Studies Towards the Total Synthesis of Manzamine A

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (D.Phil.)

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Wadham College

University of Oxford

Hilary Term 2013

For my family

Past, present and future

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Abstract

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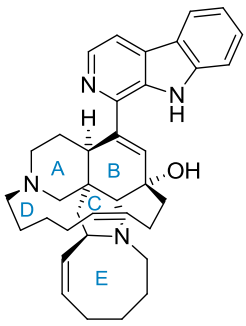
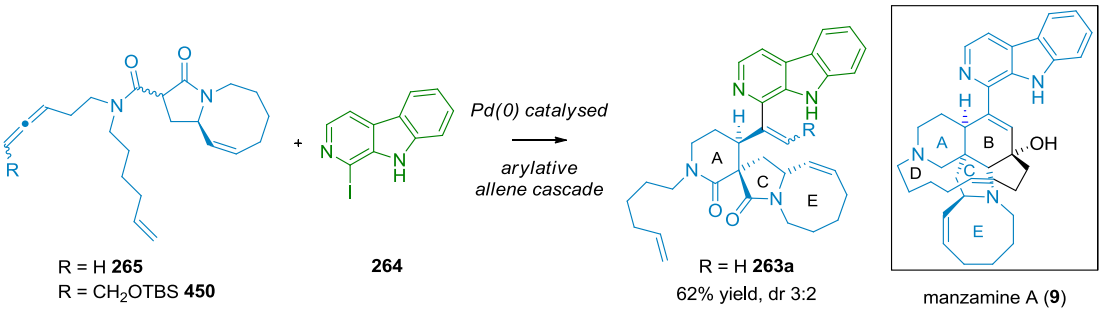


manzamine A (**9**)

This thesis describes studies towards the total synthesis of manzamine A (**9**), a marine alkaloid. Two routes are presented.

The first route applied a novel palladium-catalysed arylative allene spirocyclisation cascade to the synthesis of manzamine A (**9**). In the first generation, a short route was developed to access the tricyclic ACE core **263a** in only nine steps. The second generation applied the palladium-catalysed cascade to a similar system which utilised non-terminal allene pro-nucleophile **450** in an attempt to access a homologated derivative of the ACE core.



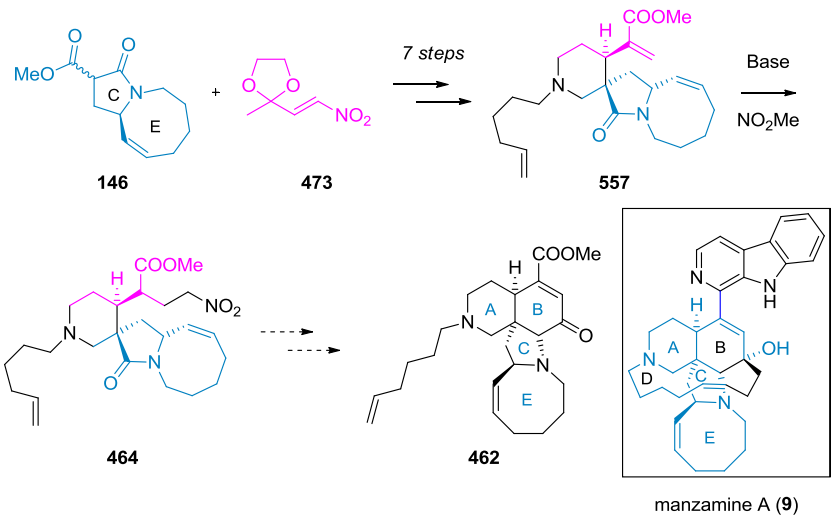
R = H **265**
R = CH_2OTBS **450**

264

R = H **263a**
62% yield, dr 3:2

manzamine A (**9**)

The second route relied on a diastereoselective Michael addition between nitro-olefin **473** and 8,5-fused ring system **146** comprising rings C and E of manzamine A (**9**). Further elaboration of the Michael addition product enabled the synthesis of tetracyclic ABCE core precursor **464** to be carried out and preliminary investigations into ring B formation were investigated.



146 **473** **557**

464 **462**

manzamine A (**9**)

Declarations and Copyright

I declare that this thesis has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree at this or any other university or institute of learning. Any work done in collaboration with a research colleague or undergraduate student has been fully acknowledged and referenced within the text.

I was admitted as a probationary research student in October 2009 and as a candidate for the degree of Doctor of Philosophy in October 2011; the higher study for which this is a record was carried out in the University of Oxford between 2009 and 2012.

Alison Hawkins

Date Signature of candidate

I hereby certify that the candidate has fulfilled the conditions of the Regulations appropriate for the degree of Doctor of Philosophy in the University of Oxford and that the candidate is qualified to submit this dissertation in application for that degree.

Date Signature of supervisor

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Acknowledgements

"Ever tried. Ever failed. No matter. Try again. Fail again. Fail better. Fail harder."

Samuel Beckett, *Worstward Ho*, (1983)

Throughout my DPhil., I have often felt that this is an apt quote. The total synthesis of a complex natural product is a daunting task by any standard and there are many people that deserve recognition for the help and support I have received during my DPhil.

When Darren asked me what project I wanted, in June 2009, the options were: (1) difficult, but potential gold-mine, or (2) established project, lots of papers. I chose the former, and have to say it's been quite an experience. So, thank you to my supervisor, Darren Dixon a.k.a DJD, for accepting me into his research group and trusting me with such a great project, and for providing ideas and enthusiasm when mine were lacking.

Thanks to my industrial supervisor, Alan Ironmonger at GSK for the supervision on my CASE award. Thanks to Tim, Barbara, Tina and Maria in the NMR department all for their time and effort spent helping me with interpreting NMR spectra, running NOESYs and all the ^{13}C spectra run on <5 mg of material. Thank you to Amber Thompson for making me a slightly less bad crystallographer - her patience and teaching skills are amazing.

Thanks to Marta, Gus, Bal, Andrew, Mel and Pavol for proof-reading this thesis.

So on to the Dixon group....let's start at the beginning back in first year. Thank you to Chloe Holloway for recommending the Dixon group, and for your friendship since then. Thank you to my fellow 1st year DPhils - Eddy, Dave and Matt. Wow - we made it! (Well, most of us...). Michael "Moral" Muratore, the French lover and best English speaker in the lab, you were missed! Marta Rosa Nuñez García, what can I say - I couldn't have survived G6 without you! Thank you for all our fume-hood gossips and crazy dancing (orr orr)! And of course, Andrew Kyle/AFK - thanks for all the triple whisky nights and continued jovial greetings. Second year announced the arrival of trouble-makers Alex and Alistair into G6. Thanks to fellow Michael Bublé appreciator Alex for all the duets and education into the male mind-set. Farley - I will miss the banter and your tumbling locks. In third year I was given the exciting task of managing a Part II, and in my opinion, I had the best one! Alan (A-bomb Jr.), thank you for being sor sor awesome - the shaking-hands-whilst-raising-shoulders move lives on to this day. Thank you to the rest of the Dixon group for day-to-day banter, friendship and support throughout my three years in the group.

Special thanks must be given to friend/colleague, Pavol Jakubec. Not only has he made me a nearly fluent Slovak speaker and has increased my whisky appreciation no end, he has also been the better half of Team Manzamine. Pavol, ďakujem za všetku Tvoju poskytnutú pomoc, myslím že bez Teba by som to nezvládla. Prajem Ti v budúcnosti veľa sťastia a dúfam, že zostaneme v kontakte. Daj mi vedieť, či si nazbieral veľa hríbov a ja prídem ochutnať to najlepšie zo Slovenska.

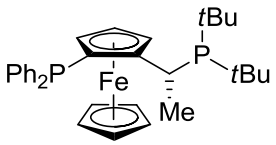
And to friends around and outside the lab, who have always provided entertainment of the non-chemistry variety and been there whenever I've needed. Gus - thank you for the Peep Show moments, morning crumpets, marmite and tea and excellent banter. Mel - I'm so pleased you asked me out on that first date, the beginning of a jubbly-filled life! Matteo - you made IRs and α_D measurements so much more entertaining. Liz, Sarah, Lucy, Alice, Rosie, Jo and Phoebe, my ladies - thank you for all the distraction from chemistry, the dinners, cocktails and general friendship over the years!

Russell Kinch a.k.a Rusty/R-bomb or otherwise - thank you for waiting - we have arrived! You have been amazingly supportive throughout, even though you have no idea what is going on (apart from the diastereomers, β-carbolines, Bunsen burners and centrifuges of course!). Your constant belief that I could do it was more valuable than I can tell you. I am the luckiest girl and I can't wait to begin the next chapter of my life with you. No more A4074!

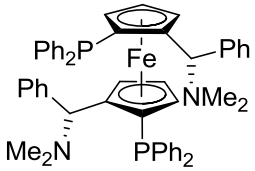
Finally, thank you to my family. Jonny - thank you for telling me to chill out, and for all our trips together! Mum and Dad - thank you for all the words of wisdom, vegetables, jam and gardening advice. I couldn't have finished my DPhil. without your support and encouragement, so thank you for always being there!

Abbreviations

˚C	degrees Celsius
≈	similar skeletal properties
Å	angstrom
Ac	acetyl
act	activation
AIBN	2,2′-azobis(2-methylpropionitrile)
aq	aqueous
Ar	(hetero)aromatic
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	(*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
brsm	based on recovered starting material
Bs	benzene sulfonate ($C_6H_5SO_2$-)
Bu	butyl
Bz	benzoyl
c	concentration
CAN	cerium ammonium nitrate
cat.	catalyst or catalytic
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
cm	centimetres
COD	cyclooctadiene
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	days
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine or 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N’-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin Periodinane

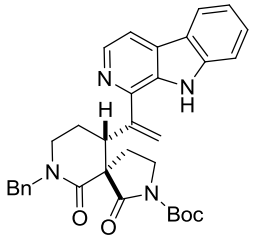
DMSO	dimethylsulfoxide
dmppp	1,3-bis(di-(2-methoxylphenyl)-phosphino)propane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBMP	di-*tert*-butyl methyl pyridine
DTBP	di-*tert*-butyl pyridine
E	$COOCH_3$
EDC.HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact
eq	equivalent
ES	electrospray
Et	ethyl
EWG	electron withdrawing group
FDA	food and drug administration
FGI	functional group interconversion
Fu	furan
G	activating species
g	gram
h	hours
Het	heterocycle
HMBC	heteronuclear multiple-bond correlation experiment
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOBt	*N*-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HSQC	heteronuclear single-quantum coherence experiment
HRMS	high-resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IPA	isopropanol
IR	infra-red
	
JOSIPHOS	(*R*)-1-[(*S*)-2-diphenylphosphinoferrocenyl]ethyldi-*tert*-butylphosphine
kg	kilogram
L	ligand or litre
LA	Lewis acid
LDA	lithium diisopropylamide
m	integer
M	metal or molar concentration/mol dm^{-3}

m/z	mass to charge ratio
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl (-$C_6H_3Me_3$)
mg	milligram
MHz	megahertz
min	minutes
mL	millilitre
mmol	millimole
mol	mole
MOM	methoxymethyl ether
mp	melting point
Ms	methanesulfonyl
Mts	mesitylenesulfonyl
MVK	methyl vinyl ketone
n	integer
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	*p*-nitrobenzenesulfonyl
Nu/Nuc	nucleophile
P	generic protecting group
p/*m*/*o*	*para*/*meta*/*ortho*
PCC	pyridinium chlorochromate
Ph	phenyl
pin	pinacolate
PMB	*p*-methoxybenzyl
PMHS	polydimethylsiloxane
PMP	*p*-methoxyphenyl
Pr	propyl
PS	polymer supported
*p*TSA	*p*-toluenesulfonic acid
Py	pyridyl
quat	quaternary
$R/R^1/R^2/R^3$	alkyl groups
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
RT	room temperature
rxn	reaction
S	solvent
SES	2-trimethylsilylethanesulfonyl
SET	single electron transfer
S_N2	bimolecular nucleophilic substitution
SPHOS	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
T	temperature
TBAF	tetrabutylammonium fluoride

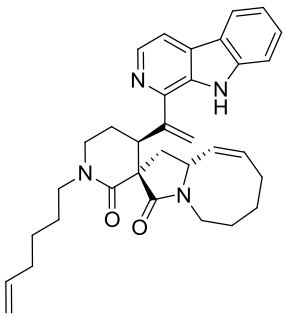
TBAI	tetrabutylammonium iodide
TBD	3,4,6,7,8,9-hexahydro-2H-pyrimido[1,2-a]pyrimidine or triazabicyclodecene
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBME	2-methoxy-2-methylpropane
TBS	*tert*-butylsilyl
Tf/triflic	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMEDA	*N*,*N*,*N*',*N*'-tetra-methylethylenediamine
TMG	1,1,3,3-tetra-methylguanidine
TMS	trimethylsilyl
Triton B	benzyl trimethylammonium hydroxide
Ts	4-toluenesulfonyl
WALPHOS	 (α*R*,α*R*)-2,2'-bis(α-N,N-dimethylaminophenylmethyl)-(*S*,*S*)-1,1'-bis(diphenylphosphino) ferrocene
wt	weight
X	unspecified functional group
µg	microgram

Stereochemistry

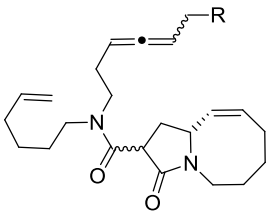
Stereochemistry is drawn in accord with the conventions proposed by Maehr.[i] Normal bond thickness is used for racemic compounds or enantioenriched compounds where stereochemistry is unknown. Solid and broken wedges are used to indicate absolute configuration when known (or inferred from other results) in enantioenriched or enantiopure compounds. Solid and broken lines are used to indicate the relative stereochemistry (when known) of diastereomerically pure or diastereo-enriched, racemic compounds.



racemic diastereopure or diastereoenriched compound with known relative stereochemistry



enantiopure or enantioenriched compound where stereochemistry is known (or assumed)



undefined bond indicates mixture of diastereomers

[i] Maehr, H. *J. Chem. Educ*. **1985**, *62*, 114–120.

Chapter 1
Introduction

1.1 Natural Product Synthesis

The synthesis of biologically active compounds is one of the most exciting areas of chemistry. The discovery and isolation, structural elucidation and synthesis of these natural products has gone from strength to strength over time, enhanced by improvements in spectroscopic techniques and a continually increasing wealth of reactions available. Natural product synthesis is, in itself, an art requiring creativity, knowledge, stamina and flair, and provides an education to all who participate.

Within the Dixon group, there is a strong interest in the total synthesis of natural products. We aim to use new reactions and methodologies discovered within the group, which usually involve the formation of multiple carbon-carbon bonds and stereocentres, and then apply them to the synthesis of biologically relevant targets. The term “cascade” is often used and the concept is outlined in Figure 1.

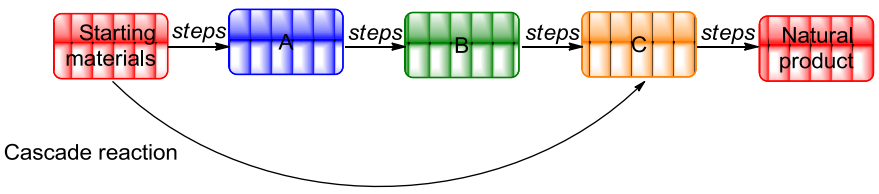


Figure 1: Concept of a cascade reaction.

The idea for the project outlined in this thesis was inspired by the discovery of such a reaction, as well as a continued interest in the synthesis of marine alkaloids within the Dixon research group.

1.2 Marine Alkaloids

The ocean covers approximately 71% of the world's surface and holds a plethora of marine life; it is estimated that biological diversity is greater in the sea than in tropical rainforests.[1] It follows that there are many natural products isolated from various sponges, seaweeds and marine micro-organisms with presumably many more undiscovered.

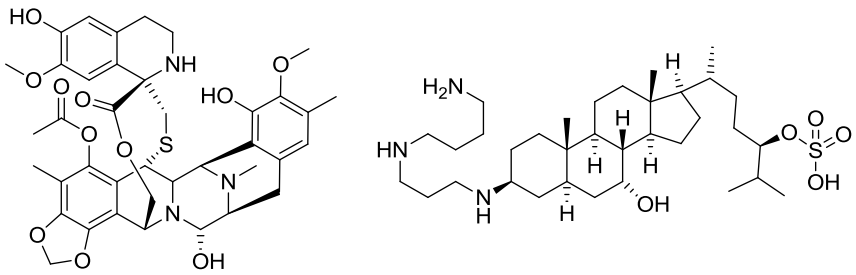


Figure 2: Biologically active marine alkaloids.

The two marine alkaloid natural products outlined in Figure 2 are both used as medicines. Trabectedin (**1**) was first isolated in the 1960s from a sea squirt and the structure was first determined in 1984 by Rinehart *et al.* who collected the sea squirts himself.[2] The first total synthesis was completed by Corey *et al.* in 1996[3] and **1** is now made by a semi-synthetic route from an antibiotic obtained by fermentation. The natural product is marketed as Yondelis™ and was approved in Europe in 2007 for use as a soft tissue anti-cancer agent and exhibits pico- to nanomolar activity. The mechanism is not yet fully understood, but it has been postulated that it involves the production of superoxide near DNA stands which cleaves the DNA backbone and results in cell apoptosis.[1] Squalamine (**2**) was first isolated from the dogfish shark *Squalus acanthias* in 1993.[4] The first total synthesis was completed by Moriarty *et al.* in 1994.[5] Squalamine is a potent antibiotic but has also been recently fast-tracked by the FDA for use in the treatment of macular degeneration. It is also in phase II clinical trials for treatment against ovarian and lung cancers.[1]

1.3 The Manzamines and Related Compounds

Manzamine A was the first of the manzamine alkaloid family to be isolated in 1986 and since then, over seventy further compounds have been isolated from the same Okinawan sponge.[6] A representative example are shown in Figure 3.[7]

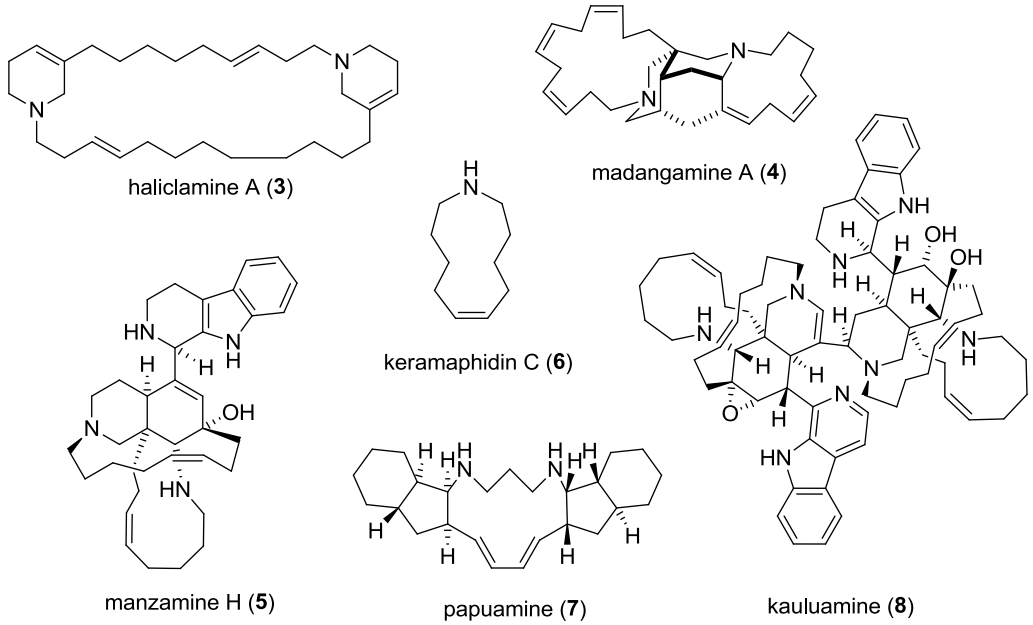


Figure 3: Representative examples from the manzamine family.

The structure of the manzamine alkaloids is highly varied, from relatively simple keramaphidin C (**6**) to dimer kauluamine (**8**). The family members often possess highly substituted and functionalised central ring systems; fused nitrogen-containing heterocycles, *Z*- and/or *E*-olefins, macrocycles (8–15-membered rings), complex carbon-skeletal frameworks and β-carboline systems can all be found.

The total synthesis of the more complex compounds is often considered in two stages; the formation of the core skeleton, then construction of the external macrocycles which are usually formed either *via* a Yamaguchi lactamisation or more recently, ring-closing metathesis (RCM). Problems of *E*/*Z* selectivity when RCM in used often arise to which end there has been a lot of investigation. The complex nature of these natural products as well as interesting biological activity has resulted in significant interest from the synthetic community. As many as eight of the family members have been synthesised: manzamine A

(including common precursors, ircinol A, ircinal A, and manzamine D),[8–12] papuamine (**7**),[13,14] nakadomarin A (see Section 4.2.4),[15–17] less complex manzamine C (see Section 1.4.1),[18–22] and haliclamine A (**3**).[23–25]

This thesis is concerned with investigating a new route to arguably the most important member, manzamine A, the father of this diverse and massive family.

1.3.1 Manzamine A

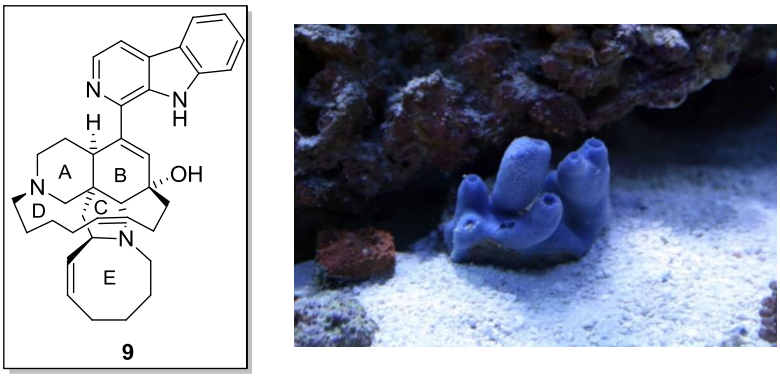


Figure 4: Manzamine A (**9**) and the *Haliclona sponge*.

Manzamine A (Figure 4, (**9**)) was first isolated in 1986 by Higa *et al*.[26] when investigating new anti-tumour activity in marine organisms, specifically from marine sponges in the Okinawa Sea. Manzamine A contains eight rings in total; five aliphatic (ABCDE) including one 13-membered and one 8-membered ring, and a β-carboline system. It also possesses two *Z*-olefins and five stereocentres including four contiguous and two fully substituted centres.

Manzamine A, found in the *Haliclona sponge*, was extracted from the sponge with ethyl acetate and purified by flash column chromatography eluting with acetone (100 mg of manzamine hydrochloride obtained from 735 g of wet sponge).[26] It exhibits interesting biological activity, not least its potent antimalarial activity, but also insecticidal, antibacterial, anti-inflammatory and antitumour properties: manzamine A exhibits high *in vitro* activity against P388 mouse leukaemia cells (IC_{50} 0.07 μg/mL).[27] Perhaps the most notable activity is its antimalarial properties: over 90% of activity in *Plasmodium (P.)*

berghei, a malaria parasite was inhibited after a single injection of manzamine A in infected mice.[28] Indeed, in highly parasitemic mice, after 60 days of exposure to the malaria parasite, 40% of mice recovered after a single injection.[27] Manzamine A's potent activity against malaria is incredibly important as it opens a new door in the fight against one of the most serious global health challenges for which there is still no cure. Malaria is a disease that affects between 300 – 500 million people a year, resulting in 1 – 2 million deaths.[29] *P. falciparum* is the main cause of death out of the four species of plasmodium and it is quickly becoming more resistant to standard antimalarial drugs. Therefore, there is an urgent need to develop new methods to control malaria which should include utilising natural products and their analogues.

Studies in other assays have shown the ability of a β-carboline unit to bind to biological receptors. For example, β-carboline-3-carboxylates are known to bind with high affinity and high selectivity to the neurotransmitter GABA (*γ*-amino butyric acid) receptor; GABA is responsible for reducing the activity of neurons it binds to and is linked to diseases such as insomnia and anxiety.[30] Indeed, manzamine A is one of the few natural products that can permeate the blood-brain barrier in an *in vitro* model.[28] On the other hand, in kinase inhibition such as the inhibition of glycogen synthase kinase-3 (GSK-3), a key protein in type-2 diabetes and neurogenerative conditions such as Alzheimer's disease, it has been shown that neither the β-carboline unit nor ircinal A, which are chemical precursors to manzamine A, will inhibit the protein; manzamine A in its entirety is required (IC_{50} = 10 μM).[31]

Aside from the clear pharmaceutical benefits gained from exploring manzamine A and its related analogues, from a synthetic chemist's view it poses a challenging target to inspire, educate and push the boundaries of organic chemistry for anyone in the synthetic community. Indeed, it is a testament to the complex structure of manzamine A that it has

only been fully synthesised four times in the last 25 years since its discovery. Many groups have attempted routes of the core and these, along with the full syntheses will be discussed.

The antimalarial and antitumor properties of manzamine A, as well as its complex structure make it a highly desirable target for synthesis.

1.4 Approaches to the Synthesis of Manzamine A

1.4.1 Biosynthetic Route

The biosynthetic route to form manzamine A was postulated by Baldwin *et al.* in 1992, six years after its discovery and isolation.[32] When manzamine A's structure was determined by Higa *et al.*, it prompted the quote:

"*its (i.e. manzamine A's) provenance is problematical as there appears to be no obvious biogenetic path*"[26]

As mentioned previously, the manzamine alkaloid family contains amongst others, the following three structurally similar compounds; manzamines A (Figure 5, (**9**)), B (Figure 5, (**10**)) and C (Figure 5, (**11**)).

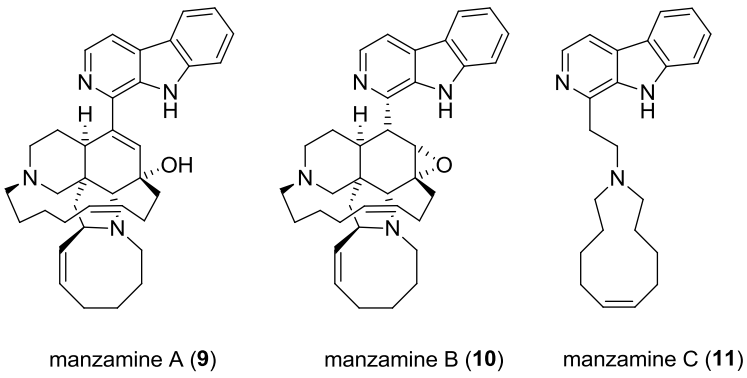


Figure 5: Manzamines A (**9**), B (**10**) and C (**11**).

Baldwin proposed that manzamine C, a relatively structurally simple member of the family, could be "broken up" in to three fragments, and that by considering the biosynthesis of

manzamine C, biosynthetic links could be made between manzamine C and the more structurally complex analogues, A and B.[32]

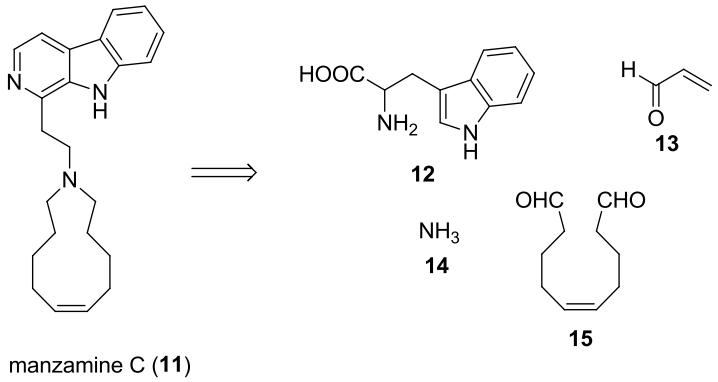


Figure 6: Biosynthetic retrosynthesis to manzamine C (**11**). No stereochemistry defined for tryptophan **12**.

Manzamine C was proposed to have been formed by the reductive condensation of ammonia **14** with tryptophan **12**, acrolein **13**, and bis-aldehyde olefin **15** (Figure 6). By analogy, the path to manzamine B and consequently manzamine A was proposed (Figure 7).

Baldwin proposed that manzamine B, in a similar fashion to manzamine C, was formed by the reductive condensation between two units of ammonia **14**, acrolein **13** and bis-aldehyde olefin **15** to give macrocycle **16**. The tautomer **17** could undergo a Diels-Alder reaction to form bis-dihydropyridine **18**. Redox exchange between the two piperidine rings and hydrolysis of the subsequent iminium ion could then form aldehyde **20**. Coupling to the tryptophan unit and epoxidation would give manzamine B (**10**). Further derivatisation would give manzamine A (**9**); *trans*-eliminative opening of the epoxide and allylic oxidation of a double bond followed by ring closure provides a feasible biosynthetic route to manzamine A. The postulated biosynthetic route was further confirmed in 1994 when Kobayashi *et al*. isolated and characterised keramaphidin B (**19**), which had the same skeletal structure that was proposed by Baldwin two years earlier.[33] As discussed in this thesis, some aspects of the proposed biosynthetic route have been used to inspire synthetic pathways. Condensation of tryptophan or related tryptamine derivative has been used in three of the four total syntheses that have been published to date as a way to

introduce the β-carboline system, and inter/intramolecular Diels-Alder reactions have often been used to synthesise the core.

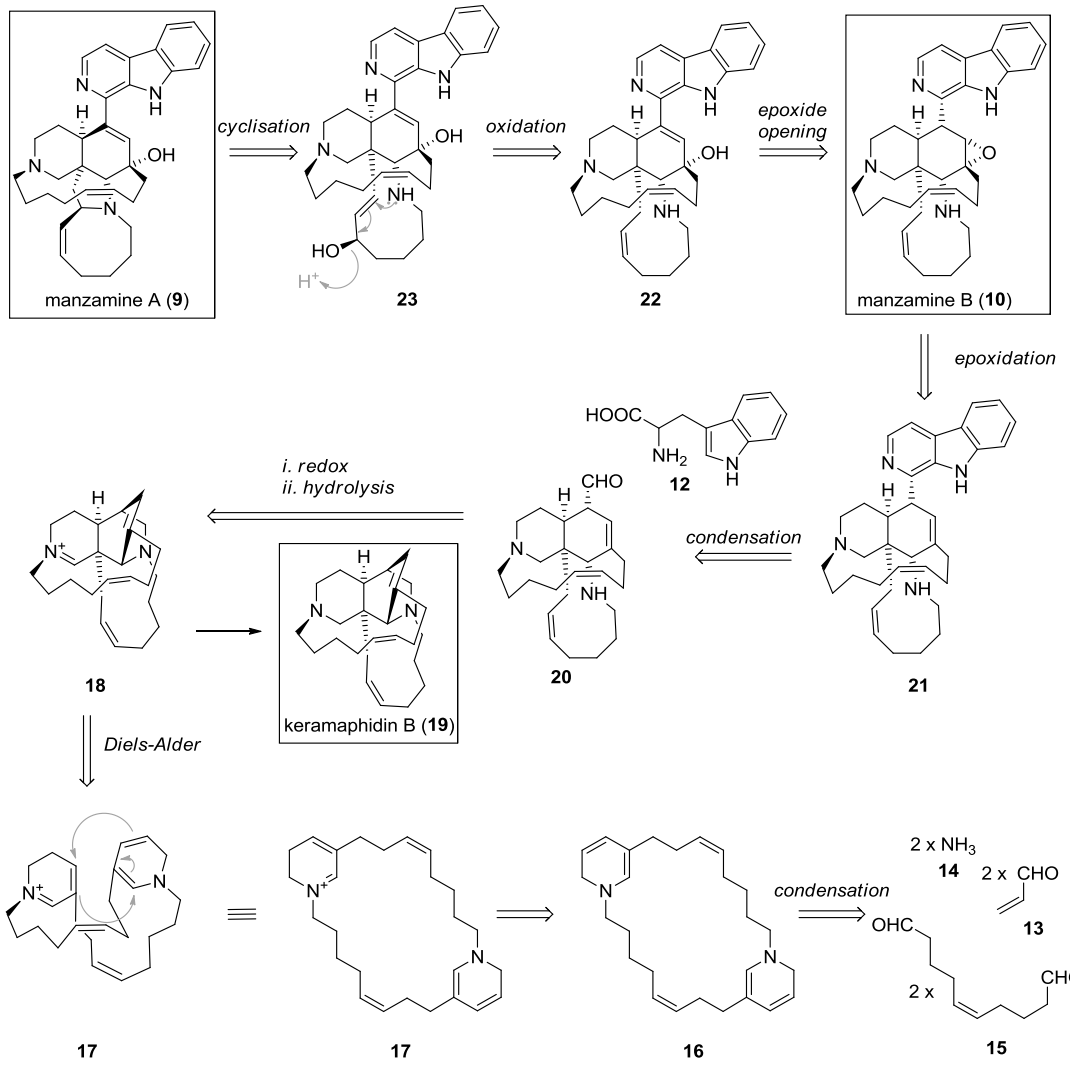
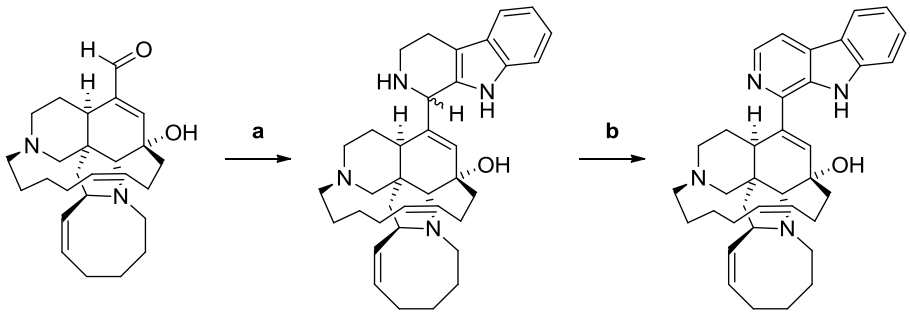


Figure 7: Biosynthetic route retrosynthesis to manzamine B (**10**) and manzamine A (**9**).

