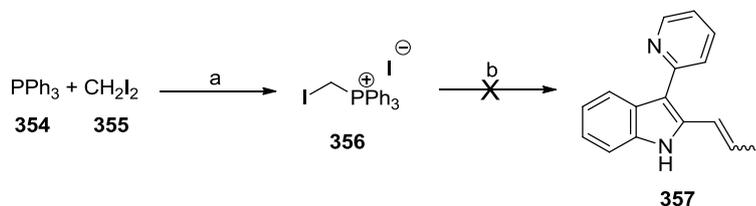


Figure 13: ^{31}P NMR spectra of phosphonium salt **346** (1.5 eq.) with NaHMDS (1.3 eq.) in THF.

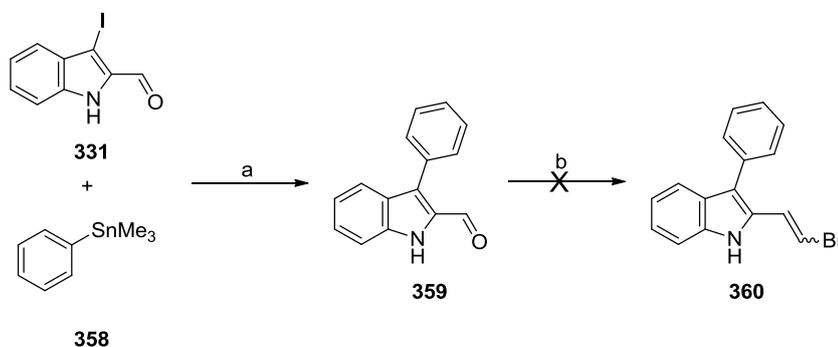
Pleasingly, signals indicative of dibrominated phosphonium salt formation were identified. Although no direct spectral evidence for the presence of dibrominated phosphonium salt **349** could be detected at the time intervals analysed, the formation of phosphonium salt **352** (22.4 ppm) was evident at $t=15$ h. The formation of dibrominated phosphonium salt **349** can be inferred from the observed presence of methyltriphenylphosphonium salt **352**, which ties in with the mechanistic postulate.

Phosphonium iodide **356** was also synthesised in 95% yield during the course of the Wittig optimisation studies. However, when used in the Wittig reaction no vinyl iodide product **357** was isolated (Scheme 82). The low yielding Wittig transformation could be due to either the steric bulk of the system or pyridyl $N \rightarrow ^+PR_4$ coordination. To ascertain whether either of these explanations was indeed affecting the Wittig transformation, phenyl substituted indole **359** was synthesised by the Stille coupling of iodide **331** and trimethylphenyltin **358** (Scheme 83). Indole **359** was formed as an inseparable mixture with unreacted iodide **331**. However, when subjected to the Wittig conditions no product was observed. As a result we suspect the reason for the poor Wittig yield to be a steric issue rather than one resulting from N -coordination.



a) PhMe, 100 °C, 20 h, 95%; b) $ICH_2PPh_3^+I^-$, NaHMDS, THF, -78 °C-RT, 16 h.

Scheme 82

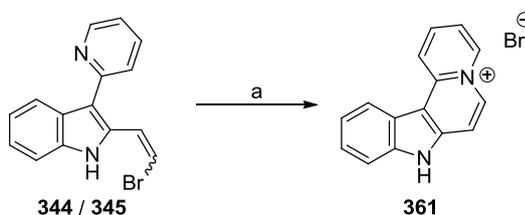


a) $Pd(PPh_3)_4$, CuI, DMF, Δ , 3 h, 41% as a 1.2:1 (**359**:**331**) inseparable mixture.

Scheme 83

5.5 Radical Cyclisation

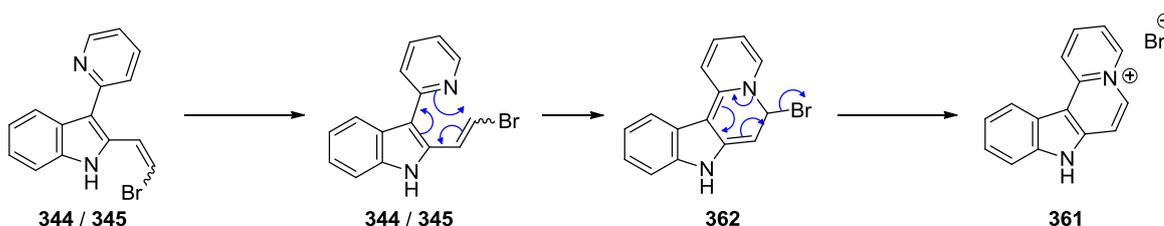
With key precursors **344** and **345** in hand, our investigation of the key radical cyclisation began. As the first action of the radical cyclisation process is homolysis of the C–Br bond, and it is known that vinyl radical intermediates are configurationally labile, mixtures of *cis* / *trans* / dibromoalkene **344**, **345** and **343** were subjected to the radical forming conditions. When vinyl bromide (as a 5:1 *cis* / *trans* mixture) was treated with tributyltin hydride and VAZO at reflux a precipitate was observed. Interestingly pyridinium salt **361** had been formed in 60% yield, rather than the desired 6-*exo/endo*-trig cyclisation product (Scheme 84). To the best of our knowledge pyridinium salt **361** represents a unique structural motif.



a) Bu₃SnH, VAZO, PhMe, Δ, 16 h, 60%.

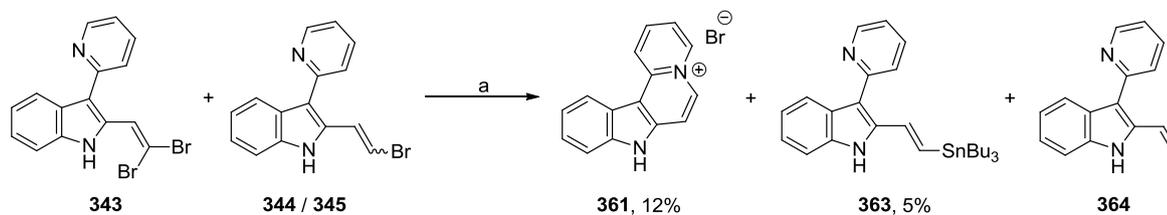
Scheme 84

Subsequently we discovered that the tributyltin hydride used in the reaction had decomposed prior to use. Consequently, the rearrangement of vinyl bromides **344** / **345** to the condensed heteroaromatic **361** was, in all probability, induced by thermolysis. This led us to postulate that pyridinium salt **361** arose from a 6π-electrocyclisation reaction followed by rearomatisation with loss of bromide in a manner akin to that outlined in Scheme 85. It is worth noting that although this leads to a loss of aromaticity in both heterocyclic rings, the 'enamine' nature of the indole should accelerate the 6π-electrocyclisation process.



Scheme 85: Postulated mechanism.

In repeating the reaction with fresh reagents, we hoped that the desired radical cyclisation reaction might outpace the 6π -electrocyclisation, allowing us access to the desired *ABCE* ring system of aspidospermidine **6**. As such, a mixture of bromoalkenes **343**, **344** and **345** (1:1.5:1) was heated at reflux with tributyltin hydride and radical initiator VAZO (Scheme 86). Pleasingly, considerably less pyridinium salt **361** was isolated. However after 16 h at reflux, and despite the complete consumption of vinyl bromide, none of the desired *6-exo/endo*-trig product was observed. Furthermore, vinyl stannane **363** was isolated as a minor by-product. The remainder of the mass balance was attributed by crude NMR analysis to be terminal alkene **364**, resulting from either C–Br bond homolysis followed by H-atom abstraction from tributyltin hydride or, protodestannylation of **363**, although it was not possible to isolate this product.



a) Bu_3SnH , VAZO, PhMe, Δ , 16 h.

Scheme 86

5.6 Conclusions

The key intermediates for both the model and natural product systems, aldehydes **334** and **342**, were successfully synthesised using high yielding palladium-catalysed coupling reactions. In addition, robust routes to the individual Stille coupling partners were identified. A Wittig reaction then provided small quantities of the key intermediate vinyl bromides **343**, **344** and **345** in the model system, though their synthesis in large quantities was precluded due to a low yield even after optimisation.

The key radical cyclisation was investigated on the model system with little success. However, an interesting product arose as a result of competing 6π -electrocyclisation. This provided tetracyclic pyridinium salt **361** as the major product which, to the best of our knowledge, represents a unique structural motif. Work is currently ongoing to investigate the scope of the 6π -electrocyclisation with a variety of *N*-containing heterocycles.

Chapter 6: Experimental

6.1 General Experimental

Melting Points: Melting points were recorded on Reichert Austria apparatus and are uncorrected.

NMR Spectra: Proton (^1H) and carbon (^{13}C) spectra were recorded on a Bruker AVX300 (300/75 MHz) or Bruker DPX400 (400/100 MHz) spectrometer at 298 K unless otherwise stated. Chemical shifts are quoted in parts per million downfield of tetramethylsilane with residual solvent as the internal standard. Assignments were made on the basis of chemical shifts, coupling constants, DEPT-135, COSY, HMQC, HMBC and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), app. (apparent) and br. (broad). Coupling constants (J) are given in Hz and are rounded to the nearest 0.1 Hz.

Infrared Spectra: Infrared spectra were recorded neat as an oil film or solid compression using the ATR/golden gate method. Absorption maxima (ν_{max}) are described as s (strong), m (medium) and w (weak) and are quoted in wavenumbers (cm^{-1}).

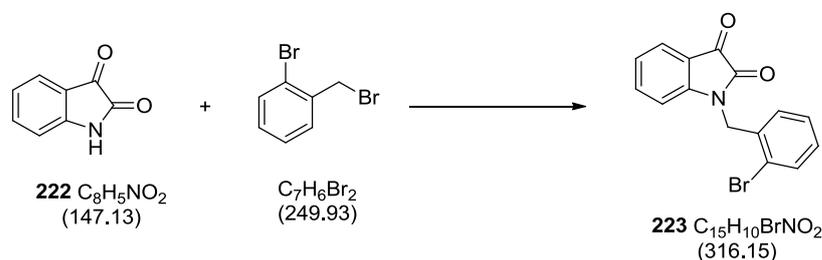
Mass Spectra: ESI mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring mono-isotopic masses (mode: ES+ or ES-). EI and CI were measured on a Thermoquest Trace MS. m/z values are reported with their percentage abundance relative to the most intense signal and, where known, the relevant fragment ion in parentheses. Values for the most abundant isotope combination are reported. High resolution mass spectra were recorded by Dr. John Langley or Ms. Julie Herniman at the University of Southampton and are calculated to four decimal places from the molecular formula.

Chromatography Techniques: Thin layer chromatography was performed on Merck DC-Alufolien 60 F₂₅₄ 0.2 mm precoated plates. Product spots were visualised by UV fluorescence ($\lambda_{\text{max}}=254$ nm) then stained and heated using, most

commonly, 5% potassium permanganate in 5% aqueous NaOH solution or 6% vanillin in ethanol as appropriate. Flash column chromatography was carried out on silica gel (200–400 mesh) with the solvent system used given in parentheses.

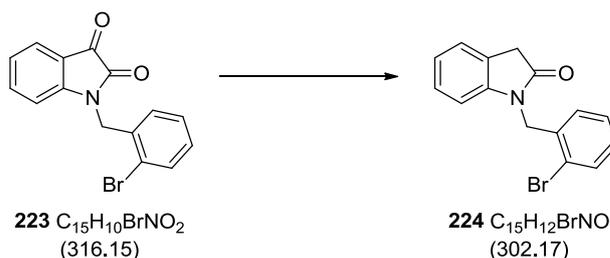
Solvents and Reagents: Commercially available reagents were purchased and used without further purification. THF and diethyl ether were freshly distilled and dried over a purple solution of sodium and benzophenone, toluene and acetonitrile were freshly distilled over sodium and dichloromethane and chloroform were distilled and dried over CaH_2 immediately prior to use.

6.2 Experimental Procedures for Chapter 3

1-(2-Bromobenzyl)-1*H*-indole-2,3-dione (**223**)

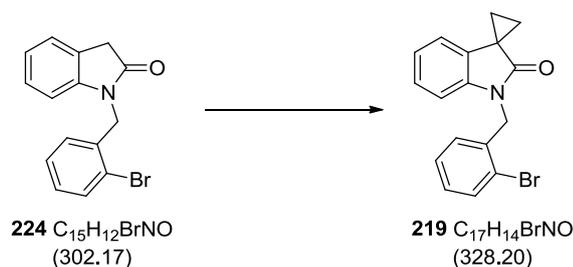
To a solution of isatin **222** (2.00 g, 13.6 mmol) in acetonitrile (100 mL) was added K_2CO_3 (3.76 g, 27.2 mmol) and KI (230 mg, 1.36 mmol). After 45 min, 2-bromobenzyl bromide (3.40 g, 13.6 mmol) in acetonitrile (30 mL) was added dropwise over 30 min. After 17 h ethyl acetate (100 mL) and water (100 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (3 \times 100 mL) then the combined organic phases were washed with brine (100 mL), dried (MgSO_4) and the solvent removed *in vacuo* to afford the title compound as an orange solid (4.19 g, 13.3 mmol, 98%). These data are in accordance with those reported in the literature.¹⁷

MP	177–181 °C (EtOH), Lit. 180–182 °C (EtOH). ¹⁷
ν_{max}	3334 (w), 3097 (w), 2930 (w), 1735 (s), 1643 (m), 1610 (s), 1530 (m), 1470 (m), 1439 (w), 1373 (m), 1350 (m), 1279 (w), 1197 (w).
δ_{H} (300 MHz, CDCl_3)	7.67–7.50 (2H, m, 2 \times ArH), 7.43 (1H, app. td, $J=7.8, 1.3$ Hz, ArH), 7.26–6.95 (4H, m, 4 \times ArH), 6.67 (1H, d, $J=7.7$ Hz, ArH), 4.98 (2H, s, NCH_2Ar).
δ_{C} (75 MHz, CDCl_3)	182.9 (C=O), 158.4 (C=O) 150.5 (C), 138.5 (CH), 133.2 (CH), 129.6 (CH), 128.1 (CH), 128.1 (CH), 125.5 (CH), 124.1 (CH), 122.8 (C), 117.7 (C), 111.1 (CH), 44.0 (CH_2). <i>N.B.</i> One quaternary signal not discreetly observed.
LRMS (ES⁺)	⁷⁹ Br: 338 ($[\text{M}+\text{Na}]^+$, 100%).

1-(2-Bromobenzyl)-1,3-dihydroindol-2-one (224)

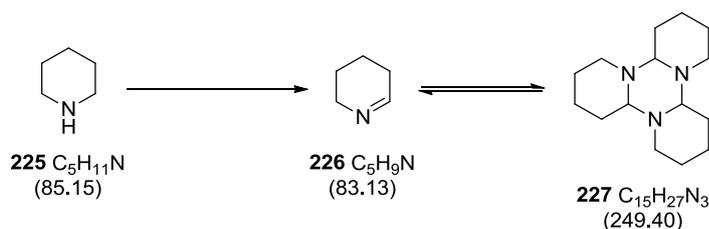
A suspension of *N*-benzylated isatin **223** (3.28 g, 10.4 mmol) in hydrazine monohydrate (20 mL) was heated at reflux for 2 h, then cooled to RT and poured into ice water (100 mL). Following extraction with ethyl acetate (4 × 100 mL), the combined organic phases were washed with brine (100 mL), dried (MgSO₄) and the solvent removed *in vacuo* to afford the title compound as an orange solid (2.83 g, 9.37 mmol, 90%). These data are in accordance with those reported in the literature.¹⁷

MP	88–97°C (EtOH), Lit. 102–104°C (EtOH). ¹⁷
ν_{max}	3057 (w), 1710 (s), 1615 (m), 1489 (m), 1466 (m), 1440 (w), 1376 (w), 1348 (m), 1310 (w), 1268 (w), 1227 (w), 1196 (w), 1169 (w), 1098 (w).
δ_H (300 MHz, CDCl₃)	7.52 (1H, dd, <i>J</i> =7.7, 1.1 Hz, <i>ArH</i>), 7.22 (1H, d, <i>J</i> =7.6 Hz, <i>ArH</i>), 7.17–7.02 (3H, m, 3 × <i>ArH</i>), 7.01–6.92 (2H, m, 2 × <i>ArH</i>), 6.59 (1H, d, <i>J</i> =7.8 Hz, <i>ArH</i>), 4.95 (2H, s, CH ₂), 3.61 (2H, s, CH ₂).
δ_C (75 MHz, CDCl₃)	175.2 (C=O), 144.0 (C), 134.5 (C), 132.9 (CH), 129.0 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 124.5 (CH), 124.3 (C), 122.8 (C), 122.6 (CH), 109.2 (CH), 43.8 (CH ₂), 35.8 (CH ₂).
LRMS (ES⁺)	⁷⁹ Br: 324 ([M+Na] ⁺ , 100%).

1'-(2-Bromobenzyl)-spirocyclopropane-1,3'-indol-2'-one (219)

To a solution of oxindole **224** (2.77 g, 9.17 mmol) in DMF (50 mL) at 0 °C was added NaH (60% in mineral oil, 810 mg, 20.2 mmol). After 1 h at 0 °C, 1,2-dibromoethane (3.16 mL, 36.7 mmol) was added dropwise over 5 min. The reaction mixture was warmed to RT and after 72 h water (100 mL) and ethyl acetate (100 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phases were washed with water (4 × 100 mL) and brine (200 mL), then dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% ethyl acetate in hexanes) afforded the title compound as an orange solid (2.06 g, 6.28 mmol, 69%). These data are in accordance with those reported in the literature.¹⁷

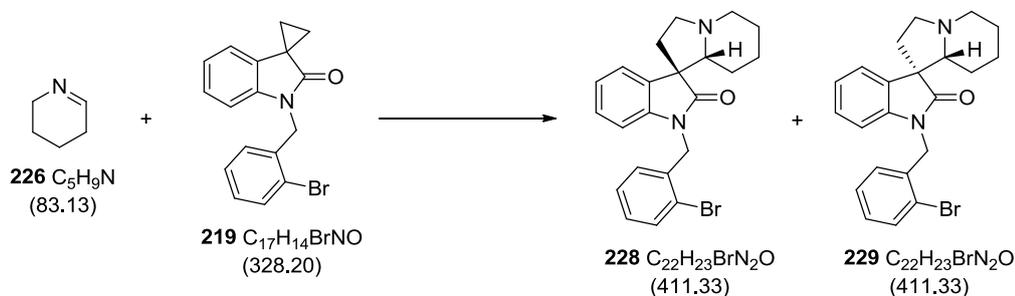
MP	129–131 °C (EtOAc/hexanes), Lit. 115–117 °C (EtOH). ¹⁷
ν_{max}	3057 (w), 1709 (s), 1615 (m), 1568 (w), 1489 (m), 1466 (s), 1440 (m), 1420 (w), 1369 (s), 1349 (m), 1309 (w), 1264 (w), 1230 (w), 1178 (s), 1122 (w).
δ_H (300 MHz, CDCl₃)	7.51 (1H, dd, <i>J</i> =7.9, 1.3 Hz, <i>ArH</i>), 7.15–7.00 (3H, m, 3 × <i>ArH</i>), 6.99–6.88 (2H, m, 2 × <i>ArH</i>), 6.80 (1H, d, <i>J</i> =7.3 Hz, <i>ArH</i>), 6.65 (1H, d, <i>J</i> =7.7 Hz, <i>ArH</i>), 5.01 (2H, s, NCH ₂ Ar), 1.94–1.76 (2H, m, CHHCHH), 1.57–1.43 (2H, m, CHHCHH).
δ_C (75 MHz, CDCl₃)	177.3 (C=O), 142.4 (C), 134.8 (C), 132.9 (CH), 130.7 (C), 128.9 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 122.7 (C), 122.3 (CH), 118.4 (CH), 109.0 (CH), 44.1 (CH ₂), 27.1 (C), 19.5 (2 × CH ₂).
LRMS (ES⁺)	⁷⁹ Br: 350 ([M+Na] ⁺ , 100%).

2,3,4,5-Tetrahydropyridine (226)

To a solution of piperidine **225** (4.60 mL, 47.0 mmol) in water (4 mL) was added glacial acetic acid (3.80 mL, 61.6 mmol). This solution was then added dropwise to a slurry of calcium hypochlorite (4.64 g, 32.4 mmol) stirred in water (10 mL) and MTBE (10 mL) at $-10\text{ }^{\circ}\text{C}$ over 10 min. After 0.5 h the organic phase was separated and a solution of KOH (3.80 g, 68.8 mmol) in MeOH (10 mL) added dropwise at $0\text{ }^{\circ}\text{C}$ over 15 min. The reaction mixture was warmed to RT and stirred for 16 h. The resultant precipitate was isolated by filtration, washed with methanol and the filtrate concentrated *in vacuo*. The residue and precipitate were combined in water (100 mL) and extracted with diethyl ether ($3 \times 80\text{ mL}$). The combined organic phases were washed with brine (100 mL), dried (MgSO₄), then concentrated *in vacuo* to give a pale yellow oil. The oil was taken up in acetone (10 mL) and cooled to $-20\text{ }^{\circ}\text{C}$ overnight. The resultant precipitate was isolated by filtration and washed with cold acetone to afford the title compound as a white solid (433 mg, 5.21 mmol, 11%). These data are in accordance with those reported in the literature.⁴⁷

MP	50–54 $^{\circ}\text{C}$ (acetone)
ν_{max}	2930 (s), 2856 (m), 2813 (w), 2783 (w), 2725 (w), 1446 (m), 1378 (w), 1343 (w), 1312 (w), 1286 (w), 1271 (w), 1257 (w), 1240 (s), 1204 (w), 1188 (m), 1157 (w).
δ_{H} (300 MHz, CDCl₃)	3.21–3.00 (3H, m, NCH), 2.81 (3H, m, 3 \times NCHH), 2.10–1.97 (3H, m, 3 \times NCHH), 1.80–1.47 (15H, m, 3 \times CH ₂ CH ₂ CHH), 1.40–1.10 (3H, m, 3 \times CHH).
δ_{C} (75 MHz, CDCl₃)	81.9 (CH), 46.3 (CH ₂), 29.1 (CH ₂), 25.7 (CH ₂), 22.2 (CH ₂).
LRMS (ES⁺)	167 ([2M+H] ⁺ , 100%), 250 ([M+H] ⁺ , 6%).

***rel*-(1'*S*,8'*aR*)-Spiro[3H-indole-3,1'(5'H)-indolizin]-2(1H)-one,2',3',6',7',8',8'*a*-hexahydro-1-(2-bromobenzyl)(228) and *rel*-(1'*R*,8'*aR*)-spiro[3H-indole-3,1'(5'H)-indolizin]-2(1H)-one,2',3',6',7',8',8'*a*-hexahydro-1-(2-bromobenzyl)(229)**



A solution of cyclopropane **219** (100 mg, 0.31 mmol), imine **226** (67 mg, 0.27 mmol) and MgI₂ (36 mg, 0.13 mmol) in THF (2 mL) was degassed for 30 min. The reaction vessel was then heated under microwave irradiation (150 W, 125 °C) for 5 h. After cooling to RT water (10 mL) and ethyl acetate (10 mL) were added. The aqueous phase was separated and extracted with ethyl acetate (2 × 10 mL), then the combined organic phases were washed with brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (40% ethyl acetate in hexanes–1% methanol in ethyl acetate) afforded firstly **228** as a colourless oil (80 mg, 0.20 mmol, 74%) and then **229** as a colourless oil (11 mg, 0.03 mmol, 11%) in a diastereomeric ratio of 88:12 based on isolated mass.

Data for 228:

ν_{\max}	2931 (m), 2855 (w), 2793 (w), 1716 (s), 1612 (m), 1486 (m), 1466 (m), 1440 (m), 1382 (m), 1359 (m), 1318 (w), 1263 (w), 1200 (w), 1171 (m), 1150 (w), 1113 (w).
δ_{H} (300 MHz, CDCl ₃)	7.52 (1H, dd, $J=7.8, 1.4$ Hz, ArH), 7.40 (1H, d, $J=7.4$ Hz, ArH), 7.16–7.01 (3H, m, 3 × ArH), 6.98 (1H, app. td, $J=7.5, 1.1$ Hz, ArH), 6.89 (1H, dd, $J=7.5, 1.7$ Hz, ArH), 6.56 (1H, d, $J=7.5$ Hz, ArH), 5.03 (1H, d, $J=16.7$ Hz, NCHHAr), 4.85 (1H, d, $J=16.7$ Hz, NCHHAr), 3.34–3.20 (1H, m, NCHH), 3.15 (1H, app. d, $J=10.6$ Hz,

NCHH), 2.55–2.39 (2H, m, NCH₂), 2.36 (1H, ddd, $J=15.1, 9.2, 2.3$ Hz, NCH), 2.11–1.93 (2H, m, 2 × CHH), 1.68–1.47 (2H, m, 2 × CHH), 1.46–1.26 (1H, m, CHH), 1.25–1.01 (3H, m, 3 × CHH).

δ_C (75 MHz, CDCl₃) 179.9 (C=O), 141.9 (C), 134.7 (C), 133.5 (C), 133.0 (2 × CH), 128.9 (CH), 127.7 (CH), 127.6 (CH), 125.0 (CH), 122.8 (C) 122.6 (CH), 108.7 (CH), 72.1 (CH), 56.6 (C), 54.2 (CH₂), 53.6 (CH₂), 43.9 (CH₂), 35.1 (CH₂), 26.5 (CH₂), 25.1 (CH₂), 23.7 (CH₂).

LRMS (ES⁺) ⁷⁹Br: 411 ([M+H]⁺, 99%).

HRMS C₂₂H₂₄BrN₂O [M+H]⁺ requires 411.1067; found: 411.1066.

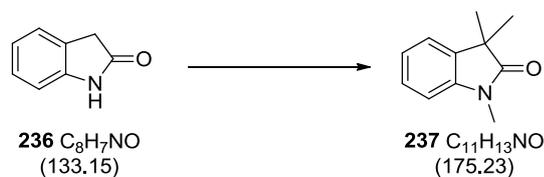
Data for 229:

ν_{max} 3057 (w), 2924 (m), 2853 (w), 2788 (w), 2364 (w), 1716(s), 1612 (m), 1488 (m), 1467 (m), 1441 (m), 1355 (m), 1267 (w), 1171 (m), 1113 (w), 1028 (w), 749 (m).

δ_H (300 MHz, CDCl₃) 7.60 (1H, dd, $J=7.8, 1.3$ Hz, ArH), 7.24–6.97 (6H, m, 6 × ArH), 6.60 (1H, d, $J=8.0$ Hz, ArH), 5.17 (1H, d, $J=16.9$ Hz, NCHHAr), 4.86 (1H, d, $J=16.9$ Hz, NCHHAr), 3.47–3.36 (1H, m, NCHH), 3.35–3.26 (1H, m, NCHH), 2.60–2.40 (2H, m, NCH₂), 2.32–2.21 (1H, m, NCH), 2.14–1.86 (2H, m, 2 × CHH), 1.84–1.39 (4H, m, 4 × CHH), 1.34 (1H, m, CHH), 1.20–1.05 (1H, m, CHH).

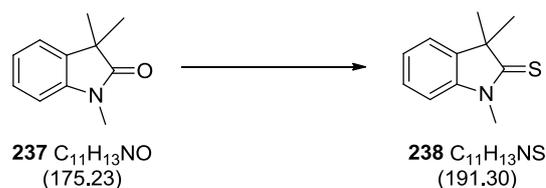
LRMS (ES⁺) ⁷⁹Br: 411 ([M+H]⁺, 99%).

HRMS C₂₂H₂₄BrN₂O [M+H]⁺ requires 411.1067; found: 411.1070.

1,3,3-Trimethyloxindole (237)

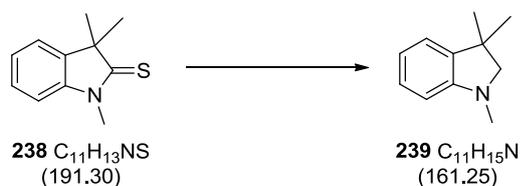
To a solution of oxindole **236** (1.00 g, 7.51 mmol) in THF (24 mL) was added NaH (1.20 g, 30.0 mmol) and MeI (1.64 mL, 26.3 mmol) at 0°C. The reaction mixture was warmed to RT and after 18 h was poured onto saturated NH₄Cl (40 mL) and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (30% ethyl acetate in petroleum ether) afforded the title compound as a pale red oil (1.23 g, 7.02 mmol, 93%). These data are in accordance with those reported in the literature.⁷⁹

ν_{max}	2967 (w), 2927 (w), 1702 (s), 1612 (s), 1492 (m), 1471 (m), 1459 (m), 1382 (m), 1373 (m), 1347 (m), 1305 (m), 1247 (m), 1195 (w), 1157 (w).
δ_{H} (300 MHz, CDCl ₃)	7.27 (1H, app. td, $J = 7.5, 1.3$ Hz, ArH), 7.21 (1H, dd, $J = 7.3, 0.9$ Hz, ArH), 7.07 (1H, app. td, $J = 7.5, 0.9$ Hz, ArH), 6.85 (1H, d, $J = 7.7$ Hz, ArH), 3.22 (3H, s, CH ₃), 1.38 (6H, s, CH ₃).
δ_{C} (75 MHz, CDCl ₃)	181.4 (C=O), 142.6 (C), 135.8 (C), 127.6 (CH), 122.4 (CH), 122.2 (CH), 108.0 (CH), 44.1 (C), 26.1 (CH ₃), 24.3 (2 × CH ₃).
LRMS (ES ⁺)	198([M+Na] ⁺ , 100%).

1,3,3-Trimethyl-1,3-dihydroindole-2-thione (238)

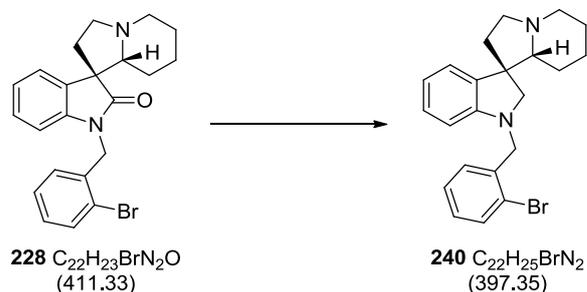
To a solution of oxindole **237** (115 mg, 0.66 mmol) in DCM (2 mL) was added POCl_3 (0.12 mL, 1.32 mmol) dropwise over 5 min. The reaction mixture was then heated at reflux for 2.5 h, then cooled to RT and TMS_2S (0.43 mL, 2.05 mmol) added. After a further 18 h at reflux the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by column chromatography (2% diethyl ether in petroleum ether) afforded the title compound as a pale yellow oil (54 mg, 0.28 mmol, 43%). These data are in accordance with those reported in the literature.⁸⁰

ν_{max}	2967 (w), 2923 (w), 2860 (w), 1613 (m), 1600 (w), 1458 (m), 1429 (m), 1364 (s), 1306 (s), 1259 (m), 1154 (m), 1106 (s), 1071 (w).
δ_{H} (300 MHz, CDCl_3)	7.39–7.29 (2H, m, ArH), 7.24–7.15 (1H, m, ArH), 7.06 (1H, d, $J=7.7$ Hz, ArH), 3.67 (3H, s, CH_3), 1.45 (6H, s, CH_3).
δ_{C} (75 MHz, CDCl_3)	211.9 (C=S), 143.8 (C), 140.4 (C), 127.8 (CH), 124.2 (CH), 122.7 (CH), 109.5 (CH), 54.9 (C), 31.4 (CH_3), 28.0 ($2 \times \text{CH}_3$).
LRMS (ES^+)	192 ($[\text{M}+\text{H}]^+$, 100%).

1,3,3-Trimethyl-2,3-dihydro-1H-indole (239):

To a solution of thioamide **238** (134 mg, 0.70 mmol) in DCM (3 mL) at 0°C was added $\text{Me}_3\text{O}^+\text{BF}_4^-$ (108 mg, 0.73 mmol) and then warmed to RT. After 18 h the reaction mixture was concentrated *in vacuo* to afford an off-white solid which was then taken up in methanol (3 mL). NaBH_4 (68 mg, 1.79 mmol) was then added at 0 °C and after 10 min was warmed to RT. After 4 h 2 M HCl (4 mL) was added and after a further 5 min the reaction mixture was basified with 2 M NaOH (~pH 10). The reaction mixture was extracted with diethyl ether (3 × 20 mL) and the combined organic phases washed with brine (40 mL), then dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (15–25% DCM in petroleum ether) afforded the title compound as a colourless oil (12 mg, 0.074 mmol, 11 %). These data are in accordance with those reported in the literature.⁸¹

ν_{max}	3024 (w), 2954 (m), 2858 (m), 2801 (m), 2158 (w), 2025 (w), 1607 (m), 1490 (m), 1461 (m), 1422 (w), 1385 (w), 1372 (w), 1298 (m), 1279 (m), 1261 (m), 1200 (m).
δ_{H} (300 MHz, CDCl_3)	7.13 (1H, app. t, $J=7.7$ Hz, ArH), 7.05 (1H, d, $J=7.0$ Hz, ArH), 6.74 (1H, app. t, $J=7.3$ Hz, ArH), 6.52 (1H, d, $J=8.1$ Hz, ArH), 3.10 (2H, s, CH_2), 2.79 (3H, s, CH_3), 1.34 (6H, s, CH_3).
δ_{C} (75 MHz, CDCl_3)	152.0 (C), 139.2 (C), 127.2 (CH), 121.5 (CH), 117.8 (CH), 107.3 (CH), 70.3 (CH_2), 40.2 (C), 36.0 (CH_3), 27.4 (2 × CH_3).
LRMS (ES^+)	162 ($[\text{M}+\text{H}]^+$, 100%).