It was Kobayashi who demonstrated the utility of this chemistry from the biosynthetic route for the first time in a synthetic setting (Scheme 1).[34] Kobayashi *et al.* isolated and elucidated the structures of new marine alkaloids ircinal A (**24**) and manzamine D (**25**) from the marine sponge, *Ircinia sponge*. A Pictet-Spengler reaction with tryptamine and aldehyde **24** under acidic conditions gave manzamine D (**25**) which upon oxidation using DDQ gave manzamine A (**9**) in 54% yield.



ircinal A (**24**) manzamine D (**25**) manzamine A (**9**)

Scheme 1: Kobayashi's synthesis of manzamine D (**25**) and manzamine A (**9**) from naturally occurring ircinal A (**24**). **(a)** tryptamine, trifluoroacetic acid, toluene, RT, 6 h, 18%, no dr given; **(b)** DDQ, EtOH, $CHCl_3$, RT, 30 min, 44%. Kobayashi synthesised manzamine D as a mixture of diastereomers. The correct stereochemistry at undefined stereocentre is (*R*).

This discovery set the precedent for the synthesis of manzamine A and most groups who have attempted the synthesis of the core or have completed a total synthesis, aimed towards ircinal A, after demonstration by Kobayashi *et al.* that ircinal A (**24**) is only two relatively simple steps from manzamine A.

1.4.2 Synthetic Approaches of the Core of Manzamine A

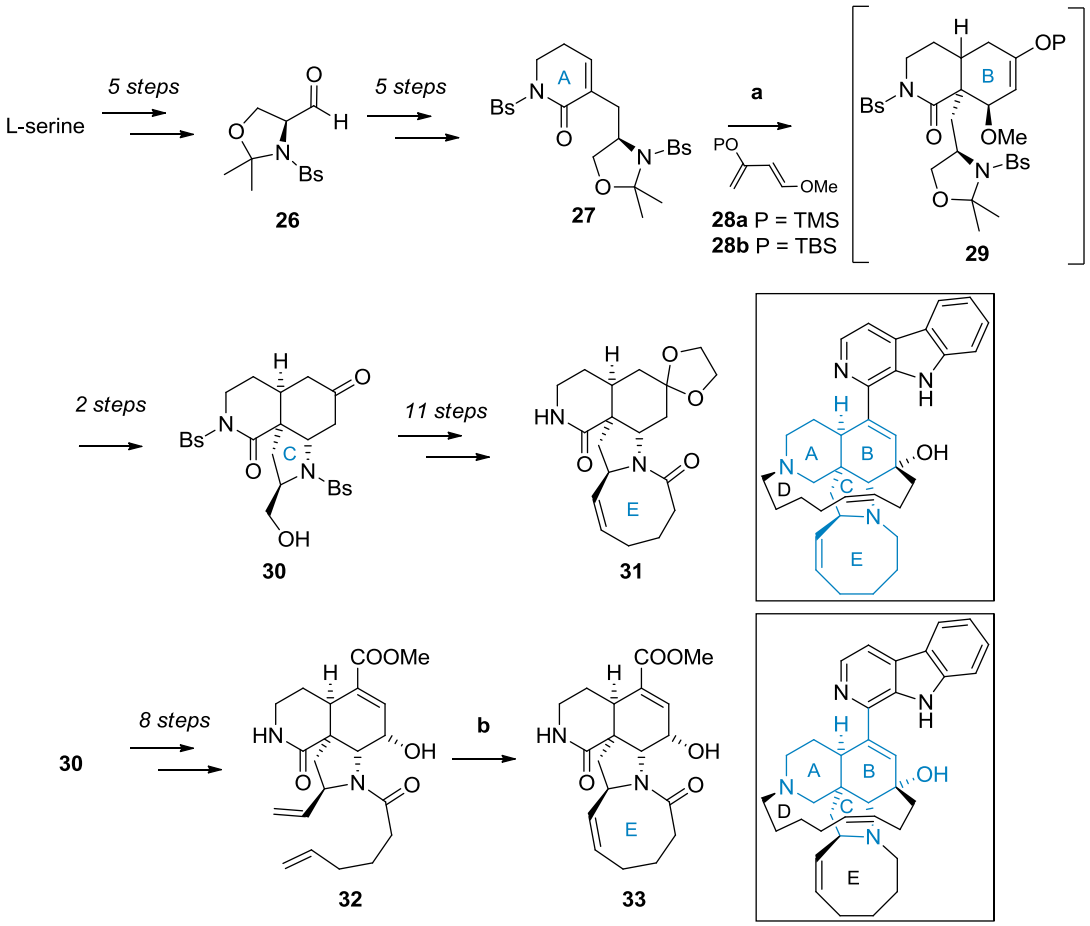
There have been many papers published reporting synthetic efforts towards skeletal cores of manzamine A. The author defines a core as at least a bicyclic carbon skeleton which could be fused or spirocyclic. This thesis has grouped the publications according to the type of chemistry used to access ring systems and will focus on representative examples from each category. The vast majority of syntheses of cores of manzamine A rely on a Diels-Alder reaction, as it is a classic way to access fused ring systems and is undoubtedly based partially on the biosynthetic route. The standard lettering annotation referring to the ring system of manzamine A (Figure 4) is shown throughout in schemes and referred to in the text as such.

1.4.2.1 Intermolecular Diels-Alder Reaction

A Diels-Alder reaction is a powerful synthetic tool and can be used to access fused ring systems, with excellent stereochemical control. In the case of manzamine A, a common retrosynthesis for the formation of rings A and B is the use of an inter- or intramolecular Diels-Alder reaction. With suitably functionalised substrates, the majority of the carbon skeleton, including stereocentres, of manzamine A can be introduced in a single step. There are four groups that have published routes of the core that utilise this type of chemistry to synthesise the AB system.[35–37,38–41,42–44]

Both Marazano[37] and Nakagawa published routes to the ABC core of manzamine A using an intermolecular Diels-Alder reaction. Nakagawa and co-workers have published extensively in the field of manzamine A core synthesis[35,38–41] and a summary is outlined in Scheme 2. The tricyclic core **30** was accessed *via* an intermolecular Diels-Alder reaction with substituted piperidenone **27** and the highly reactive Danishefsky diene **28**.[35] It was found that the nitrogen of the lactam ring must be protected with a strongly electron-withdrawing group; Boc proved too thermally unstable, Ts was used in the original work (30% yield)[35] and Bs was used in a later route (66–85% yield).[35,40] It was found that when TMS- or TBS-protected diene **28a**/**28b** was used, treatment of Diels-Alder product **29** with acid gave the tricyclic ABC system **30** in 36% (TMS) or 45% (TBS) yield *via* elimination of MeOH and a stereoselective 1,4-Michael addition.[40] It required a further eleven steps to form tetracycle **31**;[41] a Wittig reaction was used to introduce the *cis*-double bond in the 8-membered ring following chemistry first developed in an earlier report,[39] and most other steps are protecting group manipulations. The synthesis of another tetracyclic core **33** was reported which used similar chemistry. Mander's reagent[45] (MeCOCN) was used to introduce the α,β-unsaturated ester moiety. Some protecting group exchange, functional group interconversion and redox chemistry gave tetracycle precursor **32**. A ring-closing

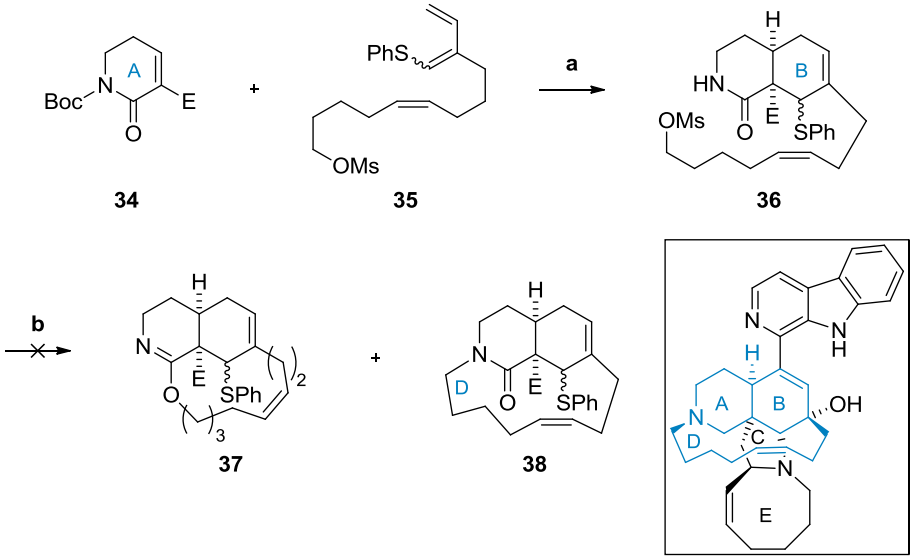
metathesis reaction using 50 mol% Grubbs second generation catalyst formed ring E in 75% yield (*Z*:*E* ratio not specified).



Scheme 2: Nakagawa's syntheses of the core of manzamine A. **(a) 28**, *p*-cymene, 180 ˚C, 20 h, P = TMS 36%, or P = TBS 45%; **(b)** 50 mol% Grubbs' second generation, CH_2Cl_2, RT, 21 h, 75%, *Z*:*E* ratio not specified. P = TMS (**28a**) or TBS (**28b**).

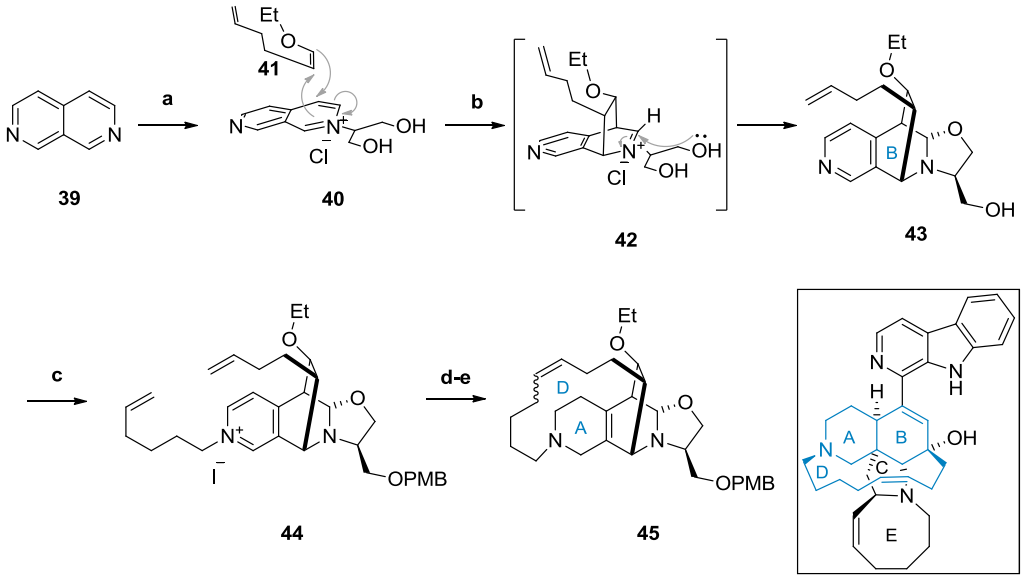
Both Simpkins and Langlois synthesised the AB core of manzamine A *via* an intermolecular Diels-Alder reaction and then extended their route to introduce ring D. Simpkins was an early contributor to the manzamine field[42] and reported the use of a Diels-Alder reaction using suitably substituted diene **35** to enable later construction of ring D. The *cis*-double bond on the mesylate chain in **35** was introduced by a Ni(II)/$NaBH_4$ hydrogenation of an internal alkyne. The Diels-Alder reaction gave bicyclic core **36** in 27% yield using optimised conditions ($ZnBr_2$ in dichloromethane) with concomitant loss of the Boc group. The instability of Boc-lactam **34** was the reason given for the low yield. The S_N2-like ring closing sequence was problematic. After a wide screen of conditions (Scheme 3), minute quantities

of material was obtained after purification by HPLC which Simpkins tentatively assigned to **37** and **38**, although no characterisation data were reported.[42]



Scheme 3: Simpkins' synthesis of the core of manzamine A. **(a)** $ZnBr_2$, dichloromethane, 0 ˚C, 27% (46% brsm), dr 1:1; **(b)** basic conditions (NaH, DMF; K_2CO_3, DMF; CsF, THF; K_2C0_3, 18-crown-6, benzene). E = COOMe. No isomeric ratio of **37** and **38** given.

Langlois also employed a Diels-Alder reaction but in a different way to Nakagawa, Marazano and Simpkins (Scheme 4).[43,44] A Zincke reaction[46] in water with 2-amino-1,3-propanediol using fused di-pyridine **39** gave *N*-alkylated pyridinium substrate **40**.



Scheme 4: Langlois' synthesis of the core of manzamine A. **(a)** 1-chloro-2,4-dinitrobenzene, 2-amino-1,3-propanediol, H_2O, reflux, 16 h; **(b)** 10 eq **41**, $CaCO_3$, H_2O:THF 8:2, 20 ˚C, 3 d, 25% over two steps; **(c) (i)** NaH, PMBCl, THF:DMF 8:2, 20 ˚C, 6 h, 90% **(ii)** $I(CH_2)_4CH{=}CH_2$, MeCN, reflux, 6 h, 95%; **(d)** 10 mol% Grubbs' second generation, benzene, 60 ˚C, 2 d, 95%, 7:3 *Z*:*E*; **(e)** $NaBH_4$, MeOH:THF 1:1, 0 ˚C, 1 h, 80%.

A Bradsher cycloaddition[47] was performed with 10 equivalents of vinyl ether dienophile **41** and the reaction proceeded in water at room temperature in 25% yield over two steps. The stereochemistry was confirmed by nOe experiments and single crystal X-Ray diffraction. Further *N*-alkylation gave pyridinium **44** and ring D was synthesised *via* a ring-closing metathesis in 95% yield with a 7:3 inseparable mixture of *Z* and *E* isomers. Subsequent reduction of the pyridinium ring gave tricyclic core **45**.

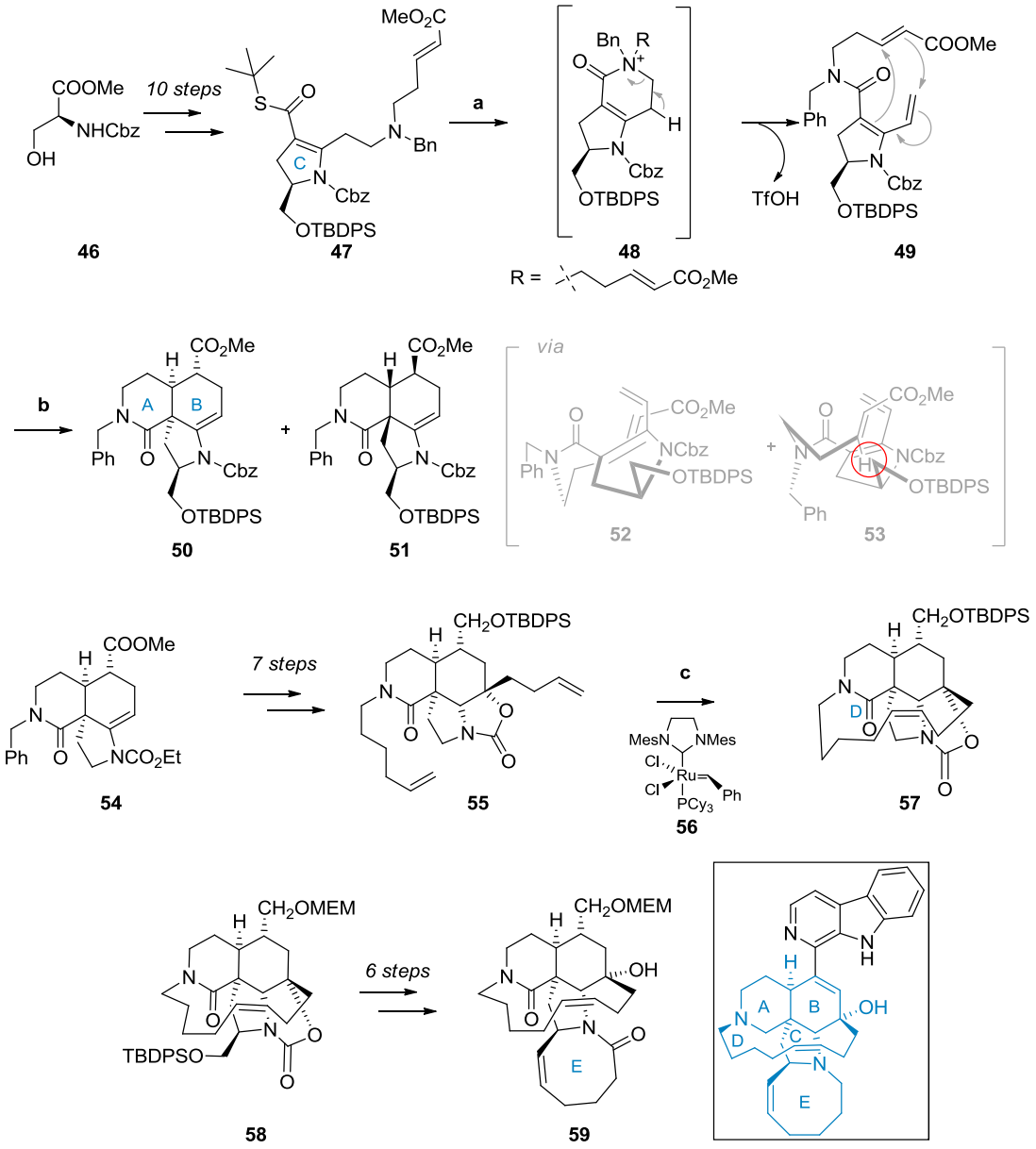
1.4.2.2 Intramolecular Diels-Alder

Intramolecular Diels-Alder reactions have also been applied to the synthesis of the core of manzamine A, as well as in one total synthesis by Martin *et al.* (discussed in Section 1.4.3.2.). Reports from Marko *et al.*[48,49] and Leonard *et al.*[50] also outlined the use of an intramolecular Diels-Alder reaction and are not discussed. Pandit and co-workers have made considerable contributions to the field and their synthetic efforts are outlined in Scheme 5.[51–55]

Pandit *et al.* were the first group to coin the term "the heart" of manzamine A which referred to rings ABC; their synthetic efforts were directed towards forming these three rings (Scheme 5). An intramolecular Diels-Alder route was chosen based on the biomimetic pathway and introduced the desired substitution pattern.

Thiol-ester **47** was synthesised in ten steps from L-serine derivative **46**. One interesting reaction that was developed was a Ag(I) catalysed rearrangement of **47**: the tertiary amine attacked a silver-activated electrophilic thiol-ester carbon which generated putative bicyclic intermediate **48**, presumably *via* formation of a ketene. Elimination and subsequent fragmentation gave Diels-Alder precursor **49**. The intramolecular Diels-Alder reaction then proceeded with the electron rich diene and electron poor dienophile. Two diastereomeric products were formed in a 3.5:1 ratio in 90% combined yield. Transition state **53** was postulated to be disfavoured due to the steric hindrance between highlighted atoms

(Scheme 5) and therefore transition state **52** led to the preferred and required diastereomer **50** for manzamine A in 67% yield.[51]



Scheme 5: Pandit's synthesis of the core of manzamine A. **(a)** DIPA, AgOTf, MeCN, RT, 18 h, 67%; **(b)** xylene, N_2, 130 ˚C, 4 h, 90%, 3.5:1 **50**:**51**; **(c)** 10 mol% **56**, benzene-d_6, RT, 5 d, 30%.

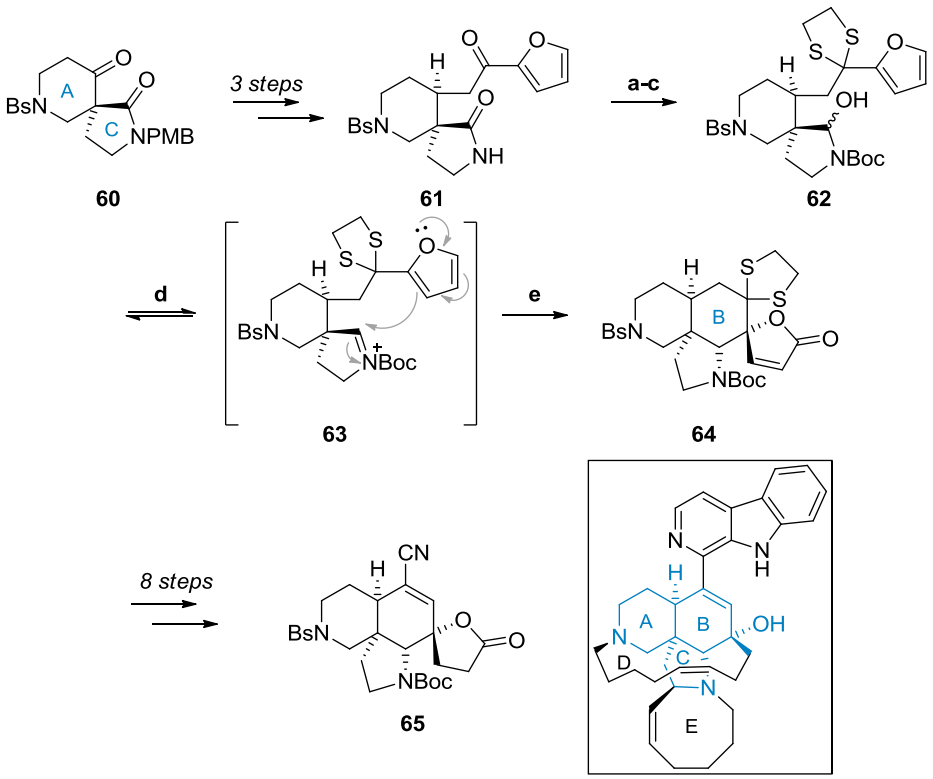
On related system **54**, seven steps were required to form ring-closing metathesis precursor **55**. On exposure to Grubbs' second generation catalyst **56**, tetracycle **57** was formed in 30% yield and this was the first report of metathesis being used to form ring D.[52] Pandit also reported that the β-carboline could be introduced from an ester moiety on the ABCE ring system but no yields or conditions were given.[53] A further paper reported the synthesis of

pentacycle **59** (Scheme 5), accessed in six steps from pentacycle **58**, using a more advanced system and similar chemistry that was used to form tetracyclic core **57**.[54] The -OTBDPS group was removed and the subsequent alcohol was converted to a terminal two-carbon olefin *via* an oxidation and Wittig reaction. The hydroxyl functionality was liberated *via* basic hydrolysis of the cyclic carbamate. Amidation of the pyrrolidine nitrogen using a six-carbon olefinic carboxylic acid gave the precursor to **59** and ring-closing metathesis was utilised to form ring E (**59**), but again no yields were reported.[54]

1.4.2.3 Intramolecular Mannich Ring-Closure

The use of an intramolecular Mannich ring-closing reaction has also been used to form the core of manzamine A. Both Nishida and Overman independently used this strategy, to introduce ring B and A respectively.[56] A modified approach to Nishida's work was employed by Dixon *et al*. in the total synthesis of manzamine alkaloids.[11,16]

Nishida *et al.* set out to use a furan-iminium cation cyclisation to construct the ABC ring system of manzamine A (Scheme 6).[57] This transformation has been applied to other total syntheses of manzamine alkaloids, notably towards the synthesis of nakadomarin A carried out firstly by Nishida followed by Dixon and co-workers.[15,17] Three steps were required to synthesise furyl derivative **61** from spirocycle **60**. *N*-Boc protection of amide **61** followed by Lewis acid promoted partial reduction of the pyrrolidinone carbonyl gave aminol **62**. On exposure to acidic conditions, elimination of water occurred to give iminium **63**. Nucleophilic attack by the furan onto the iminium ion proceeded and impressive diastereoselectivity was observed; a single diastereoisomer **64** in 80% yield was achieved, whilst implementing two correct stereocentres in one step. The structure was confirmed by single crystal X-ray diffraction (Scheme 6).[57]



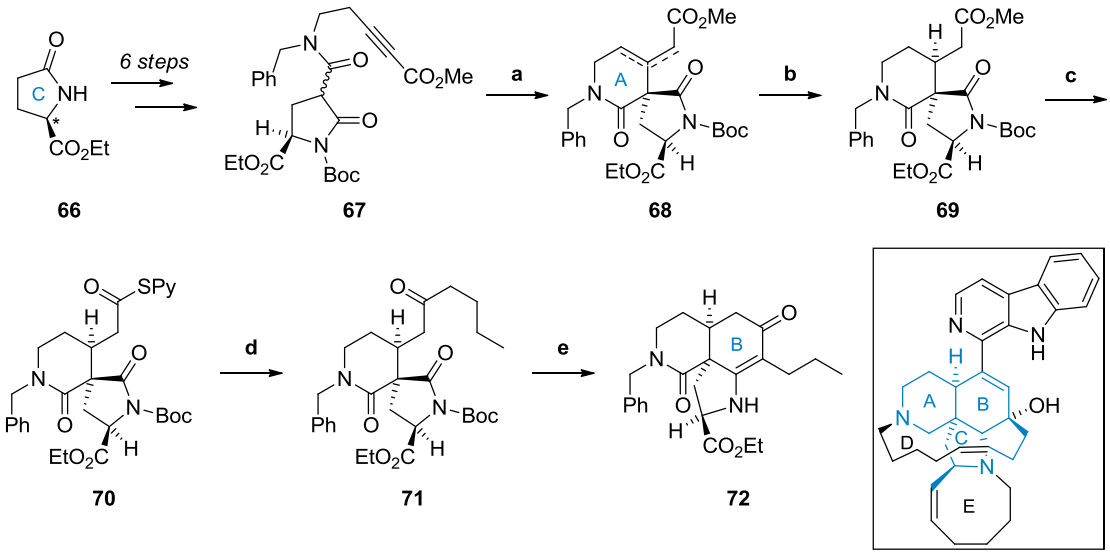
Scheme 6: Nishida's synthesis of the tricyclic core of manzamine A. **(a)** $HSCH_2CH_2SH$, $BF_3.OEt_2$, RT, 24 h, 78%; **(b)** Boc_2O, Et_3N, DMAP, THF, RT, 6 h, 82%; **(c)** $LiBEt_3H$, THF, −78 ˚C to 0 ˚C, 5 h, 78%; **(d)** *p*TsOH•H_2O, acetone-H_2O, RT, 96 h; **(e)** IBX, DMSO, 50 ˚C, 6 h, 60% over two steps.

1.4.2.4 Intramolecular Michael Addition

An intramolecular Michael addition has been used by both Brands and Furstner to form the ABC and ACE tricyclic cores respectively.[58,59] Brands and DiMichele opted to make the pyrrolo[*2,3-i*]isoquinoline ABC ring system by using an intramolecular Michael addition. The stereochemistry of the newly formed spirocyclic carbon was controlled by the inherent stereochemistry at C*; the ester moiety blocked the top face which led to the formation of a single diastereomer at the spirocyclic centre (Scheme 7, **68**).[58]

Michael addition precursor **67** was synthesised in six steps from commercially available pyroglutamic acid ester **66** using chemistry similar to that presented in Chapter 2 of this thesis. On exposure of pro-nucleophile **67** to diisopropylethylamine in acetonitrile, the Michael addition occurred affording a mixture of three products in a ratio of 2.7:2.2:1.0 which were not fully assigned but were tentatively suggested to be *E*-α,β, *Z*-α,β and β,γ-

isomers of **68** respectively. However, under hydrogenation conditions, all three products were converted to single diastereomer **69** in 85% yield over the two steps (Scheme 7).

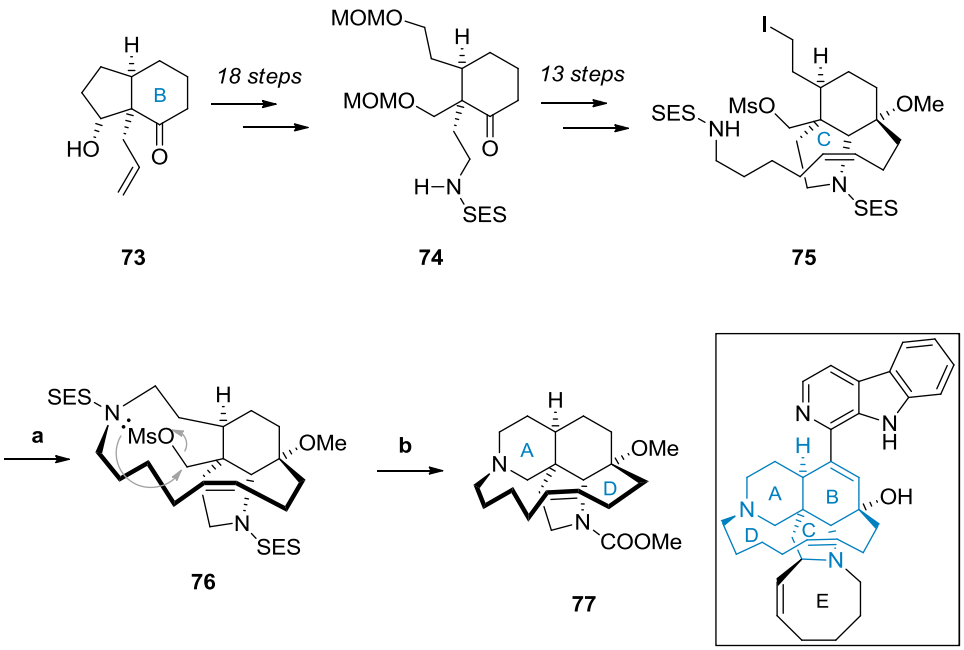


Scheme 7: Brands' synthesis to the tricyclic core of manzamine A. **(a)** DIPEA, MeCN; **(b)** H_2, Pd/C, MeOH, 85% over two steps, no further details given; **(c) (i)** LiOH, THF/H_2O **(ii)** PySSPy, Ph_3P, MeCN, 69% over two steps, no further details given; **(d)** BuMgBr, THF, 71%, no further details given; **(e) (i)** KO*t*Bu, THF **(ii)** TFA, CH_2Cl_2, 60% from **71**, no further details given.

After successfully implementing two rings of manzamine A, the synthesis of ring B was attempted. Hydrolysis of ester **69** followed by introduction of the butyl chain *via* a Grignard addition into pyridyl thiol-ester **70** gave cyclisation precursor **71**. A Dieckmann-type cyclisation was performed; exposure of **71** to basic conditions and subsequent treatment with trifluoroacetic acid gave amine **72** in 60% overall yield (Scheme 7). This chemistry was not pursued further by these authors.

1.4.2.5 Intramolecular Substitution

Yamamura *et al.* took a different approach and used multiple intramolecular S_N2 reactions to synthesise the tetracyclic ABCD core **77** (Scheme 8).[60] The synthesis is long and only ring-closing reactions are highlighted. Bicycle **73** was accessed in two steps from cyclohexenone which was converted to MOM-protected alcohol **74** in eighteen steps. A further thirteen steps gave bicycle **75**; ring C was synthesised *via* an acid-mediated cyclisation of the secondary amine onto the ketone.

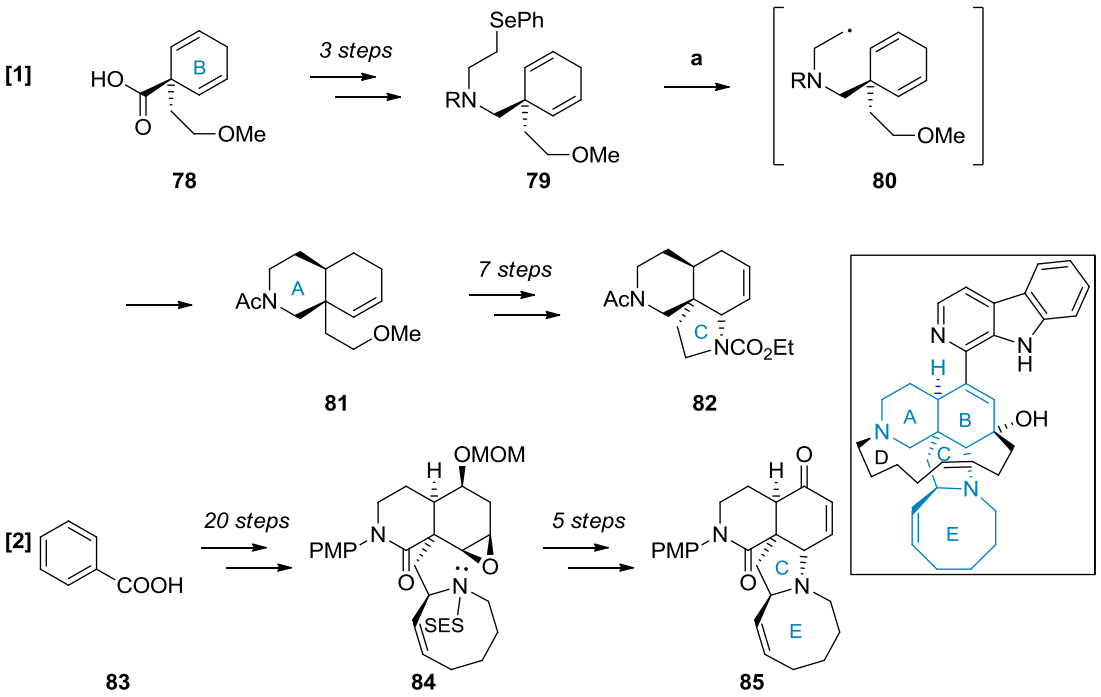


Scheme 8: Yamamura's synthesis of the tetracyclic core of manzamine A. **(a)** Cs_2CO_3, DMF, 60 °C, 30 h, 82%; **(b) (i)** TBAF, THF, reflux, 4.5 h **(ii)** $ClCO_2Me$, Et_3N, CH_2Cl_2, −50 ˚C to RT, 16 h, 57% in 2 steps. SES = 2-trimethylsilylethanesulfonyl.

Macrocyclisation using Cs_2CO_3 gave **76** in 82% yield. Removal of the silyl protecting group and subsequent double cyclisation gave rings A and D (**77**) in a single step. Concomitant protection of the pyrrolidine nitrogen (ring C) was also carried out but no reason was given for choice of protecting group. No further work has yet been published using this route.

1.4.2.6 Miscellaneous

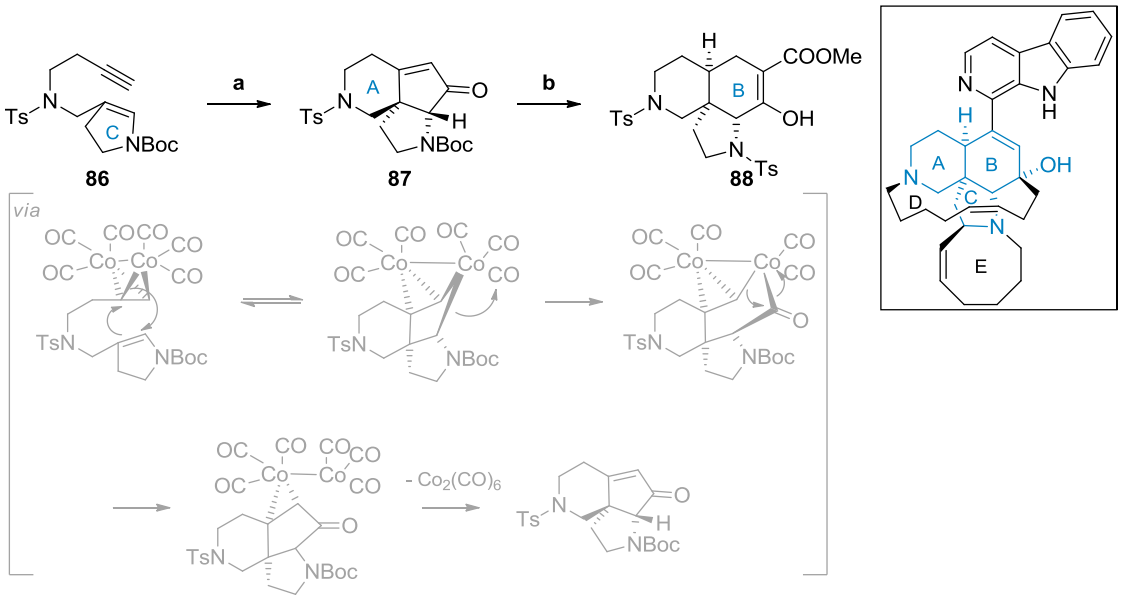
Hart *et al*. were the first group to report a synthetic route of the core of manzamine A. In 1989, they used a *6-exo-trig* radical cyclisation to access hydroisoquinoline skeleton **81** (rings A and B) (Scheme 9, **[1]**). After functional group interconversion, an electrophile-initiated ring closing sequence was performed which, after subsequent elimination, gave tricycle **82** in 62% yield.



Scheme 9: Two syntheses of the core of manzamine A by Hart. **(a)** nBu$_3$SnH, AIBN, benzene, heat, 54%. R = Ac.

In 1992, Hart reported the synthesis of the tetracyclic core of manzamine A which used a different route and started from benzoic acid **83**. Ring C was formed *via* an intramolecular nucleophilic epoxide-opening reaction by the nitrogen of the azocine ring **84** to eventually give the ABCE core of manzamine A, **85** (Scheme 9, **[2]**). No further work has been published on this highly advanced core.

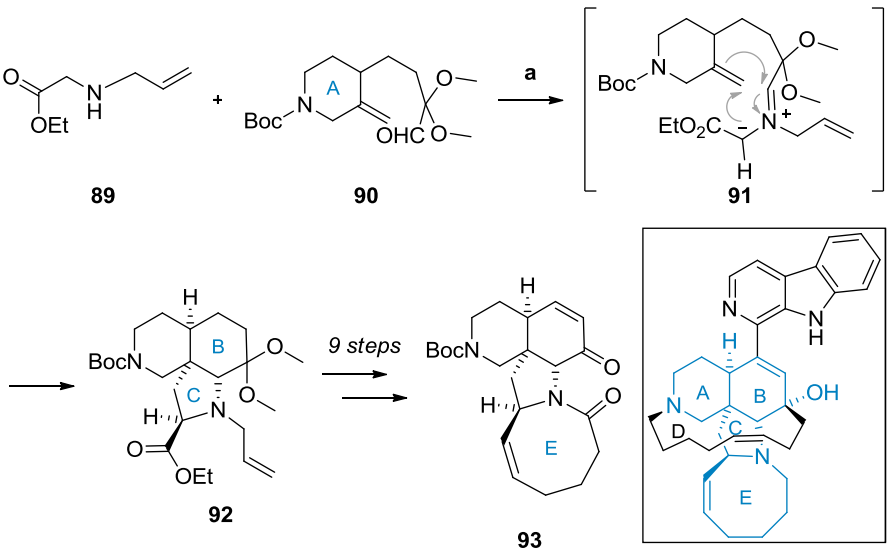
Magnus *et al.* took a different approach altogether, and used a Pauson-Khand reaction with an enamide or enamine followed by a ring expansion to give rings ABC (Scheme 10).[61] Enamide **86** was accessed in five steps from *N*-Boc pyrrolidinone in an average 44% yield. Extensive optimisation for the Pauson-Khand reaction was carried out. It was found that using Sugihara conditions,[62] a modified Pauson-Khand reaction that utilises alkyl methyl sulfides, the desired tricycle **87** was isolated in 53% yield and introduced two stereocentres including one quaternary centre. Magnus *et al.* were the first people to use an enamide as the alkene reaction partner for a Pauson-Khand reaction.



Scheme 10: Magnus' synthesis to the tricyclic core of manzamine A. **(a)** $Co_2(CO)_8$, DCE, *n*BuSMe, 83 ˚C, 63–69%; **(b) (i)** 10% Pd/C, H_2, EtOAc, 63% **(ii)** TFA, CH_2Cl_2 **(iii)** TsCl, pyridine **(iv)** EtO_2CCHN_2, BF_3•OEt_2, CH_2Cl_2, 53%. No further details given.

After the successful Pauson-Khand reaction, [6,5,5] tricycle **87** was converted to [6,6,5] tricycle **88**. Reduction followed by ring expansion *via* Lewis acid activation and the use of ethyl diazoacetate gave **88** in 53% yield and the stereochemistry was confirmed by single crystal X-ray diffraction.

Coldham *et al.* also set out to form the ABC rings of manzamine A, using a [3+2] azomethine ylide intermolecular cycloaddition reaction (Scheme 11).[63]

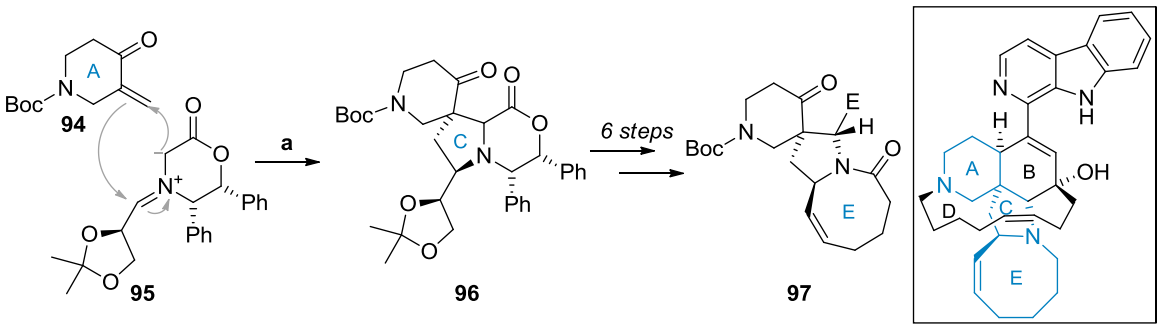


Scheme 11: Coldham's synthesis to the tetracyclic core of manzamine A. **(a)** toluene, reflux, 16 h, 43%.

Aldehyde **90** was accessed in ten steps from commercially available arecoline and was poised to perform the [3+2] cycloaddition reaction. A condensation with amino-ester **89** and aldehyde **90** gave the iminium ion intermediate **91**. Coldham *et al.* found that the subsequent intramolecular cycloaddition yielded a single diastereomeric product **92**. The stereochemistry of **92** was determined unambiguously by single crystal X-ray diffraction on the dithiane derivative.[64]

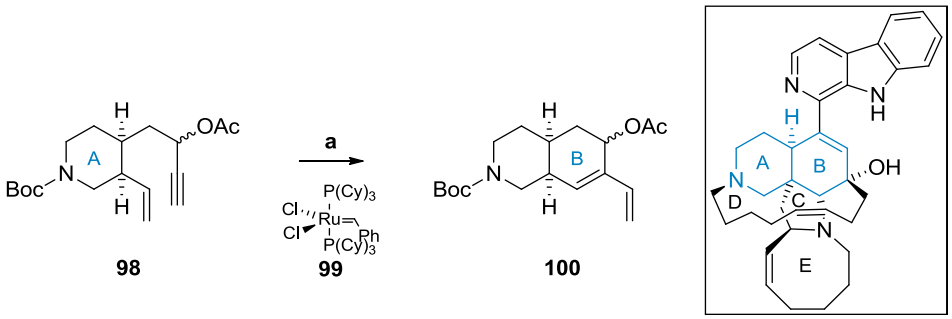
In 2005, Coldham published a third paper outlining a route to tetracyclic core **93** (Scheme 11).[65] Nine steps were required from cycloaddition product **92**; proto-deallylation followed by *N*-acylation and some functional group manipulation of ester **92** gave the tetracycle precursor with two terminal double bonds in place. A ring-closing metathesis was performed using 15 mol% Grubbs' second generation catalyst which gave tetracycle **93** in 75% yield. No *Z*:*E* ratio was given, although postulated isomeric products were observed by ^{1}H NMR spectroscopy.

Williams *et al.* performed an intermolecular [3+2] cycloaddition outlined in Scheme 12 to form the ACE ring system **97**. Ring-closing metathesis was employed to synthesise ring E.[66]



Scheme 12: Williams' synthesis to the tricyclic core of manzamine A. **(a)** 3Å molecular sieves, toluene, 50 ˚C, 35%.

Clark *et al.* used an enyne ring-closing metathesis to synthesise the AB ring system (Scheme 13). Eight steps were used to synthesise **98** from quinine. Grubbs' first generation catalyst **99** (10 mol%) was used in toluene and bicycle **100** was synthesised in 46% yield. No further work has been published.

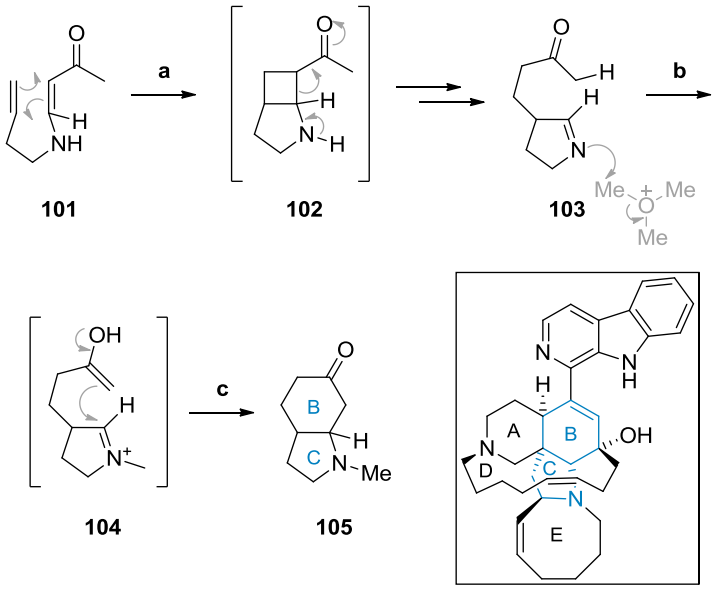


Scheme 13: Clark's synthesis of the bicyclic core of manzamine A. **(a)** 10 mol% **99**, toluene, CH_2Cl_2, 46% yield. No other conditions given.

1.4.3 Total Syntheses of Manzamine A

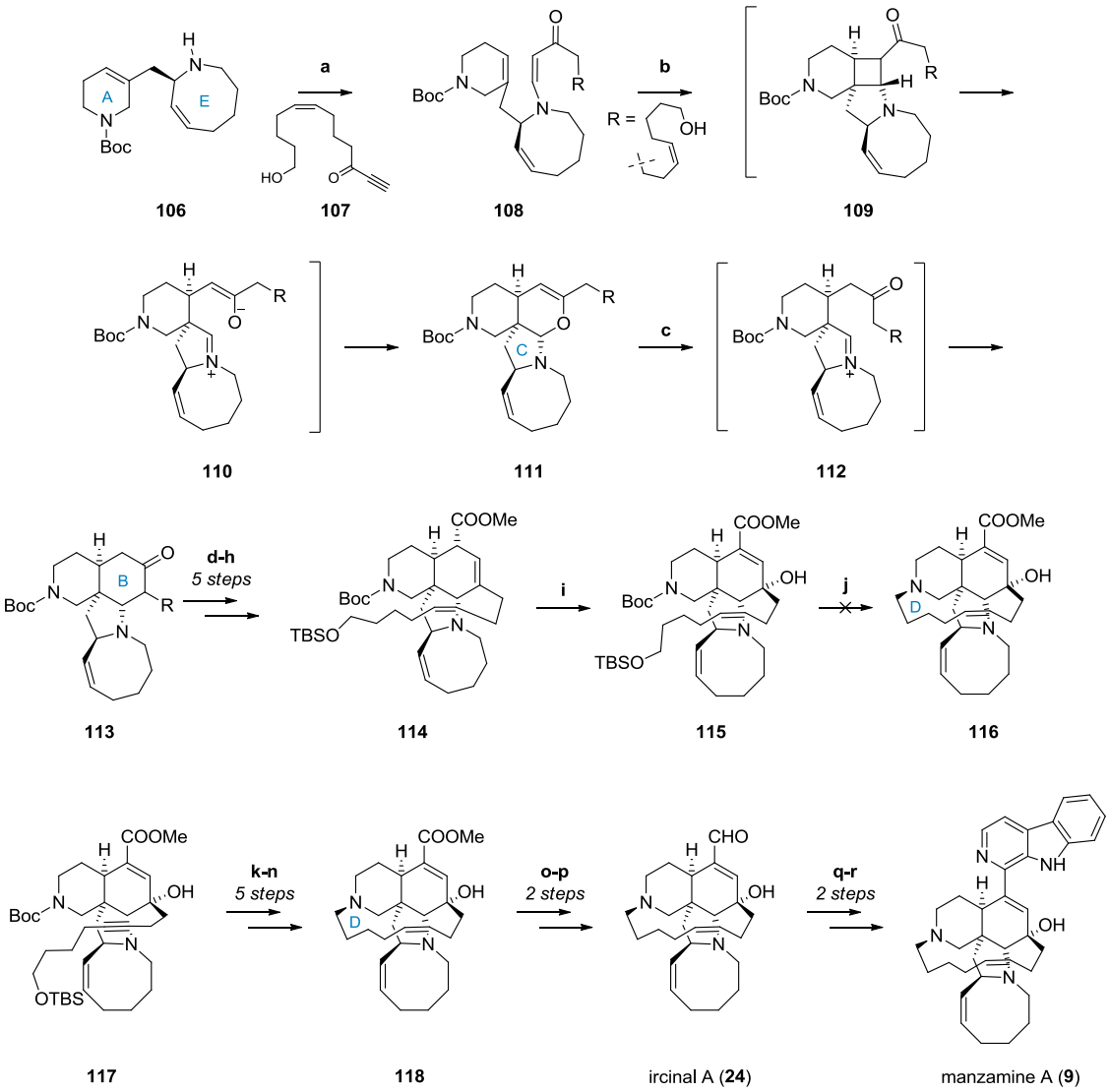
1.4.3.1 Winkler and Co-Workers' Total Synthesis of Manzamine A

Winkler *et al.* were the first group to report the total synthesis of manzamine A and related alkaloids ircinal A, ircinol A and manzamine D.[8] They had previously developed an intramolecular vinylogous amide photoaddition/fragmentation/Mannich closure sequence (Scheme 14).[67,68]



Scheme 14: Winkler's initial methodology towards manzamine A. **(a)** hυ; **(b)** $[Me_3O^+][^-BF_4]$, DCM; **(c)** 15% aqueous HCl, 50% over three steps. No further details given including stereochemistry.

Winkler observed that by exposing vinylogous amides such as **101** to light, the photoaddition and retro-Mannich fragmentation product keto-imine **103** was formed presumably *via* the formation of amine **102**. Subsequent exposure of **103** to trimethyloxonium tetrafluoroborate in dichloromethane followed by acidic treatment gave the photocycloaddition-retro-Mannich-Mannich product **105** in 50% yield.[67] This methodology was then used to synthesise the tetracyclic core **113**[69] using substrates suitably functionalised for manzamine A. This was shortly followed by the publication of the first total synthesis (Scheme 15).[8]



Scheme 15: Winkler's total synthesis of manzamine A. **(a)** (7*Z*)-12-hydroxydodec-7-en-1-yn-3-one **107**, CH_2Cl_2, 0 ˚C to RT, 4 h, 99%; **(b)** hυ, Et_2O, argon, 15 ˚C, 6 h; **(c)** pyridine, AcOH, MeCN, reflux, 4 h, 20% over four steps; **(d)** TBSCl, imidazole, CH_2Cl_2, 0 ˚C, 1 h, 87%; **(e)** LHMDS, HMPA, THF, then MeOCOCN, −78 ˚C, 1 h, 90%; **(f)** $NaBH_4$, MeOH, 0 ˚C, 1 h, 93%; **(g)** MsCl, Et_3N, CH_2Cl_2, 0 ˚C, 30 min, 95%; **(h)** DBU, benzene, reflux, 12 h, 30%; **(i) (i)** *m*CPBA, $NaHCO_3$ (solid), CH_2Cl_2, 0 ˚C to 15 ˚C, 3 h **(ii)** NaOMe, MeOH, RT, 4 h, 69% over two steps; **(j) (i)** TBAF, THF, RT, 3 h, 94%; **(ii)** TsCl, Et_3N, CH_2Cl_2, RT, 24 h, 96%; **(iii)** TFA, CH_2Cl_2, no temp. given, 1 h, 100% **(iv)** $(i\text{-Pr})_2NEt$, MeCN, reflux, 20 h, 12%; **(k)** TBAF, THF, RT, 3 h, 94%; **(l)** TsCl, Et_3N, CH_2Cl_2, RT, 24 h, 96%; **(m)** TFA, CH_2Cl_2, no temp. given, 1 h then $(i\text{-Pr})_2NEt$, MeCN, reflux, 20 h, 89%; **(n)** 5% $Pd/CaCO_3$/Pb (Lindlar catalyst), quinoline, MeOH, H_2, 4 h, no temp. given, 94%; **(o)** DIBAL, CH_2Cl_2, −78 ˚C to −50 ˚C, 2 h, 83%; **(p)** Dess-Martin periodinane, CH_2Cl_2, 0 ˚C, 15 min, 90%; **(q)** tryptamine, TFA, $CHCl_3$, 4Å molecular sieves, 18 h, no temp. given, 58%; **(r)** DDQ, benzene, 1 h, no temp. given, 50%.

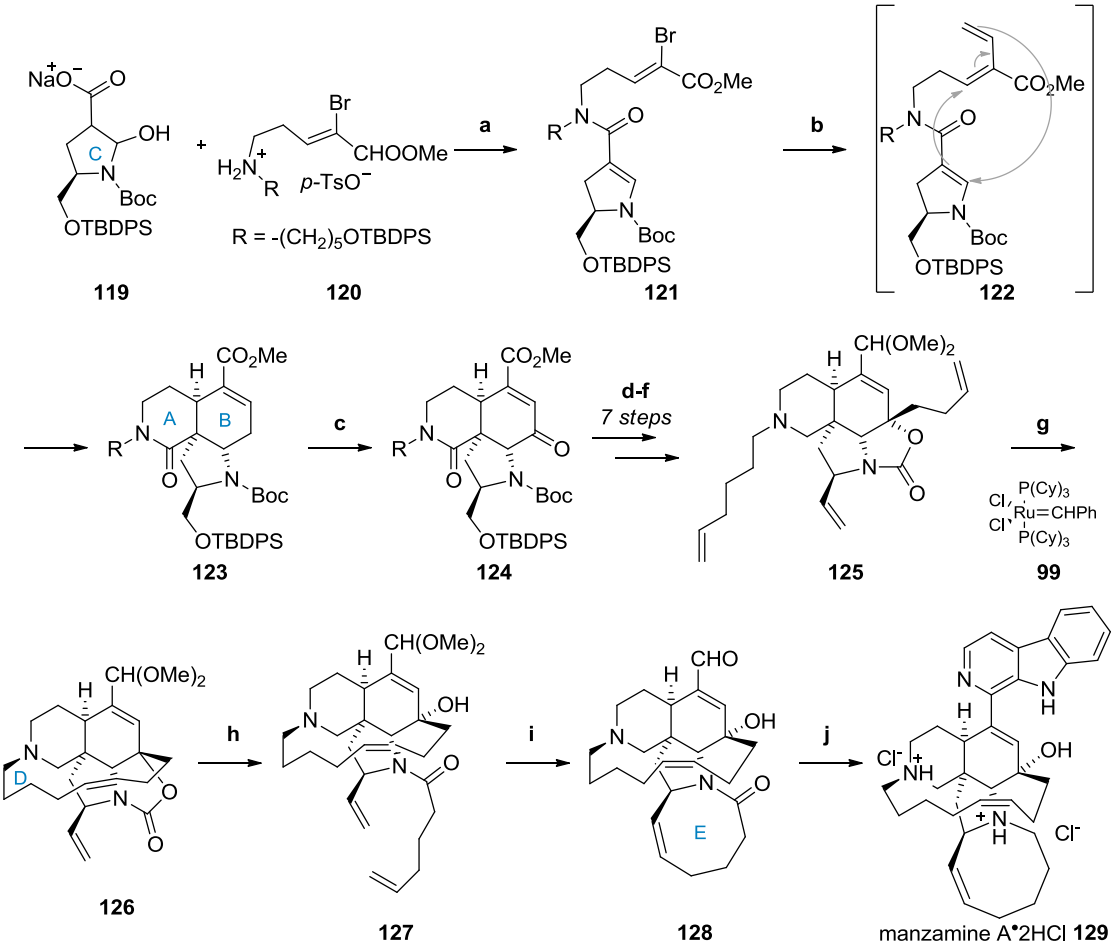
Azocine **106** was prepared in fourteen steps from commercially available pyridine-3-methanol. As Kobayashi had previously shown that manzamine A was readily accessible in two steps from ircinal A (**24**),[34] Winkler *et al.* directed their synthetic efforts towards **24**. Intramolecular [2+2] photoaddition/fragmentation/Mannich precursor **108** was synthesised in one step from azocine **106** and alkyne **107** in 99% yield. The cascade reaction proceeded in 20% yield over four steps from vinylogous amide **108** to tetracyclic core **113**. Winkler and

co-workers were the first to suggest that the stereochemistry of manzamine A could be controlled by the one stereocentre on the 8-membered ring E, a feature our group has exploited.[12,70]

Ester **115** was a key intermediate for Winkler and was accessed through elaboration of ring B. TBS-protection of the hydroxy group was followed by the use of Mander's reagent[45] which introduced the ester in a similar manner to Nakagawa *et al.*. Reduction of the ketone followed by activation and elimination gave β,γ-unsaturated ester **114** in 21% overall yield over five steps. In the presence of DBU at reflux, the carbon-carbon double bond (originally in the α,β-position) became deconjugated (β,γ-position) due to unfavourable steric interactions with the fused [6,6]-ring system. Subjection of ester **114** to *m*CPBA gave the epoxide intermediate (no diastereomeric ratio given) which under basic conditions eliminated to form hydroxy-ester **115** in 69% yield over two steps. Closure of macrocyclic ring D (**116**) proved difficult and after a disappointing 12% initial yield when **115** and Hünig's base were used, the acetylenic substrate **117** was successfully employed. This was followed by a Lindlar reduction which gave ircinal A precursor **118** in 75% over five steps. DIBAL reduction gave ircinol A in 83% yield which was subsequently oxidised to give ircinal A (**24**) in 90% yield. The group were now set up for the end game and the now often used method to complete the total synthesis of manzamine A was tested for the first time. Exposure of ircinal A to tryptamine under acidic conditions, followed by DDQ oxidation completed the first total synthesis of manzamine A in thirty-one steps (longest linear sequence from commerically available starting materials).

1.4.3.2 *Martin and Co-Workers' Total Synthesis of Manzamine A*

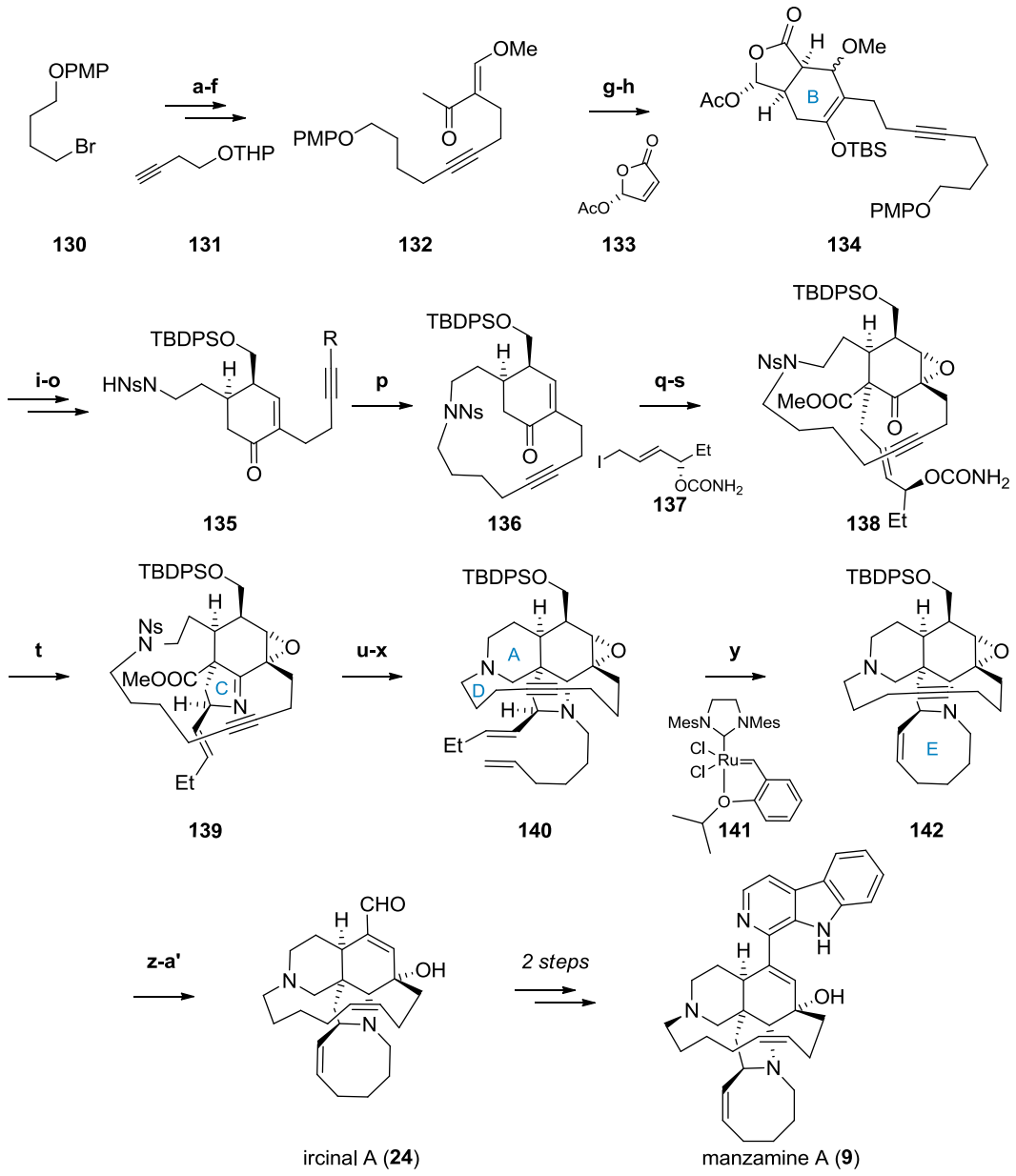
Martin *et al*. published their route outlining the formal synthesis of manzamine A in 1999,[9] and was followed by the total synthesis in 2002 (Scheme 16).[10] Their synthesis was based on a previously reported intramolecular Stille/Diels-Alder reaction which was utilised to form the ABCE tetracyclic core.[71] Accordingly, chiral dienophilic precursor **119** was synthesised in five steps from commercially available pyroglutamol. Tosylate salt **120** was synthesised from 1-amino-5-hydroxypentane in five steps and 53% overall yield. The two compounds **119** and **120** were stored as salts for stability reasons.



Scheme 16: Martin's total synthesis of manzamine A. **(a)** $(COCl)_2$, then **120**, Et_3N, 79%, no further details given; **(b)** tributyl(vinyl)stannane, 4 mol% $Pd(Ph_3P)_4$, toluene, reflux, 30 h, 68%; **(c)** CrO_3, 3,5-$Me_2C_3H_2N_2$, 63%, no further details given; **(d) (i)** HCl, MeOH **(ii)** DMSO, $(COCl)_2$, Et_3N **(iii)** $Ph_3P{=}CH_2$, −78 to 0 °C, 47% over three steps, no further details given; **(e) (i)** Excess DIBAL **(ii)** Dess-Martin periodinane, 53% over two steps, no further details given; **(f) (i)** MeOH, $HC(OMe)_3$, HCl **(ii)** $CH_2{=}CHCH_2CH_2Li$, –78 to –20 °C, 15 min, 55% over two steps; **(g)** 10 mol% **99**, CH_2Cl_2, reflux, 5 h, 75%, 67:8 *cis*:*trans*; **(h) (i)** 40% soln. KOH in MeOH, 75 ˚C, 30 min **(ii)** hex-5-enoyl chloride, 2,6-lutidine, toluene, no temp. given, 75% over two steps; **(i)** 100 mol% **99**, benzene, reflux, 30 min, then 1 M HCl, 2 min, 26%; **(j) (i)** DIBAL, CH_2Cl_2, −78 ˚C (15 min) to 0 ˚C (20 min) to RT (1 h), 63% **(ii)** Dess-Martin periodinane, CH_2Cl_2, 0 ˚C to RT, 40 min, 89% **(iii)** tryptamine, TFA, 4Å molecular sieves, CH_2Cl_2, RT, 13 h **(iv)** DDQ, $CHCl_3$, EtOH, RT, 45 min, then HCl, 52% over two steps. R = -$(CH_2)_5$OTBDPS.

The key Stille-Diels-Alder reaction precursor **121** was synthesised by a coupling reaction in 79% yield. On exposure to tributyl(vinyl)stannane and catalytic Pd(0), vinyl-bromide **121** underwent a Stille cross-coupling reaction to form diene **122** which underwent a spontaneous Diels-Alder cyclisation to form tricycle **123** in 68% overall yield. Once again, it was found that the stereocentre on ring C was key for controlling the stereochemistry in tricycle **123** and only a single diastereomer was observed. Subsequent allylic oxidation using modified Salmond conditions (20 eq of CrO_3 and 30 eq of 3,5-dimethylpyrazole) gave intermediate **124** in 63% yield.[72] Seven steps were then required to access ring-closing metathesis precursor acetal **125**. A Wittig reaction and stereoselective addition of an alkyl chain possessing a terminal olefin were used to introduce the two terminal double bonds required for the ring-closing metathesis. Ring D (**126**) was formed using 10 mol% Grubbs' first generation catalyst in 67% yield with 8% of the undesired *trans* isomer observed. Hydrolysis of the cyclic carbamate followed by *N*-acylation gave amide **127** and the stereochemistry of the structure was confirmed by single crystal X-ray diffraction. The ring-closing metathesis to form ring E was problematic: Martin had to use stoichiometric Grubbs' first generation catalyst to form ring E which gave the ABCDE pentacyclic core. Subsequent hydrolysis of the acetal gave amide **128** in 26% yield over two steps.[9] The total synthesis was not published until three years later; complete reduction of the amide and aldehyde before re-oxidation gave ircinal A (**24**) in 56% yield over two steps before conversion to the manzamine A dihydrochloride salt **129**, a stable derivative of manzamine A was performed in 52% yield.[10] In a similar fashion to Winkler, an elegant key step was employed to introduce three stereocentres and two rings in a single step. Martin also demonstrated the possibility of using ring-closing metathesis as well as other transformations in highly functionalised molecules that could be employed in our synthesis of manzamine A.