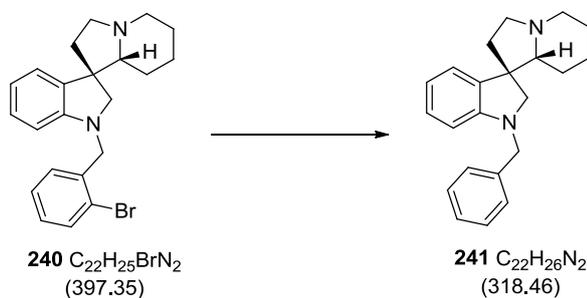
***rel*-(1'S,8a'R)-1-(2-Bromobenzyl)-3',5',6',7',8',8a'-hexahydro-2'H-spiro[indoline-3,1'-indolizine] (240)**

To a solution of **228** (80 mg, 0.19 mmol) in toluene (2 mL) at $-78\text{ }^{\circ}\text{C}$ was added AlH_3 (0.5 M in toluene, 0.96 mL, 0.48 mmol) dropwise over 5 min. After a further 20 min the reaction mixture was warmed to RT for 4 h and then cooled to $0\text{ }^{\circ}\text{C}$. Methanol (1 mL) was added dropwise and then 1 M HCl (1 mL). The reaction mixture was basified with saturated NaHCO_3 ($\sim\text{pH } 10$) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with brine (30 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (25–40% ethyl acetate in hexanes) afforded the *title compound* as a colourless oil (49 mg, 0.12 mmol, 63%).

ν_{max}	3047 (w), 2928 (m), 2852 (w), 2781 (w), 1716 (w), 1604 (m), 1568 (w), 1486 (m), 1460 (m), 1440 (m), 1380 (w), 1343 (m), 1152 (m), 1108 (w), 1087 (w), 1024 (m).
δ_{H} (400 MHz, CDCl_3)	7.57 (1H, d, $J=7.8$ Hz, ArH), 7.37 (1H, d, $J=7.5$ Hz, ArH), 7.30–7.22(2H, m, 2 x ArH), 7.13 (1H, app. td, $J=7.6, 1.1$ Hz, ArH), 7.05 (1H, app. td, $J=7.6, 1.1$ Hz, ArH), 6.71 (1H, app. t, $J=7.1$ Hz, ArH), 6.41 (1H, d, $J=7.7$ Hz, ArH), 4.36 (1H, d, $J=16.1$ Hz, NCHHAr), 4.20 (1H, d, $J=16.1$ Hz, NCHHAr), 3.39 (1H, d, $J=9.0$ Hz, NCHH), 3.33 (1H, d, $J=9.0$ Hz, NCHH), 3.24–3.05 (2H, m, 2 x NCHH), 2.27–2.11 (2H, m, 2 x NCHH), 1.99–1.85 (2H, m, CHH and NCH), 1.80 (1H, d, $J=10.6$ Hz, CHH), 1.68 (1H, d, $J=12.8$ Hz, CHH), 1.60–1.37 (3H, m, 3 x CHH), 1.15 (1H, qt, $J=12.9, 4.0$ Hz, CHH), 1.02–0.82 (1H, m, CHH).

δ_{C} (100 MHz, CDCl_3)	150.7 (C), 136.5 (C), 134.8 (C), 131.8 (CH), 128.30 (CH), 127.50 (CH), 126.44 (2 x CH), 123.97 (CH), 122.46 (C), 116.85 (CH), 105.65 (CH), 73.38 (CH), 64.96 (CH_2), 53.05 (CH_2), 52.95 (CH_2), 52.83 (CH_2), 51.50 (C), 37.21 (CH_2), 25.39 (CH_2), 24.26 (CH_2), 23.15 (CH_2).
LRMS (ES^+)	^{79}Br : 397 ($[\text{M}+\text{H}]^+$, 100%).

***rel*-(1'*S*,8*a'**R*)-1-Benzyl-3',5',6',7',8',8*a'*-hexahydro-2'*H*-spiro[indoline-3,1'-indolizine] (241)**



A solution of **240** (35 mg, 0.09 mmol), tributyltin hydride (0.05 mL, 0.20 mmol) and VAZO (5 mg, 0.02 mmol) in toluene (4 mL) was heated at reflux for 18 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 25% ethyl acetate in hexanes) afforded the title compound as a colourless oil (25 mg, 0.08 mmol, 89%). These data are in accordance with those reported in the literature.⁴⁶

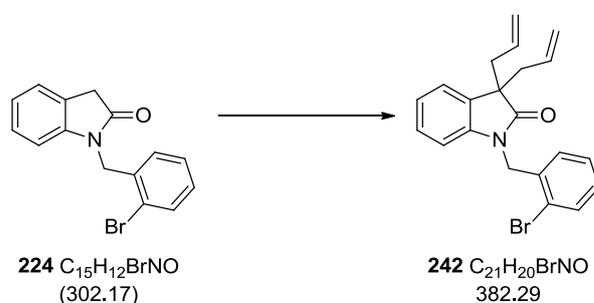
ν_{max}	3029 (w), 2931 (m), 2854 (w), 2360 (w), 1712 (w), 1603 (m), 1487 (m), 1453 (m), 1359 (w), 1259 (m), 1152 (w), 1075 (w), 1046 (w), 1026 (w).
δ_{H} (300 MHz, CDCl_3)	7.34–7.16 (6H, m, 6 x <i>ArH</i>), 7.01 (1H, app. td, $J=7.6, 1.3$ Hz, <i>ArH</i>), 6.65 (1H, app. td, $J=7.4, 0.9$ Hz, <i>ArH</i>), 6.43 (1H, d, $J=7.8$ Hz, <i>ArH</i>), 4.26 (1H, d, $J=14.9$ Hz, <i>NCHHP</i>), 4.08 (1H, d, $J=14.9$ Hz, <i>NCHHP</i>), 3.23 (1H, d, $J=9.1$ Hz, <i>NCHH</i>), 3.15 (1H, d, $J=9.1$ Hz, <i>NCHH</i>), 3.13–3.00 (2H, m, 2 x <i>NCHH</i>), 2.19–2.00 (2H, m, 2 x <i>NCHH</i>), 1.92–1.29 (7H, m, 6 x <i>CHH</i> and

NCH), 1.09 (1H, app. qt, $J=12.7$, 4.0 Hz, CHH), 0.97–0.77 (1H, m, CHH).

δ_C (75 MHz, $CDCl_3$) 152.0 (C), 138.6 (C), 136.0 (C), 128.5 (2 × CH), 127.8 (2 × CH), 127.4 (CH), 127.0 (CH), 125.0 (CH), 117.7 (CH), 106.7 (CH), 74.4 (CH), 65.5 (CH₂), 54.1 (CH₂), 53.9 (CH₂), 53.5 (CH₂), 52.3 (C), 38.1 (CH₂), 26.4 (CH₂), 25.3 (CH₂), 24.2 (CH₂).

LRMS (ES⁺) 319 ([M+H]⁺, 100%).

3,3-Diallyl-1-(2-bromobenzyl)indolin-2-one (242)



To a solution of **224** (1.00 g, 3.31 mmol) in DMF (50 mL) was added NaH (60% in mineral oil, 0.331 g, 8.28 mmol) at RT. After 2 h allyl bromide (0.72 mL, 8.28 mmol) in DMF (10 mL) was added dropwise over 15 min. After 16 h water (75 mL) and ethyl acetate (75 mL) were added and the phases separated. The aqueous phase was then extracted with ethyl acetate (2 x 75 mL). The combined organics were washed with water (250 mL), brine (250 mL), then dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (25–50% DCM in petroleum ether) afforded the *title compound* as a yellow solid (922 mg, 2.41 mmol, 73%).

MP 118–121 °C.

ν_{max} 3057 (w), 2905 (w), 1700 (s), 1641 (w), 1614 (m), 1568 (w), 1490 (m), 1466 (s), 1440 (m), 1383 (m), 1366 (m), 1349 (m).

δ_H (300 MHz, $CDCl_3$) 7.62–7.55 (1H, m, ArH), 7.29–7.02 (6H, m, ArH), 6.62 (1H, app. dq, $J=7.7$, 0.6 Hz, ArH), 5.57–5.41 (2H, m,

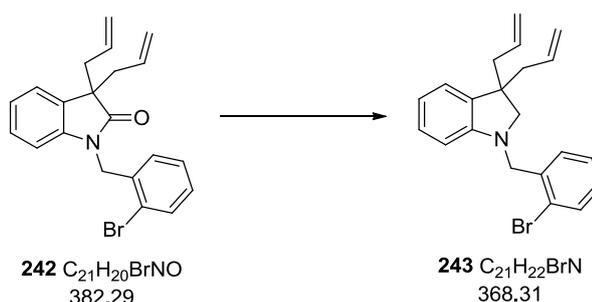
2 x CH₂CH=CH₂), 5.06 (2H, ddt, *J*=17.0, 2.1, 1.2, Hz, 2 x CH₂CH=CHH), 4.98 (2H, ddt, *J*=10.0, 2.0, 0.8 Hz, 2 x CH₂CH=CHH), 4.99 (2H, d, *J*=0.5 Hz, NCH₂Ar), 2.75–2.58 (4H, m, 2 x CH₂CH=CH₂).

δ_c (75 MHz, CDCl₃) 134.5 (C), 132.8 (CH), 132.4 (2 x CH), 131.1 (C), 128.9 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 123.4 (CH), 122.5 (CH), 119.1 (2 x CH₂), 109.0 (CH), 53.0 (C), 43.7 (CH₂), 41.5 (2 x CH₂), *N.B. Three Quaternary signals not observed.*

LRMS (ES⁺) ⁷⁹Br: 785 ([2M+Na]⁺, 29%), 404 ([M+Na]⁺, 100%).

HRMS C₂₁H₂₁BrNO requires 382.0801; Found: 382.0808.

3,3-Diallyl-1-(2-bromobenzyl)indoline (243)



To a solution of **242** (113 mg, 0.30 mmol) in toluene (3 mL) at –78 °C was added AlH₃ (0.5 M in toluene, 1.2 mL, 0.60 mmol) dropwise. After 20 min the reaction mixture was warmed to RT for 4 h and then cooled to 0 °C. Methanol (1.5 mL) was added dropwise and then 1 M HCl (1.5 mL). The reaction mixture was basified with saturated NaHCO₃ (~pH 10) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo* to afford the *title compound* as a yellow oil (105 mg, 0.29 mmol, 97%).

ν_{max} 3676 (w), 3647 (w), 3628 (w), 3071 (w), 2976 (w), 2913 (w), 2838 (w), 2359 (m), 2341 (m), 2194 (w), 2177 (w), 2158 (m), 2035 (w), 2012 (w), 1969 (w), 1942 (w), 1716 (w), 1698 (w), 1605 (m), 1489 (s), 1459 (m), 1439 (m).

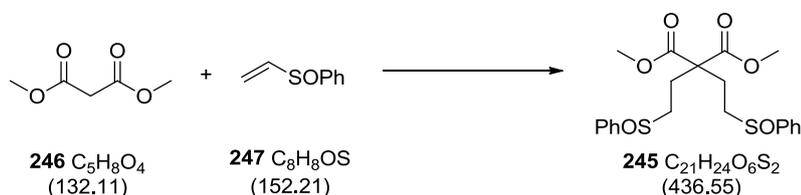
δ_{H} (300 MHz, CDCl_3) 7.48 (1H, dd, $J=7.9, 1.1$ Hz, ArH), 7.32 (1H, dd, $J=7.6, 1.5$ Hz, ArH), 7.18 (1H, app. td, $J=7.5, 1.1$ Hz, ArH), 7.04 (1H, app. td, $J=7.6, 1.8$ Hz, ArH), 7.01–6.90 (2H, m, 2 \times ArH), 6.61 (1H, app. td, $J=7.4, 1.0$ Hz, ArH), 6.31 (1H, d, $J=7.9$ Hz, ArH), 5.76–5.53 (2H, m, 2 \times $\text{CH}_2\text{CH}=\text{CH}_2$), 5.03–4.92 (4H, m, 2 \times $\text{CH}_2\text{CH}=\text{CH}_2$), 4.22 (2H, s, NCH_2Ar), 3.17 (2H, s, NCH_2C), 2.45–2.28 (4H, m, 2 \times $\text{CH}_2\text{CH}=\text{CH}_2$).

δ_{C} (75 MHz, CDCl_3) 151.6 (C), 137.4 (C), 134.7 (C), 134.6 (2 \times CH), 132.7 (CH), 129.2 (CH), 128.5 (CH), 127.8 (CH), 127.4 (CH), 123.3 (C), 123.2 (CH), 117.8 (2 \times CH_2), 117.4 (CH), 106.6 (CH), 63.0 (CH_2), 53.41 (CH_2), 47.0 (C), 43.0 (2 \times CH_2).

LRMS (ES^+) ^{79}Br : 368 ($[\text{M}+\text{H}]^+$, 100%).

HRMS $\text{C}_{21}\text{H}_{23}\text{BrN}$ requires 368.1008; Found: 368.1014.

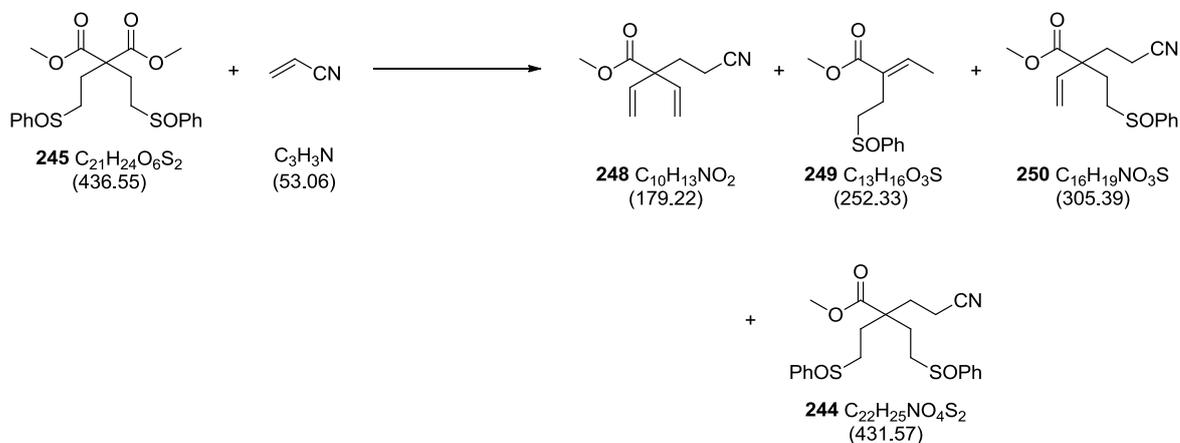
2,2-Bis-(2-phenylsulfinyl-ethyl)malonic acid dimethyl ester (245)



To a solution of dimethyl malonate **246** (8.30 mL, 72.7 mmol) in DMF (160 mL) at 0 °C was added NaH (60% in mineral oil, 580mg, 14.6 mmol). After 20 min the reaction mixture was warmed to RT and phenyl vinyl sulfoxide (25.0 g, 0.16 mol) in DMF (40 mL) added dropwise over 20 min. After 4 days ethyl acetate (150 mL) and water (150 mL) were added and the phases separated. The aqueous phase was washed with ethyl acetate (200 mL). The organic phases were combined and washed with water (3 \times 200 mL) and brine (200 mL), then dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (50% ethyl acetate in hexanes–2% methanol in ethyl acetate) afforded the title compound as a colourless oil (23.83 g, 54.6 mmol, 75%). These data are in accordance with those reported in the literature.¹⁷

ν_{\max}	3468 (br. w), 3050 (w), 2953 (w), 1730 (s), 1477 (w), 1443 (m), 1308 (w), 1265 (m), 1217 (m), 1170 (m), 1086 (m), 1041 (m), 998 (w).
δ_{H} (300 MHz, CDCl_3)	7.66–7.36 (10H, m, ArH), 3.77–3.48 (6H, m, 2 × OCH_3), 2.75 (2H, m, 2 × $\text{CH}_2\text{CHHSOPh}$), 2.64–2.42 (2H, m, 2 × $\text{CH}_2\text{CHHSOPh}$), 2.32–2.11 (2H, m, 2 × $\text{CHHCH}_2\text{SOPh}$), 2.05–1.85 (2H, m, 2 × $\text{CHHCH}_2\text{SOPh}$).
δ_{C} (75 MHz, CDCl_3)	170.3 (2 × C=O), 143.0+142.9 (2 × C), 131.2 (2 × CH), 129.3 (4 × CH), 124.0 (4 × CH), 55.9+55.8 (C), 52.9 (2 × CH_3), 51.1+51.0 (2 × CH_2), 25.4+25.3 (2 × CH_2).
LRMS (ES^+)	459 ($[\text{M}+\text{Na}]^+$, 100%).

4-Cyano-2,2-divinylbutyric acid methyl ester (248), (*E*)-methyl-2-(2-phenylsulfinyl-ethyl)but-2-enoate (249), methyl-2-(2-cyanoethyl)-2-(2-phenylsulfinyl-ethyl)but-3-enoate (250), 2,2-bis(2-phenylsulfinyl-ethyl)-4-cyano-butyric acid methyl ester (244)



To a solution of malonate **245** (7.28 g, 16.7 mmol) in DMF (150 mL) was added sodium iodide (5.0 g, 33.4 mmol) and acrylonitrile (5.5 mL, 90.2 mmol) and then heated at 120 °C for 12 h. The reaction mixture was cooled to RT, ethyl acetate (100 mL) and water (100 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phases were washed with water (4 x 100 mL), brine (100 mL), then dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (5% ethyl

acetate in hexanes–5% MeOH in ethyl acetate) afforded a mixture of compounds (248, 249, 250 and 244). Yields of each product varied with reaction time and temperature. These data are in accordance with those reported in the literature.¹⁷

Data for 248:

Light yellow oil.

ν_{\max}	2954 (w), 2247 (w), 1728 (s), 1633 (w), 1434 (m), 1245 (m), 1200 (m), 1121 (w), 1084 (w), 997 (w), 927 (m), 806 (w), 752 (w).
δ_{H} (300 MHz, CDCl_3)	5.89 (2H, dd, $J=17.6, 11.0$ Hz, $2 \times \text{CH}=\text{CH}_2$), 5.27 (2H, d, $J=11.0$ Hz, $2 \times \text{CH}=\text{CH}_2$), 5.10 (2H, d, $J=17.6$ Hz, $2 \times \text{CH}=\text{CH}_2$), 3.67 (3H, s, OCH_3), 2.38–2.22 (2H, m, $\text{CH}_2\text{CH}_2\text{CN}$), 2.22–2.06 (2H, m, $\text{CH}_2\text{CH}_2\text{CN}$).
δ_{C} (75 MHz, CDCl_3)	172.9 (C=O), 136.9 ($2 \times \text{CH}$), 119.5 (CN), 117.3 ($2 \times \text{CH}_2$), 54.7 (C), 52.6 (CH_3), 31.4 (CH_2), 13.0 (CH_2).
LRMS (ES^+)	202 [$\text{M}+\text{Na}$] ⁺ (100).

Data for 249:

Clear oil.

ν_{\max}	3460 (w), 3057 (w), 2950 (w), 2360 (w), 2340 (w), 2246 (w), 2153 (w), 1708 (s), 1647 (w), 1582 (w), 1477 (w), 1441 (m), 1384 (w), 1295 (w), 1260 (m), 1193 (w), 1160 (m), 1123 (w), 1085 (w), 1040 (s), 999 (w), 928 (w).
δ_{H} (300 MHz, CDCl_3)	7.66–7.48 (5H, m, $5 \times \text{ArH}$), 6.96 (1H, q, $J=7.2$ Hz, $\text{C}=\text{CHCH}_3$), 3.70 (3H, s, OCH_3), 3.04–2.91 (1H, m, $\text{CH}_2\text{CHHSOPh}$), 2.89–2.73 (2H, m, CHHCHHSOPh), 2.69–2.51 (1H, m, $\text{CHHCH}_2\text{SOPh}$), 1.81 (3H, d, $J=7.2$ Hz, $\text{C}=\text{CHCH}_3$).
δ_{C} (75 MHz, CDCl_3)	167.4 (C=O), 143.5 (C), 140.3 (CH), 130.9 (CH), 129.7 (C), 129.1 ($2 \times \text{CH}$), 124.0 ($2 \times \text{CH}$), 55.5 (CH_2), 51.8 (CH_3), 19.3 (CH_2), 14.3 (CH_3).
LRMS (ES^+)	316 ([$\text{M}+\text{MeCN}+\text{Na}$] ⁺ , 100%), 275 ([$\text{M}+\text{Na}$] ⁺ , 23%).

Data for 250:

Clear oil, 1:1 mixture of diastereoisomers.

ν_{\max}	3460 (w), 3057 (w), 2952 (w), 2360 (w), 2247 (w), 1727 (s), 1636 (w), 1582 (w), 1476 (w), 1444 (m), 1306 (w), 1254 (m), 1204 (m), 1155 (w), 1085 (m), 1042 (s), 999 (w), 932 (w).
δ_{H} (300 MHz, CDCl_3)	7.68–7.45 (5H+5H, m, 2 × (5 × ArH)), 5.88 (1H, dd, $J=17.8, 11.0$ Hz, CH=CH ₂), 5.85 (1H, dd, $J=17.8, 11.0$ Hz, CH=CH ₂), 5.34 (1H, d, $J=11.0$ Hz, CH=CHH), 5.30 (1H, d, $J=11.0$ Hz, CH=CHH), 5.15 (1H, d, $J=17.8$ Hz, AH=CHH), 5.05 (1H, d, $J=17.8$ Hz, CH=CHH), 3.71 (3H, s, OCH ₃), 3.69 (3H, s, OCH ₃), 2.92–2.76 (1H+1H, m, 2 × CHH), 2.70–2.56 (1H+1H, m, 2 × CHH), 2.35–2.22 (2H+2H, m, 2 × 2 CHH) 2.05 - 2.21 (2H+2H, m, 2 × 2 CHH) 1.82 - 2.04 (2H+2H, m, 2 × 2 CHH).
δ_{C} (75 MHz, CDCl_3)	173.2 (C=O), 143.1+143.0 (C), 136.5+136.4 (CH), 131.2 (CH), 129.3 (2 × CH), 123.9 (2 × CH), 119.0 (CN), 117.7+117.6 (CH ₂), 52.6+52.6 (OCH ₃), 51.5+51.3 (CH ₂), 50.9 (C), 32.3+32.1 (CH ₂), 27.9+27.6 (CH ₂), 12.8+12.72 (CH ₂).
LRMS (ES ⁺)	369 ([M+MeCN+Na] ⁺ , 20%), 328 ([M+Na] ⁺ , 100%).

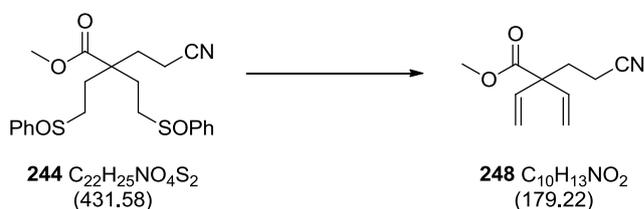
Data for 244:

Brown oil, complex mixture of diastereoisomers.

ν_{\max}	3449 (br. w), 3056 (w), 2952 (w), 2250 (w), 1725 (s), 1477 (w), 1443 (m), 1306 (w), 1207 (m), 1165 (m), 1086 (m), 1038 (s), 998 (m), 920 (w).
δ_{H} (300 MHz, CDCl_3)	7.74–7.48 (10H, m, ArH), 3.67–3.51 (3H, m, OCH ₃), 2.83–2.55 (2H, m, CH ₂ CH ₂ SOPh), 2.54–2.32 (2H, dddd, $J=12.4, 12.4, 12.2, 4.8$ Hz, CH ₂ CH ₂ SOPh), 2.19–2.04

	(2H, m, 2 × CHH), 2.04–1.85 (2H, m, 2 × CHH), 1.85–1.74 (2H, m, 2 × CHH), 1.74–1.61 (2H, m, 2 × CHH).
δ_c (75 MHz, CDCl ₃)	173.8 (C=O), 142.9+142.8+142.8+142.7 (2 × C), 131.3 (2 × CH), 129.4 (4 × CH), 124.0 (4 × CH), 118.6 (CN), 52.7 (OCH ₃), 5.06+50.4+50.3+50.2 (2 × CH ₂), 47.1+47.1 (C), 30.7+30.6+30.5 (CH ₂), 25.6+25.4+25.2 (2 × CH ₂), 12.3 (CH ₂).
LRMS(ES ⁺)	454 ([M+Na] ⁺ , 100%).

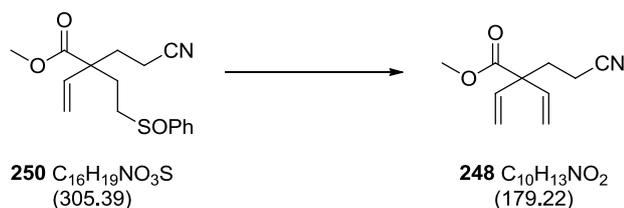
4-Cyano-2,2-divinylbutyric acid methyl ester (248)



A solution of nitrile **244** (73 mg, 0.169 mmol) in DMF (5 mL) was heated to reflux. After 5 h the reaction mixture was cooled to RT then water (10 mL) and ethyl acetate (10 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases washed with water (4 x 10 mL), brine (20 mL), then dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (0–25% diethyl ether in petroleum ether) afforded the title compound as a pale yellow oil (12 mg, 0.067 mmol, 40%).

Data as previously reported.

4-Cyano-2,2-divinylbutyric acid methyl ester (248)



A solution of nitrile **250** (444 mg, 1.45 mmol) in DMF (18 mL) was heated to reflux. After 5 h the reaction mixture was cooled to RT then water (50 mL) and ethyl acetate (50 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases washed with water (4 x 100 mL), brine (200 mL), then dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (0–25% diethyl ether in petroleum ether) afforded the title compound as a pale yellow oil (197 mg, 1.10 mmol, 76%).

Data as previously reported.

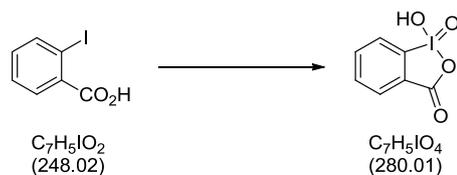
4-Hydroxymethyl-4-vinylhex-5-enenitrile(251)



To a solution of ester **248** (200mg, 1.12 mmol) in THF (12 mL) at $-78\text{ }^\circ\text{C}$ was added LiAlH_4 (1.0 M solution in THF, 2.64 mL, 2.64 mmol) dropwise over 5 min. After 6 h the reaction mixture was warmed to $0\text{ }^\circ\text{C}$ and water (4 mL) added dropwise maintaining a temperature of $0\text{ }^\circ\text{C}$. The reaction mixture was warmed to RT and 2 M HCl (7 mL) and diethyl ether (15 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether ($2 \times 15\text{ mL}$). The combined organic phases were washed with brine (40 mL), then dried (MgSO_4) and the solvent removed *in vacuo* to afford the title compound as a pale yellow oil (156 mg, 1.03 mmol, 92%). These data are in accordance with those reported in the literature.¹⁷

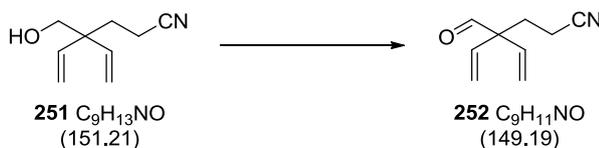
ν_{\max}	3447 (br. m), 3084 (w), 3004 (w), 2933 (w), 2360 (w), 2339 (w), 2249 (w), 1920 (w), 1853 (w), 1635 (w), 1453 (w), 1419 (w), 1044 (m), 1004 (m), 924 (s), 741 (w).
δ_{H} (300 MHz, CDCl_3)	5.67 (2H, dd, $J=17.9, 11.0$ Hz, $2 \times \text{CH}=\text{CH}_2$), 5.26 (2H, d, $J=11.0$ Hz, $2 \times \text{CH}=\text{CHH}$), 5.08 (2H, d, $J=17.9$ Hz, $2 \times \text{CH}=\text{CHH}$), 3.47 (2H, s, CH_2OH), 2.34–2.15 (2H, m, $\text{CH}_2\text{CH}_2\text{CN}$), 1.96–1.81 (2H, m, $\text{CH}_2\text{CH}_2\text{CN}$), 1.58 (1H, br. s, CH_2OH).
δ_{C} (75 MHz, CDCl_3)	139.2 ($2 \times \text{CH}$), 120.3 (CN), 117.5 ($2 \times \text{CH}_2$), 67.1 (CH_2), 48.5 (C), 30.1 (CH_2), 12.6 (CH_2).
LRMS (CI)	169 ($[\text{M}+\text{NH}_4]^+$, 100 %), 140 (87%), 138 (77%).

2-Iodoxybenzoic acid, IBX (365)



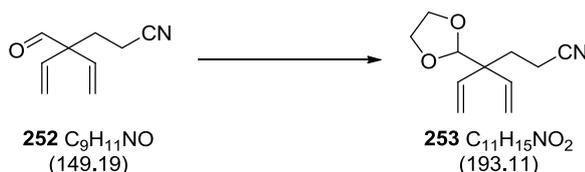
To a suspension of 2-iodobenzoic acid (10.0 g, 40.3 mmol) in aq. H_2SO_4 (0.73 M, 100 mL) was added KBrO_3 (8.75 g, 52.4 mmol) and heated to 75 °C. The reaction gases were scrubbed through saturated sodium thiosulfate solution. After 4.5 h the reaction mixture was cooled to RT and the precipitate collected by filtration, washed with water (200 mL) and ethanol (100 mL) and dried under vacuum to afford the title compound as a white solid (9.71 g, 34.7 mmol, 86%). These data are in accordance with those reported in the literature.⁷⁸

ν_{\max}	3430 (br. m), 2998 (w), 2914 (w), 1663 (w), 1436 (m), 1406 (m), 1311 (m), 1017 (s), 952 (s).
δ_{H} (300 MHz, DMSO)	8.15 (1H, d, $J=7.7$ Hz, ArH), 8.08–7.95 (2H, m, ArH), 7.84 (1H, app. t, $J=7.1$ Hz, ArH).
δ_{C} (75 MHz, DMSO)	167.5 (C=O), 146.6 (C), 133.4 (CH), 132.9 (CH), 131.5 (C), 130.1 (CH), 125.0 (CH).

4-Formyl-4-vinylhex-5-enitrile (252)

To a solution of Dess-Martin Periodinane (690mg, 1.63 mmol) in chloroform (14 mL) at RT was added alcohol **251** (182 mg, 1.20 mmol) in chloroform (3.5 mL) dropwise over 5 min. After 4 h the reaction mixture was concentrated *in vacuo* and dry loaded onto silica. Purification by column chromatography (30% diethyl ether in petroleum ether) afforded the title compound as a yellow oil (172 mg, 1.15 mmol, 96%). These data are in accordance with those reported in the literature.¹⁷

ν_{max}	3088 (w), 2935 (w), 2822 (w), 2723 (w), 2248 (w), 1722 (s), 1630 (w), 1450 (w), 1421 (w), 1355 (w), 1165 (w), 996 (m), 931 (s), 797 (w).
δ_{H} (300 MHz, CDCl ₃)	9.32 (1H, s, CHO), 5.78 (2H, dd, $J=17.8$, 10.8 Hz, 2 × CH=CH ₂), 5.52 (2H, d, $J=10.8$ Hz, 2 × CH=CHH), 5.24 (2H, d, $J=17.8$ Hz, 2 × CH=CHH), 2.44–2.27 (2H, m, CH ₂ CH ₂ CN), 2.19–2.06 (2H, m, CH ₂ CH ₂ CN).
δ_{C} (75 MHz, CDCl ₃)	197.5 (C=O), 134.8 (2 × CH), 120.5 (2 × CH ₂), 119.5 (CN), 59.1 (C), 29.4 (CH ₂), 12.6 (CH ₂).
LRMS (ES ⁺)	259 (100%), 172 ([M+Na] ⁺ , 24%).

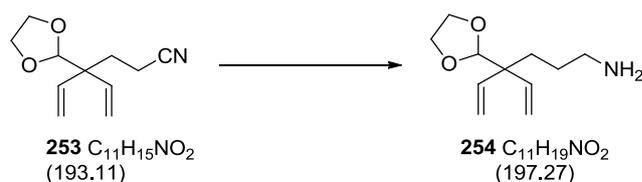
4-[1,3]Dioxolan-2-yl-4-vinylhex-5-enitrile (253)

To a solution of aldehyde **252** (172 mg, 1.15 mmol) in toluene (20 mL) was added *p*TSA (11 mg, 0.06 mmol) and ethylene glycol (0.32 mL, 5.75 mmol). The reaction mixture was heated at reflux under Dean and Stark conditions for 6 h. The

reaction mixture was cooled to RT and then diethyl ether (10 mL) and saturated K_2CO_3 solution (20 mL) were added and the phases separated. The organic phase was washed with brine (20 mL), then dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound as a yellow oil (212 mg, 1.10 mmol, 95%). These data are in accordance with those reported in the literature.¹⁷

ν_{max}	3085 (w), 2980 (w), 2955 (w), 2887 (m), 2246 (m), 1636 (w), 1455 (w), 1418 (w), 1377 (w), 1146 (m), 1114 (m), 1081 (m), 1032 (m), 1002 (m), 925 (s), 774 (w).
δ_H (300 MHz, $CDCl_3$)	5.76 (2H, dd, $J=17.8, 11.0$ Hz, $2 \times CH=CH_2$), 5.30 (2H, dd, $J=11.0, 0.6$ Hz, $2 \times CH=CHH$), 5.18 (2H, dd, $J=17.8, 0.6$ Hz, $2 \times CH=CHH$), 4.68 (1H, s, $CHOCH_2$), 3.96–3.70 (4H, m, OCH_2CH_2O), 2.35–2.25 (2H, m, CH_2CH_2CN), 2.00–1.90 (2H, m, CH_2CH_2CN).
δ_C (75 MHz, $CDCl_3$)	137.3 ($2 \times CH$), 120.3 (CN), 117.7 ($2 \times CH_2$), 107.4 (CH), 65.3 ($2 \times CH_2$), 50.2 (C), 28.3 (CH_2), 12.5 (CH_2).
LRMS (ES^+)	216 ($[M+Na]^+$, 100%).