1.4.3.3 Fukuyama and Co-Workers' Total Synthesis of Manzamine A



Scheme 17: Fukuyama's total synthesis of manzamine A. **(a) 131**, *n*BuLi, TMEDA, nBu$_4$N$^+$I$^-$, THF:HMPA, −78˚C to RT, 4 h, 91%; **(b)** CSA, MeOH, RT, 1 h, 93%; **(c)** I_2, PPh_3, imidazole, MeCN:Et_2O, 0 °C to RT, 2 h, 97%; **(d)** methyl acetoacetate, NaH, THF, reflux, 18 h, 86%; **(e)** $LiAlH_4$, THF, RT, 18 h, 91%; **(f) (i)** Dess-Martin periodinane, *t*BuOH, CH_2Cl_2, RT, 3 h **(ii)** *p*TsOH•H_2O, Na_2SO_4, MeOH, RT, 1 h, 66% over two steps; **(g)** TBSOTf, Et_3N, Et_2O, 0 °C, 30 min; **(h) 133**, NaOAc, toluene, 3Å molecular sieves, reflux, 2 h, 97% over two steps (endo/exo = 2:1); **(i) (i)** Et_3N, MeOH, RT, 1 h, evaporation **(ii)** $MeOCH_2PPh_3Cl$, KHMDS, THF, −78 to 0 °C, 2 h **(iii)** MeI, *i*Pr_2NEt, DMF, 0 °C, 2 h, 89% (*E*/*Z* 1:1 for endo, 1:4 for exo); **(j)** $LiAlH_4$, Et_2O, 0 °C, 1 h, 99%; **(k)** TBDPSCl, imidazole, CH_2Cl_2, RT, 3 h, 99%; **(l)** *p*TsOH•H_2O, acetone, RT, 3 h, 97%; **(m)** $NaBH(OAc)_3$, AcOH, benzene, 40 °C, 8 h, 88%; **(n)** NsNHBoc, DEAD, PPh_3, benzene, RT, 30 min, 97%; **(o) (i)** TFA, RT, 30 min, evaporation **(ii)** CAN, MeCN:H_2O, 0 °C, 5 min, 81%; **(p)** DEAD, PPh_3, toluene, RT, 10 min, 85%; **(q)** LHMDS, THF, −78 °C, 40 min then $NCCO_2Me$, −78 °C to RT; **(r) 137**, K_3PO_4, DMF, RT, 5 h, 69% over two steps; **(s)** TBHP, Triton B, MeCN:benzene, RT, 12 h, 62%; **(t) (i)** TFAA, Et_3N, CH_2Cl_2, 0 °C, 5 min, evaporation **(ii)** AcOH, $Mg(ClO_4)_2$, benzene, 40 °C, 30 min; **(u) (i)** $NaBH(OCOCF_3)_3$, THF, RT **(ii)** TFA **(iii)** 5-hexenoylchloride, Et_3N, 0 °C, 2.5 h, 80% over five steps; **(v)** $LiAlH_4$, $AlCl_3$, Et_2O, −20 to −10 °C, 2 h, 93%; **(w)** IBX, *t*BuOH, 70 °C, 1 h; **(x) (i)** PhSH, Cs_2CO_3, MeCN, 50 °C, 30 min **(ii)** $NaBH(OCOCF_3)_3$, THF, RT, 3 h, 89% over three steps; **(y)** 100 mol% **141**, *p*-$MeOC_6H_4$-OH,CH_2Cl_2, RT, 3 h, 41%; **(z) (i)** TBAF, THF, 50 °C, 1 h, evaporation **(ii)** H_2, Lindlar catalyst, quinoline, MeOH, RT, 2 h, 84%; **(a')** Dess-Martin periodinane, CH_2Cl_2, RT, 30 min, 87%. R = -$(CH_2)_4OH$.

Fukuyama *et al.* published their route in 2010 and is the longest synthesis; thirty six steps compared to thirty-one by Winkler and twenty-four by Martin.[11] Only ring-forming reactions will be discussed in detail although all reagents and conditions are outlined in Scheme 17.

Methoxy vinyl ketone **132** was synthesised in seven steps from PMP-protected alcohol **130**. TBS-protection of ketone **132** induced a rearrangement to a moisture sensitive diene which subsequently underwent an intermolecular Diels-Alder reaction with dienophile **133** to give bicycle **134**. Ten steps, mainly functional group manipulations, were then required to form *N*-nosyl cyclohexenone **135** for which the reagents and conditions are outlined in Scheme 17. An intramolecular Mitsunobu reaction was employed to form the strained 15-membered ring which would eventually become rings A and D, and the reaction proceeded in 85% yield without need for high dilution. Acylation following Mander's protocol,[73] followed by allylation with **137** (made in six steps from known compounds in >99% ee) and epoxidation with TBHP and Triton B gave epoxy-ketone **138** in 43% yield. Ring C proved difficult to form because imine **139** was susceptible to hydrolysis triggering irreversible lactamisation with the methyl ester. This was avoided by forming the isocyanate *via* a [3,3]-sigmatropic rearrangement and using anhydrous conditions, AcOH, $Mg(ClO_4)_2$, in benzene with molecular sieves, and the reaction proceeded to give bicycle **139** in 80% yield over five steps. Reduction of the imine and *N*-acylation introduced the six-carbon olefinic chain needed for ring E. The ring-closing metathesis to form ring E failed at this point, so ring A was constructed first. A reductive amination was employed; reduction of methyl ester to the alcohol and re-oxidation to the aldehyde[ii] followed by nosyl-deprotection allowed the reductive amination to proceed in 83% yield over four steps forming ring A (**140**). The same ring-closing metathesis that was a problem for Martin *et al.* caused similar issues for Fukuyama *et al.* who attributed the low yield to the presence of tertiary amines and the

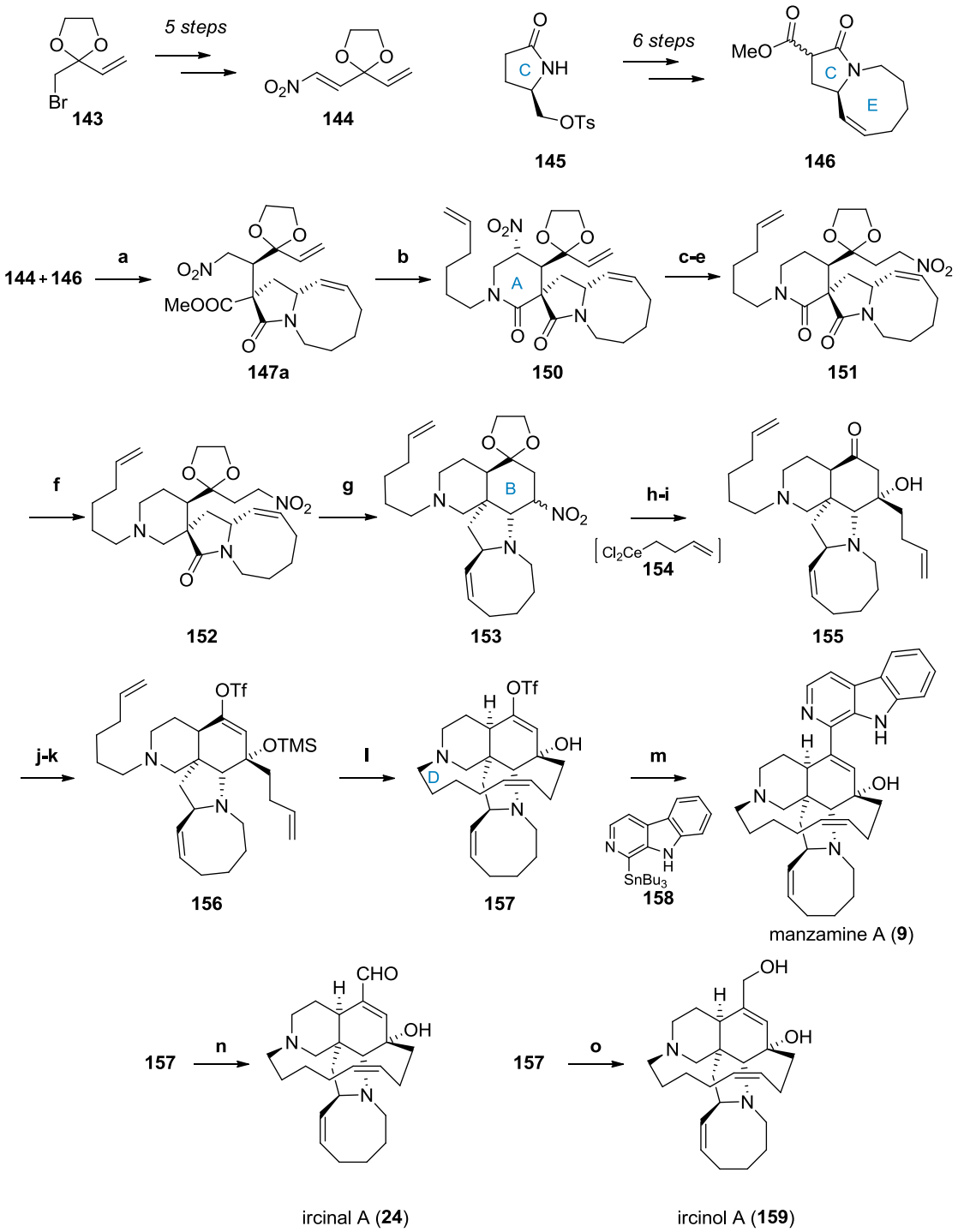
[ii] There is no mention of attempts to reduce the ester directly to the aldehyde.

alkyne. However, with stoichiometric Grubbs-Hoveyda second generation catalyst **141** and *para*-methoxyphenol, the reaction proceeded in 41% yield to form ring E (**142**). To finish, removal of the TBDPS- group, reduction of the alkyne to the *cis*-alkene and oxidation gave ircinal A (**24**) in 73% yield over three steps. Using literature conditions by Winkler[8] and Martin,[10] tryptamine was condensed with ircinal A which gave manzamine D. This was oxidised using DDQ to give manzamine A (**9**) in 75% yield over three steps.

1.4.3.4 Dixon and Co-Workers' Total Synthesis of Manzamine A

The three syntheses completed so far all have similar end games: the synthesis of ircinal A followed by introduction of the β-carboline system. The routes are also all quite long (>20 steps) with many protecting groups employed and step-wise reactions being carried out. Dixon *et al.* set out to decrease the step count and aimed to synthesise a common advanced key intermediate that could be transformed into the three natural products seen so far as well as other manzamine A analogues with potentially interesting biological activities. The route was based on their previously successful route to related alkaloid, nakadomarin A.[17] This route is also the basis for the third generation synthesis in this thesis.

Nitro-olefin **144** was synthesised in five steps from bromo-acetal **143** (Scheme 18). The 8,5-bicycle **146** was synthesised from tosylated pyroglutamol **145** and possessed two rings of manzamine A. The synthesis of ester **146** will be discussed in further detail in Chapter 2. One interesting point is the synthesis of the *cis*-double bond. Instead of using a ring-closing metathesis which was found to be very low yielding in previous syntheses, an intramolecular Julia-Kocienski reaction was employed. Only the *cis*-double bond was observed and it was the first use of such a reaction in a total synthesis.



Scheme 18: Dixon's total synthesis of manzamine A, ircinal A and ircinol A. **(a)** KHMDS, 18-crown-6, −94 °C, THF, 1 h, **147a** 65%, **147b** 21%; **(b)** CH_2=O (**148**), hex-5-en-1-amine (**149**), MeOH, reflux, 10 h, 88%; **(c)** AIBN, Bu_3SnH, toluene, reflux, 30 min, 77%; **(d)** TMSCl, KI, 4Å molecular sieves, MeCN, RT, 50 min, 81%; **(e)** $AgNO_2$, Et_2O, RT, 48 h, 63%; **(f)** DIBAL, toluene, −78 to −20 °C, 1 h, 74% of **152** (dr 83:17), 7% of **153**; **(g)** $Ti(OiPr)_4$, Ph_2SiH_2, hexane, 0 °C, 2 h, 81% (dr 83:17); **(h)** $TiCl_3$, THF, water, RT, 5 h, 56% of ketone, 21% of oxime; **(i)** 3-butenylmagnesium bromide, THF, $CeCl_3$, 0 °C, 30 min, then HCl, 40 h, RT, 91%; **(j)** TMSOTf, Et_3N, Et_2O, RT, 30 min, 72%; **(k)** Comins' reagent, KHMDS, THF, −78 °C, 20 min, 90%; **(l)** 20 mol% Grubbs' 1st generation catalyst, CH_2Cl_2, reflux, 3 h, 73%, 70:30 *Z*/*E*; **(m)** **158**, 12 mol% $Pd(PPh_3)_4$, DMF, 60 °C, 1 h, 52%; **(n)** 10 mol% $Pd(PPh_3)_4$, CO, LiCl, Bu_3SnH, toluene, 50 °C, 30 min, 58%; **(o)** **(i)** 18 mol% $Pd(OAc)_2$, 40 mol% PPh_3, CO, Et_3N, MeOH, DMF, 60 °C, 1 h, 78% **(ii)** DIBAL, toluene, –78 °C, 2 h, 82%.

A diastereoselective Michael addition between nitro-olefin **144** and bicycle **146** proceeded in 86% yield, dr 3:1. A minor isomer **147b** was isolated but no stereochemical information was deduced. However, single crystal X-ray diffraction determined the relative configuration of desired Michael addition product **147a**. A nitro-Mannich lactamisation cascade was employed to synthesise ring A (**150**); *p*-formaldehyde (**148**) and hex-5-en-1-amine (**149**) formed an imine ($pKa_H \approx 11$) which was basic enough to deprotonate the α-nitro carbon (pKa ≈ 10) initiating an irreversible lactamisation. Three steps were required to form nitro-acetal **151**; radical initiated proto-denitration followed by anti-Markovnikov addition of HI across the double bond and S_N2 displacement with $AgNO_2$ (40% yield over three steps). A chemoselective reduction of the piperidinone in the presence of the pyrrolidinone proceeded in 74% yield (**152**) and this remarkable reactivity difference is discussed further in Chapter 4. Small amounts (7% yield) of tetracycle **153** were also isolated, however synthesis of ring B proceeded using conditions introduced by Buchwald.[74] $Ti(OiPr)_4$ and Ph_2SiH_2 were used to partially reduce the pyrrolidinone to the aminol *via* a single hydride delivery; subsequent cyclisation from the α-nitro carbon onto the iminium gave tetracycle **153** in 81% yield, dr 4:1, and was epimeric at the nitro carbon. This step was similar to the furan cyclisation reported by Nishida and co-workers.[57] A Nef reaction was required to convert the nitro group to a carbonyl, although caution was needed due to the acid-labile acetal group, the retro-Mannich-prone skeleton and the oxidisable tertiary amine moieties. However, using McMurry conditions,[75] the desired transformation proceeded in 56% yield and 21% yield of the corresponding oxime was isolated. A stereoselective organometallic addition which used alkyl cerium reagent **154** proceeded in 91% yield to form alcohol **155**. It was found that for the ring-closing metathesis, the alcohol group needed to be protected. A TMS-group was used before carrying out a triflation of the ketone using Comins' reagent, which gave triflate **156** in 90% yield.[76] To form ring D, a ring-closing metathesis was used; 20 mol% Grubbs' first generation catalyst was employed and

gave pentacyclic triflate **157** was isolated in 73% yield as a 70:30 *Z*/*E* mixture separable by flash column chromatography. Triflate **157** was the desired key intermediate that could now be transformed into three natural products, manzamine A (**9**), ircinal A (**24**) and ircinol A (**159**). Manzamine A (**9**) was accessed *via* a Stille cross coupling with β-carboline **158** in 52% yield. Ircinal A (**24**) was synthesised *via* a reductive carbonylation in 58% yield. Methyl ircinate was synthesised *via* an alkoxycarbonylation which was readily reduced using DIBAL to form ircinol A (**159**) in 64% overall yield (Scheme 18).

1.5 Summary

From the previously reported efforts and successes, the main points to consider when attempting an improved synthesis of this natural product can be summarised:

1. Ring-closing metathesis is seemingly the best method to synthesise ring D, however, high amounts of catalyst (>10 mol%) are required and *Z*:*E* selectivity is poor with commercially available metathesis reagents. An intramolecular S_N2 reaction to form ring D is difficult.

2. Ring-closing metathesis is undesired to form ring E; low yields and poor *Z*:*E* selectivity is observed. A Wittig or intramolecular Julia-Kocienski reaction is the best method in terms of cost and selectivity.

3. The stereochemistry of the system can be controlled by the stereocentre at the CE fused ring junction.

4. Many of the total syntheses are long, and would be impractical to carry out to synthesise significant quantities of manzamine A. A protecting group free strategy involving many "one-pot" reactions should be aimed towards.

1.6 Objectives of this Thesis

The objective of this thesis was to investigate a novel and stereoselective route to marine alkaloid manzamine A, utilising existing chemistry whilst developing new chemistry to complete the total synthesis. A novel palladium-catalysed arylative allene spirocyclisation cascade reaction would be applied as our key step to implement two stereocentres and two new carbon-carbon bonds. This thesis aims to present a route to manzamine A that is not only novel, but shorter and more efficient than others presented so far in the literature.

The following chapters detail our synthetic efforts towards the total synthesis of manzamine A. Three approaches will be discussed individually and are as follows;

1. A palladium-catalysed arylative allene spirocyclisation cascade approach using a terminal allene system;
2. A palladium-catalysed arylative allene spirocyclisation cascade approach using a non-terminal allene system;
3. An intermolecular Michael addition approach.

Chapter 2
1st Generation: Use of Terminal Allenes in the Synthesis of Manzamine A

2.1 Introduction

2.1.1 Allenes

An allene is a hydrocarbon possessing three carbon atoms with two cumulative double bonds; the central carbon is sp hybridised and the two terminal carbons are sp^2 hybridised. The π-bonds that form are a result of the overlapping p-orbitals and therefore must be perpendicular to each other, which aligns the terminal CH_2 groups perpendicular to each other (Figure 8).[77]

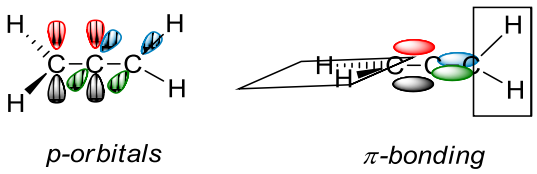


Figure 8: Allene electronic structure.

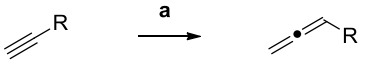
Although the first allene derivatives were synthesised in 1887 by Burton and von Pechmann,[78] the structure was only determined in 1954.[79] Interestingly, the existence of unsymmetrically substituted allenes and the fact that they should exist in two enantiomeric forms was first predicted in 1875 by van't Hoff.[80] In 1924, Staudinger and Ruzicka discovered a 1,2-diene moiety, which was previously thought to have been unstable, existing in natural products.[81] Their discovery initiated research into developing synthetic methods to access allenes.

2.1.1.1 Synthesis of Allenes

Arguably the most convenient ways to synthesise allenes require only the use of commercially available starting materials using only one step to access the allenic functionality. Two commonly used approaches, which are used in this thesis, are discussed.

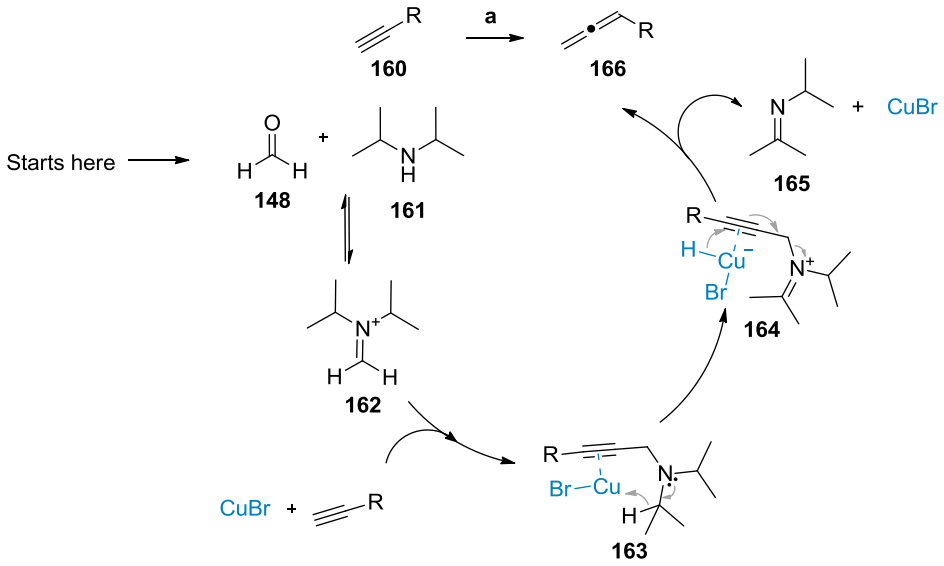
2.1.1.1.1 Crabbé Homologation

The Crabbé homologation converts alkynes to allenes in one step using *p*-formaldehyde, diisopropylamine, and a Cu(I) source (Scheme 19). 1,4-Dioxane is frequently used as solvent, but the reaction can also be carried out in tetrahydrofuran or toluene (see Chapter 2.2.2).



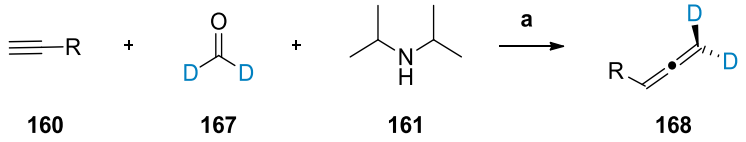
Scheme 19: Crabbé homologation of an alkyne to form an allene. **(a)** *p*-formaldehyde, DIPA, CuBr, 1,4-dioxane, reflux, 2–24 h.

There is much discussion about the mechanism of the reaction and it is still not completely understood. The first mechanism, proposed by Crabbé *et al.*[82] in 1984, is outlined in Scheme 20.



Scheme 20: Crabbé's proposed mechanism. **(a)** CuBr, 1,4-dioxane, reflux, 2–24 h, 40–62%. R = $Me(CH_2)_4CH(OH)$, $(CH_2)_4C(OH)$, $Me_2C(OH)$, Ph.

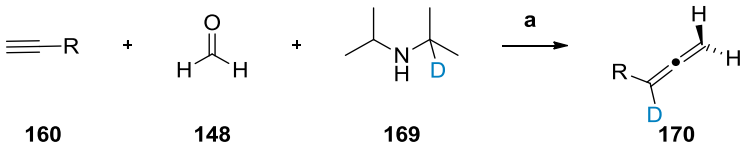
Crabbé postulated that iminium ion formation to give **162** was followed by a copper(I) catalysed addition to afford amine **163**. The formation and presence of **163** was established by GC analysis. Subsequent iminium ion formation was followed by an intramolecular hydride shift to give hydrido-copper intermediate **164**. Collapse of intermediate **164** would yield allene **166**, imine **165** and regenerate the Cu(I) catalyst. Extensive reasoning for this mechanism was given and the most conclusive evidence was their deuterium labelling experiments. When using [$^2H_2$]-formaldehyde, di-deutero allene **168** was formed (Scheme 21).



160 **167** **161** **168**

Scheme 21: Synthesis of deuterated allene **168**. **(a)** CuBr, 1,4-dioxane, reflux, 2.5–4 h, no yields specified. R = $Me(CH_2)_4CH(OH)$, $(CH_2)_4C(OH)$, $Me_2C(OH)$.

Furthermore, Fillion *et al.*[83] reported that when α-monodeuteriodiisopropylamine was used (Scheme 22, **169**), 20% deuteration was observed at C–3 (Scheme 22, **170**) which supported the 1,5-sigmatropic hydride shift.



160 **148** **169** **170**

Scheme 22: Synthesis of deuterated allene **170**. **(a)** CuBr, 1,4-dioxane, reflux, no time specified, 20% deuterium incorporation. R= $C_5H_{11}CH(OH)$.

Lastly, when the reaction was carried out with alkyne **160**, aldehyde **148** and amine **161** in dioxane-d_8 and a D_2O quench was used, no compounds showed any deuterium labelling indicating that there was no external deuterium incorporation from solvent. The rate-determining step from preliminary kinetic studies was postulated to be the 1,5-sigmatropic hydride shift. Fillion *et al.*[83] found k_H/k_D = 4 for the α-deuterium substitution. In addition, Crabbé *et al.*[82] observed that when using amines such as diethyl- or di-*n*butylamine, the rate was reduced, which implied development of electron deficiency at the α-amino carbon

in the rate determining step. This would agree with the loss of hydride from the α-amino carbon during this step.

However recent computational studies published by González *et al.*[84] investigated the mechanism and their results contradicted those of Fillion and Crabbé. González suggested that intermediate **164** (Scheme 20) was too unstable to form. Instead, they proposed a retro-imino-ene reaction of the Mannich-base intermediate in a stepwise manner (Figure 9). They postulated that the role of Cu(I) was to stabilise the intermediate zwitterionic species that formed; $\Delta G^{\ddagger}_{uncat.}$ = +39.7 kcal/mol compared to $\Delta G^{\ddagger}_{cat.}$= +4.9 kcal/mol, and $\Delta G_{uncat.\ total}$ is +116.8 kcal/mol whereas $\Delta G_{cat.\ total}$ = +40.5 kcal/mol.[84] The mechanism was in some ways similar to that postulated by Fillion, however there is a key difference: the role of the copper.

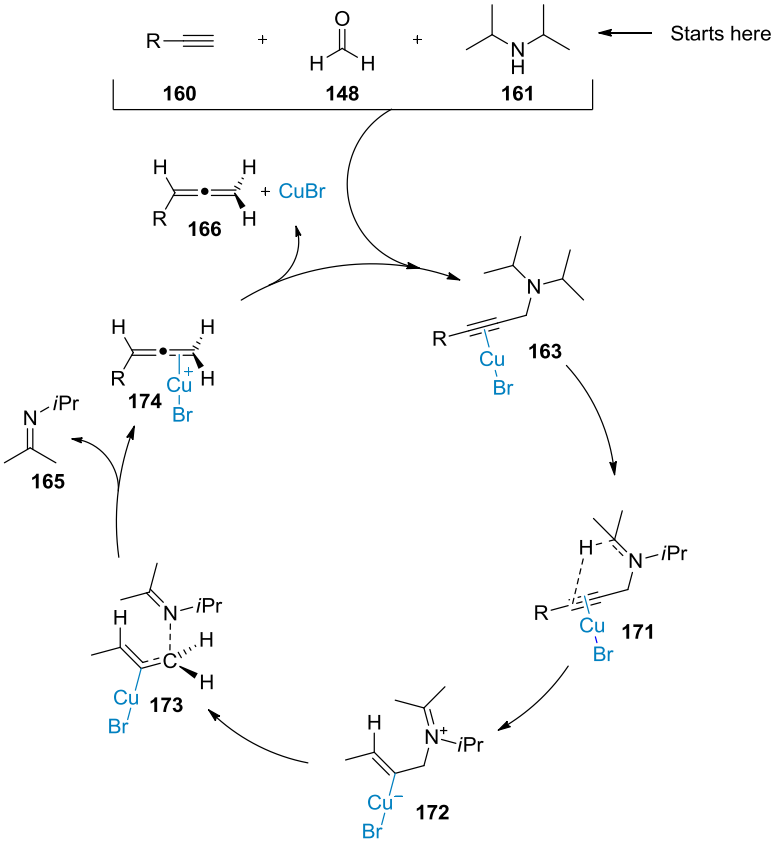
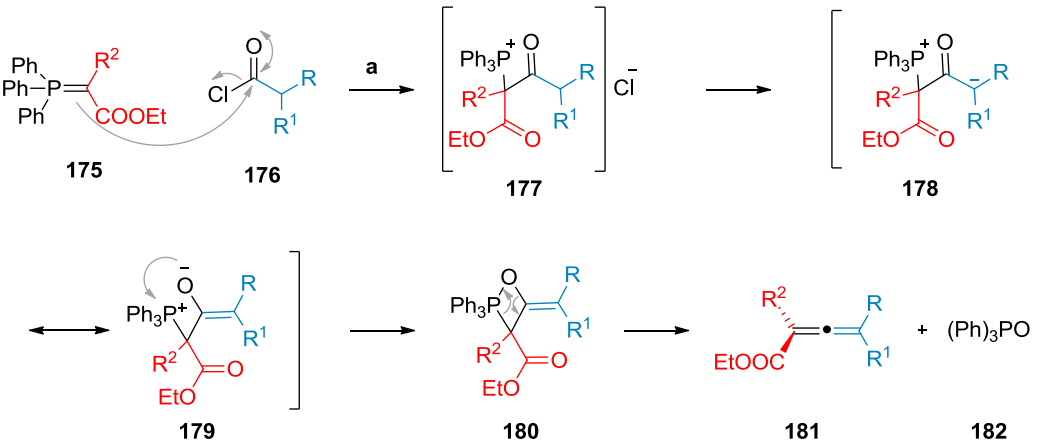


Figure 9: González's postulated mechanism. Uncatalysed (black) and catalysed (blue) pathways are shown.

Whereas Fillion suggested the role of the copper is catalytic only, González suggested that copper can not only lower the energy of the transition states of the reaction by stabilising intermediates **171**, **172** and **173** but also suggested that the only thermodynamically feasible way for the reaction to proceed was when the Cu(I) was *anti* with respect to the hydride that was abstracted (**171**). However, Gonzalez's rate determining step was the same as Fillion's: theoretical KIE values were calculated for the hydride transfer (k_H/k_D = 4.12[iii] and 4.09[iv]) which strongly agreed with experimental KIE values from Fillion (k_H/k_D = 4).[83]

2.1.1.1.2 Wittig Olefin Synthesis

The Wittig olefin synthesis (Chapter 3) of allenes was first described by Bestmann and Hartung in 1966 (Scheme 23).[85]



Scheme 23: Wittig olefination mechanism. **(a)** Base, solvent.

The mechanism follows the classic Wittig olefination sequence, except with an extra enolisation step (**177** to **178** and **179**). Since its discovery, the reaction has been used many times to access a wide variety of terminal (R and R^1 = H) and non-terminal (R and/or R^1 = alkyl) allenes and proceeds under mild conditions to access allenes bearing a synthetically useful ester functionality.

[iii] derived from ΔG values of H/D migration
[iv] derived from zero point vibrational energies of H/D migration

2.1.2 Palladium-Catalysed Reactions with Allenes

Allenes are synthetically very versatile and can undergo a wide variety of reactions including cycloaddition ([2+2], [4+2], [3+2]), oxidation, radical and nucleophilic addition, as well as intra- and intermolecular cyclisation reactions. The area is vast and the chemistry and reactions of allenes are covered in detail in reviews by Taylor (1967)[86] and more recently, Ma (2005).[87] This thesis will focus on palladium-catalysed reactions with allenes.

Palladium-catalysed reactions of allenes with *C*-centred or hetero-atom-centred nucleophiles involve the formation of a π-allyl system which was isolated independently by Schultz[88] and Shaw.[89] The formation of the π-allyl system is thought to proceed *via* the mechanism outlined in Figure 10.[87]

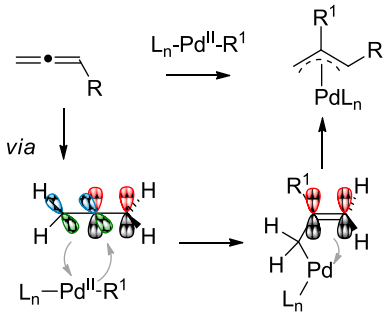


Figure 10: Coordination of palladium to form a π-allyl system.[87] For hydropalladation R^1 = H. For carbopalladation R^1 = C.

The electron deficient π-allyl system can then be attacked by nucleophiles and this was first demonstrated by Coulson who used different amines as nucleophiles.[90] More recently, it has been postulated that there are three possible mechanisms for the formation of the π-allyl system and the subsequent nucleophilic attack, which are dependent on the species present.[91,92] It should be noted that the mechanisms are complex and there is little hard evidence for any that are proposed.

The first potential pathway proceeds when the metal complex has a σ-bonded ligand such as an H, alkyl or halogen (Figure 11, R) and when the pendant nucleophile is less

nucleophilic than R. Allene **183** is more likely to form η^3-complex **186** before subsequent cyclisation (Figure 11, **187**).[92]

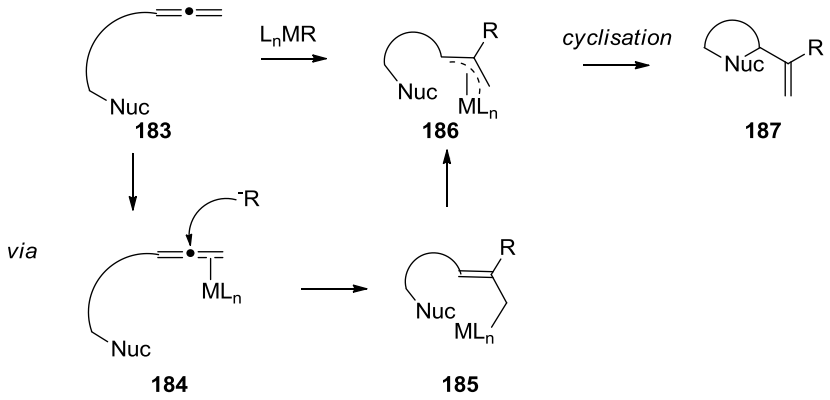


Figure 11: 1st possible mechanism for nucleophilic attack to π-allyl system.

The second potential mechanism is analogous to the Wacker reaction. In the presence of an electrophilic metal complex (such as palladium(II)) an η^2-complex could form with complexation of the metal to one of the allene double bonds (Figure 12, **188** or **190**).

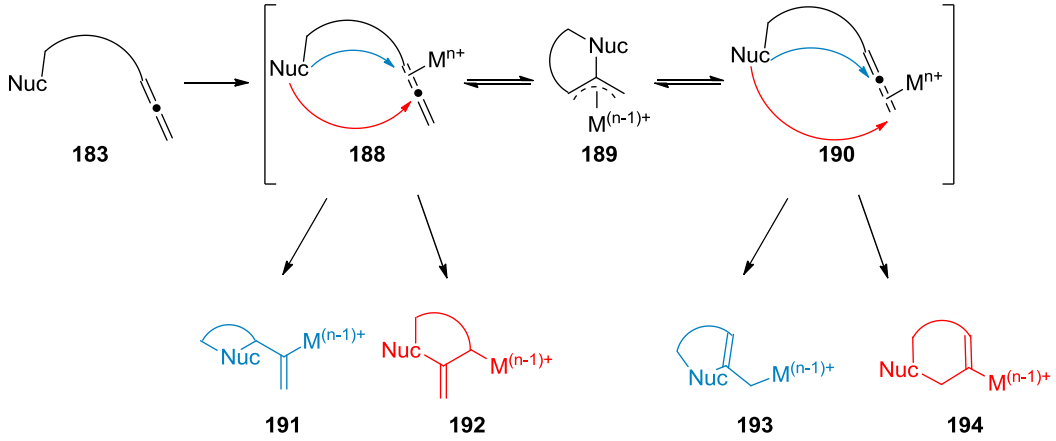


Figure 12: 2nd possible mechanism for nucleophilic attack to π-allyl system.

Complexes **188** and **190** would be in equilibrium *via* the cyclised π-allyl system (Figure 12, **189**). The pendant nucleophile could then attack the open form at either carbon of the allene to form four isomeric η^1-complexes **191–194**. These η^1-complexes can then participate in subsequent reactions, such as a carbonylation or proto-demetalation.[92]

The third possible mechanism occurs when the nucleophile can interact with the metal catalyst (Figure 13, **195**). Insertion into either allene double bond (Figure 13, **196** or **197**) followed by reductive elimination would give **187**, **198** or **199** (Figure 13).[92]

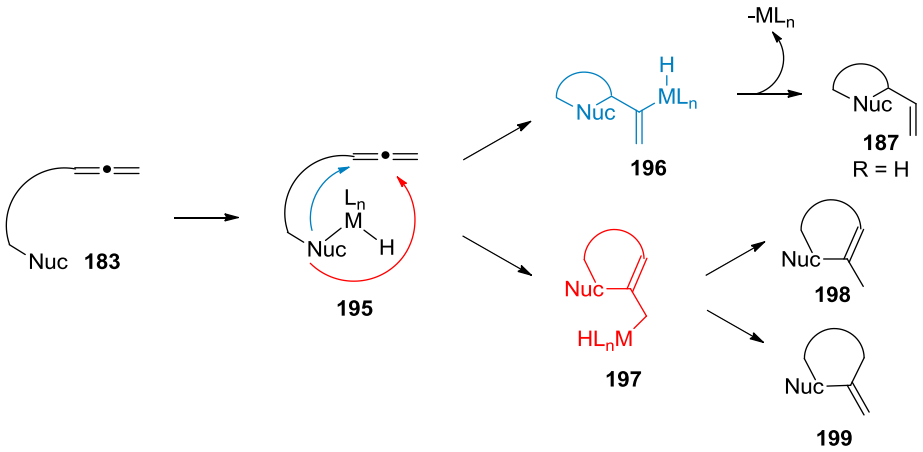
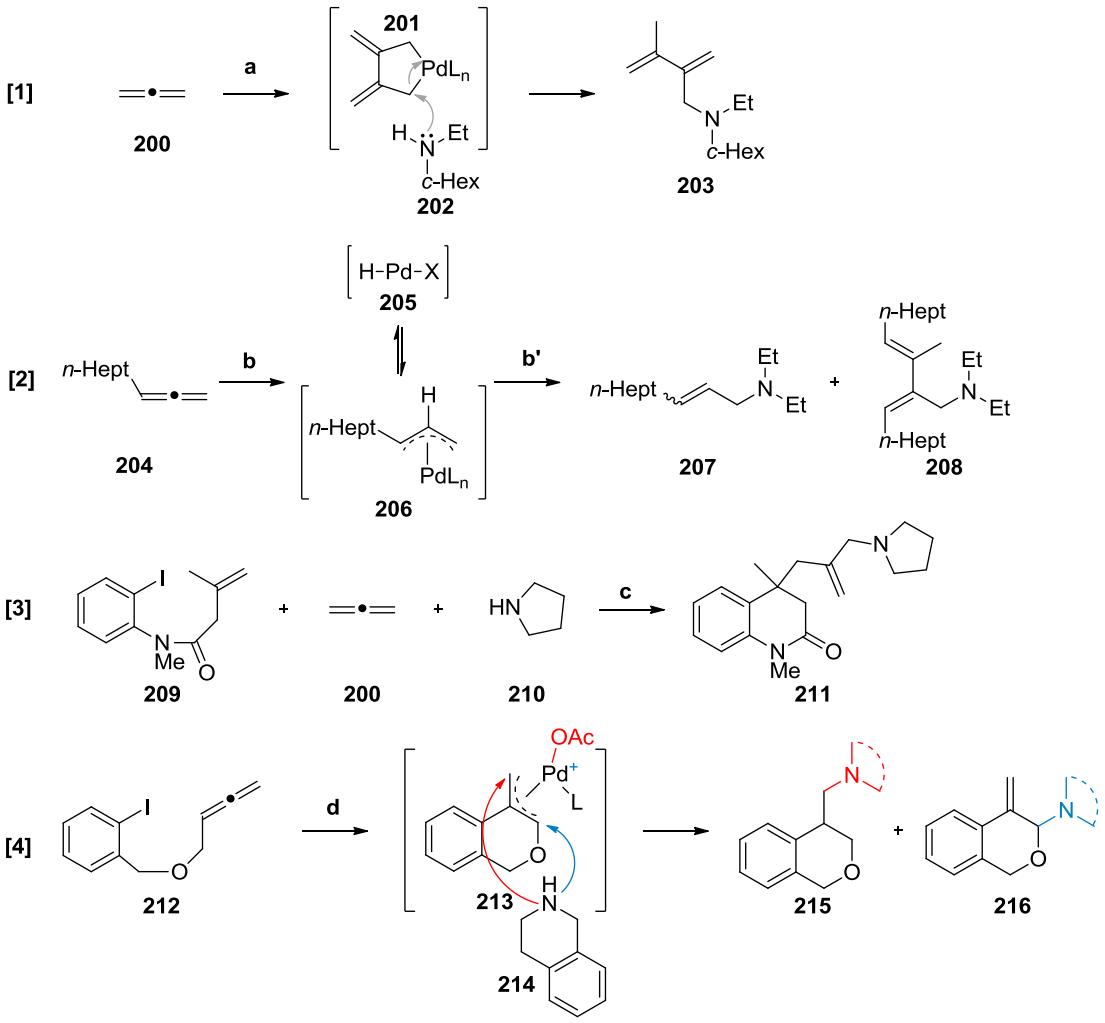


Figure 13: 3rd possible mechanism for nucleophilic attack to π-allyl system.

The reactions of π-allyl systems will be discussed with particular emphasis on nucleophilic attack by heteroatom and carbon nucleophiles.

2.1.2.1 Reactions of Allenes with Heteroatom Nucleophiles

The first report of *N*-centred nucleophiles reacting with allenes under transition metal catalysed conditions was by Coulson *et al.*[90] who found that in the presence of Pd^0 or Rh^0 catalysts at high temperatures, a wide range of amines reacted to form the corresponding amino-1,3-diene **203** (Scheme 24, **[1]**) *via* palladacycle **201**. Secondary and cyclic amines all proceeded well giving derivatives of amine **203** in 30–84% yield. Aniline and ammonia did not work as well: 23% and 12% yield was obtained respectively. Cazes *et al.*[93] demonstrated that when $Pd(dba)_2$ and PPh_3 in tetrahydrofuran with NEt_3HI as an additive was used, the reaction proceeded in up to 89% yield with mono-substituted allenes (Scheme 24, **[2]**).



Scheme 24: Examples of nitrogen centred nucleophiles attacking allenes. **(a)** 1 mol% [$(PPh_3)_2$(2,5-dioxofuran)Pd], tetrahydrofuran, 120 ˚C, sealed vessel, 6 h, 84%; **(b)** 4 mol% $Pd(dba)_2$, 8 mol% PPh_3, NEt_3HI, tetrahydrofuran, then Et_2NH, 65 ˚C, 18 h, 70%, 6:1 **207**:**208**, **207** 96:4 *E*:*Z*; **(c)** 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, Et_4NCl, K_2CO_3, toluene, 90 ˚C, 20 h, 82%; **(d)** 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Ag_2CO_3 or K_2CO_3, MeCN, reflux, 4 h, **215** 36% (K_2CO_3), **216** 88% (Ag_2CO_3).

When dimethylformamide as solvent was used, a significant quantity of **208** was observed (~1:1 **207**:**208**) however no explanation was offered. Independently, Yamamoto *et al.*[94] reported the use of acetic acid as an additive with a different catalytic system, $Pd_2(dba)_3$•$CHCl_3$/dppf, and almost quantitative yields were achieved. The beneficial addition of either NEt_3HI or acetic acid effects a different mechanism, which is postulated to proceed *via* hydropalladium species **205**, and can insert into the allene to form the π-allyl species (**206**) before nucleophilic attack by the amine occurs (Scheme 24, **[2]**).

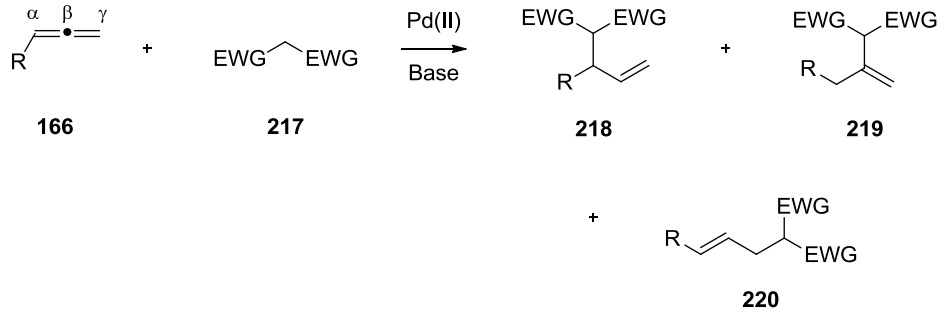
Grigg *et al.* have carried out a significant amount of work on *N*-centred nucleophiles and were first to coin the term "allene insertion-anion capture cascades".[95] This is effectively a three-component palladium-catalysed cyclisation. The palladium inserted into the allene and concomitant trapping of a nucleophile such as an amine[96] or azide[97] gave tertiary amines similar to **211** or, after a further 2,3-dipolar cycloaddition reaction, triazoles (Scheme 24, **[3]**, if the nucleophile is N_3^-). Grigg further extended the methodology to an intramolecular two-component palladium-catalysed reaction where the aryl iodide and allene were in the same molecule and a range of *N*-centred nucleophiles were trapped (Scheme 24, **[4]**). It was found that by changing the base from K_2CO_3 to Ag_2CO_3, the product of the reaction changed.[98] Under K_2CO_3 conditions, amine **215** was obtained exclusively, in 36% yield. However, when Ag_2CO_3 was employed, regio-isomer **216** was the sole product isolated in 88% yield. The reason given was that with Ag_2CO_3, the blue pathway (Scheme 24, **[4]**) proceeded; a cationic complex formed and subsequent nucleophilic attack at the most electron deficient allylic centre in the α-oxygen position occured with no further rearrangement. Meanwhile, with K_2CO_3 the red pathway dominates: there is little difference between each terminus of the π-allyl system and therefore the more stable, less sterically hindered terminus is attacked and then undergoes rearrangement to give amine **215**.

Zimmer *et al.*[87] have reviewed the field of palladium-catalysed reactions of allenes including an extension of the *N*-centred nucleophiles covered in thesis to *O*-, *S*- and *Se*-nucleophiles. There is a much smaller scope so far for the use of these nucleophiles and the chemistry is still in its infancy compared to the broad scope of *N*-centred nucleophiles.

A review by Ma in 2005 gave a comprehensive overview of other nucleophiles such as radicals, alkynes, phosphonates, stannanes, germananes, silanes and boronic esters.[99]

2.1.2.2 *Reactions of Allenes with Carbon Nucleophiles*

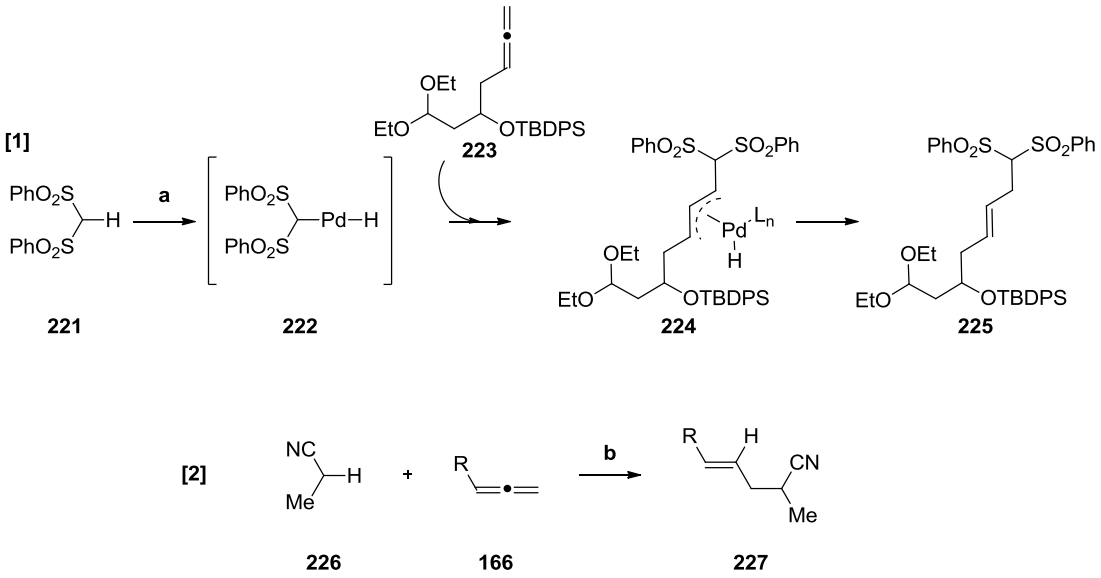
The addition of *C*-centred nucleophiles to allenes can give rise to a wide variety of compounds including alkenes, carbocycles and heterocycles of different ring sizes. The carbon nucleophiles tend to be of type **217** outlined in Scheme 25 or organometallic reagents.



166 **217** **218** **219** **220**

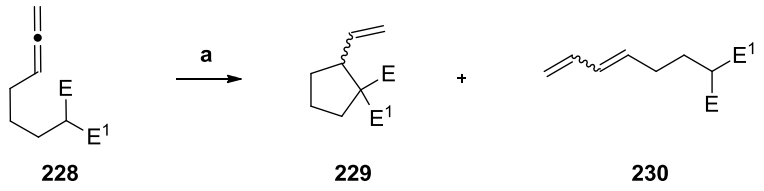
Scheme 25: Addition of carbon nucleophiles to allenes. EWG = electron-withdrawing group. R = aryl, aryloxy, alkoxy.

Mechanistic studies by Yamamoto showed that the α- (Scheme 25, **218**), β- (Scheme 25, **219**) and γ-regioisomer (Scheme 25, **220**) formation was controlled by the nature of the R group. Alkoxy/aryloxy allenes gave α-adducts due to stabilisation of the cation by OR,[100] aryl-allene with an electron-withdrawing group at the *p*-position gave β-adducts,[101] whereas an electron-donating group at the *p*-position and mono/di-alkyl-substituted allenes gave γ-adducts.[101,102] In 1973, Coulson reported the first reaction of an intermolecular addition of a pro-nucleophile (malonate) to an allene *via* a π-allyl system,[90] and this was further developed by Cazes and Goré.[103–107] Most work used malonates as the nucleophile[107] but bis-sulfones (Scheme 26, **[1]**)[108] and nitriles (Scheme 26, **[2]**)[102] have also been reported. Both carbopalladation (Scheme 26, addition of C–Pd to the allene) and hydropalladation (Figure 14, addition of H–Pd to the allene) mechanisms have been postulated for the reaction pathways.



Scheme 26: Carbopalladation mechanism using bis-sulfone **221 [1]** and nitrile **226 [2]**. (a) 5 mol% [π-allyl-PdCl]$_2$, 12 mol% dmppp, 5 mol% KOtBu, THF, reflux, 65%, no further details given; **(b)** 5 mol% $Pd_2(dba)_3$•$CHCl_3$, 26 mol% dppb, THF, reflux, 48 h, 60%. R = Bn.

In 1996, Yamamoto *et al.* reported an intramolecular palladium-catalysed carbocyclisation under neutral conditions to access carbocycles (Scheme 27).[109]



Scheme 27: Synthesis of carbocycles **222** and dienes **223**. **(a)** 5 mol% [(η^3-C_3H_5)PdCl]$_2$, 20 mol% dppf, THF, 70 ˚C, 5 h, **222**:**223** 9:1–0:1. E/E^1 = CN, COOMe, SO_2Ph, Meldrum's acid.

Yamamoto postulated that the first step of the mechanism is the insertion into the (E)(E^1)C-H bond. Either hydropalladation or carbopalladation mechanisms would give cyclic product **229** but the Yamamoto suggested that the formation of diene **230** strongly supported a hydropalladation mechanism outlined briefly in Figure 14 (**231–233)** i.e. the addition of Pd-H to the allene.

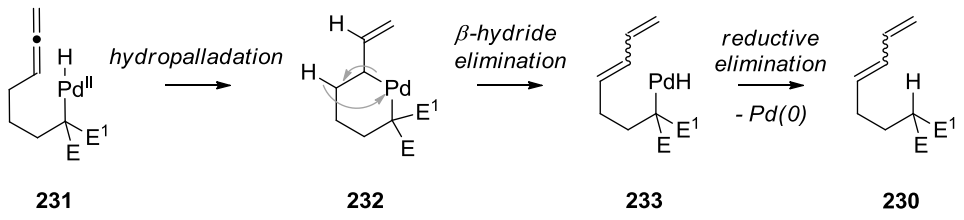
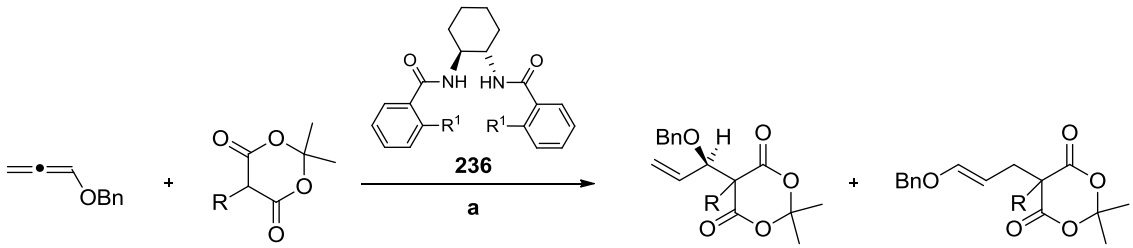


Figure 14: Hydropalladation leading to the formation of **230**.

However, the same diene **230** could also be accessed from coordination of the palladium to the allene which would form the π-allyl system, followed by subsequent β-hydride elimination, without the initial insertion/hydropalladation step.

More recently, Trost *et al.* used Meldrum's acid as the pro-nucleophile (Scheme 28).[110] They obtained yields ranging from 61–90% and 82–99% enantiomeric excess when R was varied; alkyl, alcohols, benzyl, olefins and ethers were all tolerated.



234 **235** **237** **238**

Scheme 28: Use of Meldrum's acid **235** with allene **234**. **(a)** 1 mol% $Pd(OC(O)CF_3)_2$), 1.25 mol% ligand, 1 mol% TFA, CH_2Cl_2, RT, 61–90%, ee 82–99%. R = alkyl, OH, Bn, olefins, ethers, $R^1 = PPh_2$.

Their proposed hydropalladation mechanism, which was also applicable to 1,3-diketone asymmetric addition to allenes, is outlined in Figure 15.[111] The yields were in the range of 36–73% and excellent enantioselectivities were obtained (96–98%).

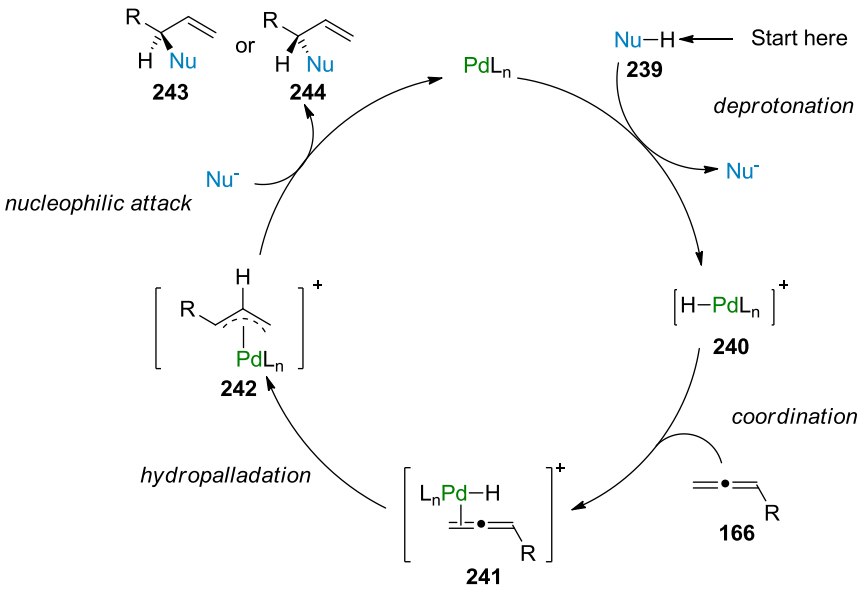


Figure 15: Hydropalladation mechanism to synthesise chiral derivatives **243** and **244**.

It was found that a substoichiometric amount of acid was required, akin to the addition of quaternary ammonium salts or AcOH in Section 2.1.2.1. When base was employed to generate the enolate nucleophile, yields of up to 69% and enantioselectivities of 38% or less were reported. Trost *et al.* found that one equivalent of acid (with respect to Pd) was required to achieve the highest yields which they postulated formed the protonated palladium species **240**, giving weight to their proposed hydropalladation mechanism. This example was the first reported palladium-catalysed asymmetric addition of pro-nucleophiles to allenes.

2.1.3 Previous Work Leading to this Project

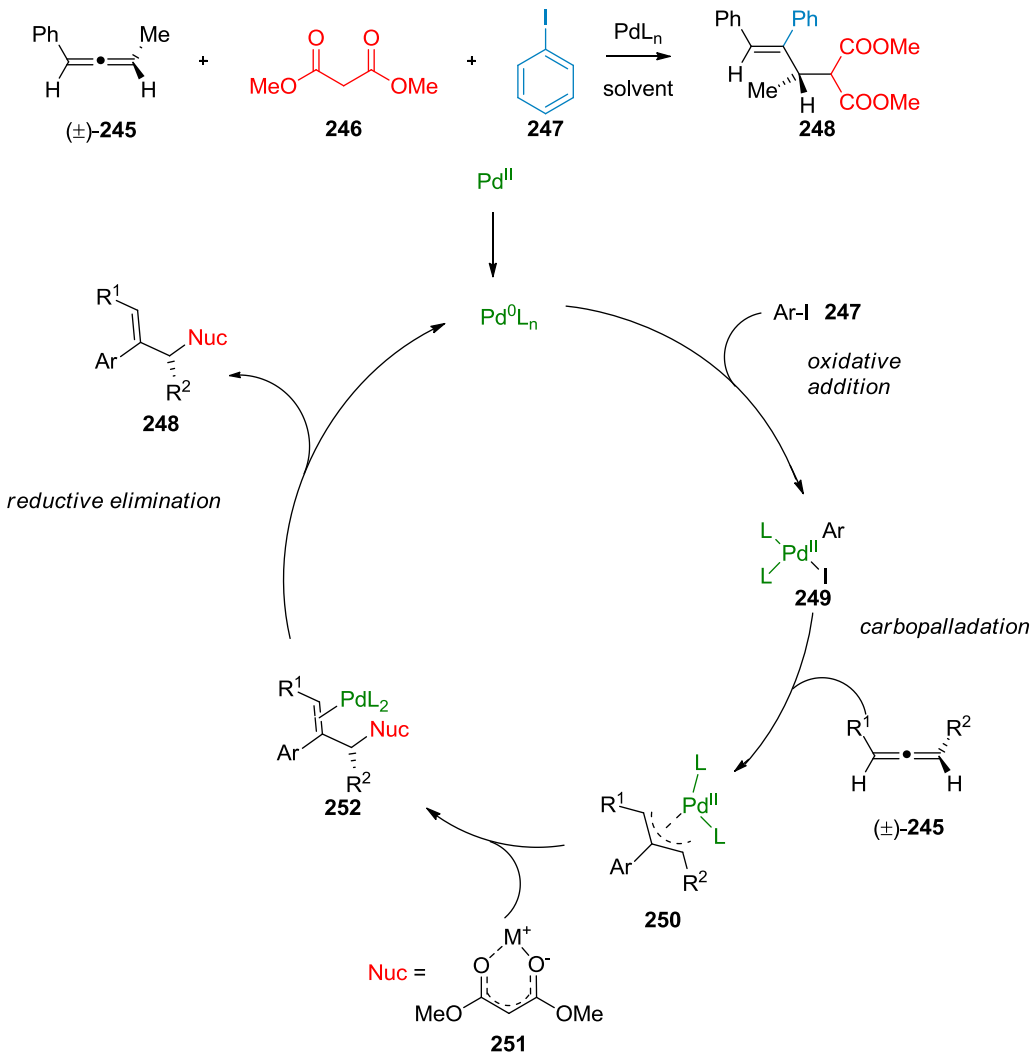
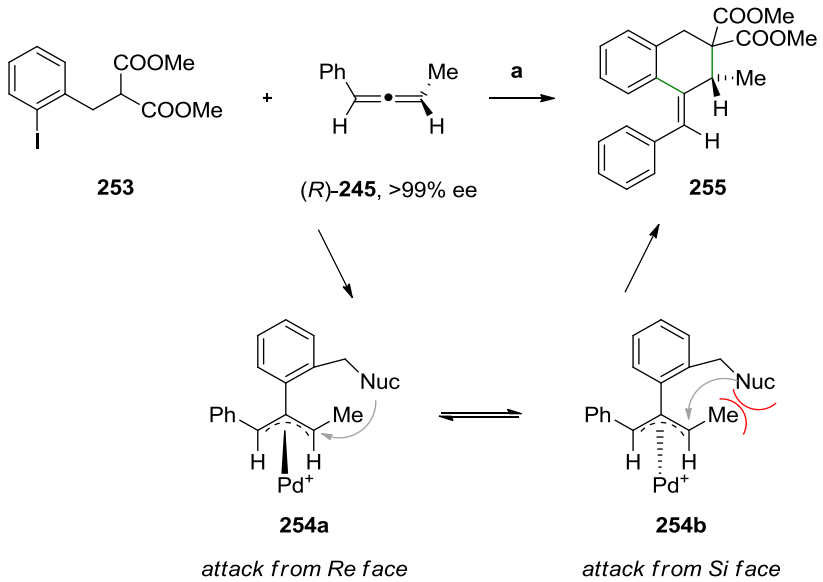


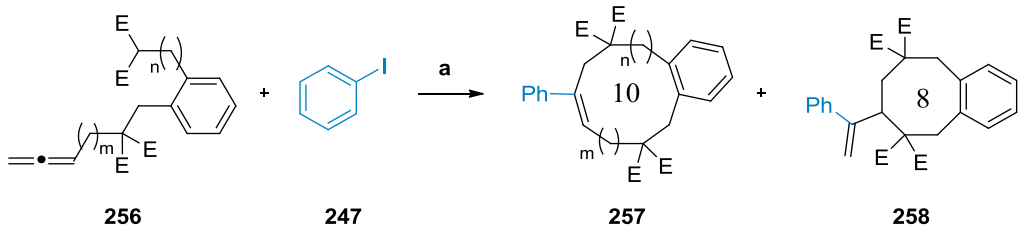
Figure 16: Catalytic cycle for carbopalladation reaction to form **248**.

In 1998, Hiroi *et al.* reported an asymmetric 1,2-functionalisation of an allenic olefin *via* a carbopalladation reaction using chiral phosphine ligands (Figure 16).[112] They began using a three-component system; the allene, the nucleophile and the aryl iodide. Iodobenzene **247**, racemic 1-phenyl-3-methyl-1,2-diene **245** and dimethyl malonate **246** were used for optimisation and in dimethylsulfoxide at 66 ˚C, yields of up to 69% were achieved. When 4 mol% $Pd(OAc)_2$ and 8 mol% (*S*)-(–)-BINAP were used, enantioselectivities of >96% were achieved. In 2004, Hiroi *et al.*[113] extended the methodology to an intramolecular two-component carbopalladation cyclisation where two of the three moieties were in the same molecule (Scheme 29, **253**). This reaction, using enantiopure, chiral allene **245** and racemic phosphine ligands proceeded with average yields of 30% but a loss of enantiomeric excess was observed; 11–50% ee was obtained. Hiroi *et al.* attributed this to the fact that there was an equilibrium between the corresponding **254a** and **254b** π-allyl complexes which existed to alleviate steric interference of the methyl group with the aryl group. The nucleophile could therefore attack either isomer with a preference for **254a**, leading to a loss of chirality in products **255** (Scheme 29).



Scheme 29: Asymmetric palladium-catalysed reaction. **(a)** 4 mol% $Pd(dba)_2$, 10 mol% PPh_3, dppf or dppb, NaH, THF or DME, reflux, 7–88%, 11–50% ee.

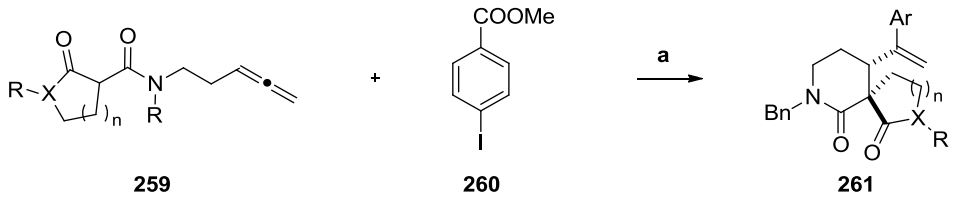
More recently, Ma *et al.*[114] reported the synthesis of nine- to twelve-membered rings using a palladium-catalysed cyclisation cascade between an allene with a nucleophilic functionality and organic halides.



Scheme 30: Synthesis of 10-membered rings **257**. **(a)** 5 mol% $Pd(PPh_3)_4$, K_2CO_3, DMA, N_2, 80 ˚C, 11–72 h, **257**: 70–89%. E = COOMe. n = 0, 1 or 2; m = 1 or 2.

Exposure of a variety of allenes **256** to the conditions outlined in Scheme 30 allowed 9-, 10-, 11- and 12-membered rings to be synthesised in yields ranging from 70–89%. None of the 8-membered ring (Scheme 30, **258**) was observed, demonstrating excellent regioselectivity, but no reason was given for this. The intramolecular nucleophile was also changed from a malonate to *N*-tosyl, and the reaction proceeded in 83% yield.

In 2010, Dixon *et al.* reported that exposure of allenic pro-nucleophiles of type **259** to palladium-catalysed conditions in the presence of a range of aryl iodides, spirocycles **261** could be synthesised (Scheme 31).[115]



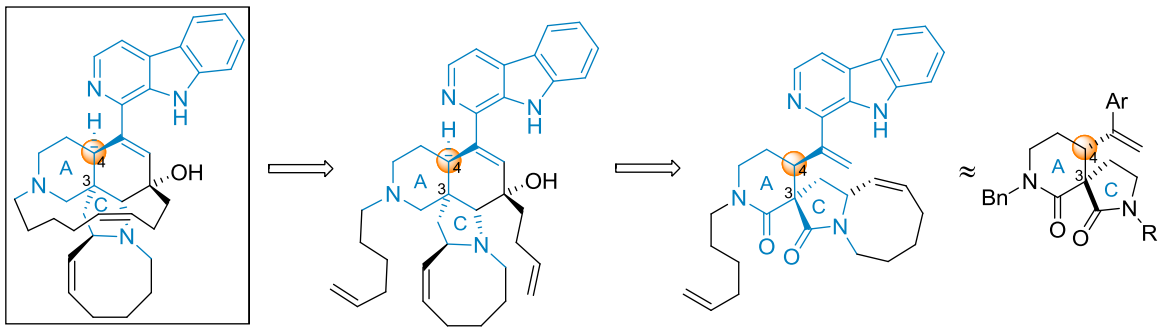
Scheme 31: Synthesis of spirocycles **261**. **(a)** 5 mol% $Pd_2(dba)_3$, 10 mol% dppe, K_2CO_3, DMSO, 70 ˚C, 16 h, 63–86%. When X = N, R = Boc, Bn, Me, Ts; when X = C, R = H; n = 1–4.