4-[1,3]Dioxolan-2-yl-4-vinylhex-5-en-1-amine (254)

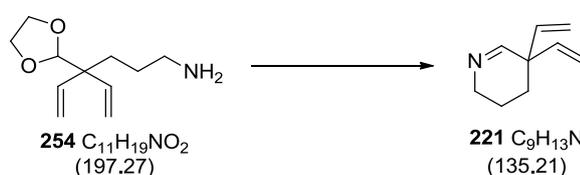


To a solution of nitrile **253** (178 mg, 0.92 mmol) in THF (8 mL) at 0 °C was added $LiAlH_4$ (1.0 M in THF, 0.9 mL, 0.9 mmol) dropwise over 5 min. The reaction mixture was then heated to 60 °C for 4 h. The reaction mixture was cooled to 0 °C and water (8 mL) was added, followed by 2 M NaOH (5 mL). The reaction mixture was extracted with diethyl ether (3×10 mL) and the combined organic phases washed with brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a yellow oil (174 mg, 0.90 mmol, 96%). These data are in accordance with those reported in the literature.¹⁷

ν_{\max}	3082 (w), 2947 (m), 2879 (m), 1634 (w), 1572 (m), 1473 (m), 1383 (m), 1318 (m), 1112 (s), 1033 (m), 920 (s).
δ_{H} (300 MHz, CDCl_3)	5.87 (2H, dd, $J=17.8, 11.1$ Hz, $2 \times \text{CH}=\text{CH}_2$), 5.25 (2H, dd, $J=11.1, 1.3$ Hz, $2 \times \text{CH}=\text{CHH}$), 5.14 (2H, dd, $J=17.8, 1.3$ Hz, $2 \times \text{CH}=\text{CHH}$), 4.80 (1H, s, CHOCH_2), 4.01–3.75 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 2.66 (2H, t, $J=7.0$ Hz, CH_2NH_2), 1.70–1.56 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), 1.49–1.39 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$).
δ_{C} (75 MHz, CDCl_3)	138.9 ($2 \times \text{CH}$), 116.2 ($2 \times \text{CH}_2$), 107.8 (CH), 65.2 ($2 \times \text{CH}_2$), 50.3 (C), 42.9 (CH_2), 30.4 (CH_2), 28.2 (CH_2).
LRMS (ES^+)	198 ($[\text{M}+\text{H}]^+$, 100%).

N.B. This compound is prone to decomposition.

5,5-Divinyl-2,3,4,5-tetrahydropyridine (221)



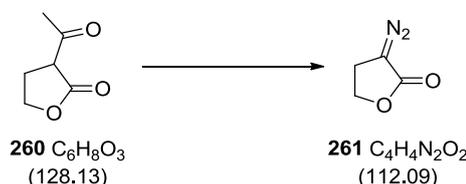
To a solution of **254** (74 mg, 0.38 mmol) in diethyl ether (1 mL) was added 10% HCl (1 mL) and after 2 h 10% NaOH (~pH 10) was added. After a further 2.5 h the reaction mixture was then extracted with diethyl ether (3×10 mL) and the combined organic phases then dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (100% diethyl ether) afforded the title compound as a colourless oil (18mg, 0.13mmol, 34%). These data are in accordance with those reported in the literature.¹⁷

ν_{\max}	3075 (w), 2924 (m), 2953 (m), 2361 (m), 2332 (w), 2160 (m), 2018 (w), 1716 (w), 1647 (w), 1540 (w), 1457 (w), 1115 (w), 1003 (w), 920 (w).
δ_{H} (300 MHz, CDCl_3)	7.55 (1H, br. s, $\text{N}=\text{CH}$), 5.76 (2H, dd, $J=17.6, 10.6$ Hz, $2 \times \text{CH}=\text{CH}_2$), 5.21 (2H, dd, $J=10.6, 0.7$ Hz,

	2 × CH=CHH), 5.08 (2H, dd, $J=17.6$, 0.7 Hz, 2 × CH=CHH), 3.70–3.46 (2H, m, NCH ₂), 1.79–1.67 (2H, m, NCH ₂ CHHCHH), 1.68–1.49 (2H, m, NCH ₂ CHHCHH).
δ_C (75 MHz, CDCl ₃)	164.1(CH), 141.3 (2 x CH), 115.7 (2 x CH), 49.4 (CH ₂), 47.6 (C), 30.3 (CH ₂), 18.2 (CH ₂).
LRMS (ES ⁺)	136 ([M+H] ⁺ , 100%).

N.B. This compound is prone to decomposition.

3-Diazodihydrofuran-2(3H)-one (261)



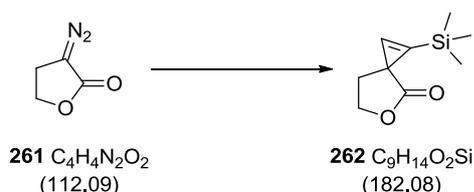
To a solution of sodium azide (2.42 g, 37.2 mmol), tetrabutylammonium bromide (15 mg, 0.047 mmol) and 2 M NaOH (70 mL) in hexanes (35 mL) at 0 °C was added Tf₂O (3.13 mL, 18.6 mmol) dropwise over 5 min. After 10 min 2-acetyl-butylolactone **260** (0.60 g, 4.68 mmol) in acetonitrile (45 mL) was added in one portion. After 30 min the reaction mixture was diluted with ice water (20 mL) and ethyl acetate (25 mL) added. The phases were separated and the aqueous phase washed with ethyl acetate (2 × 25 mL). The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (50% ethyl acetate in petroleum ether) afforded the title compound as a bright yellow solid (211 mg, 1.73 mmol, 37%). These data are in accordance with those reported in the literature.⁵²

MP	34–36 °C (EtOAc / petroleum ether), Lit. 35–36 °C. ⁵²
ν_{\max}	3525 (w), 3270 (w), 2925 (w), 1754 (s), 1664 (w), 1623 (w), 1521 (w), 1482 (w), 1453 (w), 1419 (w), 1257 (m), 1226 (m), 1176 (m), 1108 (m), 1020 (s), 953(w).
δ_H (300 MHz, CDCl ₃)	4.38 (2H, t, $J=7.8$ Hz, CH ₂ CH ₂), 3.36 (2H, t, $J=7.8$ Hz, CH ₂ CH ₂).

δ_C (75 MHz, $CDCl_3$) 170.6 (C=O), 65.2 (CH_2), 23.03 (CH_2).
N.B. One quaternary centre not observed.

LRMS (EI) 84 ($[M-N_2]^+$, 100%), 51 (72%).

1-(Trimethylsilyl)-5-oxaspiro[2.4]hept-1-en-4-one (262)

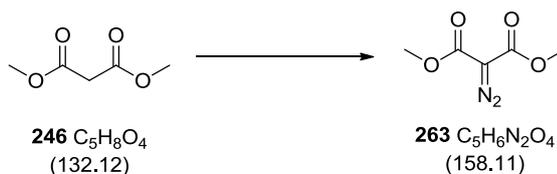


To a solution of $Rh_2(OAc)_4$ (8 mg, 0.018 mmol) in trimethylsilyl acetylene (3 mL) at reflux was added a suspension of **261** (145mg, 1.29 mmol) in trimethylsilyl acetylene (4.5 mL) dropwise over 5 h. After 16 h the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by column chromatography (25% ethyl acetate in petroleum ether) afforded the title compound as a pale brown oil (28mg, 0.15 mmol, 12%). These data are in accordance with those reported in the literature.⁵²

δ_H (300 MHz, $CDCl_3$) 7.21 (1H, s, CH), 4.42 (2H, app. t, $J=7.7$ Hz, CH_2CH_2), 2.26–2.08 (1H, m, CH_2CHH), 2.06–1.91 (1H, m, CH_2CHH), 0.25 (9H, s, $Si(CH_3)_3$).

δ_C (75 MHz, $CDCl_3$) 181.1 (C=O), 116.8 (C), 114.9 (CH), 65.1 (CH_2), 30.3 (CH_2), 24.0 (C), -1.5 ($Si(CH_3)_3$).

Dimethyl 2-diazomalonate (263)

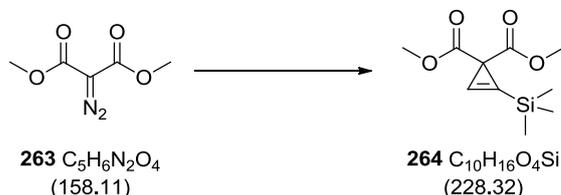


To a solution of dimethyl malonate **246** (1.00 g, 7.57 mmol) and *p*-toluenesulfonyl azide (1.49 g, 7.57 mmol) in diethyl ether (10 mL) at 0 °C was added diethylamine

(0.78 mL, 7.57 mmol). After 15 min the reaction mixture was warmed to RT for 60 h. Hexanes (75 mL) was added and the resultant precipitate removed by filtration. The filtrate was concentrated *in vacuo*. Purification by column chromatography (25% diethyl ether in petroleum ether) afforded the title compound as a pale yellow oil (638 mg, 4.04 mmol, 53%). These data are in accordance with those reported in the literature.⁸²

ν_{\max}	2993 (w), 2958 (w), 2132 (s), 1758 (s), 1734 (s), 1687 (s), 1435 (s), 1353 (m), 1326 (s), 1271 (s), 1189 (m), 1083 (s), 972 (w), 934 (w), 820 (w), 758 (s).
δ_{H} (300 MHz, CDCl_3)	3.84 (6H, s, 2 \times OCH_3).
δ_{C} (75 MHz, CDCl_3)	161.4 (2 \times C=O), 52.5 (2 \times CH_3). <i>N.B. One quaternary centre not observed.</i>
LRMS (EI)	222 ($\text{M}+\text{MeCN}+\text{Na}^+$, 100%).

Dimethyl 2-(trimethylsilyl)cycloprop-2-ene-1,1-dicarboxylate (**264**)

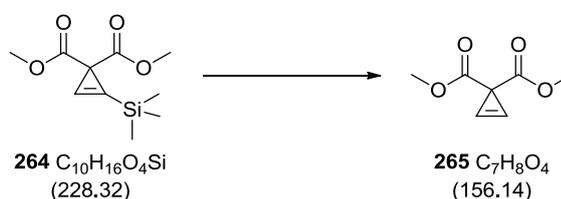


To a solution of $\text{Rh}_2(\text{OAc})_4$ (6 mg, 0.013 mmol) in trimethylsilyl acetylene (1.9 mL) at 55 °C was added a solution of diazomalonate **263** (200 mg, 1.26 mmol) in trimethylsilyl acetylene (0.6 mL) dropwise over 2 h. After 1.5 h the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by column chromatography (5–20% diethyl ether in petroleum ether) afforded the title compound as a pale yellow oil (224 mg, 0.98 mmol, 78%). These data are in accordance with those reported in the literature.⁸³

ν_{\max}	3166 (w), 3120 (m), 3003 (w), 2956 (m), 2847 (w), 2360 (w), 2192 (w), 2056 (w), 1987 (w), 1730 (s), 1670 (w),
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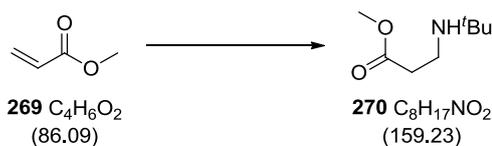
	1546 (w), 1436 (m), 1286 (s), 1252 (s), 1193 (w), 1146 (w), 1067 (s), 988 (w).
δ_{H} (300 MHz, CDCl_3)	7.05 (1H, s, CH), 3.70 (6H, s, 2 x OCH_3), 0.25 (9H, s, $\text{Si}(\text{CH}_3)_3$).
δ_{C} (75 MHz, CDCl_3)	172.1 (2 x C=O), 113.7 (C), 110.6 (CH), 52.1 (2 x OCH_3), 30.4 (C), -1.9 ($\text{Si}(\text{CH}_3)_3$).
LRMS (ES^+)	220 ($[\text{M}-\text{TMS}+\text{MeCN}+\text{Na}]^+$, 100%).

Dimethyl cycloprop-2-ene-1,1-dicarboxylate (265)



To a solution of cyclopropene **264** (201mg, 0.88 mmol) in ethanol (4.5 mL) at 0 °C was added a solution of KOH (0.25 M in ethanol, 0.13 mL) dropwise over 5 min. After 5 min the reaction mixture was neutralised with a solution of 0.25 M HCl. Ethyl acetate (10 mL) was then added and the phases separated. The aqueous phase was then washed with ethyl acetate (3 x 10 mL) and the combined organic phases washed with water (10 mL), brine (30 mL), then dried (MgSO_4) and concentrated *in vacuo* to afford the title compound as a pale yellow oil (80 mg, 0.51 mmol, 58%). These data are in accordance with those reported in the literature.⁸⁴

ν_{max}	3853 (w), 3734 (w), 3167 (w), 3121 (m), 3004 (w), 2956 (m), 2848 (w), 2361 (m), 2340 (m), 2179 (w), 2163 (w), 1723 (s), 1672 (w), 1435 (m), 1247 (s), 1192 (w), 1144 (w), 1062 (s), 987 (w), 949 (w).
δ_{H} (300 MHz, CDCl_3)	6.91 (2H, s, $\text{CH}=\text{CH}$), 3.73 (6H, s, 2 x OCH_3).
δ_{C} (75 MHz, CDCl_3)	171.3 (2 x C=O), 102.4 (2 x CH), 52.4 (2 x OCH_3), 29.8 (C).
LRMS (ES^+)	220 ($[\text{M}+\text{MeCN}+\text{Na}]^+$, 100%).

Methyl 3-(*tert*-butylamino)propanoate (270)

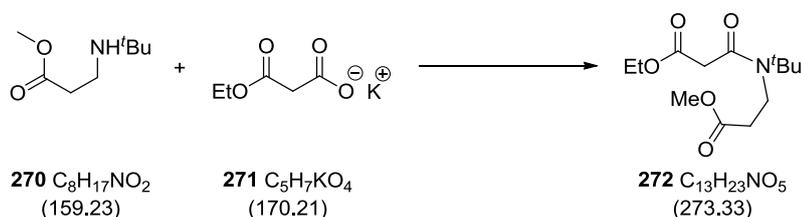
To a solution of methyl acrylate **269** (1.05 mL, 11.62 mmol) in methanol (2.5 mL) was added $^t\text{BuNH}_2$ (1.22 mL, 11.62 mmol) at RT. After 60 h the reaction mixture was concentrated *in vacuo* to afford the title compound as a colourless oil (1.24 g, 7.79 mmol, 67%). These data are in accordance with those reported in the literature.⁸⁵

ν_{max} 2961 (m), 2867 (w), 2361 (w), 2339 (w), 2179 (w), 2163 (w), 1737 (s), 1438 (w), 1391 (w), 1362 (m), 1317 (w), 1231 (m), 1212 (m), 1170 (m), 1102 (w), 1065 (w).

δ_{H} (300 MHz, CDCl_3) 3.66 (3H, s, OCH_3), 2.80 (2H, t, $J=6.7$ Hz, CH_2), 2.49 (2H, t, $J=6.7$ Hz, CH_2), 1.08 (9H, s, $\text{NHC}(\text{CH}_3)_3$).

δ_{C} (75 MHz, CDCl_3) 173.3 (C=O), 51.4 (OCH_3), 50.3 (C), 38.0 (CH_2), 35.4 (CH_2), 28.9 ($3 \times \text{CH}_3$).

LRMS (ES^+) 160 ($[\text{M}+\text{H}]^+$, 100%).

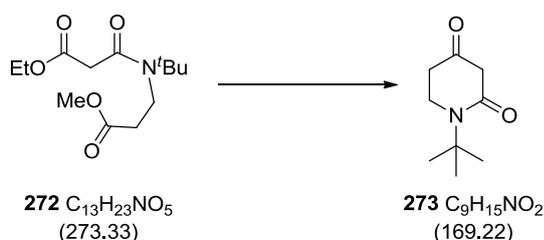
Ethyl 3-(*tert*-butyl(3-methoxy-3-oxopropyl)amino)-3-oxopropanoate (272)

To a solution of malonate **271** (6.42 g, 37.7 mmol) in diethyl ether (60 mL) was added pivaloyl chloride (0.85 mL, 6.91 mmol) at 0 °C. After 4 h NEt_3 (0.96 mL, 6.91 mmol), dimethylaminopyridine (100mg, 0.82 mmol) and **270** (1.00 g, 6.28 mmol) were added at RT. After 40 h saturated aq. NaHCO_3 (10 mL) was added and the phases separated. The organic phase was washed with saturated aq. NaHCO_3 (2×10 mL), brine (20 mL), then dried (MgSO_4) and

concentrated *in vacuo*. Purification by column chromatography (10–30% ethyl acetate in petroleum ether) afforded the *title compound* as a pale yellow oil (421 mg, 1.54 mmol, 25%).

ν_{\max}	3396 (br. w), 2981 (br. m), 2810 (br. w), 2664 (w), 2495 (w), 2361 (m), 2340 (w), 2184 (w), 1939 (w), 1732 (s), 1580 (s), 1440 (m), 1405 (m), 1379 (s), 1322 (w), 1302 (w), 1246 (w), 1205 (m), 1093 (w), 1033 (w).
δ_{H} (300 MHz, CDCl_3)	4.20 (2H, q, $J=7.1$ Hz, CH_2CH_3), 3.70 (3H, s, OCH_3), 3.66–3.57 (2H, m, CH_2CH_2), 3.46 (2H, s, $\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})$), 2.68–2.51 (2H, m, CH_2CH_2), 1.45 (9H, s, $\text{NHC}(\text{CH}_3)_3$), 1.28 (3H, t, $J=7.1$ Hz, CH_2CH_3).
δ_{C} (75 MHz, CDCl_3)	171.1 (C=O), 168.0 (C=O), 166.8 (C=O), 61.3 (CH_2), 57.8 (C), 51.9 (CH_3), 43.8 (CH_2), 41.5 (CH_2), 36.1 (CH_2), 28.8 ($3 \times \text{CH}_3$), 14.1 (CH_3).
LRMS	Did not fly by ES/EI or CI.

1-(*tert*Butyl)piperidine-2,4-dione (273)

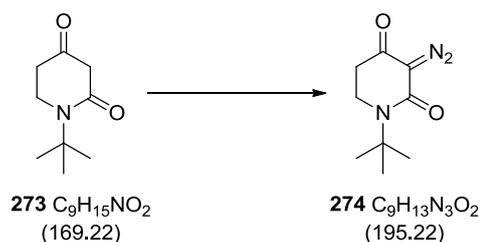


To a suspension of NaH (60% in mineral oil, 507 mg, 12.67 mmol) in cyclohexane (20 mL) at reflux was added **272** (1.69 g, 6.18 mmol) in toluene (4 mL) dropwise over 40 min. After 45 min the reaction mixture was cooled to RT and the resultant precipitate isolated by filtration and washed with cyclohexane (25 mL). The isolated solid was suspended in aqueous 10% AcOH (25 mL) and heated at reflux. After 3 h the reaction mixture was cooled to RT and neutralised with saturated aqueous NaHCO_3 and DCM added (10 mL). The phases were separated and the aqueous phase washed with DCM (2×10 mL). The combined organic phases were washed with brine (50 mL), then dried (MgSO_4) and concentrated *in vacuo* to

afford the title compound as a colourless oil (671 mg, 3.97 mmol, 64%). These data are in accordance with those reported in the literature.⁸⁶

ν_{\max}	2973 (m), 2925 (w), 2361 (w), 2339 (w), 2161 (w), 1728 (m), 1648 (s), 1477 (w), 1458 (w), 1413 (m), 1392 (m), 1364 (m), 1328 (m), 1198 (s), 1078 (w), 1034 (w).
δ_{H} (300 MHz, CDCl_3)	3.66 (2H, t, $J=5.9$ Hz, CH_2CH_2), 3.35 (2H, s, $\text{C(O)CH}_2\text{C(O)}$), 2.51 (2H, t, $J=5.9$ Hz, CH_2CH_2), 1.48 (9H, s, $\text{NHC(CH}_3)_3$).
δ_{C} (75 MHz, CDCl_3)	204.7 (C=O), 166.8 (NC=O), 57.9 (C), 52.2 (CH_2), 39.7 (CH_2), 39.5 (CH_2), 28.8 (3 \times CH_3).
LRMS (EI)	170 ($[\text{M}+\text{H}]^+$, 100%), 154 ($[\text{MCH}_3]^{++}$, 24%).

1-(*tert*-Butyl)-3-diazopiperidine-2,4-dione (274)



To a solution of **273** (634 mg, 3.75 mmol) and *p*-toluenesulfonyl azide (740 mg, 3.75 mmol) in diethyl ether (20 mL) at 0 °C was added diethylamine (0.39 mL, 3.75 mmol). After 15 min the reaction mixture was warmed to RT for 60 h. Hexanes (75 mL) were added and the resultant precipitate removed by filtration. The filtrate was concentrated *in vacuo*. Purification by column chromatography (25–35% ethyl acetate in petroleum ether) afforded the *title compound* as a pale yellow oil (548mg, 2.81 mmol, 75%).

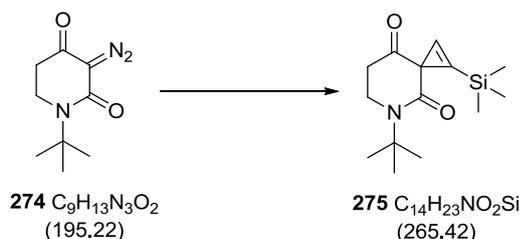
ν_{\max}	2973 (w), 2927 (w), 2361 (w), 2340 (w), 2136 (m), 1669 (m), 1639 (s), 1481 (w), 1414 (m), 1340 (s), 1327 (s), 1290 (w), 1269 (w), 1201 (m), 1062 (w), 1038 (w).
δ_{H} (300 MHz, CDCl_3)	3.51 (2H, t, $J=6.4$ Hz, CH_2CH_2), 2.56 (2H, t, $J=6.4$ Hz, CH_2CH_2), 1.49 (9H, s, $\text{NHC(CH}_3)_3$).

δ_{C} (75 MHz, CDCl_3) 188.7 (C=O), 161.6 (NC=O), 58.2 (C), 39.2 (CH_2), 37.3 (CH_2), 28.7 ($3 \times \text{CH}_3$).

N.B. One quaternary centre not observed.

LRMS (ES^+) 413 ($[\text{2M}+\text{Na}]^+$, 91%), 226 (100%).

5-(*tert*-Butyl)-1-(trimethylsilyl)-5-azaspiro[2.5]oct-1-ene-4,8-dione (275)



To a solution of $\text{Rh}_2(\text{OAc})_4$ (2.3 mg, 0.005 mmol) in trimethylsilyl acetylene (1.1 mL) at reflux was added **274** (100mg, 0.51 mmol) in trimethylsilyl acetylene (0.4 mL) dropwise over 2 h. After 2 h the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by column chromatography (25–50% ethyl acetate in hexanes) afforded the *title compound* as an orange oil (12 mg, 0.045 mmol, 9%).

ν_{max} 2962 (w), 2919 (m), 2851 (w), 2361 (w), 2339 (w), 1732(w), 1717 (w), 1646 (s), 1563 (s), 1459 (m), 1415 (w), 1365 (w), 1320 (w), 1197 (s), 1035 (w), 800 (w), 752 (s).

δ_{H} (300 MHz, CDCl_3) 6.84 (1H, s, $\text{CH}=\text{CSi}(\text{CH}_3)_3$), 3.50 (2H, t, $J=7.0$ Hz, CH_2CH_2), 2.49 (2H, t, $J=7.0$ Hz, CH_2CH_2), 1.47 (9H, s, $3 \times \text{CH}_3$) 0.24 (9H, s, $\text{Si}(\text{CH}_3)_3$).

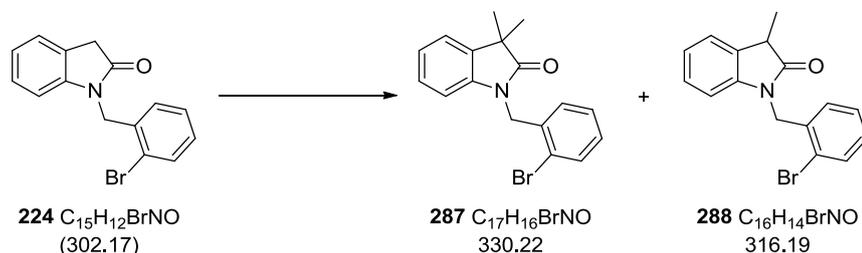
δ_{C} (75 MHz, CDCl_3) 116.8 (CH), 44.6 (CH_2), 37.4 (CH_2), 28.6 ($3 \times \text{CH}_3$), –1.84 ($\text{Si}(\text{CH}_3)_3$).

N.B. Quaternary centres not observed.

LRMS (ES^+) 288 ($[\text{M}+\text{Na}]^+$, 66%), 167 ($[\text{M}-\text{CHCSi}(\text{CH}_3)_3]^+$, 50%), 151 (100%).

HRMS Sample decomposed.

6.3 Experimental Procedures for Chapter 4

1-(2-Bromobenzyl)-3,3-dimethylindolin-2-one (**287**) and 1-(2-bromobenzyl)-3-methylindolin-2-one (**288**)

To a solution of **224** (287 mg, 0.95 mmol) in DMF (12 mL) was added NaH (60% in mineral oil, 95 mg, 2.38 mmol). After 2 h, methyl iodide (0.15 mL, 2.38 mmol) in DMF (2 mL) was added dropwise over 10 min. After 16 h water (20 mL) and ethyl acetate (20 mL) were added. The aqueous phase was separated and extracted with ethyl acetate (2 × 20 mL) then the combined organic phases were washed with water (60 mL) and brine (60 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10–30% diethyl ether in petroleum ether) afforded firstly **287** as an orange oil (126 mg, 0.38 mmol, 40%) and then **288** as an orange oil (31 mg, 0.10 mmol, 11%).

Data for 287:

ν_{\max}	3057 (w), 2967 (w), 2926 (w), 2866 (w), 1708 (s), 1612 (s), 1569 (w), 1488 (m), 1468 (m), 1458 (m), 1439 (m), 1383 (m), 1348 (s), 1308 (w), 1274 (w), 1192 (m), 1173 (m), 1120 (m).
δ_{H} (300 MHz, CDCl ₃)	7.51 (1H, dd, $J=7.7, 1.2$ Hz, <i>ArH</i>), 7.19–7.00 (4H, m, 4 × <i>ArH</i>), 6.97 (1H, app. td, $J=7.4, 0.8$ Hz, <i>ArH</i>), 6.90 (1H, dd, $J=7.4, 1.2$ Hz, <i>ArH</i>), 6.58 (1H, d, $J=7.7$ Hz, <i>ArH</i>), 4.93 (2H, s, NCH ₂ Ar), 1.39 (6H, s, 2 × CH ₃).
δ_{C} (75 MHz, CDCl ₃)	181.5 (C=O), 141.4 (C), 135.6 (C), 134.7 (C), 132.9 (CH), 128.9 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH),

122.8 (C), 122.7 (CH), 122.4 (CH), 109.1 (CH), 44.3 (C),
43.5 (CH₂), 24.6 (2 × CH₃).

LRMS (ES⁺)

⁷⁹Br: 393 ([M+Na+MeCN]⁺, 36%).

HRMS

C₁₇H₁₆BrNNaO[M+Na]⁺ requires 352.0307; found:
352.0313.

Data for 288:

ν_{max}

3025 (br. m), 3093 (w), 2961 (m), 2931 (w), 2874 (w),
2359 (w), 1698 (s), 1619 (s), 1598 (w), 1486 (m), 1470
(s), 1387 (w), 1369 (w), 1345 (m), 1318 (w), 1297 (w),
1265 (w), 1222 (m), 1202 (w), 1117 (w), 1097 (w), 1078
(w), 1019 (w).

δ_H (300 MHz, CDCl₃)

7.60 (1H, dd, *J*=7.7, 1.4 Hz, Ar*H*), 7.29 (1H, d, *J*=7.4 Hz,
Ar*H*), 7.24–7.00 (5H, m, 5 × Ar*H*), 6.67 (1H, d, *J*=7.7 Hz,
Ar*H*), 5.02 (2H, s, NCH₂Ar), 3.60 (1H, q, *J*=7.6 Hz,
CHCH₃), 1.58 (3H, d, *J*=7.6 Hz, CH₃).

δ_C (75 MHz, CDCl₃)

178.8 (C=O), 142.7 (C), 134.5 (C), 132.9 (CH), 130.5
(C), 129.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH),
123.6 (CH), 122.8 (C), 122.7 (CH), 109.0 (CH), 43.7
(CH₂), 40.6 (CH), 15.7 (CH₃).

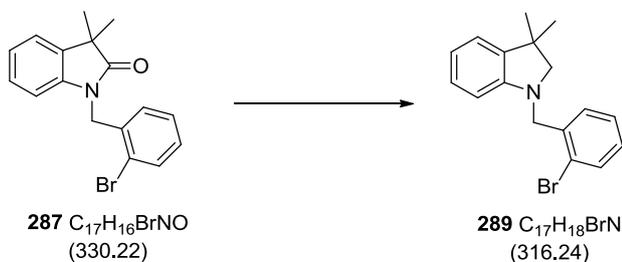
LRMS (ES⁺)

⁷⁹Br: 379 ([M+Na+MeCN]⁺, 10%).

HRMS

C₁₆H₁₅BrNO [M+H]⁺ requires 316.0332; found: 316.0335.

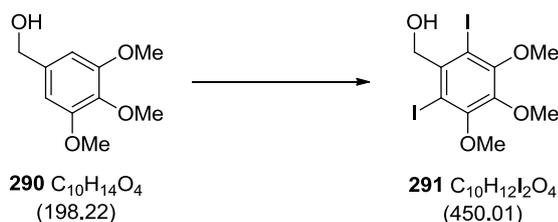
1-(2-Bromobenzyl)-3,3-dimethylindoline (289)



To a solution of **287** (126 mg, 0.38 mmol) in toluene (5 mL) at –78 °C was added AlH₃ (0.5 M in toluene, 1.52 mL, 0.76 mmol) dropwise over 10 min. After 20 min

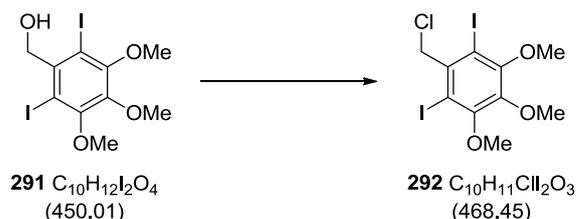
the reaction mixture was warmed to RT for 3 h and then cooled to 0 °C. Methanol (2 mL) then 1 M HCl (2 mL) were added cautiously followed after 10 min by saturated NaHCO₃ (~pH 10). The aqueous phase was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then washed with brine (60 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (5% chloroform in petroleum ether) afforded the *title compound* as a yellow oil (87 mg, 0.28 mmol, 74%).

U_{max}	3048 (w), 2955 (w), 2917 (w), 2860 (w), 2820 (w), 1605 (m), 1567 (w), 1486 (s), 1456 (m), 1439 (m), 1361 (w), 1345 (w), 1302 (w), 1263 (br. m), 1196 (w), 1157 (w), 1116 (w).
δ_H (400 MHz, CDCl₃)	7.64 (1H, dd, <i>J</i> =7.8, 1.3 Hz, <i>ArH</i>), 7.49 (1H, dd, <i>J</i> =7.6, 1.5 Hz, <i>ArH</i>), 7.34 (1H, app. td, <i>J</i> =7.5, 1.3 Hz, <i>ArH</i>), 7.20 (1H, app. td, <i>J</i> =7.8, 1.5 Hz, <i>ArH</i>), 7.15–7.09 (2H, m, 2 × <i>ArH</i>), 6.79 (1H, app. td, <i>J</i> =7.6, 1.0 Hz, <i>ArH</i>), 6.49 (1H, d, <i>J</i> =7.6 Hz, <i>ArH</i>), 4.38 (2H, s, NCH ₂ Ar), 3.26 (2H, s, NCH ₂), 1.40 (6H, s, 2 × CH ₃).
δ_C (100 MHz, CDCl₃)	150.7 (C), 138.7 (C), 137.5 (C), 132.7 (CH), 129.2 (CH), 128.5 (CH), 127.4 (2 × CH), 123.4 (C), 121.7 (CH), 117.8 (CH), 106.8 (CH), 68.2 (CH ₂), 53.4 (CH ₂), 40.4 (C), 27.6 (2 × CH ₃).
LRMS (ES⁺)	⁷⁹ Br: 316 ([M+H] ⁺ , 100%).
HRMS	Sample decomposed.

(2,6-Diiodo-3,4,5-trimethoxyphenyl)-methanol (291)

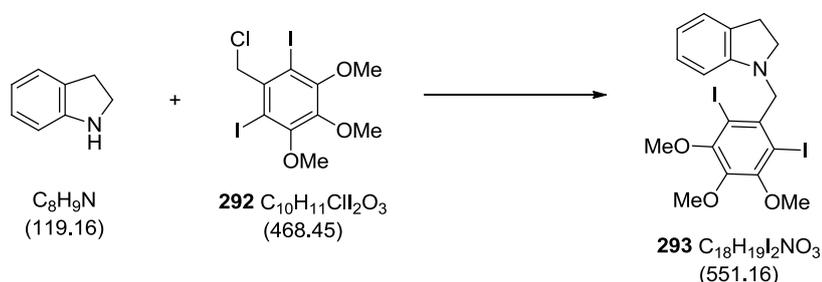
To a solution of 3,4,5-trimethoxybenzyl alcohol **290** (200 mg, 1.01 mmol) in chloroform (20 mL) at 0 °C was added silver trifluoroacetate (560 mg, 2.53 mmol). To this suspension was added a solution of iodine (640 mg, 2.53 mmol) in chloroform (100 mL) dropwise over 1 h. The reaction mixture was allowed to warm to RT and after 16 h was filtered. The filtrate was washed with saturated sodium thiosulfate (100 mL) then the organic phases were separated, dried (MgSO_4) and concentrated *in vacuo* to afford the title compound as a yellow oil (450 mg, 1.01 mmol, 99%). These data are in accordance with those reported in the literature.¹⁷

ν_{max}	2937 (w), 2362 (s), 2340 (s), 2174 (w), 2143 (w), 2115 (w), 2030 (w), 1460 (m), 1401 (s), 1371 (s), 1311 (m), 1261 (w), 1084 (w), 1004 (m), 945 (w).
δ_{H} (300 MHz, CDCl_3)	5.15 (2H, s, CH_2OH), 3.91 (3H, s, OCH_3), 3.89 (6H, s, $2 \times \text{OCH}_3$), 2.07 (1H, br. s, OH).
δ_{C} (75 MHz, CDCl_3)	154.0 ($2 \times \text{C}$), 144.9 (C), 139.4 (C), 92.6 ($2 \times \text{C-I}$), 74.8 (CH_2), 61.0 (CH_3), 60.8 ($2 \times \text{CH}_3$).
LRMS (ES^+)	923 ($[\text{2M}+\text{Na}]^+$, 49%), 505 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 100%).

1-Chloromethyl-2,6-diiodo-3,4,5-trimethoxybenzene (292)

To a solution of benzyl alcohol **291** (400 mg, 0.89 mmol) in DCM (40 mL) at 0 °C was added thionyl chloride (0.07 mL, 0.89 mmol) dropwise over 5 min. The reaction mixture was warmed to RT and after 16 h was concentrated *in vacuo* to afford the title compound as a yellow oil (420 mg, 0.89 mmol, 100%). These data are in accordance with those reported in the literature.¹⁷

ν_{max}	3005 (w), 2967 (w), 2934 (w), 2850 (w), 1785 (w), 1550 (w), 1459 (s), 1401 (s), 1371 (s), 1341 (w), 1317 (s), 1262 (w), 1216 (w), 1196 (w).
δ_{H} (300 MHz, CDCl_3)	5.13 (2H, s, ClCH_2Ar), 3.92 (3H, s, OCH_3), 3.89 (6H, s, $2 \times \text{OCH}_3$).
δ_{C} (75 MHz, CDCl_3)	154.2 ($2 \times \text{C}$), 145.0 (C), 136.8 (C), 92.7 ($2 \times \text{C-I}$), 61.0 (CH_3), 60.8 ($2 \times \text{CH}_3$), 57.9 (CH_2).
LRMS (EI)	468 ($[\text{M}]^+$, 83%), 433 ($[\text{M-Cl}]^+$, 100%), 291 (26%).

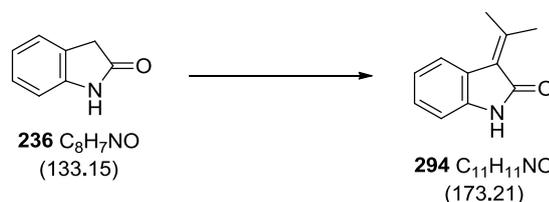
1-(2,6-Diiodo-3,4,5-trimethoxy-benzyl)indoline (293)

A solution of indoline (46 mg, 0.39 mmol), benzyl chloride **292** (272 mg, 0.58 mmol), K_2CO_3 (323 mg, 2.34 mmol) and KI (96 mg, 0.58 mmol) in acetone (40 mL) was heated at reflux for 16 h. The reaction mixture was cooled to RT and water (60 mL) and diethyl ether (60 mL) were added. The aqueous phase

was separated and extracted with diethyl ether (2 × 40 mL) then the combined organic phases were washed with brine (100 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% diethyl ether in petroleum ether) afforded the title compound as a brown oil (190 mg, 0.25 mmol, 41%).

ν_{\max}	2932 (w), 2848 (w), 2362 (w), 1606 (m), 1487 (m), 1458 (s), 1402 (s), 1371 (s), 1355 (w), 1309 (m), 1279 (w), 1251 (w), 1213 (w), 1161 (w).
δ_{H} (400 MHz, CDCl ₃)	7.18–7.09 (2H, m, 2 × ArH), 6.76 (1H, d, $J=7.7$ Hz, ArH), 6.70 (1H, app. td, $J=7.4, 0.9$ Hz, ArH), 4.69 (2H, s, NCH ₂ Ar), 3.94 (3H, s, CH ₃), 3.91 (6H, s, 2 × CH ₃), 3.27 (2H, t, $J=8.2$ Hz, CH ₂ CH ₂), 2.90 (2H, t, $J=8.2$ Hz, CH ₂ CH ₂).
δ_{C} (100 MHz, CDCl ₃)	153.8 (2 × C), 151.6 (C), 144.3 (C), 136.5 (C), 130.1 (C), 127.1 (CH), 124.4 (CH), 117.7 (CH), 107.4 (CH), 94.1 (2 × C–I), 62.2 (CH ₂), 61.0 (CH ₃), 60.8 (2 × CH ₃), 52.4 (CH ₂), 28.5 (CH ₂).
LRMS	Did not fly by ES/EI or CI

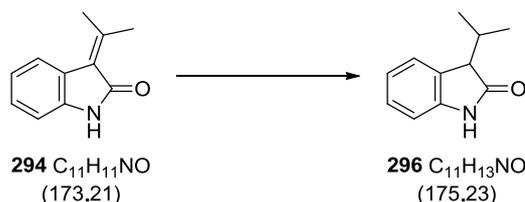
3-(Propan-2-ylidene)indolin-2-one (294)



A solution of oxindole **236** (1.00 g, 7.51 mmol), piperidine (1.49 mL, 15.02 mmol) and acetone (0.61 mL, 8.26 mmol) in ethanol (8 mL) was heated at reflux for 2.5 h, then cooled to RT. The resulting precipitate was collected by filtration, washed with cold ethanol (2 × 10 mL) and dried *in vacuo* to afford the title compound as a yellow solid (870 mg, 5.03 mmol, 67%). These data are in accordance with those reported in the literature.⁸⁸

MP	191–193 °C (EtOH), Lit. ^[14] 189–191 °C (EtOH).
ν_{max}	3139 (w), 3100 (w), 3076 (w), 3024 (w), 2893 (w), 2837 (w), 2699 (w), 2360 (w), 2341 (w), 1691 (s), 1627 (w), 1614 (m), 1587 (w), 1556 (w), 1489 (w), 1466 (m).
δ_{H} (300 MHz, CDCl_3)	8.62 (1H, br. s, NH), 7.52 (1H, d, $J=7.7$ Hz, ArH), 7.19 (1H, app. t, $J=7.7$ Hz, ArH), 7.02 (1H, app. td, $J=7.7, 1.1$ Hz, ArH), 6.89 (1H, d, $J=7.7$ Hz, ArH), 2.63 (3H, s, CH_3), 2.39 (3H, s, CH_3).
δ_{C} (75 MHz, CDCl_3)	169.7 (C=O), 155.5 (C), 139.4 (C), 127.5 (CH), 124.3 (C), 123.7 (CH), 123.0 (C), 121.5 (CH), 109.3 (CH), 25.2 (CH ₃), 23.1 (CH ₃).
LRMS (CI)	173 ($[\text{M}]^+$, 100%), 158 ($[\text{M}-\text{CH}_3]^+$, 90%), 130 ($[\text{M}-\text{C}(\text{CH}_3)_2]^+$, 21%).

3-Isopropylindolin-2-one (296)

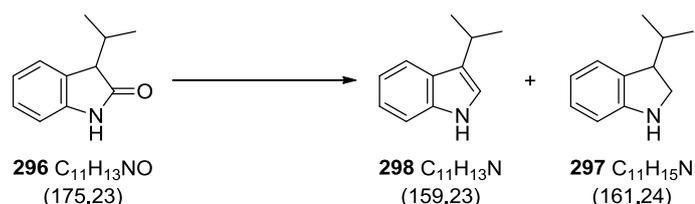


To **294** (400 mg, 2.31 mmol) and 10% Pd/C (40 mg) was added methanol:DCM (1:1, 25 mL). The mixture was degassed with argon then stirred vigorously under an atmosphere of H₂ for 4 h. The reaction mixture was purged of H₂ by flushing with argon, then filtered (Celite[®]) and washed with DCM (2 × 30 mL). The solvent was removed *in vacuo* to afford the title compound as a pale yellow solid (404 mg, 2.31 mmol, 100%). These data are in accordance with those reported in the literature.⁸⁹

MP	141–143 °C (EtOH), Lit. ^[6] 108–109 °C (EtOAc/hexanes).
ν_{max}	3057 (w), 2925 (w), 2851 (w), 1712 (s), 1613 (m), 1569 (w), 1488 (m), 1466 (m), 1440 (m), 1375 (m), 1349 (m), 1311 (w), 1265 (w), 1203 (m), 1169 (m), 1102 (w).

δ_H (300 MHz, $CDCl_3$)	8.76 (1H, br. s, NH), 7.26 (1H, d, $J=8.0$ Hz, ArH), 7.22 (1H, t, $J=7.7$ Hz, ArH), 7.02 (1H, app. td, $J=7.6, 0.9$ Hz, ArH), 6.90 (1H, d, $J=7.7$ Hz, ArH), 3.41 (1H, d, $J=3.5$ Hz, $CHC=O$), 2.52 (1H, sept. d, $J=7.0, 3.5$ Hz, $CH(CH_3)_2$), 1.14 (3H, d, $J=7.0$ Hz, CH_3), 0.93 (3H, d, $J=7.0$ Hz, CH_3).
δ_C (75 MHz, $CDCl_3$)	180.0 (C=O), 142.0 (C), 128.3 (C), 127.8 (CH), 124.6 (CH), 122.0 (CH) 109.5 (CH), 52.1 (CH), 30.7 (CH) 19.8 (CH ₃), 17.9 (CH ₃).
LRMS (EI)	175 ($[M]^+$, 23%), 133 ($[M-C(CH_3)_2]^+$, 100%).

3-Isopropyl-1H-indole (298) and 3-isopropylindoline (297)



To a solution of **296** (250 mg, 1.43 mmol) in THF (15 mL) at 0 °C was added $BH_3 \cdot DMS$ (10 M, 0.54 mL, 5.42 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to RT and after 16 h water (20 mL) was added cautiously and followed after 30 min by diethyl ether (20 mL). The aqueous phase was separated and extracted with diethyl ether (20 mL) then the combined organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (5% diethyl ether in petroleum ether) afforded firstly **298** as a colourless oil (60 mg, 0.38 mmol, 27%) and then **297** as a colourless oil (76 mg, 0.47 mmol, 33%). These data are in accordance with those reported in the literature.^{90,91}

Data for 298:

ν_{max}	3412 (br. m), 3055 (w), 2957 (m), 2868 (w), 2360 (w), 1619 (w), 1485 (w), 1456 (m), 1418 (w), 1382 (w), 1362 (w), 1338 (w), 1242 (w), 1226 (w), 1150 (w), 1097 (w).
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δ_{H} (300 MHz, CDCl_3) 7.71 (1H, br. s, *NH*), 7.65 (1H, dd, $J=7.8$, 0.5 Hz, *ArH*), 7.28 (1H, d, $J=7.8$ Hz, *ArH*), 7.20–7.05 (2H, m, 2 × *ArH*), 6.87 (1H, d, $J=2.2$ Hz, *ArH*), 3.20 (1H, sept., $J=6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.34 (6H, d, $J=6.8$ Hz, 2 × CH_3).

δ_{C} (75 MHz, CDCl_3) 136.5 (C), 126.7 (C), 123.9 (C), 121.8 (CH), 119.3 (CH), 119.2 (CH), 118.9 (CH), 111.1 (CH), 25.4 (CH), 23.3 (2 × CH_3).

LRMS (EI) 159 ($[\text{M}]^+$, 29%), 144 ($[\text{M}-\text{CH}_3]^+$, 100%).

Data for 297:

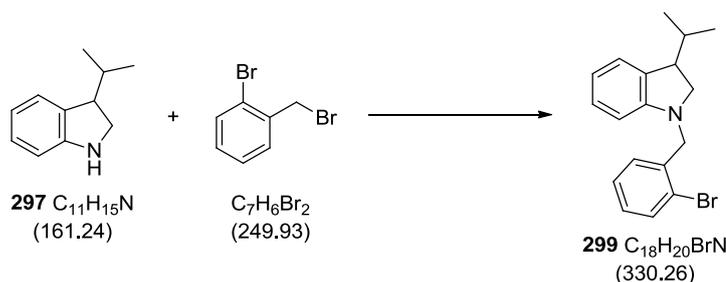
ν_{max} 3381 (w), 3031 (w), 2956 (m), 2926 (w), 2869 (m), 2360 (w), 1606 (m), 1487 (m), 1460 (m), 1385 (w), 1366 (w), 1313 (w), 1246 (m), 1151 (w), 1103 (w).

δ_{H} (300 MHz, CDCl_3) 7.14 (1H, d, $J=7.3$ Hz, *ArH*), 7.06 (1H, app. t, $J=7.6$ Hz, *ArH*), 6.75 (1H, app. t, $J=7.4$ Hz, *ArH*), 6.66 (1H, d, $J=7.7$ Hz, *ArH*), 3.60 (1H, app. t, $J=9.2$ Hz, CHCHH), 3.50 (1H, br. s, *NH*), 3.40 (1H, dd, $J=9.2$, 6.3 Hz, CHCHH), 3.26 (1H, ddd, $J=9.2$, 6.3, 5.6 Hz, CHCH_2), 2.08 (1H, sept. d, $J=6.8$, 5.6 Hz, $\text{CH}(\text{CH}_3)_2$), 1.03 (3H, d, $J=6.8$ Hz, CH_3), 0.93 (3H, d, $J=6.8$ Hz, CH_3).

δ_{C} (75 MHz, CDCl_3) 151.9 (C), 131.7 (C), 127.3 (CH), 124.7 (CH), 118.2 (CH), 109.5 (CH), 49.2 (CH_2), 48.3 (CH), 30.9 (CH), 20.4 (CH_3), 18.5 (CH_3).

LRMS (ES^+) 162 ($[\text{M}+\text{H}]^+$, 40%).

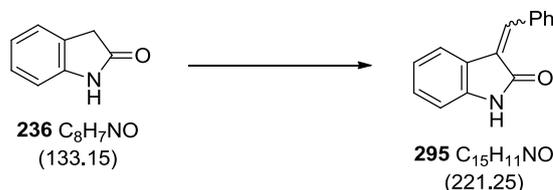
1-(2-Bromobenzyl)-3-isopropylindoline (299)



To a solution of **297** (76 mg, 0.47 mmol) in acetonitrile (8 mL) at RT was added K₂CO₃ (130 mg, 0.94 mmol) and KI (8 mg, 0.05 mmol). After 1 h, 2-bromobenzyl bromide (118 mg, 0.47 mmol) in acetonitrile (2 mL) was added dropwise over 10 min. After 12 h ethyl acetate (10 mL) and water (10 mL) were added. The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were then washed with brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (0–1% chloroform in petroleum ether) afforded the *title compound* as a colourless oil (96 mg, 0.29 mmol, 62%).

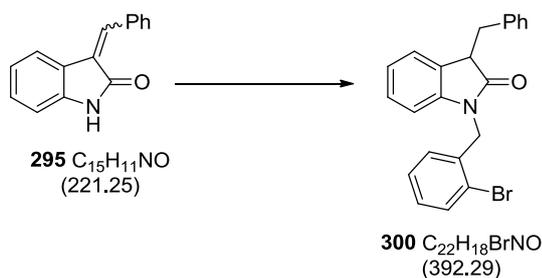
ν_{max}	3049 (w), 2955 (w), 2923 (w), 2868 (w), 1603 (m), 1567 (w), 1489 (m), 1459 (m), 1439 (m), 1384 (w), 1346 (m), 1305 (w), 1257 (m), 1156 (m), 1106 (w), 1044 (w).
δ_H (300 MHz, CDCl₃)	7.62 (1H, d, <i>J</i> =7.9 Hz, <i>ArH</i>), 7.44 (1H, d, <i>J</i> =7.6 Hz, <i>ArH</i>), 7.31 (1H, app. t, <i>J</i> =7.5 Hz, <i>ArH</i>), 7.22–7.04 (3H, m, 3 × <i>ArH</i>), 6.72 (1H, app. t, <i>J</i> =7.4 Hz, <i>ArH</i>), 6.43 (1H, d, <i>J</i> =7.8 Hz, <i>ArH</i>), 4.38 (1H, d, <i>J</i> =16.5 Hz, NCHHAr), 4.31 (1H, d, <i>J</i> =16.5 Hz, NCHHAr), 3.55–3.41 (1H, m, CHCH ₂), 3.37–3.20 (2H, m, CHCH ₂), 2.18–1.96 (1H, m, CH(CH ₃) ₂), 1.03 (3H, d, <i>J</i> =6.8 Hz, CH ₃), 0.94 (3H, d, <i>J</i> =6.8 Hz, CH ₃).
δ_C (75 MHz, CDCl₃)	152.5 (C), 137.5 (C), 132.7 (CH), 132.0 (C), 129.1 (CH), 128.4 (CH), 127.5 (CH), 127.4 (CH), 124.5 (CH), 123.3 (C), 117.3 (CH), 106.5 (CH), 56.2 (CH ₂), 53.9 (CH ₂), 46.9 (CH), 31.1 (CH), 20.4 (CH ₃), 18.6 (CH ₃).
LRMS (ES⁺)	⁷⁹ Br: 330 ([M+H] ⁺ , 79%).

HRMS

 $C_{18}H_{21}BrN$ $[M+H]^+$ requires 330.0852; found: 330.0859.**3-(Benzylidene)indolin-2-one (295)**

A solution of oxindole **236** (600 mg, 4.51 mmol), piperidine (0.9 mL, 9.02 mmol) and benzaldehyde (526 mg, 4.96 mmol) in ethanol (4 mL) was heated at reflux for 4 h. The reaction mixture was cooled to RT and ethyl acetate (20 mL) and water (20 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases washed with water (20 mL), brine (40 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20–50% diethyl ether in petroleum ether) afforded the title compound as a bright yellow solid (854 mg, 3.86 mmol, 86%). These data are in accordance with those reported in the literature.⁹²

MP	179–181 °C (MeOH).
ν_{max}	3181 (m), 3060 (m), 3024 (m), 1697 (s), 1610 (s).
δ_H (300 MHz, $CDCl_3$)	9.32 (1H, br. s, NH), 7.91 (1H, s, C=CH), 7.80–7.63 (3H, m, 3 × ArH), 7.60–7.43 (3H, m, 3 × ArH), 7.36–7.19 (1H, app. t, $J=7.8$ Hz, ArH), 7.00 (1H, d, $J=7.7$ Hz, ArH), 6.92 (1H, app. t, $J=7.7$ Hz, ArH).
δ_C (75 MHz, $CDCl_3$)	170.7 (C=O), 141.8 (C), 137.5 (CH), 134.9 (C), 129.9 (CH), 129.7 (CH), 129.4 (2 × CH), 128.7 (2 × CH), 127.7 (C), 123.0 (CH), 121.8 (CH), 121.0 (C), 110.4 (CH).
LRMS (ES⁺)	244 ($[M+Na]^+$, 100%).

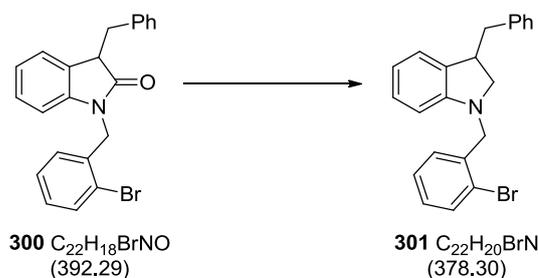
3-Benzyl-1-(2-bromobenzyl)indolin-2-one (300)

To a solution of **295** (1.00 g, 4.52 mmol) in DMF (10 mL) was added NaH (60% in mineral oil, 199 mg, 4.97 mmol). After 15 min, 2-bromobenzyl bromide (1.24 g, 4.97 mmol) in DMF (2 mL) was added dropwise over 5 min. After 16 h the reaction mixture was quenched with water (10 mL) and extracted with MTBE (2 × 10 mL). The combined organic phases were dried (MgSO₄) and the solvent removed *in vacuo* to afford a yellow oil (1.76 g, 4.51 mmol, quant.) which was diluted with acetic acid (7 mL). Zn dust (1.73 g, 0.026 g-atom) and conc. HCl (0.05 mL) were then added. After 16 h the reaction mixture was filtered through Celite[®] with additional ethyl acetate. The filtrate was washed with saturated NaHCO₃ (2 × 20 mL) and brine (20 mL), then dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% diethyl ether in petroleum ether) afforded the *title compound* as a white solid (1.13 g, 2.88 mmol, 64%).

MP	160–163 °C (EtOAc / hexanes).
ν_{max}	3059 (w), 3030 (w), 2921 (w), 2853 (w), 2248 (w), 1708 (s), 1613 (m), 1569 (w), 1488 (m), 1466 (m), 1454 (w), 1440 (m), 1422 (w), 1381 (w), 1360 (m), 1310 (w), 1268 (w), 1216 (w), 1026 (m), 907 (m), 747 (s), 725 (s), 698 (s).
δ_H (400 MHz, CDCl₃)	7.58 (1H, dd, <i>J</i> =7.9, 1.3 Hz, <i>ArH</i>), 7.41–7.22 (3H, m, 3 × <i>ArH</i>), 7.21–7.13 (4H, m, 4 × <i>ArH</i>), 7.10 (1H, app. td, <i>J</i> =7.6, 1.7 Hz, <i>ArH</i>), 7.07–6.98 (2H, m, 2 × <i>ArH</i>), 6.52 (1H, d, <i>J</i> =7.8 Hz, <i>ArH</i>), 6.22 (1H, dd, <i>J</i> =7.7, 0.8 Hz, <i>ArH</i>), 5.15 (1H, d, <i>J</i> =16.9 Hz, <i>NCHHAr</i>), 4.76 (1H, d, <i>J</i> =16.9 Hz, <i>NCHHAr</i>), 3.96 (1H, dd, <i>J</i> =7.4, 4.3 Hz,

	<i>CHCH</i> ₂ Ph), 3.56 (1H, dd, <i>J</i> =13.6, 4.3 Hz, <i>CHCHH</i> Ph), 3.30 (1H, dd, <i>J</i> =13.6, 7.4 Hz, <i>CHCHH</i> Ph).
δ_C (100 MHz, CDCl ₃)	176.8 (C=O), 143.1 (C), 137.0 (C), 133.9 (C), 132.6 (CH), 129.7 (2 × CH), 128.6 (CH), 128.2 (2 × CH), 128.0 (CH), 127.9 (C), 127.7 (CH), 127.2 (CH), 126.6 (CH), 124.4 (CH), 122.5 (C), 122.3 (CH), 108.9 (CH), 47.1 (CH), 43.5 (CH ₂), 36.2 (CH ₂).
LRMS (ES ⁺)	⁷⁹ Br: 455 ([M+Na+MeCN] ⁺ , 100%).
HRMS	C ₂₂ H ₁₉ BrNO [M+H] ⁺ requires 392.0645; found: 392.0640.

3-Benzyl-1-(2-bromobenzyl)-2,3-dihydro-1*H*-indole (301)



To a solution of **300** (100 mg, 0.25 mmol) in toluene (3 mL) at $-78\text{ }^{\circ}\text{C}$ was added AlH_3 (0.5 M in toluene, 1.0 mL, 0.50 mmol) dropwise over 5 min. After 20 min the reaction mixture was warmed to RT for 4 h and then cooled to $0\text{ }^{\circ}\text{C}$. Methanol (1.5 mL) then 1 M HCl (1.5 mL) were added cautiously followed after 10 min by saturated NaHCO_3 ($\sim\text{pH}10$). The aqueous phase was separated and extracted with ethyl acetate ($3 \times 10\text{ mL}$). The combined organic phases were washed with brine (30 mL), dried (MgSO_4) and the solvent removed *in vacuo* to afford the *title compound* as a pale yellow oil (28 mg, 0.074 mmol, 30%).

ν_{max}	3025 (w), 2916 (w), 2825 (w), 1604 (m), 1567 (w), 1487 (m), 1458 (w), 1439 (w).
δ_H (300 MHz, CDCl ₃)	7.61 (1H, dd, <i>J</i> =7.9, 1.1 Hz, <i>ArH</i>), 7.42–7.21 (7H, m, 7 × <i>ArH</i>), 7.21–7.09 (2H, m, 2 × <i>ArH</i>), 7.05 (1H, d, <i>J</i> =7.2 Hz, <i>ArH</i>), 6.74 (1H, app. t, <i>J</i> =7.3 Hz, <i>ArH</i>), 6.48 (1H, d, <i>J</i> =7.8 Hz, <i>ArH</i>), 4.37 (1H, d, <i>J</i> =16.3 Hz,

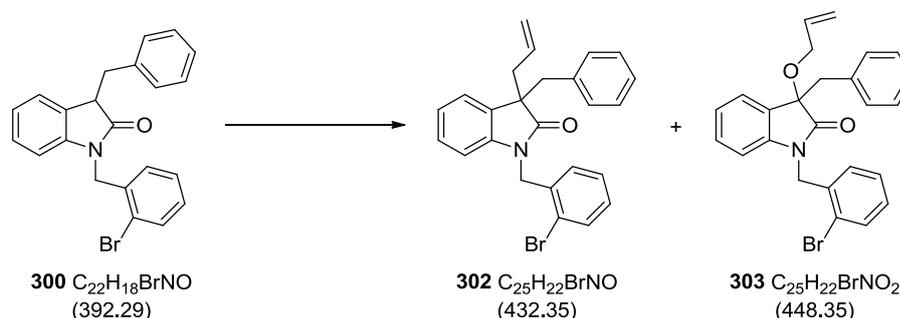
NCHHAr), 4.30 (1H, d, $J=16.3$ Hz, NCHHAr), 3.74–3.57 (1H, m, NCH₂CH), 3.49 (1H, app. t, $J=8.7$ Hz, NCHHCH), 3.29–3.10 (2H, m, NCHHCH and CHCHHPh), 2.90 (1H, dd, $J=13.6, 9.1$ Hz, CHCHHPh).

δ_c (75 MHz, CDCl₃) 152.0 (C), 139.9 (C), 137.4 (C), 132.7 (CH), 129.1 (CH), 129.0 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 127.8 (CH), 127.4 (CH), 126.2 (CH), 123.9 (CH), 123.3 (C), 117.6 (CH), 106.9 (CH), 59.5 (CH₂), 53.6 (CH₂), 42.3 (CH), 40.5 (CH₂), *N.B.* One quaternary signal not observed.

LRMS (ES⁺) ⁷⁹Br: 378 ([M+H]⁺, 100%).

HRMS Sample decomposed.

3-Allyl-3-benzyl-1-(2-bromobenzyl)indolin-2-one (302) and 3-(oxyallyl)-3-benzyl-1-(2-bromobenzyl)indolin-2-one (303)



To a solution of **300** (188 mg, 0.48 mmol) in DMF (13 mL) at 0 °C was added sodium hydride (60% in mineral oil, 29 mg, 0.72 mmol). After 1.5 h, allyl bromide (0.06 mL, 0.72 mmol) in DMF (2 mL) was added dropwise over 10 min. After 16 h at RT water (20 mL) and ethyl acetate (10 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (2 × 10 mL). The organic phases were combined, washed with water (3 × 10 mL) and brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (40% DCM in petroleum ether) afforded firstly **302** as a pale yellow oil (60 mg, 0.14 mmol, 29%) and then **303** as a colourless oil (44 mg, 0.10 mmol, 21%).

Data for 302:

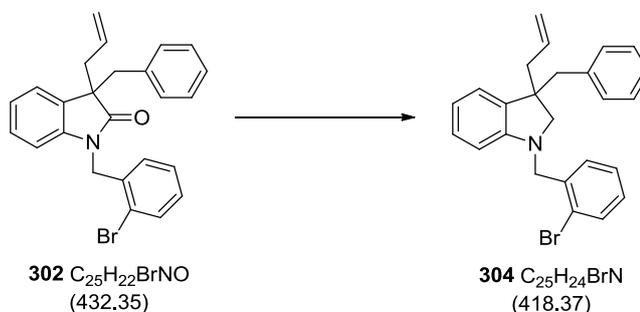
ν_{\max}	3059 (w), 3031 (w), 2915 (w), 2849 (w), 2362 (w), 2247 (w), 1709 (s), 1640 (w), 1612 (m), 1569 (w), 1489 (m), 1466 (m), 1455 (w), 1439 (m), 1382 (m), 1364 (m), 1349 (m), 1309 (w), 1269 (w), 1226 (w), 1198 (w).
δ_{H} (400 MHz, CDCl_3)	7.51 (1H, dd, $J=7.8, 1.3$ Hz, ArH), 7.41–7.34 (1H, m, ArH), 7.20–7.14 (1H, m, ArH), 7.14–7.05 (4H, m, 4 × ArH), 7.02 (1H, app. td, $J=7.5, 1.5$ Hz, ArH), 6.92 (2H, d, $J=7.0$ Hz, 2 × ArH), 6.85 (1H, app. td, $J=7.5, 1.5$ Hz, ArH), 6.36–6.31 (1H, m, ArH), 5.76 (1H, d, $J=8.0$ Hz, ArH), 5.53 (1H, ddt, $J=17.2, 9.9, 7.3$ Hz, CH=CH ₂), 5.11 (1H, dd, $J=17.2, 2.0$ Hz, CH=CHH), 5.00 (1H, dd, $J=9.9, 2.0$ Hz, CH=CHH), 4.99 (1H, d, $J=17.4$ Hz, NCHHAr), 4.60 (1H, d, $J=17.4$ Hz, NCHHAr), 3.30 (1H, d, $J=13.1$ Hz, CHHPh), 3.20 (1H, d, $J=13.1$ Hz, CHHPh), 2.82 (1H, dd, $J=13.6, 8.0$ Hz, CHHCH=CH ₂), 2.76 (1H, dd, $J=13.6, 7.0$ Hz, CHHCH=CH ₂).
δ_{C} (100 MHz, CDCl_3)	178.4 (C=O), 142.7 (C), 136.0 (C), 133.9 (C), 132.5 (CH), 132.2 (CH), 130.6 (C), 130.2 (2 × CH), 128.4 (CH), 128.0 (CH), 127.9 (2 × CH), 127.6 (CH), 127.2 (CH), 126.6 (CH), 123.7 (CH), 122.3 (C), 122.3 (CH), 119.2 (CH ₂), 108.9 (CH), 54.9 (C), 43.5 (CH ₂), 43.0 (CH ₂), 42.4 (CH ₂).
LRMS (ES ⁺)	⁷⁹ Br: 495 ([M+Na+MeCN] ⁺ , 13%), 454 ([M+Na] ⁺ , 2%).
HRMS	C ₂₅ H ₂₂ BrNNaO [M+Na] ⁺ requires 454.0777; found: 454.0793.

Data for 303:

ν_{\max}	3059 (w), 3030 (w), 2921 (w), 2853 (w), 1724 (s), 1612 (s), 1569 (w), 1487 (m), 1466 (s), 1440 (m), 1423 (w), 1378 (w), 1352 (m), 1304 (w), 1277 (w), 1199 (w), 1170 (m).
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δ_{H} (400 MHz, CDCl_3)	7.52 (1H, dd, $J=8.0, 1.0$ Hz, ArH), 7.39 (1H, dd, $J=7.3, 1.3$ Hz, ArH), 7.24–7.14 (3H, m, 3 × ArH), 7.11 (2H, app. t, $J=7.5$ Hz, 2 × ArH), 7.04 (1H, td, $J=7.5, 1.5$ Hz, ArH), 6.94 (2H, d, $J=7.5$ Hz, 2 × ArH), 6.88 (1H, app. td, $J=7.5, 1.0$ Hz, ArH), 6.36 (1H, d, $J=7.0$ Hz, ArH), 5.92 (1H, ddt, $J=17.2, 10.4, 5.7$ Hz, $\text{CH}=\text{CH}_2$), 5.73 (1H, d, $J=7.5$ Hz, ArH), 5.24 (1H, app. dq, $J=17.2, 1.5$ Hz, $\text{CH}=\text{CHH}$), 5.15 (1H, app. dq, $J=10.4, 1.5$ Hz, $\text{CH}=\text{CHH}$), 5.06 (1H, d, $J=17.1$ Hz, NCHHAr), 4.56 (1H, d, $J=17.1$ Hz, NCHHAr), 3.82 (1H, ddt, $J=11.6, 5.7, 1.4$ Hz, $\text{OCHHCH}=\text{CH}_2$), 3.69 (1H, ddt, $J=11.6, 5.7, 1.4$ Hz, $\text{OCHHCH}=\text{CH}_2$), 3.46 (1H, d, $J=12.6$ Hz, CHHPh), 3.41 (1H, d, $J=12.6$ Hz, CHHPh).
δ_{C} (100 MHz, CDCl_3)	175.7 (C=O), 143.1 (C), 134.1 (CH), 133.7 (C), 133.6 (C), 132.6 (CH), 130.8 (2 × CH), 130.0 (CH), 128.6 (CH), 128.0 (2 × CH), 127.8 (CH), 127.1 (CH), 126.9 (CH), 126.5 (C), 124.8 (CH), 123.0 (CH), 122.3 (C), 117.4 (CH_2), 109.4 (CH), 83.5 (C), 66.7 (CH_2), 43.9 (CH_2), 43.8 (CH_2).
LRMS (ES^+)	^{79}Br : 511 ($[\text{M}+\text{Na}+\text{MeCN}]^+$, 37%), 470 ($[\text{M}+\text{Na}]^+$, 33%).
HRMS	$\text{C}_{25}\text{H}_{22}\text{BrNNaO}_2[\text{M}+\text{Na}]^+$ requires 470.0726; found: 470.0726.