A range of spirocycles were synthesised (n = 1–4) and included eight-membered rings which are notoriously difficult to form. The reaction proceeded well with other aryl iodides; electron-withdrawing, such as *p*-NO_2-C_6H_4, electron-donating, such as *p*-OMe-C_6H_4 as well as bulky aryl systems such as naphthyl were all tolerated and the resulting products were

isolated in yields of 63–86%. Crucially, in DMSO, very high diastereoselectivities were observed: <47:1, with a *trans* relationship between the vinyl aryl group and the pyrrolidinone ring in the major diastereomer (Scheme 31, n = 1).

2.1.4 Application to the Synthesis of Manzamine A

Application of this reaction to the total synthesis of a complex natural product was desired, and it was believed that the reaction could be utilised in the total synthesis of manzamine A (Figure 17, (**9**)).



manzamine A (**9**) **262** **263a** **261**

Figure 17: Core of manzamine A **263a** compared to the palladium-catalysed spirocyclisation product **261**.

The core of manzamine A could be accessed using the palladium-catalysed arylative allene spirocyclisation cascade (Figure 17, highlighted in blue). However, one key problem was the diastereoselectivity on the stereocentre at C–4. Using the methodology developed by Dixon *et al.*, the wrong stereochemistry for manzamine A would be expected. A *cis* relationship between the vinyl β-carboline and the pyrrolidinone carbonyl was required, but using this methodology, a *trans* relationship between the vinyl aryl group and the pyrrolidinone carbonyl was obtained (Figure 17, **261**). Therefore, when applying the methodology to the synthesis of manzamine A, not only would reactivity have to be maintained, but crucially the diastereoselectivity would need to be inverted.

2.1.5 Retrosynthetic Analysis

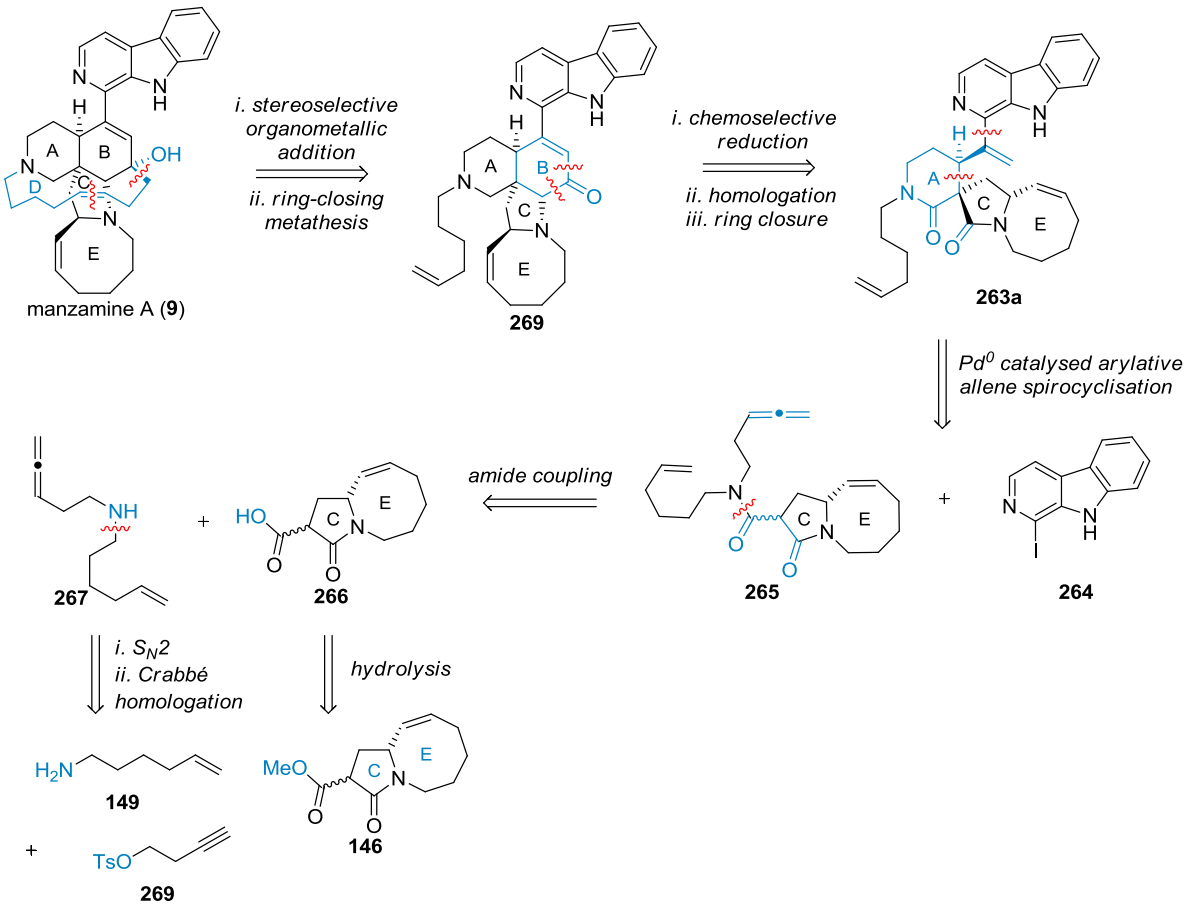


Figure 18: Retrosynthetic analysis of manzamine A using a palladium-catalysed arylative allene spirocyclisation cascade.

Our retrosynthetic analysis identified the tricyclic structure **263a** as a late stage intermediate possessing three of the five stereogenic centres, the 6,5-spirocyclic ACE core and the β-carboline moiety. Spirocycle **263a** would be accessed *via* the palladium-catalysed arylative spirocyclisation cascade between advanced pro-nucleophile **265** and β-carboline **264**. Bis-amide **265** in turn would be accessed *via* an amide coupling between secondary amine **267** and acid **266**. The acid would be synthesised from known ester **146**,[17] and amine **267** would be the product of a S_N2 reaction between **149** and **269** followed by a Crabbé homologation.

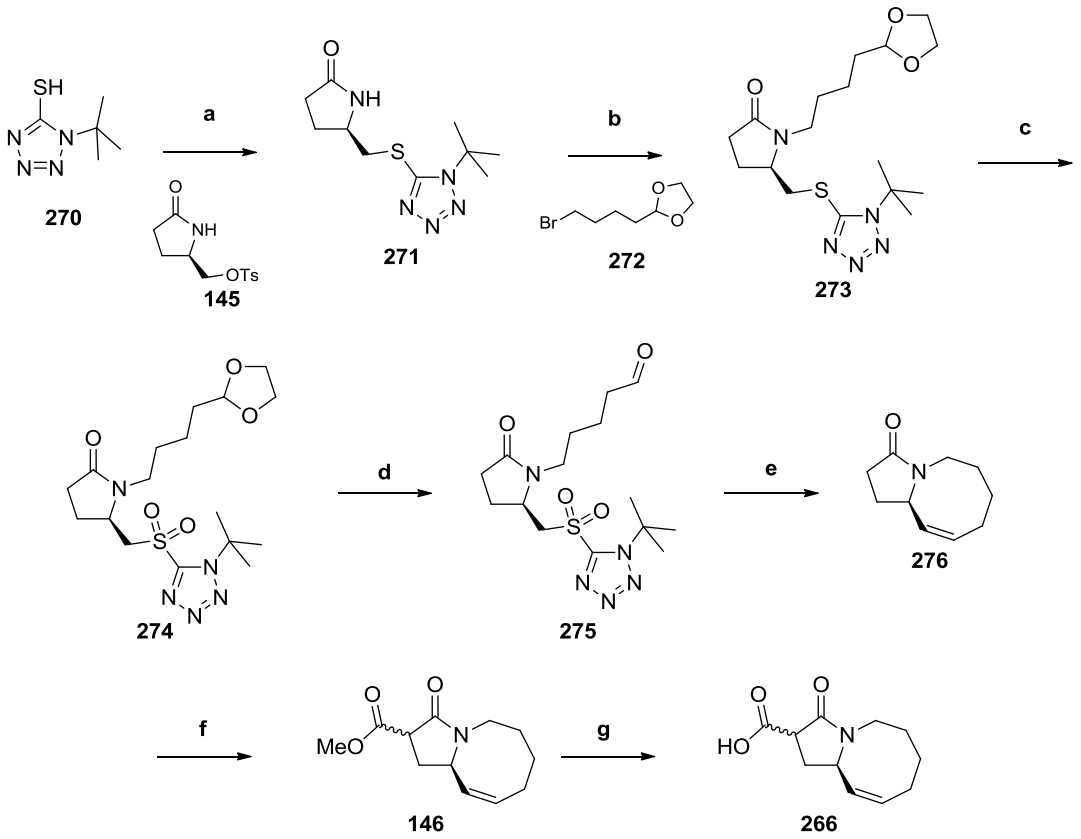
After the synthesis of **263a**, a chemoselective reduction followed by a one-carbon homologation (either to the pyrrolidinone carbonyl or the vinyl β-carboline double bond)

and a stereoselective carbocyclisation would form ring B and give **269**. Only two steps would remain, both of which had precedent in our research group on a related system;[12] a stereoselective organometallic addition followed by a ring-closing metathesis would give manzamine A (**9**).

2.2 Synthesis of the Starting Materials

*2.2.1 Synthesis of Carboxylic Acid **266***

Bicycle **146** was synthesised according to literature procedures developed by Dixon *et al.*[17] (Scheme 32) and the synthesis was further extended to form the desired carboxylic acid **266**.



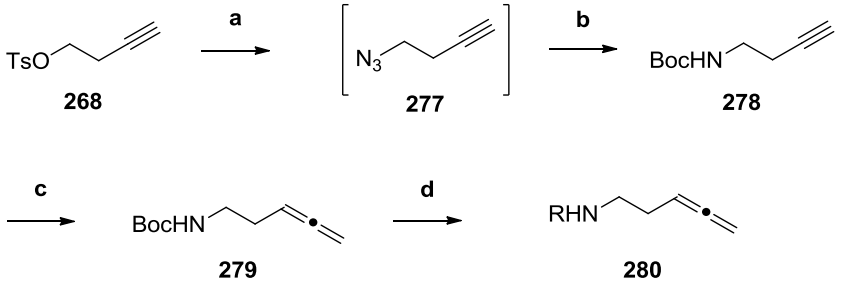
Scheme 32: Synthesis of acid **266**. **(a) (i)** NaH, THF, 0 ˚C, 10 min **(ii) 145**, THF, RT, 12 h, 89%; **(b) 272**, NaH, Bu_4NI, DMSO, 0 ˚C to RT, 12 h, 82%; **(c)** *m*CPBA, DCM, RT, 12 h, 64%; **(d)** HCl, THF, RT, 2 h, 99%; **(e)** Cs_2CO_3, THF, DMF, H_2O, 70 ˚C, 10 h, 54%; **(f)** dimethyl carbonate, LHMDS, −78 ˚C to RT, 86%, dr 1:1; **(g)** LiOH, THF, MeOH, RT, 4 h, 99%, dr 1:1.

Deprotonation of commercially available tetrazole **270** with sodium hydride in tetrahydrofuran followed by addition of tosylate lactam **145** gave sulfide **271** in 89% yield. *N*-alkylation with bromo-acetal **272** (synthesised using literature procedures[116]) gave **273** in 82% yield. Careful oxidation of sulfide **273** to sulfone **274** proceeded smoothly, in 64% yield. This low yield reflects the instability of the acetal moiety to the *m*-chlorobenzoic acid generated in the reaction. The acetal was hydrolysed in quantitative yield to give aldehyde **275**, which was used without purification. In the presence of Cs_2CO_3, aldehyde **275** underwent an intramolecular Julia-Kocienski reaction affording **276** in yields ranging from 45–65%.[117] This reaction is the first example of an intramolecular Julia-Kocienski reaction in natural product synthesis and exhibits excellent selectivity; only the *cis* isomer was observed. Subsequent alkoxycarbonylation with dimethylcarbonate gave ester **146** which after basic hydrolysis and re-acidification gave acid **266** in >99% yield. The synthesis of **146** was very robust; up to 8 g of **146** could be synthesised in a single batch from tetrazole **270**.

2.2.2 Synthesis of Secondary Amine **267**

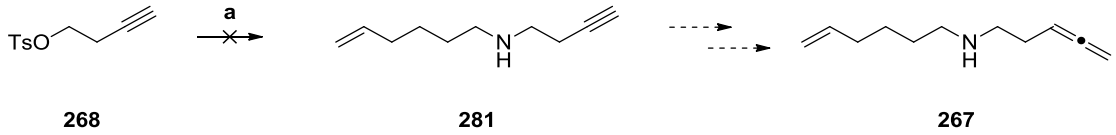
2.2.2.1 S_N2 Displacement

It was decided to synthesise the desired secondary amine containing the terminal allene moiety based on work previously carried out within our research group; the synthesis is outlined in Scheme 33.[115] Tosylate **268** underwent an S_N2 reaction with sodium azide which gave **277**. A Staudinger reaction followed by hydrolysis of the iminophosphorane and *in situ* Boc protection of the subsequent amine gave **278**. Crabbé homologation using formaldehyde, Cu(I) and diisopropylamine in 1,4-dioxane gave the Boc-protected allene-amine **279**. A subsequent deprotonation and S_N2 reaction with a selection of alkyl halides followed by removal of the Boc-protecting group gave access to a range of secondary amines **280**.



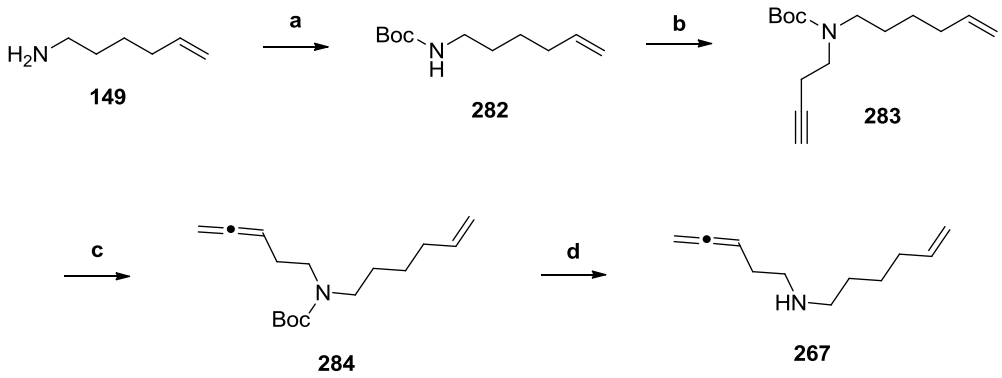
Scheme 33: Synthesis of secondary amines **280**. **(a)** NaN_3, DMSO, 45 ˚C, 16 h; **(b) (i)** $n$$Bu_3P$, Et_2O, RT, 2 h **(ii)** Boc_2O, −50 ˚C, 1 h **(iii)** $H_2O/NaHCO_3$, −50 ˚C to RT, 57% over three steps; **(c)** $(HCOH)_n$, CuBr, DIPA, 1,4-dioxane, 100 ˚C, 12 h, 65%; **(d) (i)** NaH, RX, THF, 0 ˚C to RT, 20 h, 70–83% **(ii)** TFA, CH_2Cl_2, RT, 2–7 h, 56–94%. R = Me, Et, *n*Pr, Bn, allyl.

Ideally, the number of steps required to synthesise the target amine would be cut and therefore, a direct S_N2 reaction between tosylate **268** and amine **149** was attempted (Scheme 34). Using DMSO with an excess of amine **149** at 45 ˚C, only very low yields (15–20%) were obtained. This was presumably due to competing elimination pathways as TLC analysis indicated complete consumption of tosylate **268**.



Scheme 34: Attempted synthesis of secondary amine **267. (a)** hex-5-en-1-amine (**149**), NaI, DMSO, 45 ˚C.

Subsequently, amine **149** was protected using a Boc group (Scheme 35), to aid handling issues as well as mimicking the original reaction conditions (Scheme 33). The Boc protection proceeded smoothly in >97% yield and Boc-protected amine **282** was used without further purification.

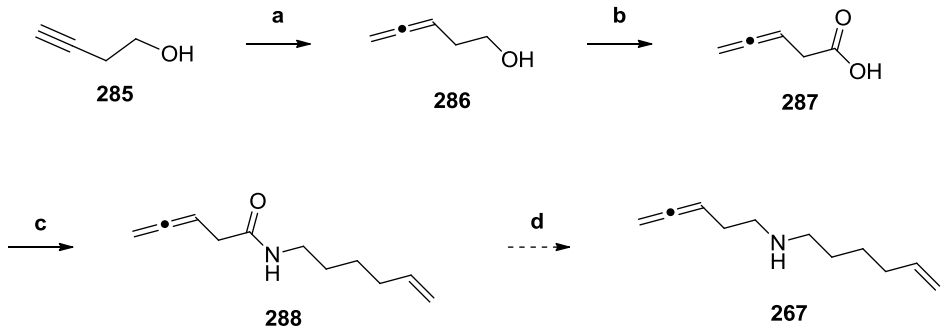


Scheme 35: Synthesis of amine **267**. **(a)** $(Boc)_2O$, MeOH, RT, 3 h, 75–97%; **(b) 268**, NaH, DMF, RT, 40 h then 110˚C, 3 h, 10–15%; **(c)** $(HCOH)_n$, CuBr, DIPA, 1,4-dioxane, 100 ˚C, 14 h, 56%; **(d)** TFA, DCM, RT, 4 h, 63%.

The following S_N2 reaction between amine **282** and tosylate **268** was low yielding (10–15%), presumably due to the decreased reactivity of the *N*-Boc protected nucleophile. Subsequent Crabbé homologation proceeded in 56% yield and removal of the Boc-protecting group gave the desired amine in 63% yield (Scheme 35). Whilst this route delivered amine **267**, the poor yields meant this pathway was not viable for scale-up. The second step was poor yielding and irreproducible. Thus, a new, shorter route that was protecting group free was sought.

2.2.2.2 Amide Coupling

With limitations of reactivity observed with amine **282**, a new amide coupling/reduction approach was attempted (Scheme 36). Allene-ol **286** was synthesised *via* Crabbé homologation of alkyne **285** in 26–34% yield. This low yield was not unexpected due to the known capricious nature of the Crabbé homologation with small (<C_5) molecules.[118] Furthermore, isolation of volatile alcohol **286** from the reaction solvent, tetrahydrofuran, proved difficult. Alcohol **286** was oxidised under standard Jones oxidation conditions which gave acid **287** in 58–67% yield.

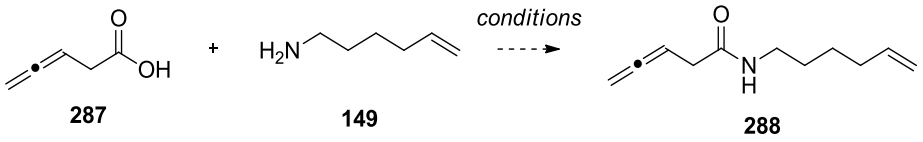


Scheme 36: Synthesis of amine **267** *via* an amide coupling. **(a)** $(HCOH)_n$, CuBr, DIPA, tetrahydrofuran, 100 ˚C, 14 h, 26–34%; **(b)** Jones' reagent, acetone, 0 ˚C, 1 h, 58–67%; **(c) 149**, CDI, THF, RT, 1 h, 71%; **(d)** Reducing reagents.

The coupling reaction was attempted with amine **149** and a range of coupling reagents were employed (Table 1). The use of ethyl chloroformate (Table 1, entry 1) gave poor conversion and a low isolated yield (22%) of **288** was obtained. When using *N*,*N*'-

dicyclohexylcarbodiimide (DCC), the final product was always contaminated with significant amounts of cyclohexyl urea residues, even after multiple purification attempts (Table 1, entry 2). The use of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) gave the desired product in 48% yield (Table 1, entry 3), however, when 1,1'-carbonyldiimidazole (CDI) in THF (Table 1, entry 5) was used, amide **288** (Scheme 36) was isolated in a satisfactory 71% yield.

Table 1: Coupling attempts between **287** and **149**.



287 **149** **288**

Entry	Reagents	Solvent	Yield/%
1	Ethyl chloroformate, Et_3N	THF	22
2	DCC, HOBt	DCM	60
3	EDC.HCl, HOBt, Et_3N	THF	48
4	CDI	DCM	21
5	CDI	THF	71

After successfully identifying the best amide forming conditions, reduction of the amide was attempted. A range of reducing agents were screened but unfortunately all attempts to synthesise amine **267** were unsuccessful. DIBAL, $LiAlH_4$ and Red-Al® (a more soluble and versatile version of $LiAlH_4$) were all employed, but analysis of the crude ^1H NMR spectra and mass spectra always indicated disappearance of the allene moiety. This undesired side-product, which was suggested to be synthesised from reduction of the allene moiety, was inseparable from the starting material and could not be isolated.

With the chemoselectivity problems arising from the reduction of amide **288**, a new route was sought.

2.2.2.3 *Reductive Amination*

A classic way to synthesise secondary amines is *via* a reductive amination. There are two potential disconnections within amine **267** that could be carried out (Figure 19).

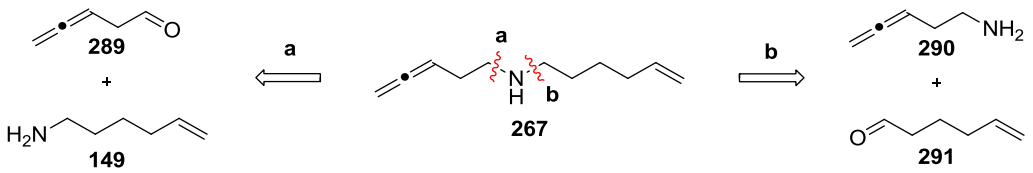
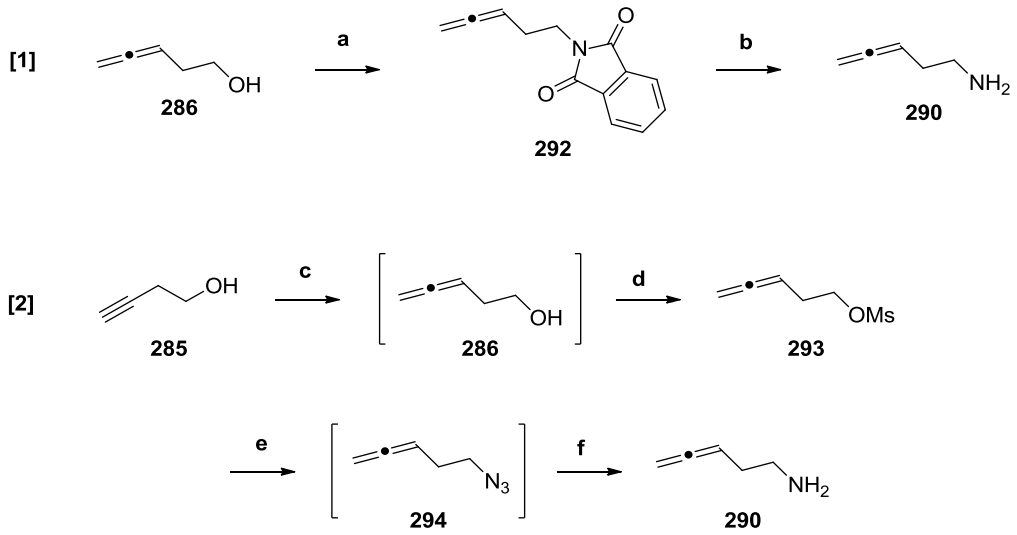


Figure 19: Two possible disconnections of amine **267**.

With multigram quantities of amine **149** available, and a robust route to synthesise it, we began with route 'a'. Novel aldehyde **289** would be accessed from an oxidation of alcohol **286**. However, on attempting the oxidation with PCC, DMP or by Swern oxidation, no aldehyde was observed. The reasons for this remain unclear, but could be due to the unstable and volatile nature of this compound.

Therefore the second route was attempted (Figure 19, route 'b'). Two methods were employed to synthesise amine **290** (Scheme 37).



Scheme 37: Synthesis of primary amine **290**. **(a)** phthalamide, DIAD, PPh_3, THF, 0 ˚C to RT, 14 h, 80%; **(b)** H_2NNH_2, EtOH, reflux, 4 h, 0–55%; **(c)** $(HCOH)_n$, CuBr, DIPA, THF, 100 ˚C, 14 h; **(d)** MsCl, Et_3N, Et_2O, 0 ˚C to RT, 3 h, 27% over two steps; **(e)** NaN_3, DMSO, 50 ˚C, 5 h; **(f)** PPh_3, H_2O, Et_2O, RT, 16 h, 100%.

The first route (Scheme 37, **[1]**) involved a Gabriel-type reaction.[119] Mitsunobu activation of alcohol **286** introduced the phthalamide moiety and subsequent cleavage with hydrazine gave amine **290** and phthalamide side products. However, the hydrazinolysis step to release the primary amine was unreliable. The best yield of amine **290** obtained was 55% but sometimes, no product was isolated. The reaction needed to be heated at reflux in ethanol, which could have led to decomposition of amine **290**. As well as this, complete separation of amine **290** from phthalamide side products was non-trivial and unsuccessful in most cases.

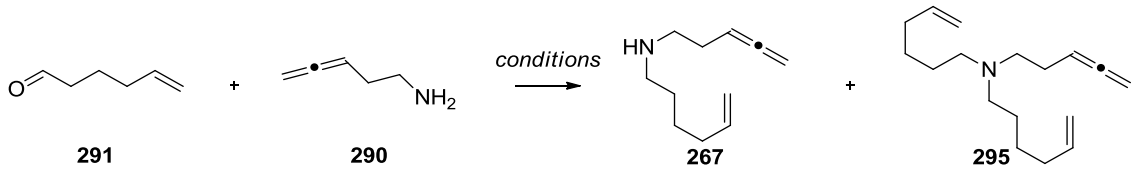
The second route (Scheme 37, **[2]**) proved to be more successful. To avoid handling volatile alcohol **286**, it was used crude in the ethereal organic extractions from the Crabbé homologation. The Crabbé homologation was carried out in tetrahydrofuran to aid separation of the organic and aqueous layers on scale-up. After an acidic work-up and extraction with diethyl ether, MsCl and Et_3N were added to the organic layer. Mesylate **293** was isolated in 27% yield over two steps from alcohol **285** with facile purification and handling. S_N2 displacement by sodium azide followed by a Staudinger reaction and subsequent hydrolysis of the formed iminophosphorane gave the desired amine **290** in quantitative yield over two steps. An acidic work-up and re-basification was successful in removing all triphenylphosphine and triphenylphosphine oxide residues, and crude ^1H NMR spectroscopy indicated the amine was of sufficient purity to be used without further purification.

2.2.2.4 Reductive Amination Studies

The crucial reductive amination was investigated and the results are outlined in Table 2. All reactions could be monitored by TLC to observe formation of the imine and subsequent reduction. Aldehyde **291** was synthesised by a Swern oxidation in 77% yield. Reactions in dichloromethane were unsuccessful with a wide range of reducing agents (Table 2, entries

1–8) and either gave no reaction or only tertiary amine formation, even with addition of drying agents such as molecular sieves (Table 2, entries 1 and 2) or Na_2SO_4 (Table 2, entries 6–10). To avoid potential tertiary amine formation, resulting from a second reductive amination between secondary amine **267** and aldehyde **291**, the equivalents of the amine used were increased (Table 2, entries 3–8), but this gave no improvement in yield. The use of formic acid as a reducing agent (Table 2, entry 5) led to extensive decomposition of all starting materials, and no product was observed in the crude ^{1}H NMR spectrum. Changing the solvent to tetrahydrofuran and using $NaBH_4$ gave improved yields (Table 2, entry 9), and the desired secondary amine **267** was isolated for the first time using this method, in 28% yield. Significant quantities of tertiary amine **295** were also observed (46% yield).

Table 2: Reductive amination studies



291 **290** **267** **295**

Entry	Aldehyde /eq	Amine /eq	Reducing agent	Additives	Solvent	Yield 267/%	Yield 295/%
1	1	1.2	$NaBH_4$	4Å MS, AcOH (cat.)	DCM	0	0
2	1	1.2	$NaBH_3CN$	4Å MS, AcOH (cat.)	DCM	0	32
3	1	3	$NaBH_3CN$	---	DCM	0	0
4	1	3	$NaBH_4$	---	DCM	0	0
5	1	3	Formic acid	---	DCM	---	---
6	1	3	$NaBH_4$	Na_2SO_4	DCM	0	0
7	1	3	$NaCNBH_3$	Na_2SO_4	DCM	0	0
8	1	3	$NaBH(OAc)_3$	Na_2SO_4	DCM	0	0
9	1	2	$NaBH_4$	Na_2SO_4	THF	28	46
10	1	2	$NaCNBH_3$	Na_2SO_4	THF	0	0
11	1	1.1	$NaBH_4$	---	MeOH	17	17
12	1	2.5	$NaBH_4$	---	EtOH	40	28
13	1	3	$NaBH_4$	---	EtOH	60	34
14	1	3	$NaBH_4$	---	EtOH	72[v]	---
15	1	1.5[vi]	$NaBH_4$	---	EtOH	88	---

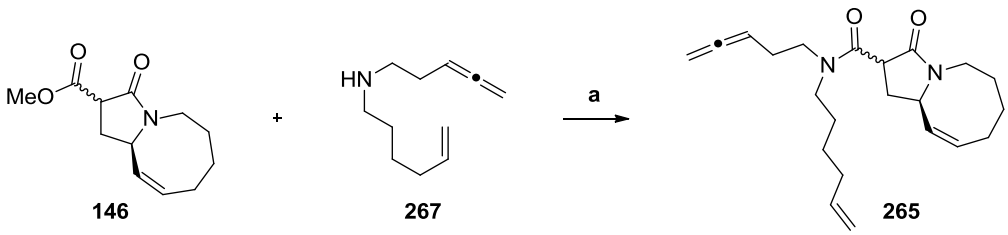
[v] On 1.00 g scale.
[vi] Using freshly distilled amine.

As solvent seemed to be very important, especially in solubilising the reducing agent, more polar solvents were employed (Table 2, entries 11–15) and, pleasingly, when using freshly distilled ethanol with an excess of amine **290**, the desired secondary amine **267** was isolated in 60% yield (Table 2, entry 13). On scale-up (1.0 g scale), the yield improved to 72% (Table 2, entry 14) and when freshly distilled amine **290** was used on the same scale, the yield improved further to 88% (Table 2, entry 15).

To summarise, the reductive amination approach was successful. When an excess of distilled primary amine **290** was employed with aldehyde **291** in freshly distilled ethanol and $NaBH_4$, 88% yield of desired amine **267** was achieved. After successfully optimising the reductive amination to form amine **267**, the route was then scaled-up to 25 g of 3-butyn-1-ol (**285**) which provided multi-gram quantities of amine **267**.

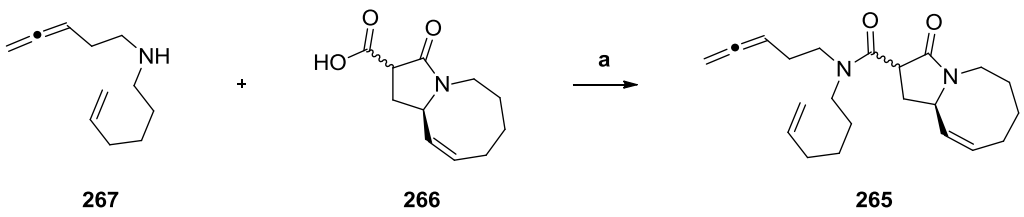
*2.2.3 Synthesis of Spirocyclisation Pro-Nucleophile **265***

Following the work of Dixon *et al.*[115] amine **267** and ester **146** were stirred in toluene at reflux (Scheme 38) but only limited reactivity was observed: amide **265** was isolated in 22% yield after 3 days. Due to the long reaction time and poor yield, a new approach was sought.



Scheme 38: Synthesis of pro-nucleophile **265**. **(a)** toluene, reflux, 3 days, 22%.

Following on the success of using CDI as a coupling reagent in Section 2.2.2.2 (acid **287** to amide **288**), it was utilised to form the spirocyclisation precursor **265**. On exposure of acid **266** to CDI in tetrahydrofuran, followed by addition of amine **267** after 10 minutes, the desired amide **265** was isolated in an average 74% yield, with a 1:1 dr (Scheme 39).



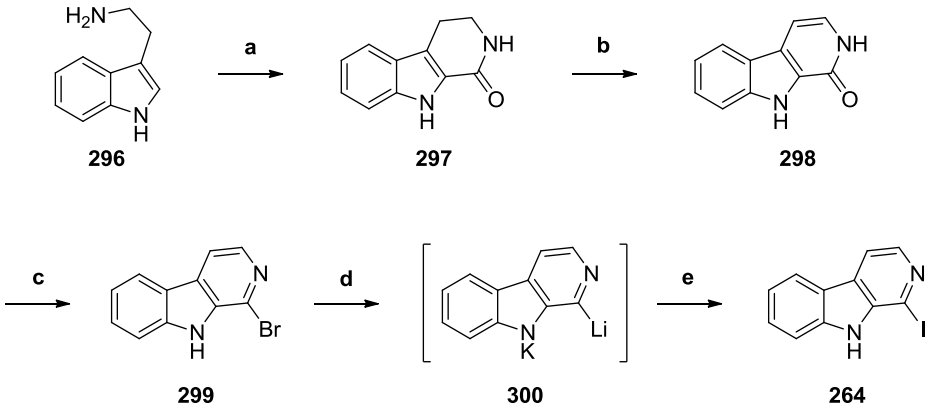
267 **266** **265**

Scheme 39: Synthesis of pro-nucleophile **265** using acid **266**. **(a)** CDI, THF, 12 h, RT, 71–77%, dr 1:1.