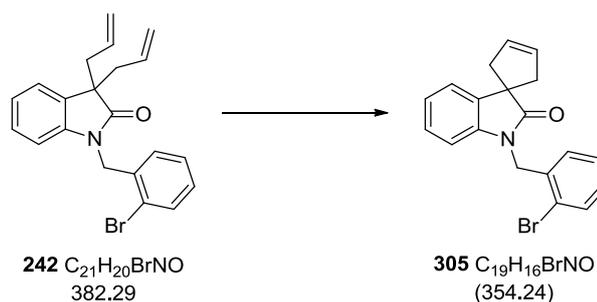
3-Allyl-3-benzyl-1-(2-bromobenzyl)indoline (304)



To a solution of **302** (60 mg, 0.14 mmol) in toluene (2 mL) at -78 °C was added AlH_3 (0.5 M in toluene, 0.56 mL, 0.28 mmol) dropwise over 5 min. After 20 min the

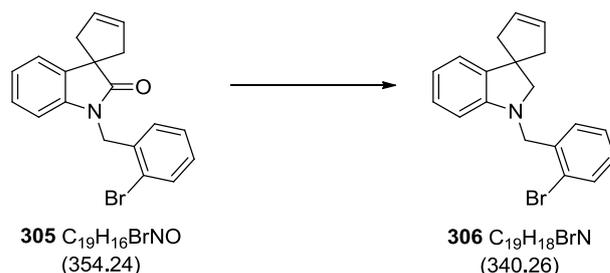
reaction mixture was warmed to RT for 4 h and then cooled to 0 °C. Methanol (1 mL) then 1 M HCl (1 mL) were added cautiously followed after 10 min by saturated NaHCO₃ (~pH 10). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were then washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10–40% chloroform in petroleum ether) afforded the *title compound* as a yellow oil (41 mg, 0.10 mmol, 71%).

U_{max}	3061 (w), 3026 (w), 2916 (w), 2849 (w), 1698 (w), 1638 (w), 1604 (s), 1567 (w), 1489 (s), 1459 (m), 1439 (s), 1346 (w), 1263 (m), 1198 (w), 1158 (w), 1111 (w).
δ_H (400 MHz, CDCl₃)	7.55 (1H, dd, <i>J</i> =7.8, 1.4 Hz, <i>ArH</i>), 7.26–7.18 (3H, m, 3 × <i>ArH</i>), 7.17 (1H, dd, <i>J</i> =7.5, 1.4 Hz, <i>ArH</i>), 7.12 (1H, dd, <i>J</i> =7.7, 1.8 Hz, <i>ArH</i>), 7.08 (1H, app. td, <i>J</i> =7.7, 1.3 Hz, <i>ArH</i>), 6.99–6.93 (3H, m, 3 × <i>ArH</i>), 6.90 (1H, dd, <i>J</i> =7.6, 1.8 Hz, <i>ArH</i>), 6.72 (1H, app. td, <i>J</i> =7.4, 0.9 Hz, <i>ArH</i>), 6.31 (1H, d, <i>J</i> =7.8 Hz, <i>ArH</i>), 5.87–5.73 (1H, m, <i>CH=CH</i> ₂), 5.13–5.11 (1H, m, <i>CH=CHH</i>), 5.09 (1H, ddt, <i>J</i> =7.2, 2.2, 1.1 Hz, <i>CH=CHH</i>), 4.28 (1H, d, <i>J</i> =16.6 Hz, <i>NCHHAr</i>), 4.15 (1H, d, <i>J</i> =16.6 Hz, <i>NCHHAr</i>), 3.40 (1H, d, <i>J</i> =9.0 Hz, <i>NCHH</i>), 3.24 (1H, d, <i>J</i> =9.0 Hz, <i>NCHH</i>), 2.99 (1H, d, <i>J</i> =13.3 Hz, <i>CHHPh</i>), 2.93 (1H, d, <i>J</i> =13.3 Hz, <i>CHHPh</i>), 2.56 (1H, ddt, <i>J</i> =14.0, 7.0, 1.4 Hz, <i>CHHCH=CH</i> ₂) 2.51 (1H, ddt, <i>J</i> =14.0, 8.0, 1.1 Hz, <i>CHHCH=CH</i> ₂).
δ_C (100 MHz, CDCl₃)	151.8 (C) 138.0 (C) 137.4 (C) 134.8 (CH) 134.5 (C) 132.5 (CH) 130.5 (2 × CH) 129.0 (CH) 128.3 (CH) 127.9 (CH) 127.8 (2 × CH) 127.4 (CH) 126.2 (CH) 123.5 (CH) 123.1 (C) 118.0 (CH ₂) 117.3 (CH) 106.7 (CH) 62.6 (CH ₂) 53.5 (CH ₂) 48.3 (C) 45.2 (CH ₂) 42.7 (CH ₂).
LRMS (ES⁺)	⁷⁹ Br: 418 ([<i>M</i> + <i>H</i>] ⁺ , 30%).
HRMS	C ₂₅ H ₂₄ BrN[<i>M</i> + <i>H</i>] ⁺ requires 418.1165; found: 418.1166.

1'-(2-Bromobenzyl)spirocyclopent-3-ene-1,3'-indolin-2'-one (305)

A solution of **242** (77 mg, 0.20 mmol) and Hoveyda-Grubbs' II catalyst (3 mg, 0.004 mmol) in toluene (2 mL) was heated at reflux for 22 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% diethyl ether in petroleum ether) afforded the *title compound* as a pale brown oil (62 mg, 0.175 mmol, 88%).

ν_{max}	3056 (w), 2921 (w), 2842 (w), 1714 (s), 1610 (m), 1569 (w), 1486 (m), 1466 (m), 1440 (m), 1381 (m), 1349 (m), 1308 (w), 1268 (w), 1206 (m), 1160 (w).
δ_{H} (400 MHz, CDCl_3)	7.61 (1H, dd, $J=7.9, 1.1$ Hz, ArH), 7.31 (1H, dd, $J=7.4, 0.8$ Hz, ArH), 7.21 (1H, app. td, $J=7.4, 1.1$ Hz, ArH), 7.18–7.11 (2H, m, 2 × ArH), 7.06–6.97 (2H, m, 2 × ArH), 6.66 (1H, d, $J=7.5$ Hz, ArH), 5.89 (2H, s, $\text{CH}_2\text{CH}=\text{CH}$), 5.04 (2H, s, NCH_2Ar), 3.12 (2H, d, $J=14.6$ Hz, 2 × $\text{CHHCH}=\text{CH}$), 2.71 (2H, d, $J=14.6$ Hz, 2 × $\text{CHHCH}=\text{CH}$).
δ_{C} (100 MHz, CDCl_3)	181.6 (C=O), 141.3 (C), 137.2 (C), 134.6 (C), 132.9 (CH), 128.9 (CH), 128.9 (2 × CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 123.1 (CH), 122.8 (C), 121.8 (CH), 108.9 (CH), 52.2 (C), 45.2 (2 × CH_2), 43.8 (CH_2).
LRMS (ES^+)	^{79}Br : 417 ($[\text{M}+\text{Na}+\text{MeCN}]^+$, 28%).
HRMS	$\text{C}_{19}\text{H}_{16}\text{BrNNaO}$ $[\text{M}+\text{Na}]^+$ requires 376.0307; found: 376.0313.

1'-(2-Bromobenzyl)spirocyclopent-3-ene-1,3'-indoline (306)

To a solution of **305** (62 mg, 0.18 mmol) in toluene (2 mL) at $-78\text{ }^{\circ}\text{C}$ was added AlH_3 (0.5 M in toluene, 0.72 mL, 0.36 mmol) dropwise over 5 min. After 20 min the reaction mixture was warmed to RT for 4 h and then cooled to $0\text{ }^{\circ}\text{C}$. Methanol (1 mL) then 1 M HCl (1 mL) were added cautiously followed after 10 min by saturated NaHCO_3 ($\sim\text{pH } 10$). The aqueous phase was separated and extracted with ethyl acetate ($3 \times 10\text{ mL}$). The combined organic phases were washed with brine (30 mL), then dried (MgSO_4) and concentrated *in vacuo* to afford the *title compound* as a yellow oil (60 mg, 0.176 mmol, 98%).

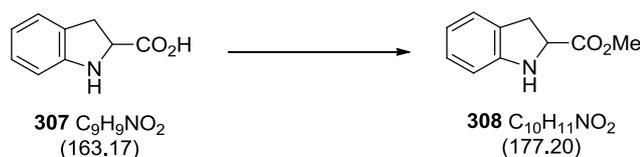
ν_{max} 3050 (w), 2917 (w), 2838 (w), 1604 (m), 1567 (w), 1485 (s), 1459 (m), 1439 (m), 1344 (m), 1260 (m), 1024 (m), 738 (s).

δ_{H} (300 MHz, CDCl_3) 7.60 (1H, dd, $J=7.9, 1.0\text{ Hz}$, ArH), 7.47 (1H, dd, $J=7.6, 0.8\text{ Hz}$, ArH), 7.31 (1H, app. td, $J=7.5, 1.2\text{ Hz}$, ArH), 7.20–7.13 (2H, m, $2 \times \text{ArH}$), 7.10 (1H, app. td, $J=7.7, 1.3\text{ Hz}$, ArH), 6.74 (1H, app. td, $J=7.4, 0.9\text{ Hz}$, ArH), 6.48 (1H, d, $J=7.9\text{ Hz}$, ArH), 5.76 (2H, s, $\text{CH}_2\text{CH}=\text{CH}$), 4.34 (2H, s, NCH_2Ar), 3.38 (2H, s, NCH_2), 2.76 (2H, d, $J=15.2\text{ Hz}$, $2 \times \text{CHHCH}=\text{CH}$), 2.65 (2H, d, $J=15.2\text{ Hz}$, $2 \times \text{CHHCH}=\text{CH}$).

δ_{C} (75 MHz, CDCl_3) 151.3 (C), 138.1 (C), 137.5 (C), 132.8 (CH), 129.3 ($3 \times \text{CH}$), 128.5 (CH), 127.6 (CH), 127.4 (CH), 123.4 (C), 121.8 (CH), 118.1 (CH), 106.9 (CH), 69.5 (CH_2), 53.5 (CH_2), 50.0 (C), 46.8 ($2 \times \text{CH}_2$).

LRMS (ES^+) ^{79}Br : 340 ($[\text{M}+\text{H}]^+$, 100%).

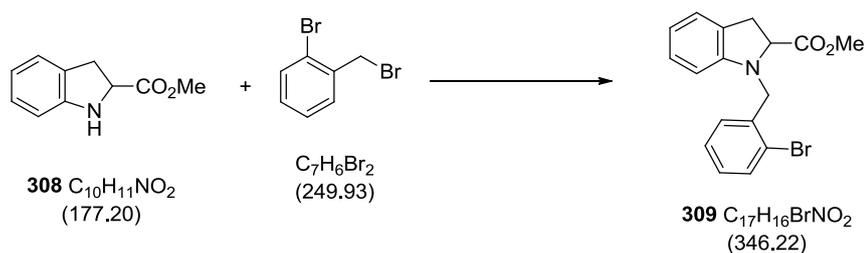
HRMS $\text{C}_{19}\text{H}_{19}\text{BrN}$ $[\text{M}+\text{H}]^+$ requires 340.0695; found: 340.0690.

Methyl indoline-2-carboxylate (308)

To a solution of carboxylic acid **307** (500 mg, 3.06 mmol) in methanol (50 mL) was added thionyl chloride (0.34 mL, 4.59 mmol) dropwise over 5 min. The reaction mixture was heated to reflux for 2 h and then cooled to RT and concentrated *in vacuo*. Saturated aq. NaHCO₃ (50 mL) was then added and the reaction mixture extracted with DCM (3 × 50 mL), the combined organic phases were washed with brine (150 mL) and concentrated *in vacuo*. Purification by column chromatography (30% ethyl acetate in hexanes) afforded the title compound as a pale brown oil (454 mg, 2.56 mmol, 84 %). These data are in accordance with those reported in the literature.⁹⁵

ν_{\max}	3368 (br. w), 3032 (w), 2951 (w), 2852 (w), 1731 (s), 1608 (m), 1531 (w), 1485 (m), 1467 (m), 1436 (m), 1405 (w), 1340 (w), 1321 (w), 1308 (w), 1199 (s), 1157 (m), 1109 (w).
δ_{H} (300 MHz, CDCl ₃)	7.13–6.99 (2H, m, 2 × ArH), 6.83–6.64 (2H, m, 2 × ArH), 4.40 (1H, dd, $J=10.1, 5.7$ Hz, CHCH ₂), 3.77 (3H, s, CO ₂ CH ₃), 3.49–3.24 (2H, m, CHCH ₂).
δ_{C} (75 MHz, CDCl ₃)	174.6 (C=O), 150.0 (C), 127.6 (CH), 126.6 (C), 124.4 (CH), 119.5 (CH), 110.1 (CH), 59.8 (CH), 52.4 (CH ₃), 33.7 (CH ₂).
LRMS (ES ⁺)	219 ([M+MeCN] ⁺ , 100%).

N.B. This compound is prone to decomposition.

Methyl 1-(2-bromobenzyl)indoline-2-carboxylate (309)

To a solution of **308** (500 mg, 2.82 mmol) in acetonitrile (40 mL) was added K_2CO_3 (780 mg, 5.64 mmol) and KI (46 mg, 0.28 mmol). After 1 h, 2-bromobenzyl bromide (705 mg, 2.82 mmol) in acetonitrile (20 mL) was added dropwise over 30 min. After 12 h ethyl acetate (50 mL) and water (50 mL) were added. The aqueous phase was separated and extracted with ethyl acetate (3 × 50 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (5% diethyl ether in petroleum ether) afforded the *title compound* as a pale brown oil (592 mg, 1.71 mmol, 61%).

ν_{max}	3053 (w), 3028 (w), 2950 (w), 2914 (w), 2850 (w), 1745 (s), 1607 (m), 1568 (w), 1485 (s), 1462 (m), 1439 (m), 1388 (w), 1347 (m), 1317 (w), 1262 (m), 1197 (s), 1168 (s), 1088 (w), 1060 (w), 1044 (w), 1024 (m), 1002 (w).
δ_H (300 MHz, $CDCl_3$)	7.59 (1H, dd, $J=8.0, 1.0$ Hz, <i>ArH</i>), 7.48 (1H, dd, $J=7.7, 0.9$ Hz, <i>ArH</i>), 7.28 (1H, app. td, $J=7.4, 1.0$ Hz, <i>ArH</i>), 7.16 (1H, dd, $J=7.8, 1.6$ Hz, <i>ArH</i>), 7.12 (1H, t, $J=8.0$ Hz, <i>ArH</i>), 7.06 (1H, app. t, $J=7.8$ Hz, <i>ArH</i>), 6.73 (1H, app. t, $J=7.4$ Hz, <i>ArH</i>), 6.34 (1H, d, $J=7.7$ Hz, <i>ArH</i>), 4.47 (2H, s, NCH_2Ar), 4.39 (1H, dd, $J=10.3, 8.0$ Hz, <i>CHCHH</i>), 3.68 (3H, s, OCH_3), 3.48 (1H, dd, $J=16.1, 10.3$ Hz, <i>CHCHH</i>), 3.27 (1H, dd, $J=16.1, 8.0$ Hz, <i>CHCHH</i>).
δ_C (75 MHz, $CDCl_3$)	173.2 (C=O), 151.0 (C), 136.9 (C), 132.6 (CH), 129.2 (CH), 128.6 (CH), 127.8 (CH), 127.5 (CH), 126.7 (C),

124.1 (CH), 123.1 (C), 118.3 (CH), 107.0 (CH), 66.1 (CH₃), 52.9 (CH₂), 52.1 (CH), 33.6 (CH₂).

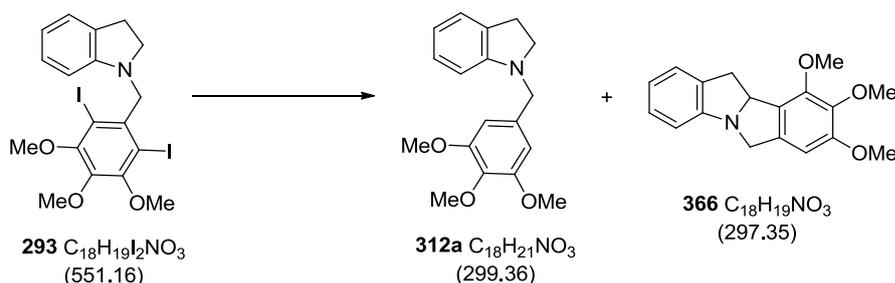
LRMS (EI)

⁷⁹Br: 207 ([M-CO₂Me-Br]⁺, 75%).

HRMS

C₁₇H₁₇BrNO₂[M+H]⁺ requires 346.0437; found: 346.0432.

1-(3,4,5-Trimethoxybenzyl)indoline (312a) and 8,9,10-trimethoxy-10b,11-dihydro-6H-isoindolo[2,1-a]indole (366)



A solution of **293** (106 mg, 0.19 mmol), tributyltin hydride (0.23 mL, 0.84 mmol) and VAZO (9 mg, 0.04 mmol) in toluene (6 mL) was heated at reflux for 18 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 20% diethyl ether in petroleum ether) afforded firstly **312a**, as a colourless oil (54 mg, 0.18 mmol, 95%) and then finally trace **366** as a pale yellow oil (3 mg, 0.01 mmol, 5%) identified by comparison with literature data.⁸⁷

ν_{max}

2923 (w), 2837 (w), 1590 (m), 1504 (m), 1487 (m), 1456 (m), 1419 (m), 1377 (w), 1357 (w), 1327 (m), 1270 (w), 1228 (m), 1181 (w), 1122 (s), 1008 (m).

δ_H (300 MHz, CDCl₃)

7.16–7.03 (2H, m, 2 × ArH), 6.71 (1H, app. td, *J*=7.4, 0.9 Hz, ArH), 6.63 (2H, s, ArH), 6.55 (1H, d, *J*=7.6 Hz, ArH), 4.19 (2H, s, NCH₂Ar), 3.88 (3H, s, OCH₃), 3.86 (6H, s, 2 × OCH₃), 3.33 (2H, t, *J*=8.3 Hz, NCH₂CH₂), 3.01 (2H, t, *J*=8.3 Hz, NCH₂CH₂).

δ_C (75 MHz, CDCl₃)

153.3 (2 × C), 152.5 (C), 136.9 (C), 134.3 (C), 130.0 (C), 127.3 (CH), 124.5 (CH), 117.9 (CH), 107.2 (CH), 104.5

(2 × CH), 60.8 (CH₃), 56.1 (2 × CH₃), 54.3 (CH₂), 53.8 (CH₂), 28.5 (CH₂).

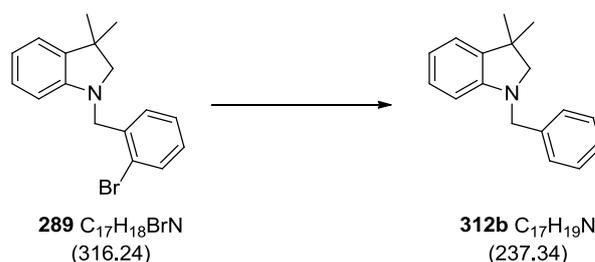
LRMS (ES⁺)

299 ([M]⁺, 13%).

HRMS

C₁₈H₂₁NNaO₃[M+Na]⁺ requires 322.1414; found: 322.1414.

1-Benzyl-3,3-dimethylindoline (312b)



A solution of **289** (87 mg, 0.28 mmol), tributyltin hydride (0.17 mL, 0.62 mmol) and VAZO (15 mg, 0.06 mmol) in toluene (9 mL) was heated at reflux for 18 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 5% chloroform in petroleum ether) afforded the *title compound* as a colourless oil (66 mg, 0.28 mmol, 100%).

ν_{max}

3025 (w), 2956 (w), 2922 (w), 2860 (w), 2803 (w), 1605 (m), 1486 (m), 1453 (m), 1361 (m), 1297 (w), 1260 (m), 1194 (m), 1157 (m), 1117 (w).

δ_H (300 MHz, CDCl₃)

7.33–7.10 (5H, m, 5 × ArH), 7.03–6.91 (2H, m, 2 × ArH), 6.62 (1H, app. td, *J*=7.3, 0.9 Hz, ArH), 6.41 (1H, d, *J*=7.8 Hz, ArH), 4.18 (2H, s, NCH₂Ph), 3.00 (2H, s, NCH₂), 1.22 (6H, s, 2 × CH₃).

δ_C (75 MHz, CDCl₃)

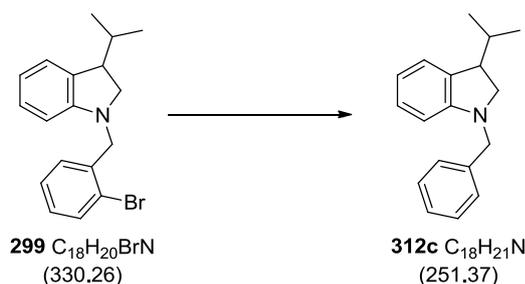
151.1 (C), 138.9 (C), 138.6 (C), 128.4 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 127.0 (CH), 121.7 (CH), 117.7 (CH), 106.9 (CH), 67.8 (CH₂), 53.0 (CH₂), 40.2 (C), 27.54 (2 × CH₃).

LRMS (ES⁺)

238 ([M+H]⁺, 28%).

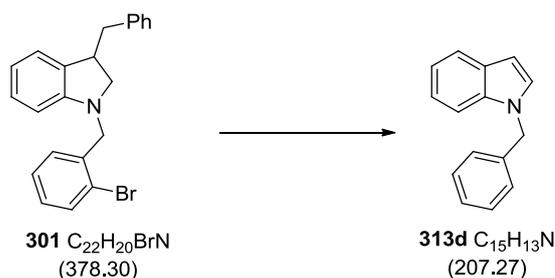
HRMS

C₁₇H₂₀N[M+H]⁺ requires 238.1590; found: 238.1590.

1-Benzyl-3-isopropylindoline (312c)

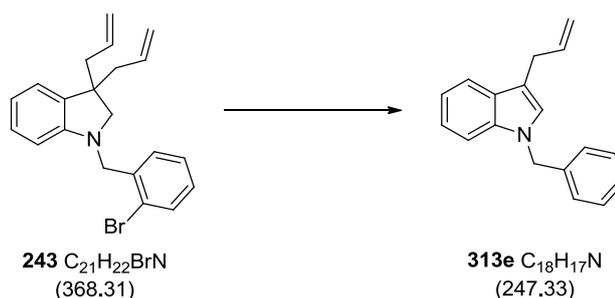
A solution of **299** (96 mg, 0.29 mmol), tributyltin hydride (0.17 mL, 0.64 mmol) and VAZO (15 mg, 0.06 mmol) in toluene (8 mL) was heated at reflux for 18 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 10% chloroform in petroleum ether) afforded the *title compound* as a pale yellow oil (70 mg, 0.28 mmol, 97%).

ν_{max}	3027 (w), 2955 (w), 2924 (w), 2869 (w), 2825 (w), 2361 (w), 1603 (m), 1490 (s), 1454 (s), 1384 (w), 1358 (w), 1309 (w), 1242 (m), 1202 (w), 1173 (w), 1154 (w), 1104 (w).
δ_{H} (300 MHz, CDCl_3)	7.31–7.11 (5H, m, 5 × ArH), 7.05–6.93 (2H, m, 2 × ArH), 6.59 (1H, app. td, $J=7.4$, 1.0 Hz, ArH), 6.39 (1H, d, $J=7.7$ Hz, ArH), 4.21 (1H, d, $J=15.1$ Hz, NCHHPh), 4.13 (1H, d, $J=15.1$ Hz, NCHHPh), 3.25 (1H, app. t, $J=11.0$ Hz, CHCH ₂), 3.14–3.04 (2H, m, CHCH ₂), 1.95 (1H, sept. d, $J=6.8$, 5.2 Hz, CH(CH ₃) ₂), 0.89 (3H, d, $J=6.8$ Hz, CH ₃), 0.79 (3H, d, $J=6.8$ Hz, CH ₃).
δ_{C} (75 MHz, CDCl_3)	152.8 (C), 138.7 (C), 132.2 (C), 128.4 (2 × CH), 127.7 (2 × CH), 127.5 (CH), 127.0 (CH), 124.5 (CH), 117.1 (CH), 106.6 (CH), 55.7 (CH ₂), 53.4 (CH ₂), 46.8 (CH), 31.0 (CH), 20.4 (CH ₃), 18.5 (CH ₃).
LRMS (ES ⁺)	252 ([M+H] ⁺ , 100%).
HRMS	Sample decomposed.

1-Benzyl-1*H*-indole (313d)

A solution of **301** (60 mg, 0.16 mmol), tributyltin hydride (0.1 mL, 0.35 mmol) and VAZO (7 mg, 0.03 mmol) in toluene (5 mL) was heated at reflux for 64 h then cooled to RT and an additional charge of tributyltin hydride (0.1 mL, 0.35 mmol) and VAZO (7 mg, 0.03 mmol) added. After a further 1 h at reflux, the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 5% DCM in petroleum ether) afforded the title compound as a colourless oil (19 mg, 0.092 mmol, 58%). These data are in accordance with those reported in the literature.⁹³

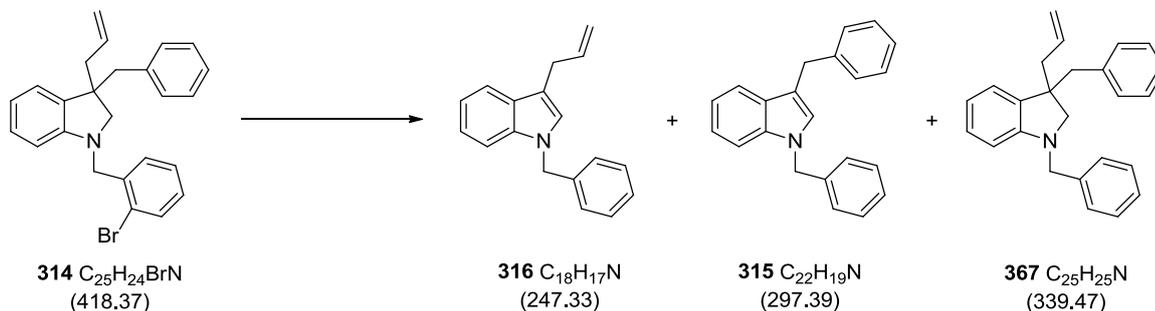
ν_{\max}	3029 (w), 2919 (w), 1612 (w), 1511 (w), 1495 (w), 1484 (w), 1463 (m).
δ_{H} (300 MHz, CDCl ₃)	7.66 (1H, dd, $J=7.9, 1.0$ Hz, <i>ArH</i>), 7.36–7.22 (4H, m, 4 × <i>ArH</i>), 7.21–7.06 (5H, m, 5 × <i>ArH</i>), 6.56 (1H, d, $J=3.2$ Hz, <i>ArH</i>), 5.32 (2H, s, NCH ₂ Ar).
δ_{C} (75 MHz, CDCl ₃)	137.7 (2 × C), 136.5 (C), 128.9 (2 × CH), 128.4 (CH), 127.8 (CH), 126.9 (2 × CH), 121.9 (CH), 121.1 (CH), 119.7 (CH), 109.9 (CH), 101.9 (CH), 50.3 (CH ₂).
LRMS (ES ⁺)	360 (100%), 208 ([M+H] ⁺ , 24%).

3-Allyl-1-benzyl-1*H*-indole (313e)

A solution of **243** (51 mg, 0.14 mmol), tributyltin hydride (0.08 mL, 0.31 mmol) and VAZO (7 mg, 0.03 mmol) in toluene (4 mL) was heated at reflux for 18 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 0–25% DCM in petroleum ether) afforded the title compound as a colourless oil (30 mg, 0.12 mmol, 86%). These data are in accordance with those reported in the literature.⁹⁴

ν_{max}	3058 (w), 3029 (w), 2917 (w), 1715 (w), 1670 (w), 1638 (w), 1604 (m), 1553 (w), 1494 (w), 1481 (w), 1465 (m), 1453 (m), 1439 (w), 1392 (w), 1356 (m), 1352 (m), 1298 (w).
δ_{H} (300 MHz, CDCl_3)	7.63 (1H, d, $J=7.7$ Hz, ArH), 7.36–7.24 (4H, m, 4 × ArH), 7.18 (1H, app. td, $J=7.5, 1.1$ Hz, ArH), 7.15–7.07 (3H, m, 3 × ArH), 6.93 (1H, s, ArH), 6.09 (1H, ddt, $J=16.9, 10.2, 6.4$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.29 (2H, s, CH_2Ph), 5.24–5.02 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.55 (2H, dd, $J=6.4, 0.9$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$).
δ_{C} (75 MHz, CDCl_3)	137.7 (C), 137.4 (CH), 128.7 (2 × CH), 128.1 (C), 127.5 (CH), 126.8 (2 × CH), 125.9 (CH), 121.7 (CH), 119.2 (CH), 118.9 (CH), 115.1 (CH_2), 113.6 (C), 109.6 (CH), 49.9 (CH_2), 29.8 (CH_2), <i>N.B. One quaternary signal not observed.</i>

3-Allyl-1-benzyl-1*H*-indole (316) and 1,3-dibenzyl-1*H*-indole (315) and 3-allyl-1,3-dibenzylindoline (367)



A solution of **314** (41 mg, 0.10 mmol), tributyltin hydride (0.06 mL, 0.22 mmol) and VAZO (5 mg, 0.02 mmol) in toluene (3 mL) were heated at reflux for 18 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 0–1% chloroform in petroleum ether) afforded an inseparable mixture of **316**, **315** and **367** (10:5:2) as a colourless oil (13 mg, 0.048 mmol, 48%).

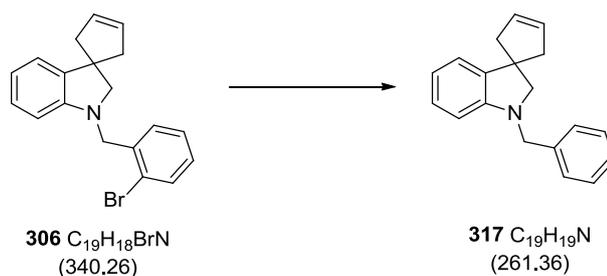
U_{max} 3059 (w), 3028 (w), 2917 (w), 2852 (w), 2358 (w), 2336 (w), 1638 (w), 1604 (w), 1553 (w), 1495 (w), 1481 (w), 1466 (m), 1453 (m), 1439 (w), 1392 (w), 1357 (m), 1332 (m), 1299 (w), 1260 (w), 1203 (w), 1173 (w), 1126 (w), 1106 (w), 1075 (w).

δ_H (400 MHz, CDCl₃) *Peaks attributed to 316* 7.60 (1H, d, *J*=7.6 Hz, Ar*H*), 7.35–6.98 (8H, m, 8 × Ar*H*), 6.90 (1H, s, Ar*H*), 6.06 (1H, ddt, *J*=17.0, 10.2, 6.4 Hz, CH₂CH=CH₂), 5.26 (2H, s, CH₂Ar), 5.19–5.01 (2H, m, CH₂CH=CH₂), 3.51 (2H, d, *J*=6.4 Hz, CH₂CH=CH₂); *Peaks attributed to 315* 7.33–6.80 (15H, m, 15 × Ar*H*), 5.27 (2H, s, NCH₂Ph), 4.11 (2H, s, CCH₂Ph); *Peaks attributed to 367* 7.51 (1H, d, *J*=7.6, 1.4 Hz, Ar*H*), 7.33–6.80 (11H, m, 11 × Ar*H*), 6.66 (1H, app. t, *J*=7.4 Hz, Ar*H*), 6.38 (1H, d, *J*=7.6 Hz, Ar*H*), 5.80–5.66 (1H, m, CH=CH₂), 5.10–5.02 (2H, obsc. m, CH₂CH=CH₂), 4.23 (1H, d, *J*=15.7 Hz, NCHHAr), 4.05 (1H, d, *J*=15.7 Hz, NCHHAr), 3.24 (1H, d, *J*=9.1 Hz,

NCHH), 3.07 (1H, d, $J=9.1$ Hz, NCHH), 2.90 (1H, s, CCH₂Ph), 2.52–2.38 (2H, m, CH₂CH=CH₂).

LRMS (ES⁺) 340 ([**367**+H]⁺, 100%), 298 ([**315**+H]⁺, 20%), 248 ([**316**+H]⁺, 20%).

1'-Benzylspirocyclopent-3-ene-1,3'-indoline (**317**)



A solution of **306** (137 mg, 0.40 mmol), tributyltin hydride (0.24 mL, 0.88 mmol) and VAZO (20 mg, 0.08 mmol) in toluene (10 mL) was heated at reflux for 18 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 0–2% diethyl ether in petroleum ether) afforded the *title compound* as a colourless oil (61 mg, 0.23 mmol, 58%).

ν_{max} 3051 (w), 3026 (w), 2918 (br. w), 2839 (w), 1716 (w), 1678 (w), 1603 (m), 1485 (s), 1459 (m), 1453 (m), 1437 (m), 1375 (w), 1357 (m), 1330 (w), 1311 (w), 1294 (w), 1260 (m), 1202 (w), 1155 (m).

δ_H (400 MHz, CDCl₃) 7.40–7.32 (3H, m, 3 × ArH), 7.31–7.26 (2H, m, 2 × ArH), 7.15–7.05 (2H, m, 2 × ArH), 6.72 (1H, app. td, $J=7.4, 0.9$ Hz, ArH), 6.55 (1H, d, $J=7.8$ Hz, ArH), 5.73 (2H, s, CH=CH), 4.27 (2H, s, NCH₂Ph), 3.25 (2H, s, NCH₂), 2.75–2.67 (2H, m, CH₂CHCH), 2.64–2.56 (2H, m, CH₂CHCH).

δ_C (100 MHz, CDCl₃) 151.6 (C), 138.5 (2 × C), 129.3 (2 × CH), 128.5 (2 × CH), 127.9 (2 × CH), 127.5 (CH), 127.1 (CH), 121.8 (CH),

118.1 (CH), 107.1 (CH), 69.0 (CH₂), 53.3 (CH₂), 49.8 (C),
46.7 (2 × CH₂).

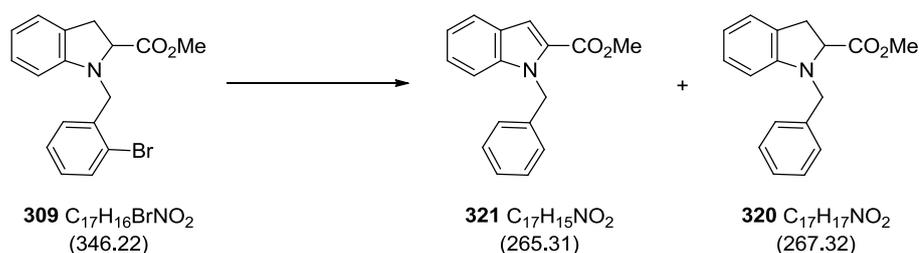
LRMS (ES⁺)

262 ([M+H]⁺, 68%).

HRMS

C₁₉H₂₀N [M+H]⁺ requires 262.1590; found: 262.1592.

Methyl 1-benzyl-1*H*-indole-2-carboxylate (321) and methyl 1-benzylindoline-2-carboxylate (320)



A solution of **309** (569 mg, 1.64 mmol), tributyltin hydride (0.97 mL, 3.61 mmol) and VAZO (81 mg, 0.33 mmol) in toluene (50 mL) was heated at reflux for 18 h, then cooled to RT and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 2–5% diethyl ether in petroleum ether) afforded firstly **321** as a colourless oil (102 mg, 0.38 mmol, 24%) and then **320** as a pale yellow oil (290 mg, 1.09 mmol, 67%).

Data for 321:

ν_{max} 3062 (w), 3031 (w), 2946 (w), 2857 (w), 1706 (s), 1614 (w), 1605 (w), 1518 (m), 1496 (w), 1480 (w), 1452 (m), 1434 (m), 1404 (w), 1353 (m), 1319 (m), 1248 (s), 1191 (s), 1163 (m), 1138 (m), 1118 (w), 1095 (m), 1076(w).

δ_{H} (300 MHz, CDCl₃) 7.76 (1H, d, *J*=8.1 Hz, Ar*H*), 7.44 (1H, s, Ar*H*), 7.41 (1H, d, *J*=8.1 Hz, Ar*H*), 7.36 (1H, dd, *J*=6.6, 1.1 Hz, Ar*H*), 7.28 (1H, d, *J*=7.5 Hz, Ar*H*), 7.33–7.17 (3H, m, 3 × Ar*H*), 7.10 (2H, m, 2 × Ar*H*), 5.89 (2H, s, NCH₂Ph), 3.91 (3H, s, OCH₃).

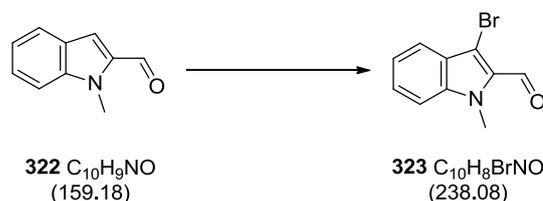
δ_{C} (75 MHz, CDCl₃) 162.3 (C=O), 139.5 (C), 138.2 (C), 128.5 (2 × CH), 127.3 (CH), 127.1 (C), 126.2 (2 × CH), 126.1 (C), 125.3 (CH),

	122.7 (CH), 120.8 (CH), 111.1 (CH), 110.8 (CH), 51.61 (CH ₃) 47.79 (CH ₂).
LRMS (EI)	265 ([M] ⁺ , 57%), 233 ([M–MeOH] ⁺ , 12%), 206 ([M–CO ₂ Me] ⁺ , 6%), 188 ([M–Ph] ⁺ , 4%), 115 ([M–CO ₂ Me–Ph] ⁺ , 5%), 91 ([Bn] ⁺ , 100%).
HRMS	C ₁₇ H ₁₅ NNaO ₂ [M+Na] ⁺ requires 288.0995; found: 288.0994.

Data for 320:

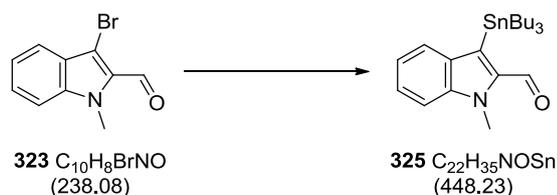
ν_{max}	3053 (w), 3027 (w), 2950 (w), 2849 (w), 1733 (s), 1605 (m), 1484 (s), 1461 (m), 1453 (m), 1435 (m), 1385 (w), 1351 (m), 1319 (w), 1265 (m), 1195 (s), 1156 (s), 1088 (w), 1076 (w), 1022 (m), 1000 (m).
δ_H (300 MHz, CDCl₃)	7.32–7.14 (5H, m, 5 × ArH), 7.02–6.93 (2H, m, 2 × ArH), 6.62 (1H, app. td, <i>J</i> =7.4, 0.7 Hz, ArH), 6.39 (1H, d, <i>J</i> =7.8 Hz, ArH), 4.44 (1H, d, <i>J</i> =15.4 Hz, NCHHPH), 4.25 (1H, d, <i>J</i> =15.4 Hz, NCHHPH), 4.19 (1H, dd, <i>J</i> =10.3, 8.1 Hz, CHCHH), 3.59 (3H, s, OCH ₃), 3.31 (1H, dd, <i>J</i> =15.9, 10.3 Hz, CHCHH), 3.12 (1H, dd, <i>J</i> =15.9, 8.1 Hz, CHCHH).
δ_C (75 MHz, CDCl₃)	173.3 (C=O), 151.3 (C), 137.7 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.2 (CH), 126.8 (C), 124.1 (CH), 118.1 (CH), 107.2 (CH), 65.2 (CH), 52.1 (CH ₂), 52.0 (CH ₃), 33.4 (CH ₂).
LRMS (EI)	267 ([M] ⁺ , 25%), 208 ([M–CO ₂ Me] ⁺ , 54%), 117 ([M–CO ₂ Me–Bn] ⁺ , 17%), 91 ([Bn] ⁺ , 100%).
HRMS	C ₁₇ H ₁₇ NNaO ₂ [M+Na] ⁺ requires 290.1151; found: 290.1156.

6.4 Experimental Procedures for Chapter 5

***N*-Methyl-3-bromo-1*H*-indole-2-carbaldehyde (323)**

To a solution of aldehyde **322** (796 mg, 5.00 mmol) in DMF (10 mL) was added *N*-bromosuccinimide (890 mg, 5.00 mmol) dropwise in DMF (5 mL). After 20 h at RT the reaction mixture was poured onto ice water (100 mL) and the resultant white precipitate collected by filtration and washed with cold ethanol to afford the title compound as a white solid (1.12 g, 4.71 mmol, 94%). These data are in accordance with that reported in the literature.⁹⁶

MP	113–116 °C (EtOH), Lit. 86–89 °C. ⁹⁶
ν_{\max}	3035 (w), 2945 (w), 2824 (m), 2724 (w), 1663 (s), 1613 (m), 1567 (w), 1507 (m), 1469 (s), 1426 (w), 1395 (m), 1350 (m), 1329 (m), 1238 (m), 1182 (m), 738 (s).
δ_{H} (300 MHz, CDCl₃)	10.13 (1H, s, CHO), 7.70 (1H, d, $J=8.1$ Hz, ArH), 7.48 (1H, ddd, $J=8.4, 7.0, 1.1$ Hz, ArH), 7.38 (1H, d, $J=8.7$ Hz, ArH), 7.26 (1H, ddd, $J=8.1, 7.0, 1.1$ Hz, ArH), 4.08 (3H, s, CH ₃).
δ_{C} (75 MHz, CDCl₃)	182.6 (CHO), 139.4 (C), 130.0 (C), 128.1 (CH), 126.2 (C), 121.6 (CH), 121.5 (CH), 110.5 (CH), 106.0 (C), 31.8 (CH ₃).
LRMS (EI)	⁷⁹ Br: 237 (M ⁺ , 100%), 207 ([M-CHO] ⁺ , 16%), 129 ([M-CHO-Br] ⁺ , 33%), 114 (32%).

***N*-Methyl-3-(tributylstannyl)indole-2-carboxaldehyde (325)**

To a stirred solution of *N,O*-dimethylhydroxylamine (147 mg, 1.51 mmol) in THF (7 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*BuLi (1.18 mL, 2.56 M in hexanes, 3.02 mmol). After 1 h a solution of aldehyde **323** (300 mg, 1.26 mmol) in THF (3 mL) was added, followed after 15 min by *n*BuLi (1.13 mL, 2.56 M, 2.90 mmol). The solution was warmed to $-40\text{ }^{\circ}\text{C}$ and after 3 h tributyltin chloride (0.41 mL, 1.51 mmol) was added. The solution was warmed to RT and after 16 h, water (5 mL) and diethyl ether (10 mL) were added. The aqueous phase was separated and washed with diethyl ether (10 mL). The combined organic phases were then washed with brine (20 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 5–10% diethyl ether in petroleum ether) afforded the *title compound* as a pale yellow oil (245 mg, 0.55 mmol, 44%).

ν_{max}	2954 (m), 2921 (m), 2870 (m), 2851 (m), 2360 (w), 2341 (w), 1662 (s), 1609 (m), 1561 (w), 1520 (w), 1464 (s), 1421 (w), 1382 (m), 1340 (s), 1234 (w), 870 (s), 740 (s).
δ_{H} (400 MHz, CDCl_3)	9.89 (1H, s, CHO), 7.75 (1H, dt, $J=8.2, 0.9$ Hz, ArH), 7.42 (2H, m, $2 \times$ ArH), 7.17 (1H, ddd, $J=8.1, 5.4, 2.6$ Hz, ArH), 4.13 (3H, s, NCH ₃), 1.61–1.52 (6H, m, $3 \times$ SnCH ₂ (CH ₂) ₂ CH ₃), 1.36 (6H, sxt, $J=7.3$ Hz, $3 \times$ Sn(CH ₂) ₂ CH ₂ CH ₃), 1.27–1.21 (6H, m, $3 \times$ SnCH ₂ CH ₂ CH ₂ CH ₃), 0.89 (9H, t, $J=7.3$ Hz, $3 \times$ Sn(CH ₂) ₃ CH ₃).
δ_{C} (100 MHz, CDCl_3)	185.0 (CHO), 142.1 (C), 141.7 (C), 134.3 (C), 129.9 (C), 127.1 (CH), 125.5 (CH), 120.9 (CH), 110.9 (CH), 32.2 (NCH ₃), 29.5 ($3 \times$ CH ₂), 27.7 ($3 \times$ CH ₂), 14.0 ($3 \times$ CH ₃), 11.8 ($3 \times$ CH ₂).

LRMS (EI) ^{120}Sn : 392 ($[\text{M}-\text{Bu}]^+$, 32%), 278 ($[\text{M}-3\text{Bu}]^+$, 21%), 159 ($[\text{M}-\text{SnBu}_3]^+$, 100%).

HRMS Sample decomposed.

Indole-2-carboxaldehyde (**327**)



To a solution of carboxylic acid **326** (500 mg, 3.10 mmol) in THF (6 mL) at 0 °C was added thionyl chloride (0.41 mL, 5.60 mmol) in THF (1 mL) dropwise over 5 min. The resulting mixture was heated to 50 °C for 4 h then cooled to RT and concentrated *in vacuo*. The residue was washed with hexanes (2 x 5 mL) then dissolved in THF (4 mL). $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.02 mmol) was then added, followed by tributyltin hydride (0.92 mL, 2.07 mmol), dropwise over 5 min. After 1 h at RT the reaction mixture was filtered through Celite[®] and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 10% ethyl acetate in petroleum ether) afforded the title compound as a white solid (87 mg, 0.60 mmol, 19% over two steps). These data are in accordance with that reported in the literature.⁹⁸

MP 141–144 °C (PhMe / hexanes), Lit. 139–140 °C.⁹⁸

ν_{max} 3310 (s), 3210 (br. w), 2861 (w), 1677 (s), 1619 (w), 1574 (w), 1527 (m), 1451 (w), 1428 (w), 1366 (w), 1341 (m), 1242 (w), 1231 (m), 1127 (m), 821 (m), 744 (m).

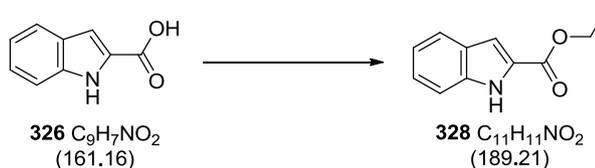
δ_{H} (300 MHz, CDCl_3) 9.87 (1H, s, CHO), 9.14 (1H, br. s, NH), 7.77 (1H, ddd, $J=8.2, 1.9, 1.0$ Hz, ArH), 7.47 (1H, ddd, $J=8.4, 1.9, 1.0$ Hz, ArH), 7.41 (1H, ddd, $J=8.4, 6.9, 1.1$ Hz, ArH), 7.30 (1H, dd, $J=2.1, 0.9$ Hz, ArH), 7.20 (1H, ddd, $J=8.1, 6.9, 1.1$ Hz, ArH).

δ_{C} (75 MHz, CDCl_3) 182.1 (CHO), 138.0 (C), 136.0 (C), 127.3 (CH), 123.4 (CH), 121.3 (CH), 114.8 (CH), 112.4 (CH).

N.B. One aromatic quaternary centre not observed.

LRMS (CI) 145 (M^+ , 88%), 116 ($[M-CHO]^+$, 26%), 89 (100%).

2-(Ethoxycarbonyl)indole (328)

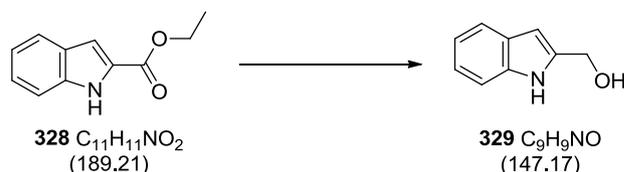


To a solution of carboxylic acid **326** (1.00 g, 6.21 mmol) in ethanol (15 mL) was added conc. H_2SO_4 (0.15 mL). The reaction mixture was heated at reflux for 20 h then cooled to RT, concentrated *in vacuo* to ~5 mL then poured into sat. $NaHCO_3$ (25 mL) at 0 °C. The resulting precipitate was dissolved in diethyl ether (50 mL) and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a white fibrous solid (1.08 g, 5.71 mmol, 92%). These data are in accordance with that reported in the literature.⁹⁹

MP	149–151 °C (EtOH), Lit. 120–121 °C. ⁹⁹
ν_{max}	3310 (s), 3081 (w), 2985 (w), 2940 (w), 2907 (w), 2360 (w), 2342 (w), 1692 (s), 1619 (w), 1528 (m), 1475 (w), 1446 (w), 1435 (w), 1397 (w), 1383 (m), 1370 (w), 1341 (m), 1310 (m), 1253 (s), 1206 (s), 773 (m), 747 (m).
δ_H (300 MHz, $CDCl_3$)	9.14 (1H, br. s, <i>NH</i>), 7.71 (1H, dd, $J=8.1, 1.1$ Hz, <i>ArH</i>), 7.45 (1H, dd, $J=8.3, 1.0$ Hz, <i>ArH</i>), 7.34 (1H, ddd, $J=8.3, 7.0, 1.1$ Hz, <i>ArH</i>), 7.26 (1H, dd, $J=2.1, 1.0$ Hz, <i>ArH</i>), 7.17 (1H, ddd, $J=8.1, 7.0, 1.0$ Hz, <i>ArH</i>), 4.45 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.44 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$).
δ_C (75 MHz, $CDCl_3$)	162.1 (C=O), 136.8 (C), 127.5 (2 × C), 125.3 (CH), 122.6 (CH), 120.7 (CH), 111.9 (CH), 108.6 (CH), 61.0 (CH_2), 14.4 (CH_3).

LRMS (CI) 189 (M^+ , 82%), 160 ($[M-Et]^+$, 8%), 143 ($[M-EtOH]^+$, 100%), 115 ($[M-CO_2Et]^+$, 82%).

2-(Hydroxymethyl)indole (**329**)



To a solution of ester **328** (4.84 g, 25.6 mmol) in THF (120 mL) at $-78\text{ }^\circ\text{C}$ was added $LiAlH_4$ (2.14 g, 56.3 mmol) portionwise. The reaction mixture was warmed to $0\text{ }^\circ\text{C}$. After 1 h water (5 mL) was added cautiously, followed by 15% aq. NaOH (5 mL) and water (15 mL). After 30 min $MgSO_4$ (25.00 g) was added and after 16 h the white suspension was removed by filtration and the filtrate concentrated *in vacuo*. Recrystallisation from benzene / petrol afforded the title compound as pale orange needles (3.72 g, 25.3 mmol, 99%). These data are in accordance with that reported in the literature.⁹⁸

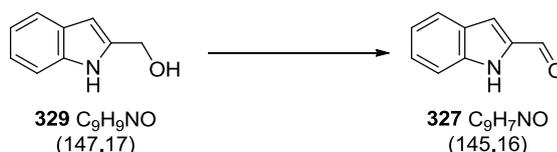
MP 71–73 $^\circ\text{C}$ (benzene / petrol), Lit.75–76 $^\circ\text{C}$.⁹⁸

ν_{\max} 3379 (s), 3300 (br. w), 3051 (w), 2859 (w), 2358 (w), 1489 (w), 1455 (m), 1417 (m), 1385 (w), 1341 (w), 1309 (w), 1291 (m), 1138 (m), 1061 (m), 1016 (m), 1004 (m), 967 (m), 929 (w), 793 (m), 782 (m), 750 (s), 736 (s).

δ_H (300 MHz, $CDCl_3$) 8.37 (1H, br. s, NH), 7.60 (1H, d, $J=7.4$ Hz, ArH), 7.32 (1H, d, $J=7.7$ Hz, ArH), 7.21 (1H, td, $J=7.4, 1.1$ Hz, ArH), 7.13 (1H, td, $J=7.7, 1.1$ Hz, ArH), 6.40 (1H, s, ArH), 4.77 (2H, s, ArCH₂OH), 2.21 (1H, br. s, ArCH₂OH).

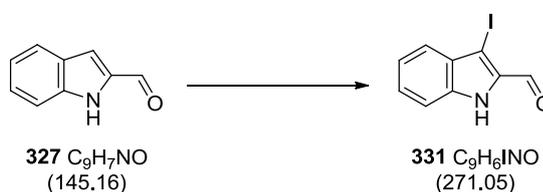
δ_C (75 MHz, $CDCl_3$) 137.5 (C), 136.3 (C), 128.0 (C), 122.2 (CH), 120.6 (CH), 119.9 (CH), 111.0 (CH), 100.5 (CH), 58.6 (CH₂).

LRMS (CI) 148 ($[M+H]^+$, 100%), 57 (31%), 43 (25%).

Indole-2-carboxaldehyde (327)

To a solution of alcohol **329** (5.13 g, 34.9 mmol) in DCM (140 mL) was added barium manganate(VI) (8.93 g, 34.9 mmol) and activated MnO₂ (72.7 g, 0.84 mol; azeotroped with toluene to activate). The reaction mixture was stirred vigorously for 5 days and then SiO₂ (73.0 g) was added. The black suspension was filtered through Celite[®], which was then washed with DCM (100 mL) and the combined organic phases concentrated *in vacuo*. Purification by column chromatography (10–25% diethyl ether in petroleum ether) afforded the title compound as a white solid (3.45 g, 23.8 mmol, 68%).

Data as previously reported.

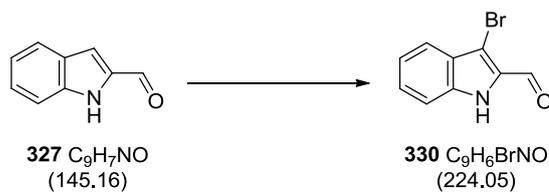
3-Iodoindole-2-carboxaldehyde (331)

To a solution of aldehyde **327** (500mg, 3.44 mmol) in DMF (3 mL) at RT was added powdered KOH (736 mg, 13.11 mmol) portionwise. After 15 min a solution of iodine (874 mg, 3.44 mmol) in DMF (2 mL) was added dropwise over 5 min. After 1.5 h in the dark the reaction mixture was poured into a stirred solution of 25% aq. NaHSO₃ (2 mL), 25% aq. NH₄OH (4 mL) and water (60 mL). The resultant pale brown suspension was collected by filtration and washed with cold ethanol (20 mL). Recrystallisation from ethanol afforded the title compound as a pale brown solid (921 mg, 3.40 mmol, 99% over two crops). These data are in accordance with that reported in the literature.¹⁰⁰

MP 196–197 °C (EtOH), Lit. 193–194 °C (EtOH).¹⁰⁰

ν_{\max}	3289 (s), 2840 (w), 2180 (w), 2146 (w), 1650 (s), 1614 (w), 1568 (w), 1503 (m), 1446 (w), 1413 (m), 1360 (w), 1334 (m), 1226 (m), 1151 (w), 1122 (w).
δ_{H} (400 MHz, acetone)	11.40 (1H, br. s, NH), 9.88 (1H, s, CHO), 7.61–7.54 (2H, m, ArH), 7.45 (1H, ddd, $J=8.3, 7.1, 1.0$ Hz, ArH), 7.26 (1H, ddd, $J=8.3, 7.1, 1.0$ Hz, ArH).
δ_{C} (100 MHz, acetone)	183.3 (CHO), 139.0 (C), 134.9 (C), 131.4 (C), 128.8 (CH), 123.7 (CH), 122.7 (CH), 114.3 (CH), 71.7 (C-I).
LRMS (CI)	271 ($[\text{M}]^+$, 100%), 215 (10%), 144 ($[\text{M}-\text{I}]^+$, 8%), 116 (16%), 89 (41%).

3-Bromoindole-2-carboxaldehyde (330)

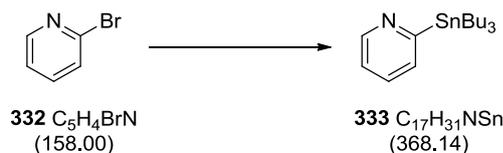


To a solution of aldehyde **327** (560 mg, 3.86 mmol) in DMF (7 mL) was added dropwise a solution of *N*-bromosuccinimide (694 mg, 3.90 mmol) in DMF (3 mL). After 20 h at RT the reaction mixture was poured onto ice water (60 mL). The resultant white precipitate was collected by filtration and washed with cold ethanol affording the title compound as a white solid (833 mg, 3.72 mmol, 96%). These data are in accordance with those reported in the literature.¹⁰¹

MP	191–193 °C (EtOH).
ν_{\max}	3284 (br. m), 1773 (w), 1695 (m), 1651 (s), 1614 (m), 1573 (w), 1515 (m), 1450 (w), 1419 (w), 1362 (w), 1338 (m), 1294 (w), 1240 (w), 1228 (w), 1189 (m), 1153 (w), 1053 (m), 863 (m), 751 (m), 740 (m).
δ_{H} (400 MHz, CDCl_3)	10.00 (1H, s, CHO), 9.49 (1H, br. s, NH), 7.72 (1H, dd, $J=8.2, 0.9$ Hz, ArH), 7.50–7.41 (2H, m, ArH), 7.30–7.21 (1H, m, ArH).

δ_{C} (100 MHz, CDCl_3)	181.3 (CHO), 136.9 (C), 131.5 (C), 128.5 (CH), 127.2 (C), 122.0 (CH), 121.5 (CH), 112.7 (CH), 104.3 (C).
LRMS (EI)	^{79}Br : 223 (M^+ , 100%), 194 ($[\text{M}-\text{CHO}]^+$, 18%), 145 ($[\text{M}-\text{Br}]^+$, 9%), 116 ($[\text{M}-\text{CHO}-\text{Br}]^+$, 34%).

2-(Tributylstannyl)pyridine (333)



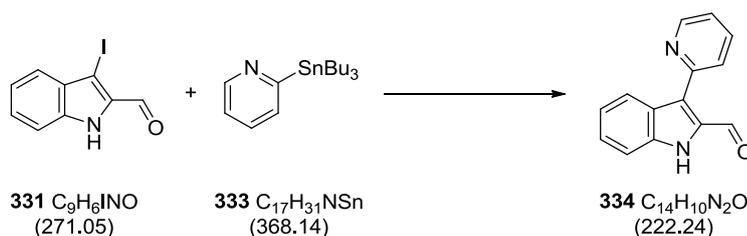
To a solution of 2-bromopyridine **332** (1.00 g, 6.33 mmol) in THF (12 mL) at $-78\text{ }^\circ\text{C}$ was added *n*BuLi (2.38 M in hexanes, 2.66 mL, 6.33 mmol) dropwise. After 0.5 h tributyltin chloride (1.72 mL, 6.33 mmol) was added dropwise. After 1 h the reaction mixture was warmed to RT and after 2 h saturated aq. NH_4Cl (25 mL) was added. The reaction mixture was extracted with diethyl ether (3 x 50 mL) then the combined organic phases were washed with brine (100 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 2% ethyl acetate in hexanes) afforded the title compound as a pale yellow oil (1.97 g, 5.35 mmol, 85%). These data are in accordance with that reported in the literature.⁹⁷

ν_{max}	3058 (w), 2955 (s), 2922 (s), 2870 (m), 2851 (m), 2360 (w), 2342 (w), 1567 (m), 1556 (m), 1463 (m), 1448 (s), 1414 (m), 1376 (m), 1358 (w), 1340 (w), 1292 (w), 1275 (w), 1263 (w), 985 (m), 748 (s), 689 (m), 667 (m).
δ_{H} (400 MHz, CDCl_3)	8.74 (1H, ddd, $J=4.9, 1.9, 1.1$ Hz, <i>ArH</i>), 7.53–7.45 (1H, m, <i>ArH</i>), 7.44–7.35 (1H, m, <i>ArH</i>), 7.16–7.06 (1H, m, <i>ArH</i>), 1.62–1.52 (6H, m, $\text{SnCH}_2(\text{CH}_2)_2\text{CH}_3$), 1.38–1.30 (6H, m, $\text{Sn}(\text{CH}_2)_2\text{CH}_2\text{CH}_3$), 1.17–1.09 (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.93–0.83 (9H, m, $\text{Sn}(\text{CH}_2)_3\text{CH}_3$).

δ_C (100 MHz, $CDCl_3$) 174.1 (C), 150.5 (CH), 133.2 (CH), 132.4 (CH), 122.0 (CH), 29.1 (3 x CH_2), 27.3 (3 x CH_2), 13.7 (3 x CH_3), 9.8 (3 x CH_2).

LRMS (EI) ^{120}Sn : 312 ($[M-Bu]^+$, 42%), 254 ($[M-2Bu]^+$, 57%), 198 ($[M-3Bu]^+$, 100%).

3-(Pyridin-2-yl)indole-2-carboxaldehyde (**334**)



To a degassed solution of indole **331** (405 mg, 1.49 mmol) and stannane **333** (659 mg, 1.79 mmol) in DMF (11 mL) at RT was added Pd(PPh₃)₄ (173 mg, 0.15 mmol) and anhydrous CuI (57 mg, 0.30 mmol). After 2 days water (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (100 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 30% diethyl ether in petroleum ether) afforded the *title compound* as a yellow solid (323 mg, 1.45 mmol, 98%).

MP 224–226°C (EtOAc / heptane).

ν_{max} 3294 (m), 3053 (w), 2907 (w), 1650 (s), 1586 (m), 1573 (w), 1531 (m), 1475 (m), 1453 (w), 1426 (m), 1383 (m), 1335 (m), 1229 (m), 1205 (w), 1145 (w), 1090 (w).

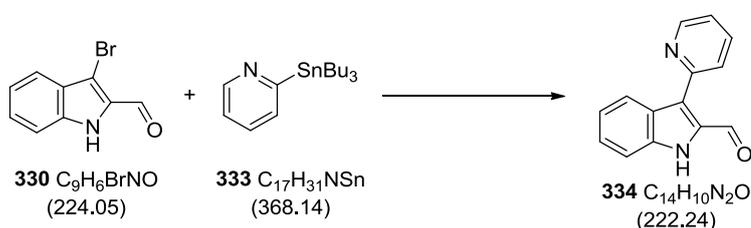
δ_H (400 MHz, $CDCl_3$) 10.33 (1H, s, CHO), 9.26 (1H, br. s, NH), 8.80 (1H, ddd, $J=4.9, 1.8, 1.0$ Hz, ArH), 8.04 (1H, dd, $J=8.2, 0.9$ Hz, ArH), 7.86 (1H, app. td, $J=7.7, 1.8$ Hz, ArH), 7.80 (1H, dt, $J=7.8, 1.1$ Hz, ArH), 7.50 (1H, dt, $J=8.3, 1.0$ Hz, ArH), 7.45 (1H, ddd, $J=8.4, 6.8, 1.1$ Hz, ArH), 7.33 (1H, ddd, $J=7.4, 4.9, 1.3$ Hz, ArH), 7.30–7.22 (1H, obsc. m, ArH).

δ_c (100 MHz, $CDCl_3$) 184.5 (CHO), 152.3 (C), 150.3 (CH), 136.9 (C), 136.7 (CH), 133.1 (C), 127.3 (CH), 126.2 (C), 124.4 (CH), 122.3 (CH), 122.2 (CH), 122.2 (C), 122.0 (CH), 112.5 (CH).

LRMS (ES+) 286 ($[M+Na+MeCN]^+$, 13%), 223 ($[M+H]^+$, 18%).

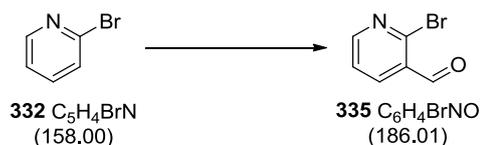
HRMS $C_{14}H_{10}N_2NaO$ $[M+Na]^+$ requires 245.0685; found: 245.0687.

3-(Pyridin-2-yl)indole-2-carboxaldehyde (**334**)



To a degassed solution of indole **330** (250 mg, 1.12 mmol) in DMF (4 mL) at RT was added $Pd(PPh_3)_4$ (127 mg, 0.11 mmol) and CuO (65 mg, 0.82 mmol). The reaction mixture was heated to reflux for 10 min then cooled to RT. Stannane **333** (302 mg, 0.82 mmol) in DMF (1 mL) was added dropwise and the reaction mixture heated at reflux for 16 h then cooled to RT. Water (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 30% diethyl ether in petroleum ether) afforded the *title compound* as a yellow solid (68 mg, 0.31 mmol, 38%).

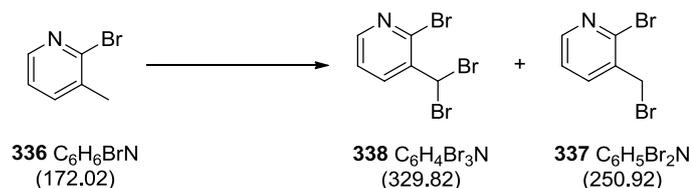
Data as previously reported.

2-Bromopyridine-3-carboxaldehyde (335)

A solution of LDA was prepared *in situ* by the dropwise addition of *n*BuLi (2.5 M in hexanes, 2.64 mL, 6.60 mmol) to a solution of *i*Pr₂NH (1.12 mL, 8.00 mmol) in THF (20 mL) at -78 °C. After warming to RT for 1 h the reaction mixture was cooled to -78 °C and 2-bromopyridine **332** (948 mg, 6.00 mmol) was added dropwise. After 4 h DMF (4 mL) was added dropwise and after a further 30 min at -78 °C the reaction mixture was warmed to RT for 16 h. Saturated aq. NH₄Cl (20 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (100 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% diethyl ether in petroleum ether) afforded the title compound as a white solid (364 mg, 1.96 mmol, 33%). These data are in accordance with those reported in the literature.⁷³

MP	61–64 °C (ether / petrol), Lit. 64–65 °C. ⁷³
ν_{\max}	3070 (w), 3053 (w), 3026 (m), 2999 (w), 2925 (w), 2873 (m), 1694 (s), 1658 (m), 1573 (s), 1557 (m), 1440 (w), 1415 (m), 1372 (s), 1272 (m), 1257 (m), 1235 (m), 1058 (m), 1050 (m), 833 (s), 803 (m), 727 (m), 705(m).
δ_{H} (300 MHz, CDCl₃)	10.35 (1H, d, $J=0.7$ Hz, CHO), 8.58 (1H, dd, $J=4.6, 2.0$ Hz, ArH), 8.19 (1H, dd, $J=7.7, 2.2$ Hz, ArH), 7.45 (1H, ddd, $J=7.7, 4.8, 0.7$ Hz, ArH).
δ_{C} (75 MHz, CDCl₃)	191.1 (CHO), 154.5 (CH), 145.4 (C), 138.0 (CH), 130.6 (C), 123.4 (CH).
LRMS (ES+)	⁷⁹ Br: 218 ([M+MeOH+H] ⁺ , 100%).