In summary, a scalable route to the spirocyclisation pro-nucleophile precursor **265** was developed in only eight steps from commercially available starting materials. The yields were high, the route was chemically robust and the materials were cheap. More than 2 g of spirocyclisation precursor **265** was synthesised allowing extensive optimisation of the palladium-catalysed arylative allene spirocyclisation reaction.

*2.2.4 Synthesis of β-Carboline **264***

The second coupling partner in the palladium-catalysed arylative spirocyclisation cascade was iodo-β-carboline **264**. The synthesis of β-carboline **264** was carried out according to modified and extended literature procedures developed by Bracher *et al*.[120] (Scheme 40).



296 **297** **298**

299 **300** **264**

Scheme 40: Synthesis of β-carboline **264**. **(a)** triphosgene, Et_3N, HBr (33 wt% in AcOH), toluene, RT to reflux, 1.5 h, 40%; **(b) (i)** DDQ, 1,4-dioxane, RT, 16 h, 54–77% or **(ii)** $Pd(OAc)_2$ (stoichiometric), mesitylene, 100 ˚C, 4 h, 94%; **(c)** $POBr_3$, anisole, 120 ˚C, 4 h, 51%; **(d) (i)** KH (30% in mineral oil), THF, 0 ˚C, 40 min **(ii)** *t*BuLi (1.7 M in pentane), −78 ˚C, 20 min; **(e)** I_2, THF, −78 ˚C to RT, 75%.

On exposure of tryptamine **296** to triphosgene, the isocyanate formed which on addition of acid, was protonated and underwent a cyclisation reaction to form tetrahydro-β-carboline **297**. Subsequent oxidation using 10% Pd/C in xylene was unsuccessful; only low crude mass

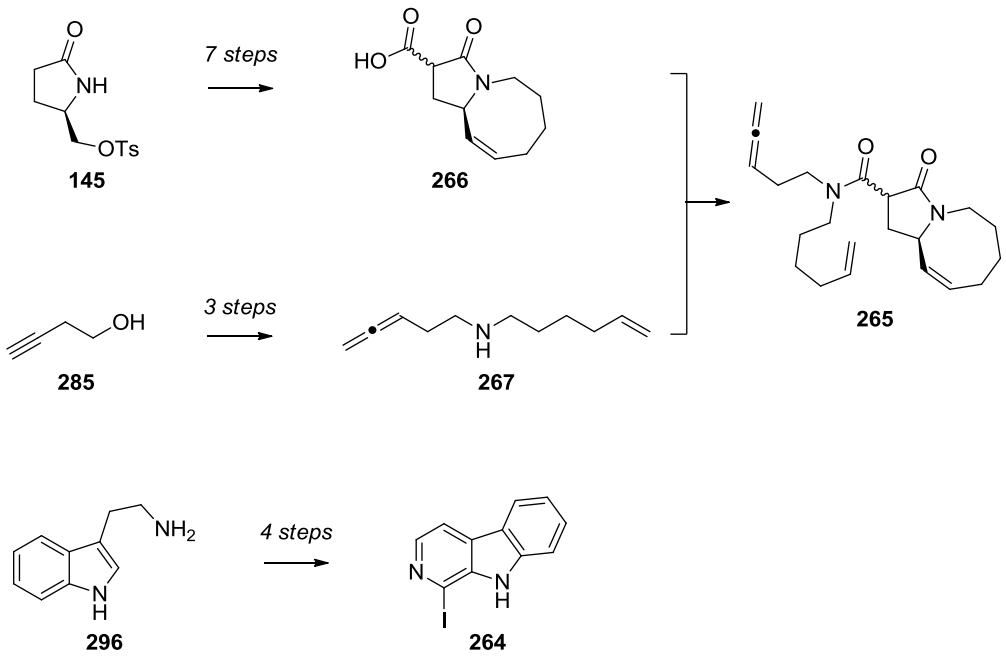
return was observed (<75%). However, changing to stoichiometric $Pd(OAc)_2$ in mesitylene gave almost quantitative yield. Using DDQ in 1,4-dioxane, a cheaper alternative oxidant, provided the desired dihydro-β-carboline **298** in up to 77% yield. Bromination of **298** proceeded using $POBr_3$ in anisole which gave the bromo-β-carboline **299** in around 50% yield.[vii] Di-anion **300** was formed[121] which was then quenched by the addition of iodine in freshly distilled tetrahydrofuran which, following an aqueous work-up, gave the desired iodo-β-carboline **264** in an average yield of 75%.

[vii] The bromo-β-carboline **299** was unsuccessful in the spirocyclisation cascade.

2.2.5 Summary

Iodo-β-carboline **264** was prepared in four steps from cheap, commercially available starting materials. Although there were many issues with the synthesis, for example, the use of *t*BuLi, triphosgene and $POBr_3$ on scale, the chemistry was carried out on large scale (30 g) and was reproducible.

Scalable and robust routes were developed to rapidly access the two advanced intermediates **264** and **265** required for the key step of our planned total synthesis (Scheme 41). With the iodo-β-carboline **264** and bis-amide pro-nucleophile **265** in hand, studies towards the palladium-catalysed spirocyclisation could be carried out.



Scheme 41: Summary of the synthesis of **264** and **265**.

2.3 Palladium-Catalysed Arylative Allene Spirocyclisation Studies

Dixon achieved excellent diastereoselectivities (dr 3:1 – 47:1) and average yields of 67% in the palladium-catalysed arylative spirocyclisation cascade.[115] Investigations began into the application of this novel reaction to the synthesis of manzamine A. However, maintaining reactivity whilst inverting stereoselectivity was crucial.

2.3.1 Mechanism

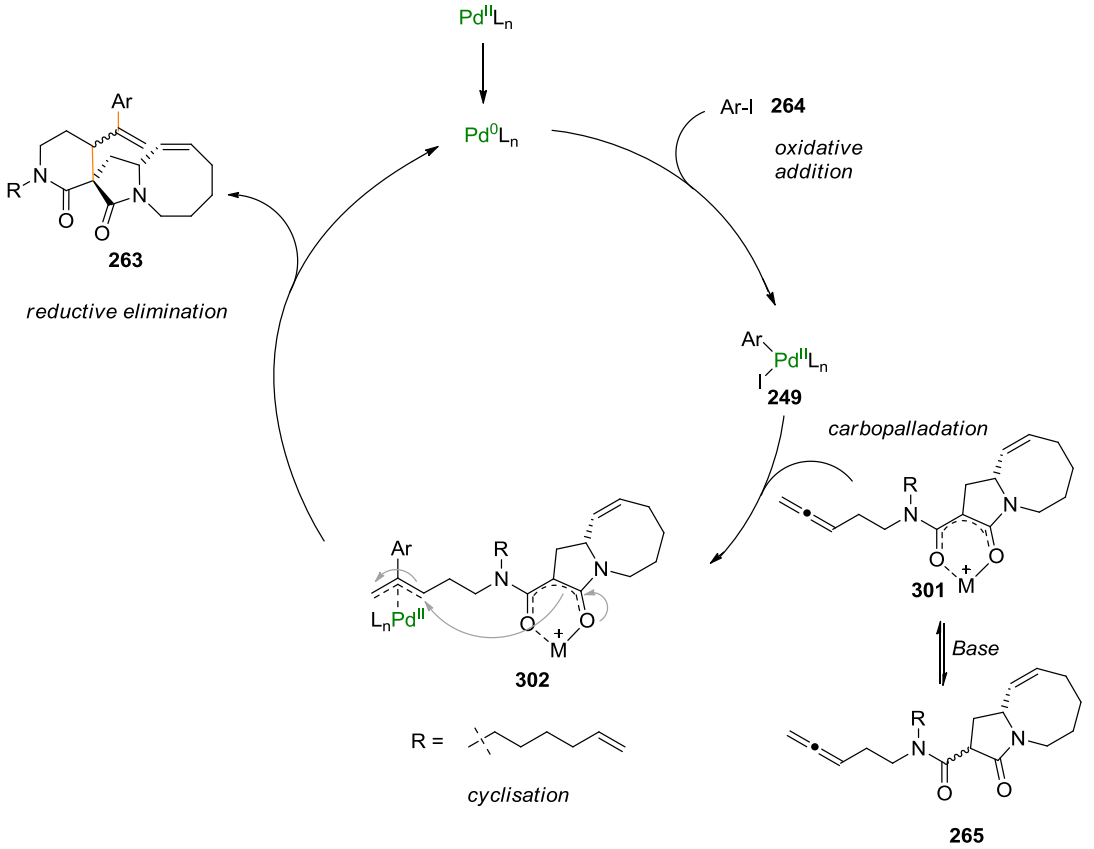


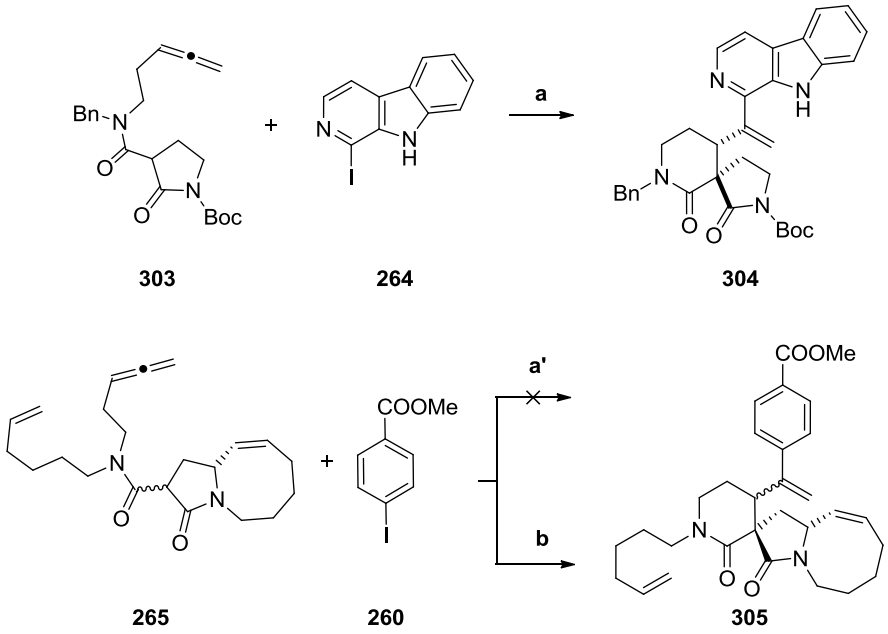
Figure 20: Possible mechanism for palladium-catalysed arylative allene spirocyclisation cascade.

The proposed mechanism is outlined in Figure 20. Overall, the reaction led to the formation of two new carbon-carbon bonds: one between the aryl-halide and sp centred allenic carbon *via* an η^3-π allyl palladium species, and one between the methine carbon and sp^2 internal carbon of the allene (Figure 20, **263**, highlighted in orange). Palladium(0) oxidatively inserts into the C-I bond in aryl iodide **264** which would give palladium(II)

complex **249**. Deprotonation of pro-nucleophile **265** occurred to form enolate **301**, which was carbopalladated resulting in the formation of η^3-π allyl palladium species **302**. The nucleophilic enolate then attacked the electrophilic π-allyl system and reductive elimination occurred releasing the spirocyclic product **263**, and regenerating the palladium(0) catalyst.

2.3.2 Validation of Coupling Partners

Investigations into whether the spirocyclisation partners **264** and **265** were able to undergo the key step began. Amide **303** and aryl-iodide **260** were both successfully employed in the original reaction methodology.[115] Thus, not knowing if our coupling partners were appropriate substituents for the reaction, **264** and **265** were validated against known compounds **303** and **260** (Scheme 42).



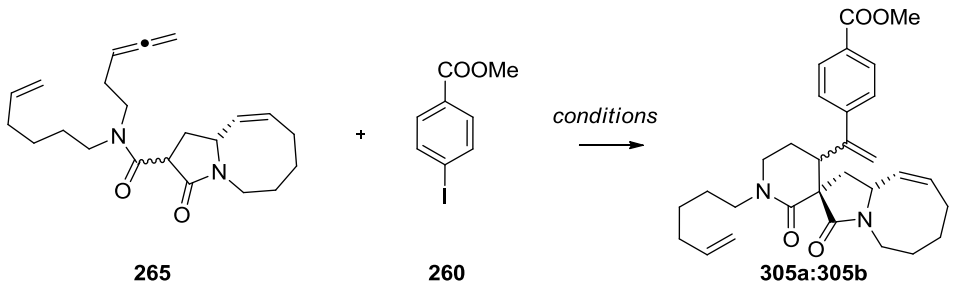
Scheme 42: Validation of β-carboline **264** and pro-nucleophile **265**. **(a/a')** 5 mol% $Pd_2(dba)_3$, 10 mol% dppe, K_2CO_3, DMSO, 70 ˚C, 16 h **(a)** 45%, dr 1:3 **(a')** no reaction; **(b)** 2.5 mol% $Pd(dppf)Cl_2$, CuI, LHMDS, THF, reflux, 16 h, 45%, dr 1:1.

Pleasingly, on exposure of β-carboline **264** to the original reaction conditions and using known *N*-Boc protected allene **303**[viii] the reaction proceeded to form the expected and undesired diastereomer **304** (Scheme 42, conditions **(a)**). Stereochemistry of **304** was

[viii] Pro-nucleophile **303** was successfully employed in the original methodology.[115]

proven by comparison of ^{1}H NMR spectra with compounds from the original work; the C_{quat}=C$\underline{H}_2$ protons are indicative of which diastereomer formed and comparisons could be made. Furthermore, in the original work, single crystal X-ray diffraction unambiguously proved the stereochemistry of a related compound.[115] When the required pro-nucleophile **265** was employed using the same reaction conditions (Scheme 42, conditions **(a')**), no reaction was observed. This was presumably due to the less acidic methine proton (pKa ≈ 18 for **265** compared to pKa ≈ 13 for **303**)[122] and increased steric bulk of the 8-membered ring. A small screen of different bases and solvents was performed with the required pro-nucleophile **265** (Table 3).

Table 3: Screening of conditions for pro-nucleophile **265** and model aryl iodide **260.**



Entry	Solvent	Base	Temp/˚C	PdL_n	Additives	Yield/%, dr 305a:305b	
1	DMSO	K_2CO_3	70	$Pd_2(dba)_3$, dppe	---	---	---
2	DMSO	NaH	70	$Pd_2(dba)_3$, dppe	---	---	---
3	THF	NaH	40	$Pd_2(dba)_3$, dppe	---	---	---
4	THF	LHMDS	66	$Pd(dppf)Cl_2$	CuI	45	1:1
5	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	CuI	42	1:1

Weaker, inorganic bases were unsuccessful (Table 3, entries 1–3). The solvent system was changed from polar solvent DMSO to less polar solvents because it was known that DMSO gave solely the undesired diastereomer for manzamine A. Following conditions developed by Burton *et al.*[123] (Table 3, entry 4) which used a stronger base (LHMDS) and a different catalyst system ($Pd(dppf)Cl_2$ and CuI) in tetrahydrofuran, **305** was isolated in 45% yield, 1:1 dr (Table 3, entry 4). Further change to 1,4-dioxane, a higher boiling ethereal solvent, gave the desired product in 42% yield, 1:1 dr. Having established that both bis-amide **265** and β-

carboline **264** could independently undergo the reaction cascade, screening began to utilise **265** and **264** together.

2.3.3 Key Step Investigation

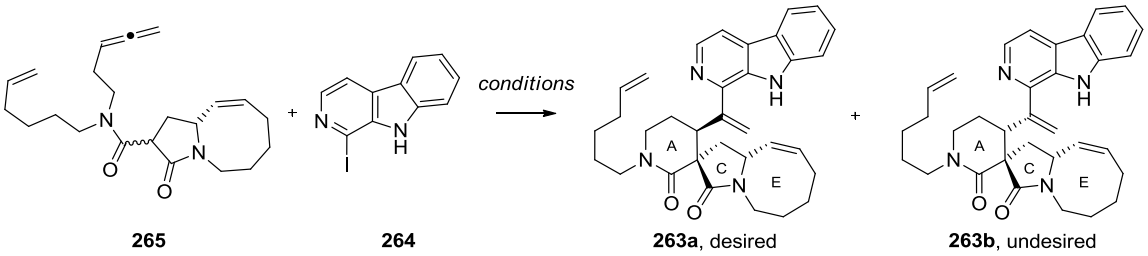
2.3.3.1 Screening and Optimisation

As discussed in Section 2.1.4, it was known from the outset that the original work developed within the research group would give the incorrect diastereomer for manzamine A. The diastereoselectivity needed to be inverted, as well as reactivity being maintained. Extensive optimisation was therefore carried out and a representative example is shown in Table 4.

All reactions were carried out on 50 mg scale using one equivalent of amide **265**, 1.5 equivalents of β-carboline **264**, 1 equivalent of base, 2.5 mol% Pd-complex, 5 mol% ligand, 5 mol% additive and at a concentration of 0.16 M.

Initially, a 1:1 diastereomeric mixture of **263a** and **263b** was obtained in 6% yield in tetrahydrofuran (Table 4, entry 1). Solvent played a significant role in determining the diastereoselectivity with non-polar solvents enhancing the diastereoselectivity to its fullest extent. Reasons for this are discussed further in Section 2.3.3.2. A solvent screen was carried out, using predominantly non-polar solvents as well as DMSO (Table 4, entries 2–9). As expected, DMSO (Table 4, entry 2) gave predominantly diastereomer **263b** which was analogous with the previous work,[115] but no major change in diastereoselectivity was observed amongst different non-polar solvents.

Table 4: Representative examples of the palladium-catalysed spirocyclisation cascade.



265 **264** **263a**, desired **263b**, undesired

Entry	Solvent	Base	Temp/˚C	PdL_n	Additives	Yield/%, dr 263a:b	
1	THF	LHMDS	66	$Pd(dppf)Cl_2$	CuI	6	1:1
2	DMSO	Cs_2CO_3	70	$Pd(dppf)Cl_2$	---	21	1:3
3	toluene	LHMDS	95	$Pd(dppf)Cl_2$	CuI	39	3:2
4	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	CuI	40	3:2
5	anisole	LHMDS	95	$Pd(dppf)Cl_2$	CuI	42	2:1
6	chlorobenzene	LHMDS	95	$Pd(dppf)Cl_2$	CuI	50	3:2
7	xylene	LHMDS	95	$Pd(dppf)Cl_2$	CuI	27	2:1
8	mesitylene	LHMDS	95	$Pd(dppf)Cl_2$	CuI	28	3:2
9	diphenyl ether	LHMDS	95	$Pd(dppf)Cl_2$	CuI	48	2:1
10	1,4-dioxane	LHMDS	60	$Pd(dppf)Cl_2$	CuI	24	3:2
11	toluene	LHMDS	60	$Pd(dppf)Cl_2$	CuI	16	1:1
12	1,4-dioxane	LHMDS	70	$Pd(dppf)Cl_2$	CuI	30	3:2
13	1,4-dioxane	KHMDS	95	$Pd(dppf)Cl_2$	CuI	---	---
14	1,4-dioxane	NHMDS	95	$Pd(dppf)Cl_2$	CuI	---	---
15	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	---	45	3:2
16	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	$AgSbF_6$	21	3:2
17	1,4-dioxane	LHMDS	95	$Pd(PPh_3)_4$	(*R*)-(*S*)-JOSIPHOS	29	3:2
18	1,4-dioxane	LHMDS	95	$Pd(OAc)_2$	(*R*)-BINAP	21	2:1
19	1,4-dioxane	LHMDS	95	$Pd(OAc)_2$	(*R*)-(*S*)-WALPHOS	41	3:2
20[a]	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	---	62	3:2

All reactions were carried out on 50 mg scale (of **265**). Standard conditions were: 1.0 eq. **265**, 1.5 eq. **264**, 1.0 eq. base, 10% Pd-complex, 20% ligand, 20% CuI, 0.16 M. (a) 1.5 eq. **265**, 1.0 eq. **264**, 1.7 eq. base.

A lower temperature led to a reduced yield, and starting material was recovered (Table 4, entries 10–12). It was found that the lithium counter-ion was required; changing the base to KHMDS or NHMDS inhibited reactivity (Table 4, entries 13–14). This may be due to the decreased stability of potassium or sodium enolates compared to the corresponding lithium enolate.[124]

It was unnecessary to use CuI for the reaction, which had also been observed by Burton *et al.* for some substrates (Table 4, entry 15 compared to entry 4).[123] A range of chiral ligands were employed in the hope that there would be an enhancement in the diastereoselectivity

(Table 4, entries 16–19) but unfortunately, no significant change was observed. A markedly improved yield of 62% was obtained when pro-nucleophile **265** was in excess (Table 4, entry 20, 1.5 equivalents relative to **264**). At this stage, it was decided that this yield and diastereomeric ratio was acceptable for introducing the majority of the carbon skeleton of manzamine A (**9**), including two new carbon-carbon bonds and two new stereocentres, in a single step to reach a key intermediate (Figure 21).

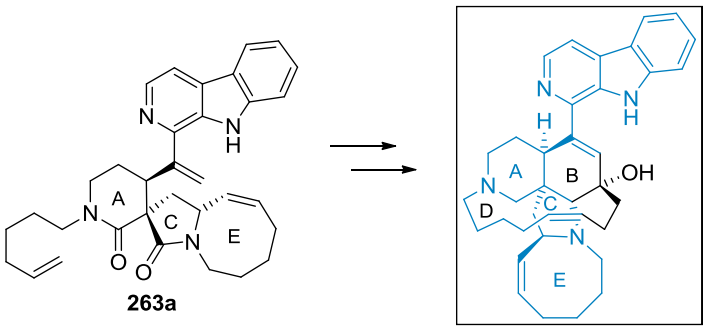


Figure 21: Highlighted carbons of the skeleton of manzamine A implemented in a single step.

2.3.3.2 *Explanation of Diastereoselectivity*

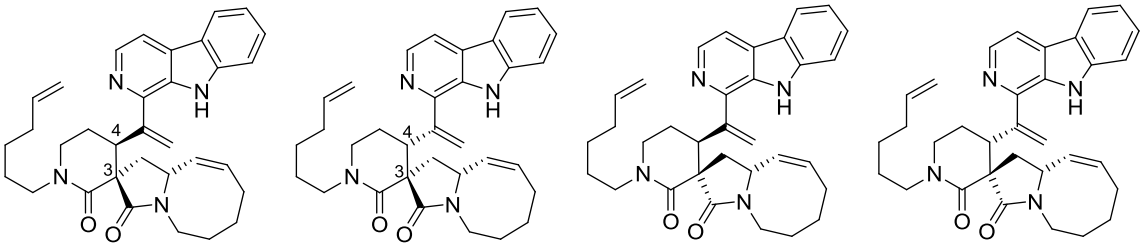


Figure 22: Four possible diastereomers from the spirocyclisation cascade.

During the spirocyclisation reaction, only two out of a possible four diastereomers were observed (Figure 22). It was clear that the existing stereochemistry of the 8,5-fused bicyclic system controlled the spirocyclic centre; only a single diastereomer was observed at C–3. Based on work by Zook *et al.*[125] it was postulated that in non-polar solvents there may be favourable chelation of the palladium to not only the η^3-π allyl system, but also to the enolate system (Figure 23, **[1]**). This may give some diastereocontrol giving **263a** in

preference to **263b**. In polar solvents such as DMSO, this chelation is disrupted (Figure 23, **[2]**) and **263b** is formed preferentially, where the vinyl aryl group is *trans* to the pyrrolidinone carbonyl. The 1,3-diaxial interactions observed in the postulated transition state would be alleviated yielding diastereomer **263b** (Figure 23, **[2]**).

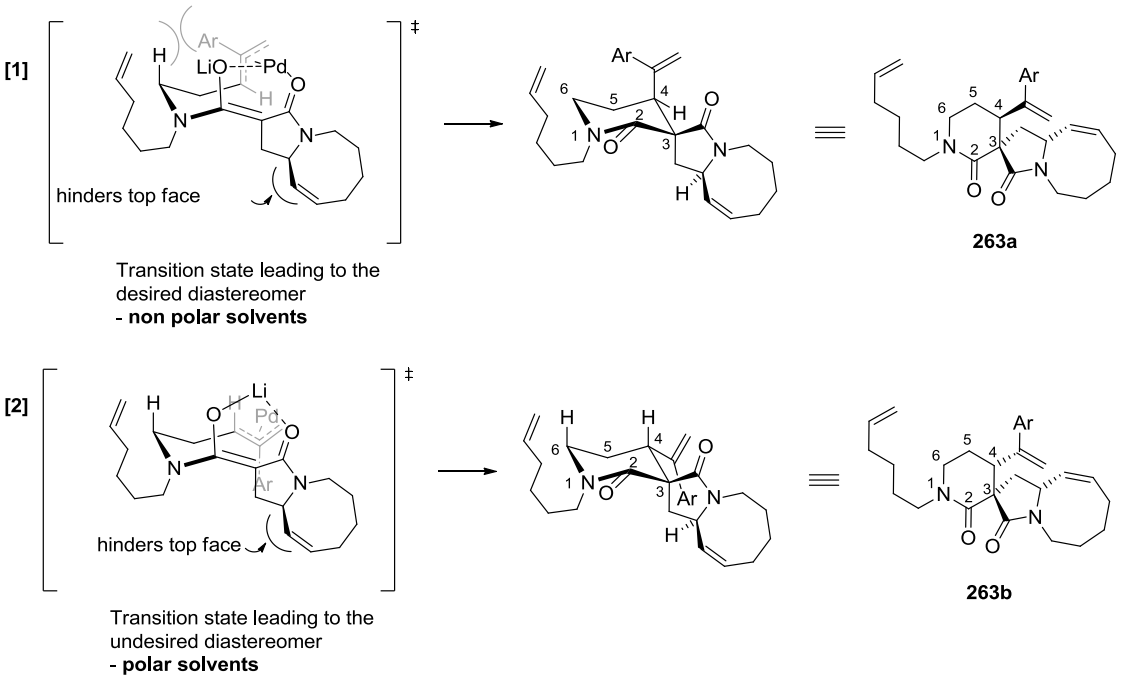


Figure 23: Possible explanation of diastereoselectivity.

2.3.4 Assignment of Stereochemistry of Separated Diastereomers

The diastereomers were not separable by flash column chromatography, however, they were separated by preparative HPLC (see Chapter 5 for details). Up to 200 mg was separated by preparative HPLC (see Appendix 1 for details) providing the pure diastereomers in the expected 3:2 ratio.

With the diastereomers separated, extensive NOESY experiments were carried out to determine the stereochemistry as it was not possible to generate crystalline material of sufficient quality for single crystal X-ray diffraction. The results from the NOESY experiments are outlined in Figure 24.

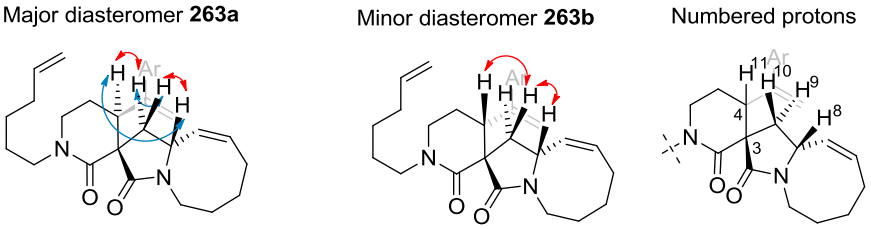


Figure 24: NOESY experiment results. Red arrows indicate strong interaction and blue arrows indicate weak interaction.

For the major desired diastereomer **263a**, very strong interactions were observed between H–8 and H–9 and also between H–9 and H–11. It can therefore be deduced, as the absolute stereochemistry at C–7 is known, that H–8 is on the same face as H–11. There was also a weak interaction observed between H–11 and H–8 and between H–8 and H–10 (Figure 24).

Conversely, for the minor undesired diastereomer **263b**, strong interactions were observed between H–8 and H–9, and H–10 and H–11. These positive interactions indicated that H–8 and H–9 are on the same face and H–10 and H–11 are also on the same face, therefore allowing the assignment of stereochemistry for the minor diastereomer.

2.3.5 Summary

A novel stereoselective route of the core of manzamine A was developed.[70] This route applied a new reaction developed within the research group as the key step in the synthesis of a complex natural product. The originally excellent, but undesired diastereoselectivity was successfully reversed, to allow access to the desired diastereomer for the synthesis.

2.4 Continuing the Synthesis: Ring B Formation Studies

As outlined in the original retrosynthesis (see Section 2.1.5), after the palladium-catalysed spirocyclisation, a chemoselective reduction, a one-carbon homologation and a stereoselective carbocyclisation were required (Figure 25). The chemoselective reduction of the piperidinone in the presence of the pyrrolidinone in the total synthesis of manzamine alkaloids is precedented (Figure 25, **263a** to **307**, discussed further in Chapter 4).[12,17]

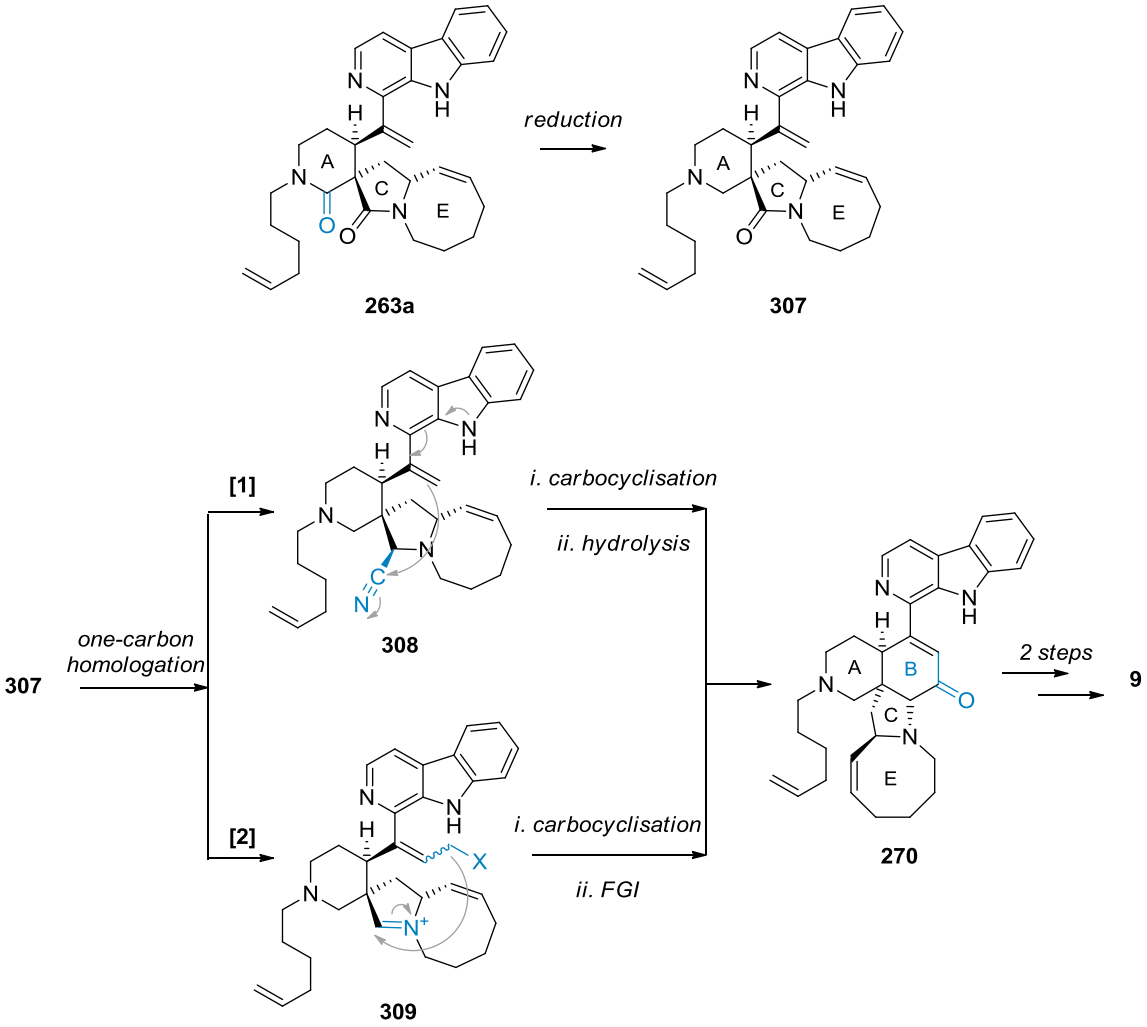
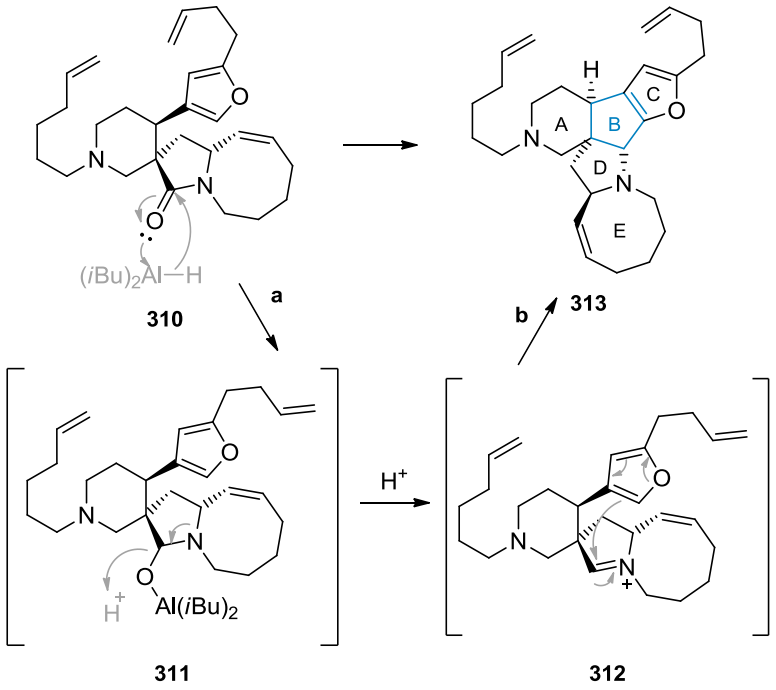


Figure 25: Planned synthetic route to advanced tetracyclic core **270.** X = activating group to allow carbanion formation.