2-bromo-3-(dibromomethyl)pyridine (**338**) and 2-Bromo-3-(bromomethyl)pyridine (**337**)



To a solution of 2-bromo-3-methylpyridine **336** (0.65 mL, 5.81 mmol) in PhCF₃ (5 mL) was added *N*-bromosuccinimide (1.14 g, 6.37 mmol), VAZO (0.171 g, 0.70 mmol) and bromine (0.02 mL, 0.29 mmol). The reaction mixture was heated to reflux for 3 h then cooled to RT, filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (10% ethyl acetate in heptane) afforded firstly **338** as a pale yellow oil (168 mg, 0.51 mmol, 9%) and then **337** as a pale yellow oil (553 mg, 2.2 mmol, 38%). These data are in accordance with those reported in the literature.^{102,103}

Data for **338**:

ν_{\max}	3116 (w), 3022 (w), 2924 (w), 2361 (w), 2175 (w), 1721 (w), 1573 (m), 1557 (m), 1446 (w), 1397 (s), 1172 (w), 1146 (m), 1121 (w), 1050 (m), 831 (m), 808 (w), 738 (m).
δ_{H} (300 MHz, CDCl ₃)	8.36–8.32 (1H, obsc. m, <i>ArH</i>), 8.31 (1H, dd, <i>J</i> =5.1, 1.9 Hz, <i>ArH</i>), 7.41 (1H, dd, <i>J</i> =7.5, 5.1 Hz, <i>ArH</i>), 7.01 (1H, s, <i>CHBr</i> ₂).
δ_{C} (75 MHz, CDCl ₃)	150.9 (CH), 139.4 (CH), 138.3 (C), 138.3 (C), 123.9 (CH), 37.7 (CH).
LRMS (EI)	⁷⁹ Br: 250 ([<i>M</i> -Br] ⁺ , 56%), 170 ([<i>M</i> -2Br] ⁺ , 11%), 104 (100%), 77 ([<i>M</i> -Br- <i>CHBr</i> ₂] ⁺ , 52%).

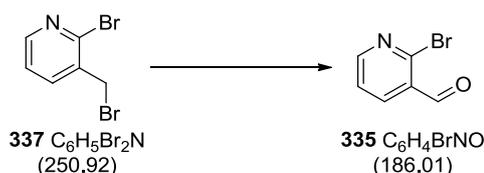
Data for **337**:

ν_{\max}	3292 (br. w), 3027 (w), 2929 (w), 2359 (w), 2118 (w), 1912 (w), 1650 (w), 1601 (m), 1577 (w), 1562 (m), 1523 (w), 1473 (w), 1450 (m), 1424 (w), 1403 (s), 1331 (w), 1311 (w), 1203 (m), 1169 (w), 1126 (w), 1053 (m).
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δ_{H} (400 MHz, CDCl_3) 8.32 (1H, dd, $J=4.7, 1.9$ Hz, ArH), 7.78 (1H, dd, $J=7.6, 1.9$ Hz, ArH), 7.29 (1H, dd, $J=7.6, 4.7$ Hz, ArH), 4.56 (2H, s, ArCH_2Br).

δ_{C} (100 MHz, CDCl_3) 149.7 (CH), 143.7 (C), 139.2 (CH), 134.6 (C), 123.2 (CH), 31.4 (CH_2).

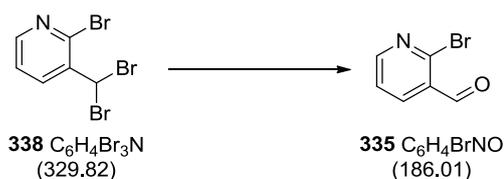
2-Bromopyridine-3-carboxaldehyde (335)



To a solution of pyridine **337** (4.93 g, 19.7 mmol) in acetonitrile (20 mL) was added 4-methylmorpholine-*N*-oxide (3.45 g, 29.5 mmol) at RT. After 3 h the solvent was removed *in vacuo*. Purification by column chromatography (20% ethyl acetate in heptane) afforded the title compound as a white solid (2.22 g, 11.9 mmol, 61%).

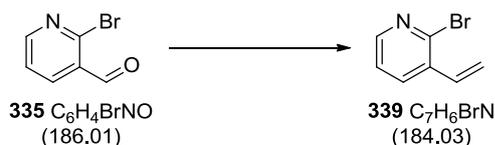
Data as previously reported.

2-Bromopyridine-3-carboxaldehyde (335)



A mixture of tribromide **338** (487 mg, 1.48 mmol) and CaCO_3 (327 mg, 3.26 mmol) in water (12 mL) was heated at reflux for 15 h then cooled to RT and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (50 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (20% ethyl acetate in heptane) afforded the title compound as a white solid (147 mg, 0.79 mmol, 53%).

Data as previously reported.

2-Bromo-3-vinylpyridine (339)

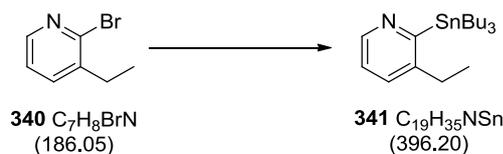
To a solution of methyltriphenylphosphonium bromide (860 mg, 2.41 mmol) in THF (20 mL) at 0 °C was added *n*BuLi (2.5 M in hexanes, 0.96 mL, 2.41 mmol). The reaction mixture was warmed to RT over 30 min then re-cooled to 0 °C and a solution of aldehyde **335** (400 mg, 2.15 mmol) in THF (20 mL) was added dropwise. After 18 h at RT, water (20 mL) and diethyl ether (20 mL) were added. The aqueous phase was separated and extracted with diethyl ether (2 x 20 mL). The combined organic phases were then washed with brine (50 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% diethyl ether in petroleum ether) afforded the title compound as a yellow oil (347 mg, 1.89 mmol, 88%). These data are in accordance with that reported in the literature.⁷³

ν_{\max}	3090 (w), 3043 (w), 1627 (m), 1572 (m), 1551 (m), 1447 (m), 1424 (m), 1375 (s), 1272 (w), 1183 (m), 1122 (m), 1048 (s), 805 (s), 666 (s).
δ_{H} (400 MHz, CDCl₃)	8.27 (1H, dd, $J=4.7, 2.0$ Hz, ArH), 7.81 (1H, ddd, $J=7.7, 2.0, 0.5$ Hz, ArH), 7.26 (1H, ddd, $J=7.7, 4.7, 0.6$ Hz, ArH), 6.99 (1H, dd, $J=17.4, 11.0$ Hz, CH=CH ₂), 5.75 (1H, dd, $J=17.4, 0.8$ Hz, CHH), 5.49 (1H, dd, $J=11.0, 0.8$ Hz, CHH).
δ_{C} (100 MHz, CDCl₃)	148.9 (CH), 142.9 (C), 134.8 (C), 134.6 (CH), 134.2 (CH=CH ₂), 123.0 (CH), 118.7 (CH ₂).
LRMS (ES+)	⁷⁹ Br: 184 ([M+H] ⁺ , 96%).

2-Bromo-3-ethylpyridine (340)

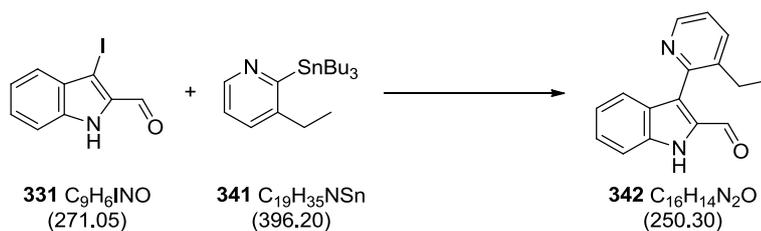
To a solution of vinylpyridine **339** (279 mg, 1.52 mmol) in THF:water (1:1, 60 mL) was added *p*-tosylhydrazide (1.70 g, 9.12 mmol) and NaOAc (1.26 g, 9.27 mmol). The reaction mixture was heated at reflux for 7 days then cooled to RT and sat. K₂CO₃ (100 mL) added. After 2 h the reaction mixture was extracted with DCM (4 x 60 mL). The combined organic phases were washed with brine (250 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (1–5% diethyl ether in petroleum ether) afforded the *title compound* as a yellow oil (212 mg, 1.14 mmol, 75%).

ν_{\max}	3048 (w), 2970 (m), 2934 (w), 2875 (w), 1577 (m), 1557 (m), 1460 (w), 1427 (w), 1400 (s), 1322 (w), 1266 (w), 1073 (m), 1057 (s), 805 (m), 659 (m).
δ_{H} (400 MHz, CDCl₃)	8.20 (1H, dd, <i>J</i> =4.8, 1.5 Hz, Ar <i>H</i>), 7.51 (1H, dd, <i>J</i> =7.5, 1.5 Hz, Ar <i>H</i>), 7.20 (1H, dd, <i>J</i> =7.5, 4.8 Hz, Ar <i>H</i>), 2.73 (2H, q, <i>J</i> =7.5 Hz, CH ₂), 1.24 (3H, t, <i>J</i> =7.5 Hz, CH ₃).
δ_{C} (100 MHz, CDCl₃)	147.3 (CH), 144.2 (C), 140.3 (C), 137.3 (CH), 122.9 (CH), 28.4 (CH ₂), 13.5 (CH ₃).
LRMS (EI)	⁷⁹ Br: 185 (M ⁺ , 54%), 170 ([M-CH ₃] ⁺ , 17%), 106 ([M-Br] ⁺ , 100%), 91 ([M-Br-CH ₃] ⁺ , 10%), 78 ([M-Br-Et] ⁺ , 28%).
HRMS	C ₇ H ₉ BrN[M+H] ⁺ requires 185.9913; found: 185.9912.

3-Ethyl-2-(tributylstannyl)pyridine (341)

To a solution of ethylpyridine **340** (200 mg, 1.08 mmol) in THF (2 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*BuLi (2.5 M in hexanes, 0.43 mL, 1.08 mmol) dropwise. After 30 min Bu₃SnCl (0.29 mL, 1.08 mmol) was added dropwise. After a further 1 h the reaction mixture was warmed to RT over 3 h then sat. NH₄Cl (10 mL) was added. Following extraction with MTBE (3 x 20 mL), the combined organic phases were washed with brine (50 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 5% ethyl acetate in heptane) afforded the *title compound* as a colourless oil (372 mg, 0.94 mmol, 87%).

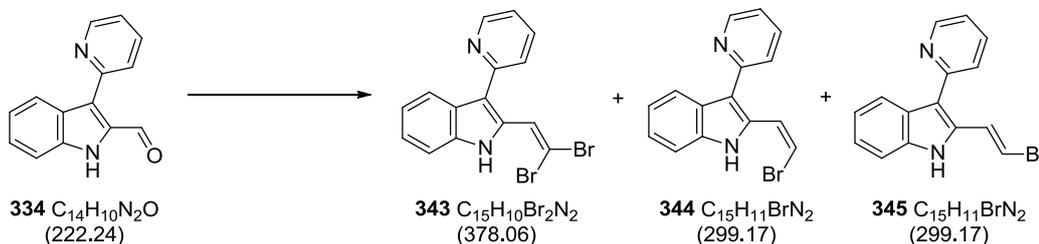
ν_{max}	3036 (w), 2956 (s), 2924 (s), 2870 (m), 2852 (m), 2360 (w), 2031 (w), 1567 (w), 1460 (m), 1404 (m), 1376 (m), 1339 (w), 1181 (w), 1150 (w), 1120 (w), 1073 (m).
δ_{H} (300 MHz, CDCl ₃)	8.57 (1H, dd, $J=4.7$, 1.6 Hz, ArH), 7.39 (1H, dd, $J=7.9$, 1.6 Hz, ArH), 7.08 (1H, dd, $J=7.9$, 4.7 Hz, ArH), 2.64 (2H, q, $J=7.5$ Hz, CH ₂ CH ₃), 1.62–1.48 (6H, m, SnCH ₂ (CH ₂) ₂ CH ₃), 1.33 (6H, sxt, $J=7.2$ Hz, Sn(CH ₂) ₂ CH ₂ CH ₃), 1.23 (3H, t, $J=7.5$ Hz, CH ₂ CH ₃), 1.18–1.09 (6H, m, SnCH ₂ CH ₂ CH ₂ CH ₃), 0.88 (9H, t, $J=7.2$ Hz, Sn(CH ₂) ₃ CH ₃).
δ_{C} (75 MHz, CDCl ₃)	173.7 (C), 147.6 (CH), 146.6 (C), 132.6 (CH), 121.7 (CH), 29.2 (3 × CH ₂), 28.7 (CH ₂), 27.3 (3 × CH ₂), 16.2 (CH ₃), 13.7 (3 × CH ₃), 10.7 (3 × CH ₂).
LRMS (EI)	¹²⁰ Sn: 226 ([M–3Bu] ⁺ , 100%), 106 ([M–SnBu ₃] ⁺ , 28%).
HRMS	C ₁₉ H ₃₆ NSn[M+H] ⁺ requires 398.1864; found: 398.1868.

3-(3-Ethylpyridin-2-yl)-1*H*-indole-2-carbaldehyde (**342**)

To a degassed solution of iodoindole **331** (198 mg, 0.73 mmol) and stannane **341** (350 mg, 0.88 mmol) in DMF (5 mL) was added Pd(PPh₃)₄ (81 mg, 0.07 mmol) and CuI (29 mg, 0.15 mmol). After 18 h at RT the solvent was removed *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 40% ethyl acetate in heptane) afforded the *title compound* as a pale orange oil (150 mg, 0.60 mmol, 82%).

ν_{\max}	3295 (w), 3060 (w), 2962 (w), 2923 (m), 2853 (m), 2361 (w), 2339 (w), 2206 (w), 1651 (s), 1618 (w), 1571 (m), 1537 (m), 1463 (m), 1368 (m), 1331 (m), 1223 (m), 1120 (m), 1055 (w), 1024 (m), 972 (w), 732 (s).
δ_{H} (300 MHz, CDCl ₃)	9.71 (1H, s, CHO), 9.63 (1H, br. s, NH), 8.62 (1H, dd, $J=4.8, 1.5$ Hz, ArH), 7.76 (1H, dd, $J=7.8, 1.5$ Hz, ArH), 7.50–7.44 (2H, m, 2 × ArH), 7.43–7.36 (1H, obsc. m, ArH), 7.36 (1H, dd, $J=7.8, 4.8$ Hz, ArH), 7.16 (1H, ddd, $J=8.1, 6.9, 1.1$ Hz, ArH), 2.66 (2H, q, $J=7.5$ Hz, CH ₂ CH ₃), 1.08 (3H, t, $J=7.5$ Hz, CH ₂ CH ₃).
δ_{C} (75 MHz, CDCl ₃)	182.7 (CHO), 150.3 (C), 147.2 (CH), 139.6 (C), 136.9 (C), 136.4 (CH), 132.8 (C), 127.4 (CH), 127.4 (C), 127.0 (C), 123.1 (CH), 122.2 (CH), 121.4 (CH), 112.6 (CH), 25.6 (CH ₂), 14.9 (CH ₃).
LRMS (ES ⁺)	342 (100%), 314 ([M+MeCN+Na] ⁺ , 43%), 251 ([M+H] ⁺ , 27%).
HRMS	C ₁₆ H ₁₅ N ₂ O[M+H] ⁺ requires 251.1179; found: 251.1178.

2-(2,2-Dibromovinyl)-3-(pyridin-2-yl)-1H-indole (343), (Z)-2-(2-bromovinyl)-3-(pyridine-2-yl)-1H-indole (344) and (E)-2-(2-bromovinyl)-3-(pyridine-2-yl)-1H-indole (345)



To a suspension of bromomethyltriphenylphosphonium bromide (589 mg, 1.35 mmol) in THF (9 mL) was added NaHMDS (1.0 M in THF, 1.17 mL, 1.17 mmol) dropwise over 10 min. After 30 min the resulting solution was added to a solution of aldehyde **334** (200 mg, 0.90 mmol) in THF (3 mL) over 20 min. After 16 h water (20 mL) and ethyl acetate (20 mL) were added and the phases separated. The aqueous phase was washed with ethyl acetate (2 × 20 mL) and the combined organic phases were washed with brine (50 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 10% ethyl acetate in heptane) afforded firstly **343** as a yellow oil (67 mg, 0.18 mmol, 20%), then an inseparable mixture of **343**, **344** and **345** (1:1.5:1) as a pale yellow oil (90 mg, 0.28 mmol, 31%) and finally recovered starting material (44 mg, 0.2 mmol, 22%).

Data for 343:

ν_{\max} 3439 (m), 3036 (m), 2925 (w), 2854 (w), 1668 (w), 1586 (s), 1562 (w), 1508 (m), 1476 (m), 1439 (w), 1421 (w), 1366 (w), 1328 (m), 1285 (w), 1242 (m), 1200 (m), 1152 (m), 1118 (w), 1095 (w).

δ_{H} (400 MHz, CDCl₃) 9.53 (1H, br. s, NH), 8.77 (1H, ddd, *J*=4.9, 1.8, 0.9 Hz, ArH), 8.23 (1H, s, CH=CBr₂), 7.89 (1H, d, *J*=8.0 Hz, ArH), 7.80 (1H, app. td, *J*=7.7, 1.8 Hz, ArH), 7.65 (1H, d, *J*=7.9 Hz, ArH), 7.44 (1H, d, *J*=8.2 Hz, ArH), 7.38–7.30 (1H, m, ArH), 7.24 (1H, obsc. ddd, *J*=7.5, 4.9, 1.2 Hz, ArH), 7.23–7.18 (1H, m, ArH).

δ_C (100 MHz, $CDCl_3$) 153.7 (C), 150.0 (CH), 136.4 (CH), 135.8 (C), 130.0 (C), 127.4 (CH), 125.8 (C), 124.4 (CH), 124.3 (CH), 121.3 (CH), 121.1 (CH), 120.1 (CH), 119.1 (C), 111.4 (CH), 86.5 (CBr_2).

LRMS (ES^+) ^{79}Br : 377 ($[M+H]^+$, 51%).

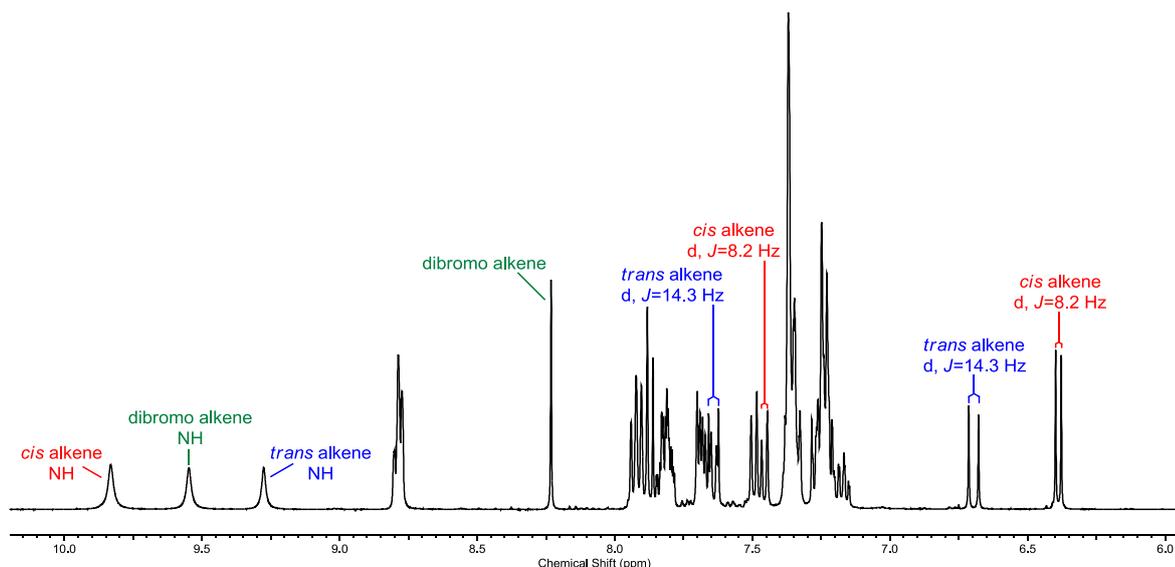
HRMS $C_{15}H_{11}Br_2N_2[M+H]^+$ requires 376.9283; found: 376.9282.

Data for inseparable mixture of 343, 344 and 345:

δ_H (400 MHz, $CDCl_3$) Peaks attributed to **343** 9.53 (1H, br. s, NH), 8.22 (1H, s, $CH=CBBr_2$), 7.86 (1H, d, $J=8.1$ Hz, ArH), 7.44 (1H, d, $J=8.2$ Hz, ArH).

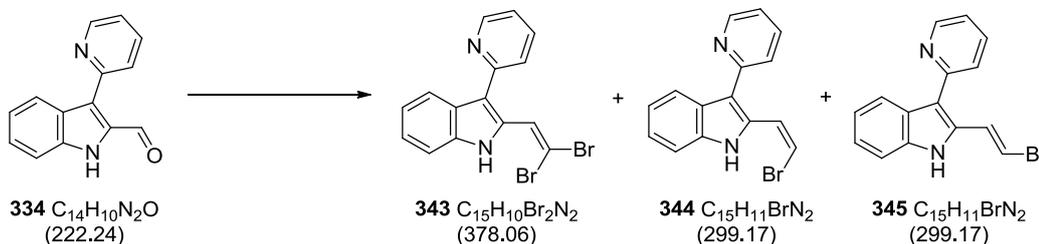
Peaks attributed to **344** 9.82 (1H, br. s, NH), 7.48 (1H, d, $J=8.2$ Hz, $CH=CHBr$), 6.37 (1H, d, $J=8.2$ Hz, $CH=CHBr$). Peaks attributed to **345** 9.26 (1H, br. s, NH), 7.63 (1H, obsc. d, $J=14.3$ Hz, $CH=CHBr$), 6.68 (1H, d, $J=14.3$ Hz, $CH=CHBr$).

Peaks not attributed 8.82–8.74 (3.5H, m, $3.5 \times ArH$), 7.95–7.88 (2H, m, $2 \times ArH$), 7.84–7.76 (3H, m, $3 \times ArH$), 7.70–7.61 (3.5H, m, $3.5 \times ArH$), 7.39–7.29 (7H, m, $7 \times ArH$), 7.26–7.13 (7H, m, $7 \times ArH$).



NMR Spectra of **343**, **344** and **345**.

2-(2,2-Dibromovinyl)-3-(pyridin-2-yl)-1H-indole (343), (Z)-2-(2-bromovinyl)-3-(pyridine-2-yl)-1H-indole (344) and (E)-2-(2-bromovinyl)-3-(pyridine-2-yl)-1H-indole (345)



To a suspension of KO^tBu (168 mg, 1.50 mmol) in THF (9 mL) at $-78\text{ }^\circ\text{C}$ was added bromomethyltriphenylphosphonium bromide (654 mg, 1.50 mmol) portionwise. The reaction mixture was warmed to $0\text{ }^\circ\text{C}$ over 1.5 h then cooled to $-78\text{ }^\circ\text{C}$ and aldehyde **334** (150 mg, 0.68 mmol) in THF (1 mL) added dropwise over 5 min. After 15 min the reaction mixture was warmed to RT and after 16 h, water (10 mL) and ethyl acetate (10 mL) were added. The aqueous phase was separated and washed with ethyl acetate ($2 \times 10\text{ mL}$) then the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (20% diethyl ether in petroleum ether) afforded firstly **343** as a yellow oil (7 mg, 0.02 mmol, 3%), then an inseparable mixture of **343**, **344** and **345** (1:1.8:0.2) as a pale yellow oil (53 mg, 0.16 mmol, 24%) and finally an inseparable mixture of **344** and **345** (1:0.4) as a yellow oil (11mg, 0.04 mmol, 6%) contaminated with $\sim 10\%$ unidentified impurities.

Data for 343:

Data as previously reported.

Data for inseparable mixture of 344 and 345:

ν_{\max}	3075 (w), 2925 (w), 2854 (w), 2449 (w), 2160 (m), 2040 (w), 2009 (w), 1975 (w), 1940 (w), 1717 (w), 1614 (m), 1539 (w), 1488 (w), 1469 (w), 1388 (m), 1264 (m).
δ_H (400 MHz, $CDCl_3$)	Peaks attributed to major regioisomer 344 9.79 (1H, br. s, NH), 8.76 (1H, app. tdd, $J=5.0, 1.8, 0.9\text{ Hz}$, ArH), 7.92–7.87 (1H, m, ArH), 7.85 (1H, d, $J=8.2\text{ Hz}$, ArH), 7.80

(1H, app. td, $J=7.7, 1.9$ Hz, ArH), 7.70–7.60 (1H, m, ArH), 7.48 (1H, d, $J=8.2$ Hz, CH=CHBr), 7.35–7.29 (1H, m, ArH), 7.26–7.14 (2H, m, ArH) 6.38 (1H, d, $J=8.2$ Hz, CH=CHBr).

Peaks attributed to minor regioisomer 345 8.56 (1H, br. s, NH), 6.73 (1H, d, $J=14.4$ Hz, CH=CHBr), remaining peaks obscured.

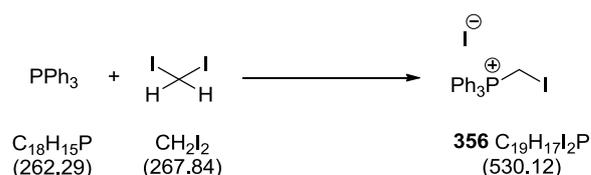
δ_C (100 MHz, CDCl₃) *Peaks attributed to major regioisomer 344* 154.1 (C), 149.8 (CH), 136.4 (CH), 135.7 (C), 131.1(C), 125.9 (C), 124.5 (CH), 124.1 (CH), 122.8 (CH), 121.1 (CH), 121.0 (CH), 120.0 (CH), 111.4 (CH), 104.4 (CH).

N.B. One aromatic quaternary centre not observed.

Peaks attributed to minor regioisomer 345 153.9 (C), 149.8 (CH), 136.5 (CH), 132.2 (C), 127.7 (CH), 126.9 (C), 124.1 (CH), 123.9 (CH), 121.0 (CH), 121.0 (CH), 120.2 (CH), 118.8 (C), 110.9 (CH), 107.7 (C), 106.2 (CH).

LRMS (ES⁺) ⁷⁹Br: 299 ([M+H]⁺, 100%).

(Iodomethyl)triphenylphosphonium iodide (356)

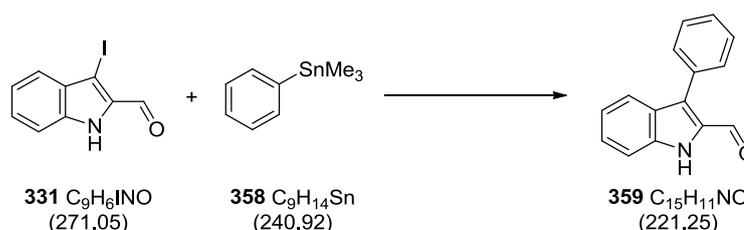


A solution of triphenylphosphine (3.00 g, 11.4 mmol) and diiodomethane (1.20 mL, 14.9 mmol) in toluene (5 mL) was protected from light, heated to 100 °C for 20 h then cooled to RT. The resulting white precipitate was collected by filtration, washed with cold toluene (50 mL) and dried *in vacuo* to afford the title compound as a white solid (5.75 g, 10.9 mmol, 95%). These data are in accordance with that reported in the literature.¹⁰⁴

MP 225–227 °C, Lit. 228–230 °C.¹⁰⁴

ν_{\max}	3040 (w), 2914 (m), 2847 (m), 2741 (w), 2326 (w), 2116 (w), 1897 (w), 1821 (w), 1680 (w), 1585 (m), 1481 (m), 1435 (s), 1334 (w), 1316 (w), 1107 (s), 996 (m).
δ_{H} (400 MHz, DMSO)	8.09–7.47 (15H, m, ArH), 5.06 (2H, d, $J=8.7$ Hz, CH_2l).
δ_{C} (100 MHz, DMSO)	135.1 (3 \times CH, d, $J=3.2$ Hz, $p\text{-Ph}$), 133.8 (6 \times CH, d, $J=10.1$ Hz, $o\text{-Ph}$), 130.1 (6 \times CH, d, $J=12.4$ Hz, $m\text{-Ph}$), 118.3 (3 \times C, d, $J=88.9$ Hz, $i\text{-Ph}$), -16.07 (1 \times CH_2 , d, $J=52.1$ Hz, CH_2l).
δ_{P} (162 MHz, DMSO)	24.2
LRMS (ES ⁺)	Did not fly by ES or EI.

3-Phenyl-1*H*-indole-2-carbaldehyde (**359**)

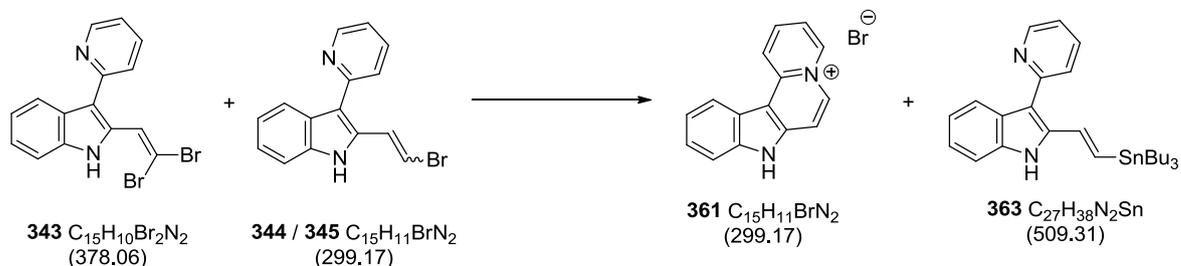


To a degassed solution of iodoindole **331** (464mg, 1.71 mmol) and stannane **358** (0.37 mL, 2.05 mmol) in DMF (12 mL) was added Pd(PPh₃)₄ (196mg, 0.17 mmol) and CuI (65 mg, 0.34 mmol). The reaction mixture heated to reflux for 3 h then cooled to RT and water (100 mL) and ethyl acetate (100 mL) added. The aqueous phase was separated and extracted with ethyl acetate (2 \times 100 mL) then the combined organic phases were washed with brine (200 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; 10% ethyl acetate in heptane) afforded the title compound as an inseparable 1.2:1 mixture of the compound **359** and recovered starting material **331** as a yellow solid (170mg, 0.70 mmol, 41%).

ν_{\max}	3308 (m), 3057 (w), 2921 (w), 2853 (w), 2059 (w), 1646 (s), 1574 (w), 1538 (w), 1490 (w), 1458 (w), 1383 (w), 1365 (w), 1335 (m), 1153 (w), 1015 (w), 932 (w).
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	(m), 1469 (s), 1452 (m), 1406 (m), 1384 (s), 1327 (m), 1286 (m), 1258 (m), 1216 (m), 1194 (m), 1168 (m).
δ_{H} (300 MHz, MeOD)	8.97 (1H, d, $J=6.9$ Hz, ArH), 8.84 (1H, d, $J=7.3$ Hz, ArH), 8.65 (1H, d, $J=9.0$ Hz, ArH), 8.24 (1H, d, $J=8.2$ Hz, ArH), 8.17 (1H, ddd, $J=8.8, 7.2, 1.2$ Hz, ArH), 7.94 (1H, d, $J=7.3$ Hz, ArH), 7.64 (1H, app. td, $J=7.0, 1.3$ Hz, ArH), 7.63 (1H, d, $J=9.0$ Hz, ArH), 7.55 (1H, app. td, $J=7.6, 1.0$ Hz, ArH), 7.39 (1H, ddd, $J=8.1, 7.0, 1.2$ Hz, ArH).
δ_{C} (75 MHz, MeOD)	141.9 (C), 141.7 (C), 140.8 (C), 137.9 (CH), 137.4 (CH), 134.7 (CH), 129.1 (CH), 124.1 (CH), 123.4 (CH), 123.0 (CH), 122.0 (C), 120.4 (CH), 114.4 (CH), 113.6 (C), 111.7 (CH).
LRMS (ES+)	219 ([M]-Br, 100%).
HRMS	$\text{C}_{15}\text{H}_{11}\text{N}_2^+$ requires 219.0917; Found: 219.0918.

8*H*-Indolo[3,2- α]quinolizin-5-ium (361) and (*E*)-3-(pyridin-2-yl)-2-(2-tributylstannyl)vinyl)-1*H*-indole (363)



To a degassed mixture of dibromoalkene **343**, *cis*-alkene **344** and *trans*-alkene **345** (~6:3:2, 157 mg, 0.46 mmol) in toluene (14 mL) was added tributyltin hydride (0.27 mL, 1.01 mmol) and VAZO (22 mg, 0.09 mmol). After 16 h at reflux the reaction mixture was cooled to RT. The precipitate was collected by filtration and washed with petroleum ether (2 x 20 mL) to afford pyridinium salt **361** (16 mg, 0.054 mmol, 12%). The filtrate was then concentrated *in vacuo* and purified by column chromatography (10% w/w anhydrous K_2CO_3 -silica; 15% ethyl acetate in heptane) to afford vinylstannane **363** (12 mg, 0.024 mmol, 5%) contaminated with ~20% of unknown impurities.

Data for 361:

Data as previously reported.

Data for 363:

ν_{\max}	3271 (br. w), 3058 (w), 2954 (s), 2923 (s), 2855 (m), 1589 (s), 1541 (w), 1454 (m), 1377 (w), 1335 (m), 1195 (w), 1150 (w), 1076 (w), 1051 (w), 1021 (w), 961 (w).
δ_{H} (400 MHz, CDCl_3)	8.75 (1H, ddd, $J=4.9, 1.9, 1.0$ Hz, ArH), 8.47 (1H, br. s, NH), 7.96 (1H, d, $J=8.0$ Hz, ArH), 7.76 (1H, app. td, $J=7.6, 1.9$ Hz, ArH), 7.60 (1H, app. dt, $J=7.9, 1.0$ Hz, ArH), 7.47 (1H, d, $J=19.9$ Hz, $\text{CH}=\text{CHSnBu}_3$), 7.38 (1H, d, $J=8.0$ Hz, ArH), 7.24 (1H, app. td, $J=7.6, 1.2$ Hz, ArH), 7.19 (1H, ddd, $J=7.6, 4.9, 1.2$ Hz, ArH), 7.18–7.13 (1H, m, ArH), 6.77 (1H, d, $J=19.9$ Hz, $\text{CH}=\text{CHSnBu}_3$), 1.63–1.50 (6H, m, $\text{SnCH}_2(\text{CH}_2)_2\text{CH}_3$), 1.36 (6H, sxt, $J=7.3$ Hz, $\text{Sn}(\text{CH}_2)\text{CH}_2\text{CH}_3$), 1.08–0.94 (6H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.91 (9H, t, $J=7.3$ Hz, $\text{Sn}(\text{CH}_2)_3\text{CH}_3$).
δ_{C} (100 MHz, CDCl_3)	149.8 (C), 149.7 (CH), 138.4 (C), 136.0 (2 × CH), 135.7 (CH), 135.2 (C), 130.1 (CH), 128.8 (C), 124.1 (CH), 123.3 (CH), 120.7 (CH), 120.5 (CH), 120.4 (C), 110.6 (CH), 29.1 (3 × CH_2), 27.3 (3 × CH_2), 13.6 (3 × CH_3), 9.8 (3 × CH_2).
LRMS (ES^+)	^{120}Sn : 511 ($[\text{M}+\text{H}]^+$, 100%), 221 ($[\text{MH}-\text{SnBu}_3]^+$, 55%).
HRMS	Sample decomposed.

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Chapter 8: Appendix

Potassium carbonate–silica: a highly effective stationary phase for the chromatographic removal of organotin impurities†‡

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Organotin impurities in product mixtures can be reduced from stoichiometric levels to ~15 parts per million by column chromatography using 10% w/w anhydrous potassium carbonate–silica as a stationary phase.

Concerns over the toxicity of organotin reagents, products and byproducts, and difficulties associated with the purification of product mixtures containing organotin residues, often limit the appeal of organotin chemistry.¹ Thus, while it is generally easy to reduce organotin impurities to below 1% w/w, their removal to a parts per million level is necessary for biological screening and health-care applications.² To address this, many methods of organotin removal have been developed,³ including water-soluble and solid-supported stannanes, catalytic procedures and alternative reagents based on metal and metalloid hydrides of lower toxicity.⁴ Though many are highly effective, their adoption usually adds to the cost or complexity of an experimental procedure.

Our groups have previously reported two simple and inexpensive procedures for the removal of organotin impurities from product mixtures.^{5,6} The first involved dilution of the concentrated product mixture with reagent grade ether, adding a slight excess of DBU then an ethereal solution of iodine until the iodine colour just persists. Elution through a plug of silica followed by standard flash column chromatography completed the purification. The second method required no pretreatment of product mixtures as, after concentration, the residue is simply eluted through a stationary phase composed of 10% finely ground potassium fluoride and 90% silica (w/w). In this way, levels of organotin impurities could be reduced from full equivalence to below 30 ppm.

The simplicity and effectiveness of the methods have ensured their widespread adoption,^{7,8} though neither is without drawbacks. One practical issue with the KF/silica protocol relates to the hygroscopic nature of the salt. On prolonged standing, this leads to a loss of fluidity in the stationary phase which in turn reduces its efficacy for both compound separation and the removal of reactive organotin species. Herein we detail an improved procedure using K₂CO₃ as an additive, making the

method cheaper and more practicable. Its effectiveness has been demonstrated in a range of common applications including the purification of tetraorganyltin and hexaorganyltin compounds from complex product mixtures. The latter observation broadens the method's scope and application considerably and offers a fresh insight into the action of the additive.

Our investigation began with an examination of stationary phases comprising silica mixed with various organic and inorganic fluorides. In our chosen test reaction, **1** → **2**,⁹ none came close to matching the success achieved using the KF–silica combination,⁶ with many performing worse than silica alone (Table 1). The results suggested that the basicity of potassium fluoride was a key factor, a hypothesis substantiated when a mixture of KOAc and silica proved highly effective for the removal of organotin impurities. Thus, in the reduction of aryl bromide **1** to arene **2** with 2 equiv. tributyltin hydride and TBAF (Scheme 1), chromatographic purification using a stationary phase of 10% KOAc and 90% silica (w/w) reduced organotin impurity levels from 2 full equivalents to 76 ppm. The result was then eclipsed by a combination of K₂CO₃ and silica, which repeatedly reduced levels of organotin impurity to below 15 ppm in this system.

We have applied the method in Bu₃SnH-mediated reductions of aryl halides and acid chlorides,^{9,10} Stille coupling¹¹ and tin-mediated radical cyclisation reactions (Scheme 1).^{12,13} In each case, ¹H NMR analysis of the purified products showed them to be free of organotin impurities (see ESI†), including situations in which a low-yielding product had to be separated from a complex product mixture containing substantial organotin residues.

Treatment of amide **9** under standard Bu₃SnH-mediated radical cyclisation conditions proved informative as cyclisation to the arene occurred with concomitant hydrostannylation of the terminal alkyne.¹³ Importantly, the resulting vinylstannane

Table 1 The effectiveness of various additives for the chromatographic removal of tin residues

Additives	Levels of tin impurity observed in 2 ^a
Potassium fluoride	28 ppm
Potassium chloride	2–5 mol%
Sodium fluoride	> 10 mol%
Calcium fluoride	> 10 mol%
Ammonium fluoride	> 10 mol%
Rochelle salt	> 10 mol%
Potassium acetate	110 ppm
Sodium acetate	76 ppm
Sodium carbonate	> 10 mol%
Potassium carbonate	13 ppm

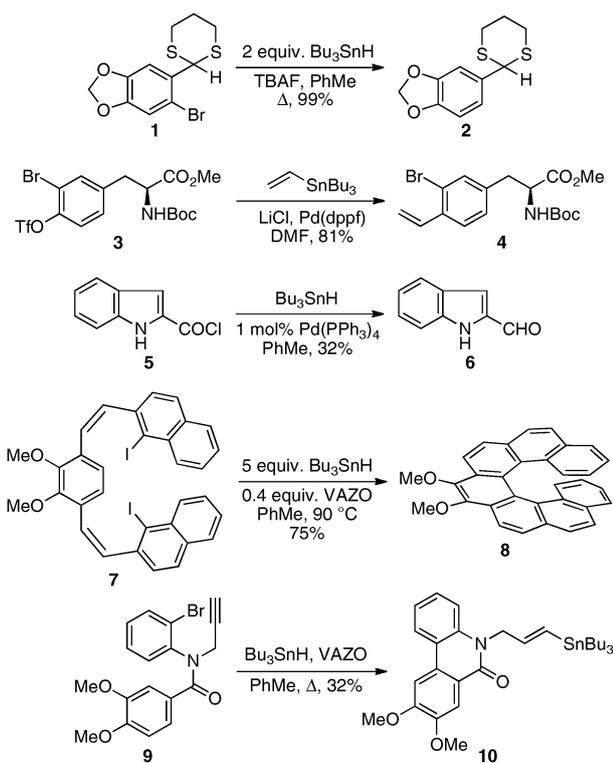
^a Tin analyses were determined independently and in duplicate at the GSK laboratories in Stevenage, UK.

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† Dedicated to Professor G. Pattenden on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental details and ¹H NMR spectra. See DOI: 10.1039/c0cc01328e



Scheme 1 Applications of the method in halide reduction, Stille coupling, Bu_3SnH -mediated radical cyclisation and hydrostannylation reactions.^{9–13}

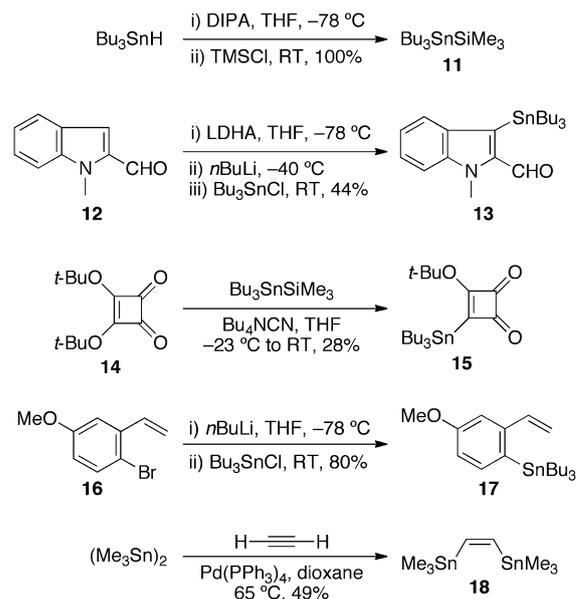
10 was amenable to chromatographic purification using K_2CO_3 -silica as the stationary phase, with residual organotin compounds being eluted close to the solvent front or retained by the stationary phase. To probe this further, a series of commercial organotin reagents was subjected to chromatographic purification using the new methodology (Table 2). The study confirmed that tributyltin hydride, tetraorganotin and hexaorganotin compounds eluted without significant loss in mass balance while reactive tributyltin halides and tributyltin oxide were retained by the stationary phase (along with carboxylic acids and phenols).

The effectiveness of the method for the purification of organotin compounds has been demonstrated further through application.^{14–17} It has proved especially valuable with products

Table 2 The behaviour of various organotin reagents on the 10% w/w anhydrous K_2CO_3 -silica stationary phase

Reagent	Outcome	% Recovery
Bu_3SnH	Eluted	100% ^a
Bu_3SnCl	Retained	0
Bu_3SnI	Retained	0
Bu_3SnOTf	Retained	0
$(\text{Bu}_3\text{Sn})_2\text{O}$	Retained	0
AllylSnBu_3	Eluted	97%
VinylSnBu_3	Eluted	98%
PhSnBu_3	Eluted	97%
$(\text{Bu}_3\text{Sn})_2$	Eluted	97% ^a

^a Recorded on pre-purified samples. Applying the method to 'aged' reagents gave poorer mass recovery and purified samples. Full details are provided in the ESI.†



Scheme 2 Applications involving the preparation of organotin compounds.

that are prone to protodestannylation on silica (*e.g.* **17**¹⁸ and **18**¹⁷) and in the separation of low-yield components from complex product mixtures containing high levels of organotin residues.¹⁹

In summary, a stationary phase composed of 10% powdered anhydrous K_2CO_3 and silica is remarkably effective for the removal of organotin impurities from product mixtures, reducing these from stoichiometric levels to ~15 ppm. The K_2CO_3 -silica mixture may be stored for many months without significant loss in fluidity or activity. Purifications are best carried out on concentrated product mixtures, eliminating the need for an aqueous work-up and treatment of the associated waste-stream. The method is compatible with tetraorganotin and hexaorganotin compounds (Table 2 and Scheme 2), which pass through the stationary phase as distinct bands at rates similar to those observed using silica alone. Separation of these from other organic components relies on polarity differences, while reactive organotin halides and oxides are captured by the stationary phase.

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Notes and references

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- 18 Compound **17** underwent rapid protodestannylation during TLC analysis and in contact with silica, but was obtained in good yield and excellent purity using the K₂CO₃ method (see ESI†).
- 19 For example, compound **15** was isolated from a complex product mixture containing both starting materials and product, which were all isolated cleanly, in addition to further unidentified side-products.

CH activation and CH₂ double activation of indolines by radical translocation: Understanding the chemistry of the indolyl radical†David C. Harrowven,^{*a} Kerri J. Stenning,^a Sally Whiting,^a Toby Thompson^b and Robert Walton^c

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CH activation and CH₂ double activation of indolines at C2 may be achieved efficiently through radical translocation. The fate of the C2 indolyl radical is dictated by the substitution at C3. Fragmentation, cyclisation and tandem cyclisation reactions leading to indole, azaheterocycle and azapropellane formation, respectively, are reported.

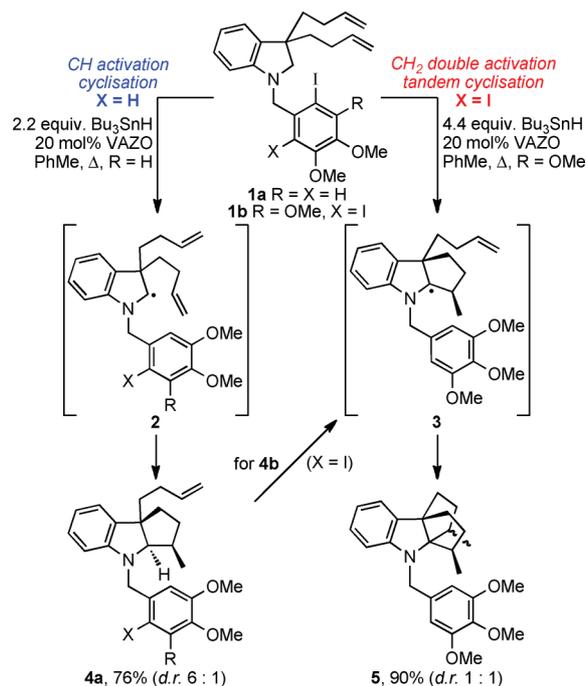
Introduction

Indoles and indolines have long been considered 'privileged structures' in medicinal chemistry owing to their ubiquitous presence in natural and pharmaceutical products. Consequently, their synthesis and functionalisation have been widely studied.^{1–4} In recent years the introduction of transition metal-catalysed cross-coupling and CH bond activation strategies has provided useful methods for the direct introduction of aryl, alkyl, vinyl and alkynyl substituents.⁵ In addition, the ability to induce intramolecular radical additions to both C2 and C3 of an indole and to metallate indolines at C2 with strong bases are notable advances.^{3,6} CH activation of indolines leading to carbon-to-carbon bond formation is less well developed than for indoles, having been demonstrated under both transition metal catalysis⁴ and, in a single example, through radical translocation and capture of samarium(II) iodide.⁷ Herein we describe a detailed examination of the chemistry of the C2 indolyl radical in which we exposed and exploited various fates including cyclisation, C3-fragmentation and tandem cyclisation reactions leading to annulation, indole and azapropellane formation, respectively.

Results and discussion

Before embarking on the study we sought an efficient method for the generation of C2 indolyl radical intermediates. Translocation of an aryl radical tethered through the nitrogen seemed an appropriate starting point as this tactic has a proven track-record in other saturated nitrogen heterocyclic ring systems.⁸ Thus,

with indoline **1a** we were pleased to find that on treatment with Bu₃SnH under standard radical-forming conditions the envisioned arene to indoline radical translocation outpaced cyclisation to C7 to give **4a** in 76% yield as a 6:1 mixture of diastereomers (Scheme 1).^{9,10} Moreover, when the same method was applied to the analogous diiodide **1b** it yielded azapropellane **5** as a 1:1 mixture of diastereoisomers in 90% yield, the result of a double activation–tandem radical cyclisation at C2.



Scheme 1 CH activation–cyclisation and CH₂ double activation–tandem cyclisation reactions. VAZO®–88: 1,1'-azobis (cyclohexane-1-carbonitrile).

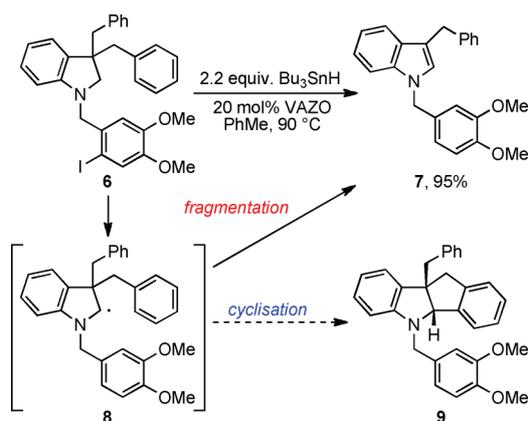
The outcome was equally clear cut with indoline **6**, where the C2 radical intermediate **8** underwent fragmentation to indole **7** rather than cyclisation to the proximal arene to form **9** (Scheme 2).

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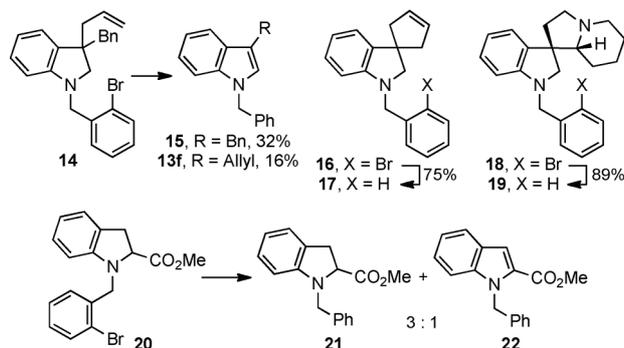
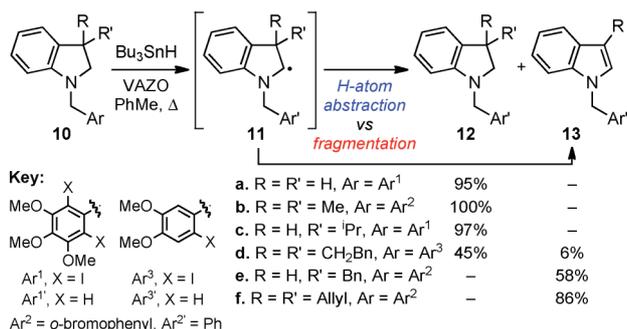
^cPfizer Ltd, Sandwich, Kent, UK CT13 9NJ

† Electronic supplementary information (ESI) available: Experimental details for the procedures described herein and for the preparation of starting materials are given, along with characterisation data and copies of recorded ¹H and ¹³C NMR spectra. See DOI: 10.1039/c1ob05527e



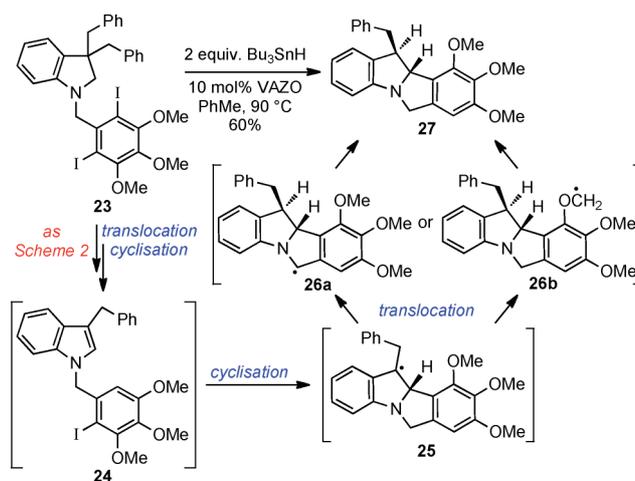
Scheme 2 Fragmentation of a C3 benzyl substituent.

Fragmentation of C3 allyl substituents was also facile (*viz.* **10f** → **13f**) and outpaced fragmentation of a C3 benzyl in the competition experiment **14** → **15** + **13f**.¹¹ Interestingly, no fragmentation was observed with spirocyclopentene **16**, which returned the product of halide reduction **17** (presumably *via* translocation and H-atom abstraction). Methyl, alkyl, aminoalkyl and hydrogen atoms at C3 resisted fragmentation (Scheme 3), though in the latter case this did compete with H-atom abstraction from tributyltin hydride when the C2 radical intermediate was stabilised by conjugation (*viz.* **20** → **21** + **22**).¹² Fragmentation of homobenzylic substituents at C3 was also observed as a minor pathway in the reaction **10d** → **12d** + **13d**, which unexpectedly gave rise to a complex product mixture.



Scheme 3 A study of C3 fragmentation reactions.

Finally, with the conversion of indoline **23** to the fused azaheterocycle **27** we have been able to show how the CH-activation/fragmentation sequence can be used to set up radical cyclisation reactions (Scheme 4). Interestingly, the product was



Scheme 4 An alternative CH activation–cyclisation strategy leading to a fused azaheterocycle.

given as a single diastereoisomer with delivery of a hydrogen atom to the concave face of intermediate **25**. It therefore seems likely that this too involves radical translocation to **26a** or **26b** providing an opportunity for further diversification.

Conclusions

In summary, access to the C2-indolinyl radical is conveniently given by translocation of an aryl radical tethered to its nitrogen centre. The fate of that radical intermediate is dictated by the substitution at C3. Hydrogen, methyl, 1°- and 2°-alkyl and homoallyl substituents at C3 are resistant to fragmentation, providing an opportunity to exploit the C2-indolinyl radical in cyclisation and tandem cyclisation reactions. By contrast, benzyl and allyl substituents at C3 readily cleave in such circumstances leading to the corresponding indole. That fate extends, in part, to hydrogen atoms at C3 when the C2-indolinyl radical is stabilised by conjugation. The CH-activation/fragmentation sequence provides further opportunities for extension, as exemplified by the conversion of indoline **23** to the fused azaheterocycle **27**.

Experimental†

General techniques

Unless specified, commercially reagents were used without further purification. All reactions were carried out in oven-dried glassware under an atmosphere of argon. Toluene, THF and diethyl ether were freshly distilled from a purple solution of sodium and benzophenone. Dichloromethane and chloroform were freshly distilled from CaH₂. Flash column chromatography was performed using silica gel (60A Particle Size 30–70 micron) with the stated solvent system. Chromatographic purification of organotin-containing reaction mixtures was performed using 10% w/w anhydrous K₂CO₃ in silica gel.¹³ Melting points were recorded on a Reichert Austria apparatus and are uncorrected. Infrared spectra were recorded neat as a film or compressed solid using the ATR/golden gate method and are quoted in wavenumbers (cm⁻¹). ¹H NMR spectra were recorded on either a Bruker AV-300 (300 MHz) or DPX-400 (400 MHz) spectrometer

operating at 298 K. ESI mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring mono-isotopic masses (mode: ES+ or ES-). EI and CI spectra were measured on a Thermoquest Trace MS.

Synthetic procedures

8b-But-3-enyl-4-(3,4-dimethoxybenzyl)-3-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indole (4a). A solution of **1a** (200 mg, 0.40 mmol), tributyltin hydride (0.24 mL, 0.87 mmol) and VAZO (20 mg, 0.08 mmol) in toluene (20 mL) was heated at reflux for 4 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica;¹³ 10% diethyl ether in petroleum ether) afforded the *title compound* as a brown oil (120 mg, 0.31 mmol, 76%), as a 6:1 mixture of diastereoisomers. ¹H NMR (400 MHz, CDCl₃) *major diastereoisomer* δ 7.48 (app. td, *J* = 7.9, 1.1 Hz, 1H), 7.43 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.34–7.28 (m, 3H), 7.13 (app. td, *J* = 7.3, 0.6 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.16 (ddt, *J* = 16.7, 10.7, 6.1 Hz, 1H), 5.39–5.31 (m, 2H), 5.04 (d, *J* = 15.9 Hz, 1H), 4.65 (d, *J* = 15.9 Hz, 1H), 4.34 (s, 3H), 4.25 (s, 3H), 4.11 (d, *J* = 5.8 Hz, 1H), 2.59–2.46 (m, 2H), 2.45–2.35 (m, 2H), 2.34–2.02 (m, 4H), 1.82 (m, 1H), 1.57 (d, *J* = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) *major diastereoisomer* δ 153.2 (C), 148.9 (C), 148.0 (C), 138.8 (CH), 136.3 (C), 131.2 (C), 127.3 (CH), 122.8 (CH), 119.8 (CH), 117.1 (CH), 113.9 (CH₂), 111.0 (CH), 110.9 (CH), 107.0 (CH), 75.0 (CH), 56.9 (C), 55.8 (CH₃), 55.7 (CH₃), 53.3 (CH₂), 41.5 (CH), 40.9 (CH₂), 40.6 (CH₂), 32.6 (CH₂), 30.1 (CH₂), 14.9 (CH₃). IR (neat) *v*_{max} 3077, 3003, 2929, 2856, 2827, 1601, 1513, 1485, 1461. LRMS-CI (*m/z*, %): 378 (30), 151 (100). HRMS-ES⁺ (*m/z*): [M + H]⁺ calcd for C₂₅H₃₂NO₂ 378.2428; found, 378.2428.

2-Aza-2-(3,4,5-trimethoxybenzyl)-8,11-dimethylbenz[c]tricyclo[3,3,3,0^{1,5}]undecane (5). A solution of **1b** (300 mg, 0.46 mmol), tributyltin hydride (0.55 mL, 2.02 mmol) and VAZO (23 mg, 0.09 mmol) in toluene (20 mL) was heated at reflux for 16 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica;¹³ 5–10% diethyl ether in petroleum ether) afforded the *title compound* as a white solid (170 mg, 0.41 mmol, 90%) as a 1:1 mixture of diastereoisomers. ¹H NMR (300 MHz, CDCl₃) δ 7.04 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.05 (dd, *J* = 7.3, 1.0 Hz, 1H), 6.92 (app. td, *J* = 7.7, 1.4 Hz, 1H), 6.91 (app. td, *J* = 7.7, 1.4 Hz, 1H), 6.63 (app. tt, *J* = 7.3, 1.0 Hz, 1H + 1H), 6.57 (br. s, 1H + 1H), 6.53 (br. s, 1H + 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 5.95 (d, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 16.8 Hz, 1H), 4.44 (s, 1H + 1H), 4.25 (d, *J* = 16.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.79 (s, 6H), 3.78 (s, 6H), 2.19–1.97 (m, 4H + 4H), 1.94–1.76 (m, 2H + 2H), 1.75–1.57 (m, 2H + 2H), 1.54–1.32 (m, 2H + 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H + 3H). ¹³C NMR (75 MHz, CDCl₃) δ 153.4 (2 × C), 152.6 + 151.8 (C), 138.5 + 137.9 (C), 135.3 (C), 135.1 (C), 127.2 + 127.2 (CH), 122.7 + 122.5 (CH), 117.3 + 117.0 (CH), 107.5 (CH), 105.7 (CH), 103.8 + 103.7 (CH), 91.4 + 87.4 (C), 67.5 + 64.3 (C), 61.1 (CH₃), 56.3 + 56.2 (2 × CH₃), 52.8 + 50.8 (CH₂), 44.0 + 43.6 (2 × CH), 41.5 + 41.1 + 40.1 (2 × CH₂), 35.0 + 34.3 + 33.8 (2 × CH₂), 16.4 + 15.2 + 15.1 (2 × CH₃). IR (neat) *v*_{max} 2933, 2868, 2848, 1687, 1588, 1499. LRMS-ES⁺ (*m/z*, %): 408 (50), 228 (100). HRMS-ES⁺ (*m/z*): [M + Na]⁺ calcd for C₂₆H₃₃NNaO₃ 430.2353; found, 430.2349.

3-Benzyl-1-(3,4-dimethoxybenzyl)-1H-indole (7). A solution of **6** (350 mg, 0.61 mmol), tributyltin hydride (0.36 mL, 1.34 mmol) and VAZO (0.12 mmol, 30 mg) in toluene (25 mL) was heated at reflux for 16 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica;¹³ 5% diethyl ether in petroleum ether) afforded the *title compound* as a brown oil (210 mg, 0.58 mmol, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.38–7.31 (m, 4H), 7.26–7.21 (m, 3H), 7.14 (ddd, *J* = 7.8, 6.9, 1.0 Hz, 1H), 6.93 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.75 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 5.27 (s, 2H), 4.20 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 149.3 (C), 148.5 (C), 141.4 (C), 136.9 (C), 130.2 (2 × C), 128.6 (2 × CH), 128.3 (2 × CH), 126.4 (CH), 125.8 (CH), 121.7 (CH), 119.3 (CH), 119.2 (CH), 119.0 (CH), 114.8 (C), 111.3 (CH), 110.1 (CH), 109.6 (CH), 55.9 (CH₃), 55.8 (CH₃), 49.7 (CH₂), 31.5 (CH₂). IR (neat) *v*_{max} 3052, 3027, 2999, 2933, 2901, 2823, 1514, 1463, 1452. LRMS-ES⁺ (*m/z*, %): 258 (100). HRMS-ES⁺ (*m/z*): [M + H]⁺ calcd for C₂₄H₂₄NO₂ 358.1802; found, 358.1804.

Methyl 1-benzylindoline-2-carboxylate (21) and methyl 1-benzyl-1H-indole-2-carboxylate (22). A solution of **20** (569 mg, 1.64 mmol), tributyltin hydride (0.97 mL, 3.61 mmol) and VAZO (81 mg, 0.33 mmol) in toluene (50 mL) was heated at reflux for 18 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica;¹³ 2–5% diethyl ether in petroleum ether) afforded firstly **22** as a colourless oil (102 mg, 0.38 mmol, 24%). ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 8.1 Hz, 1H), 7.44 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 6.6, 1.1 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.33–7.17 (m, 3H), 7.10 (m, 2H), 5.89 (s, 2H), 3.91 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.3 (C), 139.5 (C), 138.2 (C), 128.5 (2 × CH), 127.3 (CH), 127.1 (C), 126.2 (2 × CH), 126.1 (C), 125.3 (CH), 122.7 (CH), 120.8 (CH), 111.1 (CH), 110.8 (CH), 51.6 (CH₃), 47.8 (CH₂). IR (neat) *v*_{max} 3062, 3031, 2857, 1706, 1605, 1518, 1248, 1191. LRMS-EI (70 eV, *m/z*, %): 265 (57), 233 (12), 206 (6), 188 (4), 91 (100). HRMS-ES⁺ (*m/z*): [M + Na]⁺ calcd for C₁₇H₁₅NNaO₂ 288.0995; found, 288.0994. Then **21** as a pale yellow oil (290 mg, 1.09 mmol, 67%). ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.14 (m, 5H), 7.02–6.93 (m, 2H), 6.62 (app. td, *J* = 7.4, 0.7 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 4.44 (d, *J* = 15.4 Hz, 1H), 4.25 (d, *J* = 15.4 Hz, 1H), 4.19 (dd, *J* = 10.3, 8.1 Hz, 1H), 3.59 (s, 3H), 3.31 (dd, *J* = 15.9, 10.3 Hz, 1H), 3.12 (dd, *J* = 15.9, 8.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 173.3 (C), 151.3 (C), 137.7 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 127.2 (CH), 126.8 (C), 124.1 (CH), 118.1 (CH), 107.2 (CH), 65.2 (CH), 52.1 (CH₂), 52.0 (CH₃), 33.4 (CH₂). IR (neat) *v*_{max} 3053, 3027, 2950, 2849, 1733, 1605, 1484, 1195, 1156. LRMS-EI (70 eV, *m/z*, %): 267 (25), 208 (54), 117 (17), 91 (100). HRMS-ES⁺ (*m/z*): [M + Na]⁺ calcd for C₁₇H₁₇NNaO₂ 290.1151; found, 290.1156.

11-Benzyl-8,9,10-trimethoxy-10b,11-dihydro-6H-isoindolo [2,1-*a*]indole (27). A solution of **23** (500 mg, 0.68 mmol), tributyltin hydride (3.01 mmol, 0.81 mL) and VAZO (0.14 mmol, 33 mg) in toluene (40 mL) was heated at reflux for 16 h, then cooled and concentrated *in vacuo*. Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica;¹³ 5% diethyl ether in petroleum ether) afforded the *title compound* as a colourless oil (160 mg, 0.40 mmol, 60%). ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.36 (m, 4H), 7.31 (m, 1H), 7.17 (app. dt, *J* = 7.5, 1.3 Hz, 1H),

6.87–6.80 (m, 2H), 6.78 (ddd, $J = 7.9, 7.2, 0.8$ Hz, 1H), 6.51 (s, 1H), 5.06 (br. s, 1H), 4.55 (dd, $J = 14.6, 1.3$ Hz, 1H), 4.48 (d, $J = 14.6$ Hz, 1H), 4.18 (br. dt, $J = 7.5, 1.9$ Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.16 (dd, $J = 13.3, 8.2$ Hz, 1H), 3.07 (dd, $J = 13.3, 7.3$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 154.1 (C), 154.1 (C), 149.5 (C), 140.9 (C), 140.0 (C), 135.0 (C), 134.0 (C), 129.7 (2 \times CH), 128.2 (2 \times CH), 127.8 (CH), 127.1 (C), 126.1 (CH), 124.8 (CH), 120.3 (CH), 112.0 (CH), 101.3 (CH), 74.7 (CH), 60.8 (CH_3), 60.3 (CH_3), 59.4 (NCH_2), 56.1 (CH_3), 48.1 (CH), 43.2 (CH_2). IR (neat) ν_{max} 3032, 2995, 2938, 2856, 1597. LRMS-CI (m/z , %): 388 (80), 296 (100), 280 (15), 195 (20), 167 (20), 91 (30). HRMS-ES⁺ (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_3$ 388.1907; found, 388.1901.

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