Following the chemoselective reduction, there were two possible routes that would introduce one carbon into the system (Figure 25, **[1]** or **[2]**), and these are discussed in turn below.

2.4.1 Intermolecular Nucleophilic Attack

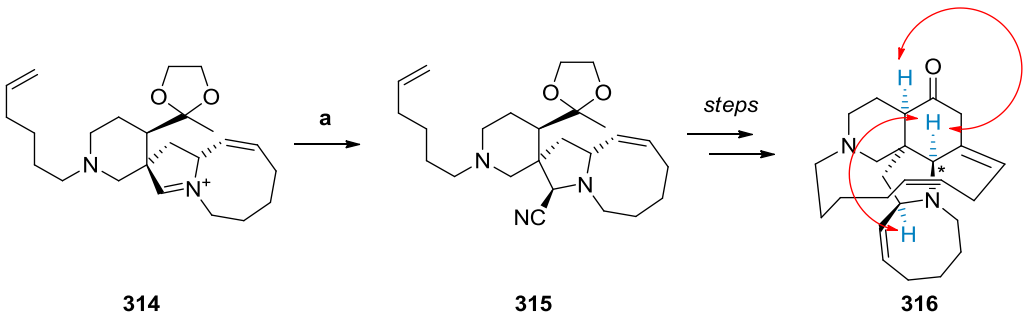
The first method was an intermolecular stereoselective cyanide addition to the pyrrolidinone carbonyl (Figure 25, **[1]**). This approach was based on a previously successful stereoselective intramolecular nucleophilic addition of a furan to an iminium ion which was utilised in the total synthesis of nakadomarin A to form ring B (Scheme 43, **313**).[17]



Scheme 43: Partial reduction/nitro-Mannich cyclisation of **310**. **(a)** DIBAL, toluene, −20 ˚C, 1 h; **(b)** HCl, 90 ˚C, 24 h, 41% over two steps.

The intermolecular stereoselective cyanide addition was performed in a parallel synthesis to form nitrile **315**. However, nOe experimental data collected on further advanced compound **316** confirmed that the cyanide had attacked from the undesired face and the carbocyclisation gave the wrong stereochemistry at C* for manzamine A (Scheme 44).[ix]

[ix] Unpublished work carried out by Dr Jakubec.



Scheme 44: Intramolecular nucleophilic addition into iminium **314**. **(a)** NaCN, phosphate buffer pH 8, RT, 2 h, 48%, dr 95:5. Red arrows indicate strong interactions by nOe experiments.

As an intermolecular addition of a nucleophile to the pyrrolidinone carbonyl gave the incorrect diastereomer for manzamine A (Scheme 44), the second approach was investigated (Figure 25, **[2]**).

2.4.2 Homologation of the Conjugated β-Carboline

The second approach was a one-carbon homologation of the conjugated double bond to introduce the extra carbon required (Figure 26). The homologation would also introduce an activating group (X) which would allow α-carbanion formation to occur.

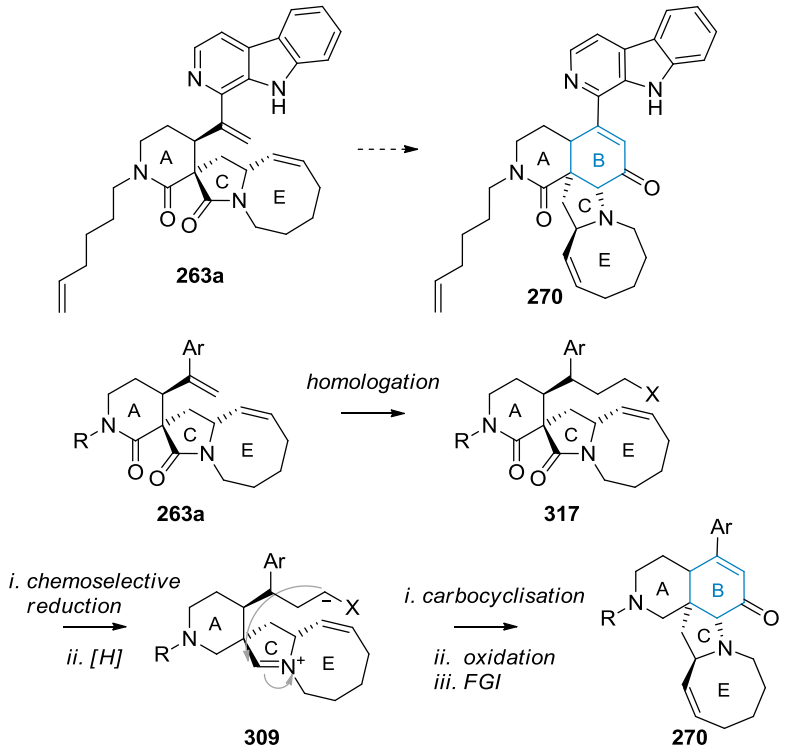
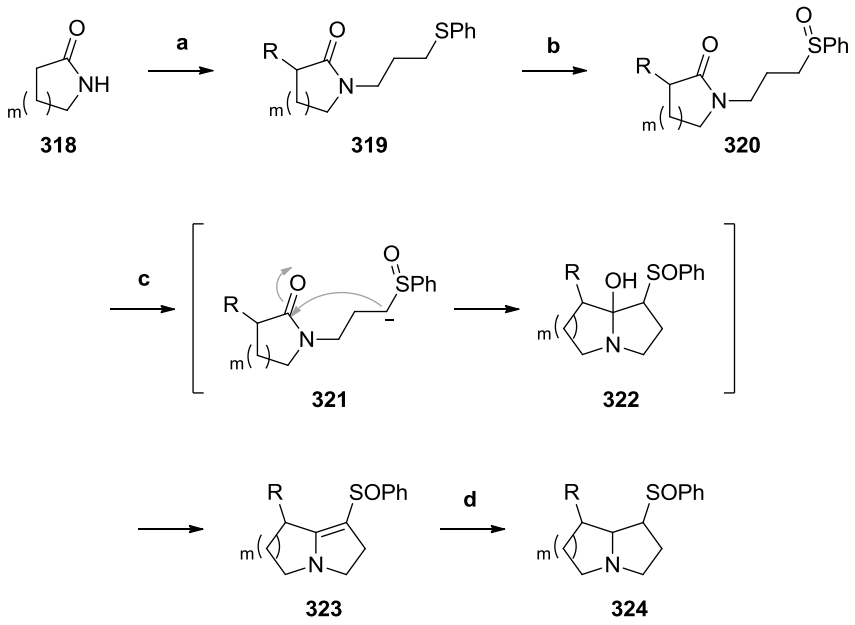


Figure 26: B-ring formation studies. X = activating group to allow α-carbanion formation.

The aim was to develop a reaction that would allow formation of a carbon-carbon bond between the α-carbon to X and the pyrrolidinone carbonyl carbon (Figure 26**, 309**). This approach also drew parallels with the original furan cyclisation used in the total synthesis of nakadomarin A by Dixon *et al.*,[17] where the use of an intramolecular nucleophile gave the desired tetracycle with the correct stereochemistry (Scheme 43). Therefore, investigations began into the identification of a suitable group for X.

2.4.3 Background: Utilising a Sulfoxide Group

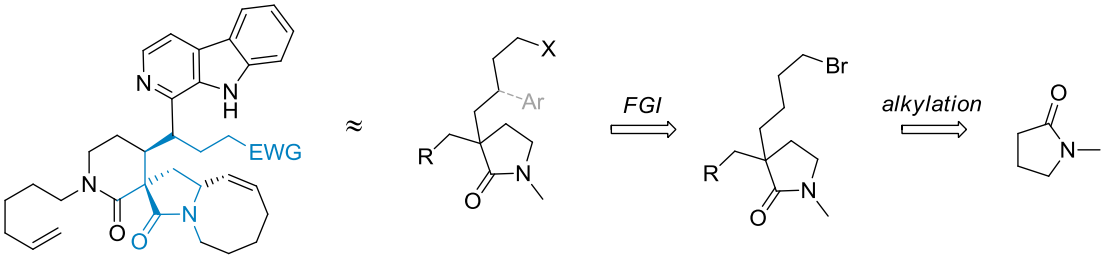
One approach was to follow methodology developed by Reutrakul *et al.*[126] who reported that *N*-alkylated sulfoxides could undergo this type of ring-closing reaction (Scheme 45).



Scheme 45: Synthesis of bicycle **324**. **(a) (i)** NaH, DMF, $BrCH_2(CH_2)_nCH_2SPh$, 0 ˚C to RT, 16 h **(ii)** LDA, THF, −78 ˚C then CH_3I**,** −78 ˚C to RT, 16 h, 74–87% over two steps; **(b)** $NaIO_4$, aq MeOH, 0 ˚C, 16 h, 86–96%; **(c)** LHMDS, THF, −78 ˚C to RT, 16 h, 85–90%; **(d)** $NaBH_4$, MeOH, 5 to 10 ˚C, 2 h, 55–59%. m = 2, 3; R = Me, H.

Reutrakul reported that under basic conditions, enolisation occurred on the α-sulfoxide carbon which subsequently underwent an intramolecular cyclisation on to the amide lactam which gave [x.3.0]-bicyclic systems **322** (x = 5–7). Elimination gave enamine **323** and subsequent reduction gave amine **324**. We believed we could utilise and extend this chemistry to form ring B.

We postulated that the sulfoxide moiety could be replaced with other electron-withdrawing groups such as a nitro group (Figure 27). One difference with our system was that, unlike Reutrakul's, it was *C*-alkylated, not *N*-alkylated and therefore, a model substrate was used to test the reactivity of the system as well as save precious front-line material. It should be noted that the reaction to form ring B used in the total synthesis of manzamine A (discussed in Chapter 1) had not been discovered.



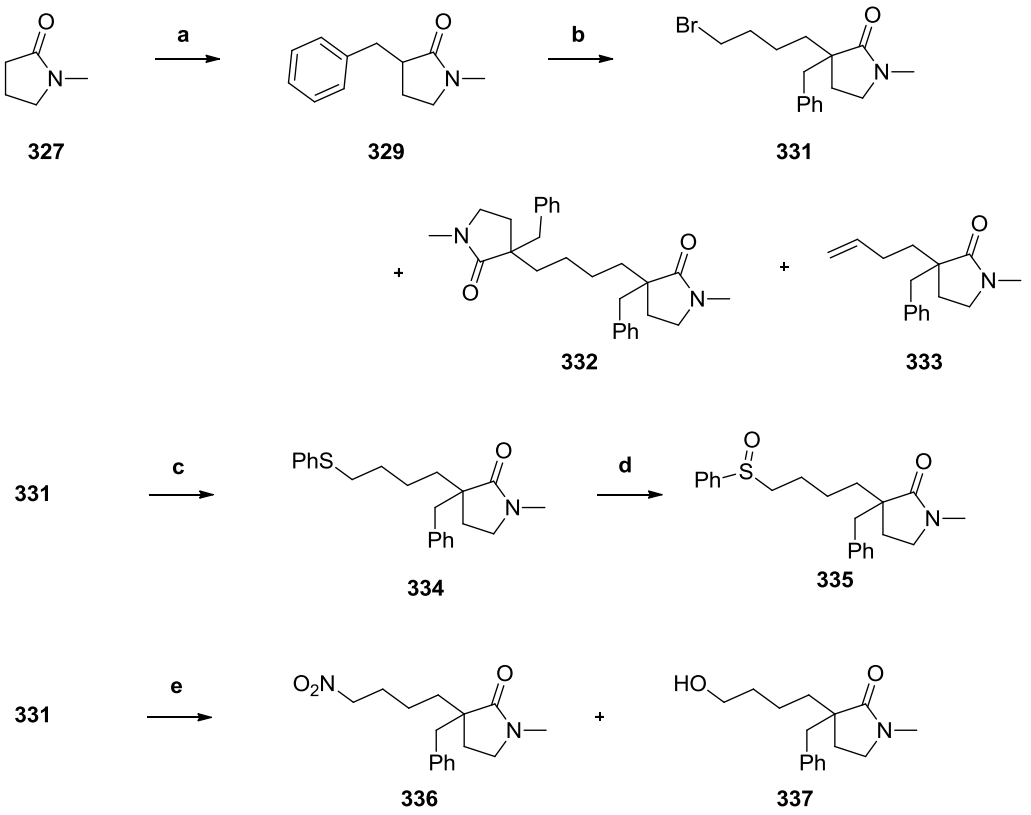
317 **325** **326** **327**

Figure 27: Retrosynthetic analysis for synthesis of B-ring formation model. X = SO_2Ph, NO_2. R = alkyl.

2.4.3.1 Synthesis of Starting Materials

The functionalised model substrates were all synthesised starting from commercially available *N*-methyl pyrrolidinone **327** (Scheme 46). Alkylation of **327** with benzyl bromide **328** gave **329** in 88% yield. Benzyl bromide was used to provide a chromophore to aid monitoring of the reaction by TLC. Subsequent alkylation with 1,4-dibromobutane **330** was low yielding (30%) and double alkylation (**332**) and eliminated (**333**) products were often observed, even after optimisation. However, this method provided ample material to investigate the ring-closing/reduction sequence.

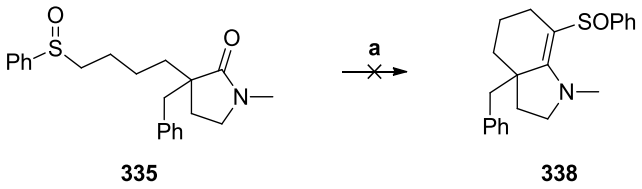
Displacement of bromide **331** with thio-phenol gave sulfide **334**, which was oxidised to sulfoxide **335** in 93% yield. Similarly, nucleophilic substitution of bromide **331** with sodium nitrite gave nitro derivative **336** in 54% yield and significant quantities of alcohol **337** (32%). With the substrates in hand, investigations in to the key ring closing/reduction sequence were then carried out.



Scheme 46: Synthesis of model cyclisation substrates **335** and **336**. **(a)** DIPA, *n*BuLi, BnBr **328**, THF, −78 ˚C to RT, 16 h, 88%; **(b)** DIPA, *n*BuLi, 1,4-dibromobutane **330**, THF, −78 ˚C to RT, 16 h, **331**: 30%, **332**: 35%, **333**: 10%; **(c)** PhSH, NaH, THF, 0 ˚C to RT, 8 h, 91%; **(d)** $NaIO_4$, MeOH, H_2O, 0 ˚C to RT, 6 h, 93%; **(e)** $NaNO_2$, DMSO, RT, 2 h, 86% overall, 1.7:1 **336**:**337**.

2.4.3.2 Cyclisation Studies

Conditions developed by Reutrakul *et al.*[126] were attempted on our system and a range of bases were explored (Scheme 47).

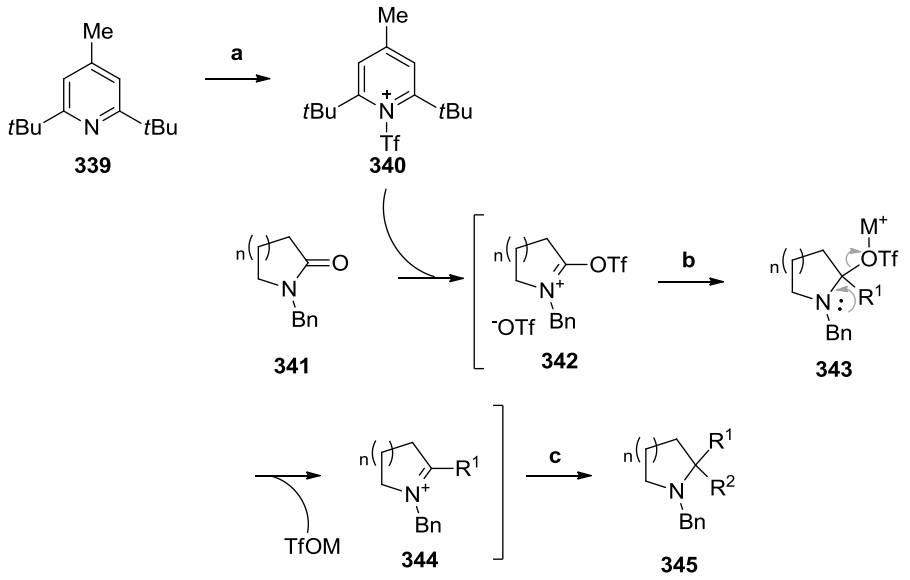


Scheme 47: Initial attempts at the cyclisation. **(a)** Base, THF.

NaH, KO^{t}Bu, KHMDS and NHMDS gave no reaction and only starting material was isolated. However, when lithium bases such as LHMDS and *n*BuLi were used, corresponding sulfide **334** was isolated.

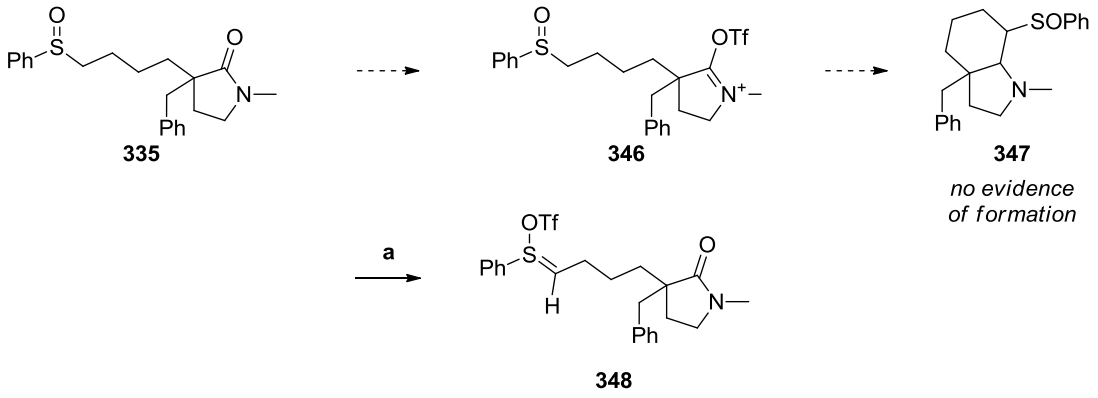
It was confirmed by deuterium experiments that the α-sulfoxide carbon was being deprotonated, as 100% deuterium incorporation was observed. It was concluded that although the anion was forming, the amide was not sufficiently reactive for the cyclisation to proceed.

Therefore, it was attempted to activate the amide towards nucleophilic attack. Xiao *et al.*[127] reported the activation of lactams followed by the addition of Grignards, using triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, (**339**)). The proposed mechanism is outlined in Scheme 48.



Scheme 48: Proposed triflic anhydride/DTBMP activation and Grignard addition. **(a)** Tf_2O, DCM, −78 ˚C, 45 min; **(b)** R^1M, Et_2O, −78 ˚C to RT, 3 h; **(c)** R^2M, Et_2O, −78 ˚C to RT, 3 h, 60–87%. n = 1, 2; R^1 = R^2 = Et, *n*Bu, allyl, Bn.

On addition of triflic anhydride, DTBMP (**339**) formed complex **340** which could react with the carbonyl of *N*-benzyl lactam **341** and form triflic imidate **342**. Addition of the first nucleophile (R^1M, **343**) and subsequent elimination of metallo-triflate TfOM gave iminium species **344**, which underwent a second nucleophilic addition, to generate the final amine **345**. Investigations into utilising this reaction to trap the triflic imidate species **346** in an intramolecular fashion with a nucleophile to form bicycle **347** began (Scheme 49).

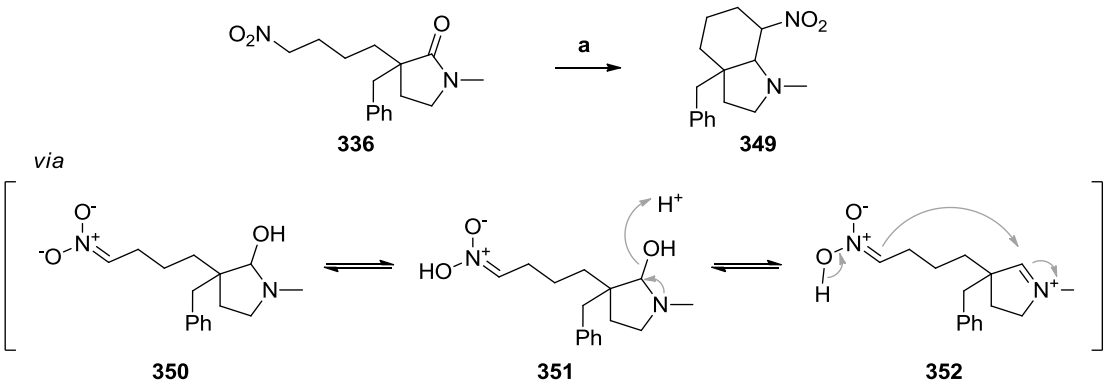


Scheme 49: Attempted triflation of **335**. **(a)** Tf_2O, DTBP, CD_2Cl_2, −78 ˚C, 2 h.

When this reaction was applied to our system, it was found that the sulfoxide was more reactive than the amide (Scheme 49); triflate **348** was observed by ^{1}H NMR (double doublet at 6.23 ppm, TfOS=C*H*) and ^{13}C NMR spectroscopy (new peak at 86 ppm, TfOS=*C*H). It was concluded that the sulfoxide was not a viable moiety to employ; attempts to activate the unreactive amide were unsuccessful and the desired cyclisation did not proceed. Therefore, a different electron-withdrawing group was used in order to harness reactivity.

2.4.3.3 Utilising a Nitro Group

After the sulfoxide approach was unsuccessful, attention turned towards another readily enolisable moiety, the nitro group. At the time of this work, there was no precedent for this type of reaction with a nitro group. This approach relied on a tandem *in situ* deprotonation/reduction process. An ambitious single hydride delivery to the amide bond and rapid cyclisation by the nucleophilic nitronate species onto the transient iminium species that formed (Scheme 50) was required.



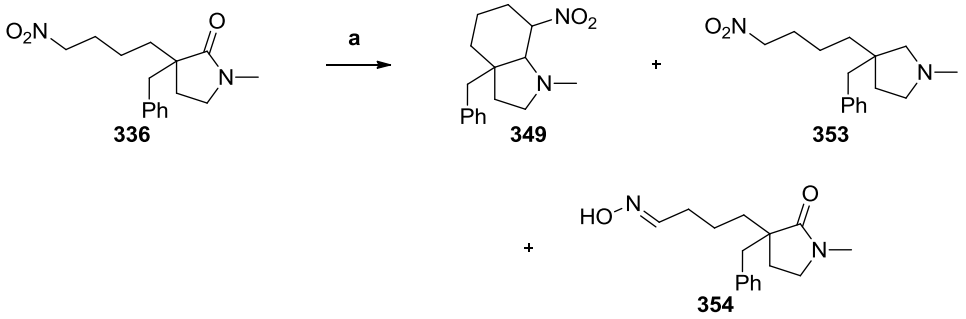
Scheme 50: Mechanism for cyclisation. **(a)** Base, reducing reagent, solvent, temperature.

Screening of a wide range of bases, reducing agents and different temperatures was carried out, and the results are outlined in Table 5. When base was used (Table 5, entries 5–10), the deprotonation step was performed first (addition of base) followed by addition of the reducing reagent.

The original reaction conditions from the Dixon nakadomarin A synthesis[17] were repeated on model system **336** (Table 5, entry 1); a slight excess of DIBAL was used and it was hoped DIBAL would act as a base as well as a reducing agent. However, only starting material and over-reduced tertiary amine **353** were isolated as well as the observation of a third minor compound which co-eluted from the column with amine **353.** The minor compound was tentatively assigned as the oxime from mass spectroscopy and characteristic ^{1}H NMR signals: a triplet at 6.7 ppm (N=C*H*) and singlet at 6.9 ppm (O*H*).

In an attempt to control over-reduction to the tertiary amine, low temperatures were employed (Table 5, entries 2–4). It was hoped that these reaction conditions would inhibit or slow the over-reduction of the tertiary amine whilst ensuring that full deprotonation was occurring. However, this only led to lower conversion, forming only the tertiary amine, and no cyclisation was observed.

Table 5: Tandem deprotonation/reduction cascade.



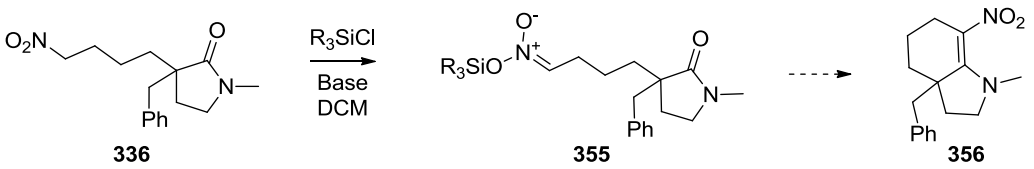
Entry	Base	Reducing reagent	Solvent	Conditions	336:353:354
1	---	DIBAL (1.45 eq)	toluene	−20 °C, 3 h	3:3:1
2	---	DIBAL (3.0 eq)	toluene	−78 °C, 3 h	20:1:0
3	---	DIBAL (3.0 eq)	toluene	−50 °C, 3 h	8:1:0
4	---	DIBAL (3.0 eq)	toluene	−50 °C, 30 min	1:1:0
5	*n*BuLi (1.0 eq)	DIBAL (1.0 eq)	toluene	0 °C, 2 h	8:2:1
6	KHMDS (1.0 eq)	DIBAL (1.0 eq)	toluene	0 °C, 2 h	2:2:1
7	NaH (1.0 eq)	DIBAL (1.0 eq)	toluene	0 °C, 2 h	1:0:0
8	KH (1.0 eq)	DIBAL (1.0 eq)	toluene	0 °C, 2 h	1:0:0
9	LHMDS (1.1 eq)	$LiAlH_4$ (1.5 eq)	toluene	−78 °C to 0 °C	---
10	LHMDS (1.1 eq)	Red-Al® (1.5 eq)	toluene	−78 °C to 0 °C	1:0:0

The sole use of DIBAL (as a base and reducing agent) had so far been unsuccessful. Therefore, it was attempted to formally synthesise the nitronate using different bases, before the addition of the reducing agent; one equivalent of base was added at 0 ˚C and after 30 min, DIBAL was added to the reaction mixture. However, this method did not improve the yields (Table 5, entries 5–8). Over-reduction to tertiary amine **353** was not observed, however only starting material was recovered (Table 5, entries 7 and 8). Changing the reducing agent to $LiAlH_4$ or Red-Al® was unsuccessful. When $LiAlH_4$ was used, ^{1}H NMR spectra of the crude reaction material indicated decomposition of the nitro group and attempts to purify baseline material were not successful (Table 5, entry 9). When Red-Al® was used, only starting material was obtained (Table 5, entry 10).

To summarise, this nitro compound **336** was unable to perform the cyclisation under the conditions outlined in Table 5, even though the reduction of the amide was observed. Therefore, we aimed to increase the nucleophilicity of the nitronate species. One potential

problem would be preferential attack by the oxygen nucleophile in the nitro-group over the desired α-nitro carbon nucleophile. To avoid this problem, the synthesis of a silyl nitronate ester was employed following work by Seebach.[128]

Table 6: Silyl nitronate formation attempts.



336 **355** **356**

Entry	Base	Silylating reagent	Conditions	Result 336:355
1	DBU (1.2 eq)	TBDMSCl (1.5 eq)	0 °C	No reaction
2	Et_3N (1.2 eq)	TMSCl (1.5 eq)	0 °C	1:2
3	Et_3N (1.2 eq)	TBDMSCl (1.5 eq)	0 °C	1:5
4	NMM (1.2 eq)	TBDMSCl (1.5 eq)	0 °C	No reaction
5	PS-BEMP (1.2 eq)	TBDMSCl (1.5 eq)	0 °C	No reaction
6	Et_3N (1.5 eq)	TBDMSCl (1.2 eq)	−78 °C	10:1
7	Et_3N (4.0 eq)	TBDMSCl (3.0 eq)	−78 °C	1:1
8	LDA (1.07 eq)	TBDMSCl (1.14 eq)	−78 °C	No reaction
9	Et_3N (1.5 eq)	TBDMSOTf (1.1 eq)	−78 °C	No reaction
10	Et_3N (1.5 eq)	TMSOTf (1.1 eq)	−78 °C	No reaction

Table 6 highlights attempts made to synthesise silyl nitronate ester **355**. All reactions were carried out in a similar manner: to **336** in dichloromethane was added the silylating reagent and base at the temperature stated before being warmed to RT and stirred for 1 h. The solvent was removed under a stream of nitrogen and the crude material was analysed by ^{1}H NMR spectroscopy. Silyl nitronate **355** had a distinctive triplet at 6.1 ppm ($CH_2\underline{H}C{=}NO_2SiR_3$) and could be integrated against the starting material. Triethylamine tended to yield the best results (Table 6, entries 2, 3, 6 and 7). The use of TMSCl was not as successful as TBDMSCl (Table 6, entry 2), presumably due to high instability levels of the TMS group, and the use of triflate analogues (Table 6, entries 9 and 10) failed. Very low temperatures (Table 6, entries 6–10) gave almost no reactivity except when using a large excess of base and silylating reagent (Table 6, entry 7). Starting material was observed in all cases, and the best result was obtained using triethylamine with an excess of TBDMSCl at 0 ˚C; a 5:1 ratio of

product to starting material was obtained, which was used crude after filtration through Celite®.

The cyclisation using silyl enol ether **355** was performed using the original reaction conditions from the Dixon nakadomarin A synthesis:[17] DIBAL (1.5 eq) and toluene at −20 ˚C before being quenched (methanol, $Na_2SO_4 \bullet H_2O$ and diethyl ether), but unfortunately no reaction was observed. The reduction of the amide bond was sluggish and only deprotected nitro compound **336** was isolated.

The nitro group, under these conditions, did not give any of the required 6,5-fused ring system. The desired single hydride delivery to the amide bond and subsequent cyclisation was unsuccessful on this substrate. Therefore a new method was sought.

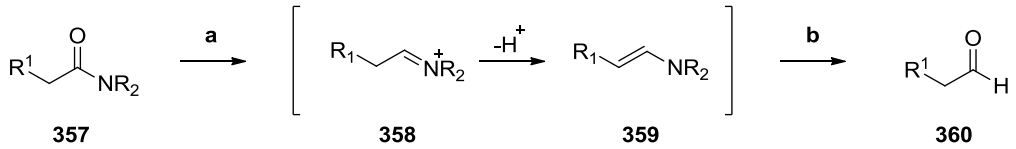
2.4.4 A Novel Intramolecular Nitro-Mannich Reaction

The following chemistry described in this section was carried out by Alan Chambers, a final year research student who worked under my day-to-day supervision.[129] It is included for continuity purposes.

The synthesis of ring B was crucial for both the total synthesis outlined in Chapter 1 as well as the synthesis described in this chapter. The intramolecular nitro-Mannich cyclisation described in Section 2.4.3.3 was completely unprecedented in the literature and was evidently non-trivial. Conditions needed to be developed that were mild and highly selective. The stable amide bond needed to be sufficiently activated or reduced in the presence of a reactive nitro moiety that would then be followed by a cyclisation reaction.

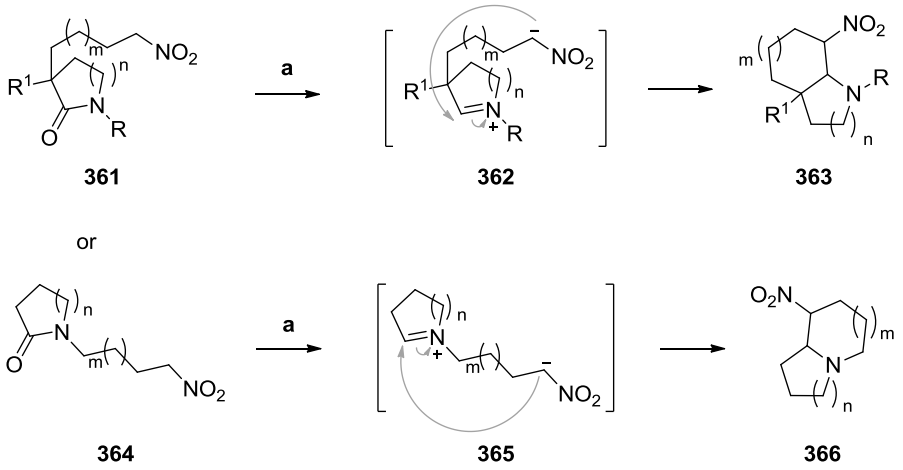
After the failed attempts using classic reducing reagents such as DIBAL to try and effect a single hydride delivery to form the aminol/iminium ion species, a new method was required. Work by Buchwald *et al.*[74] reported that amides **357** could be converted to aldehydes **360** *via* an iminium-type species (Scheme 51, **358**). This method used one

equivalent of Ti(O*i*Pr)$_4$ and one equivalent of Ph_2SiH_2 at room temperature and yields of 50–90% were obtained.



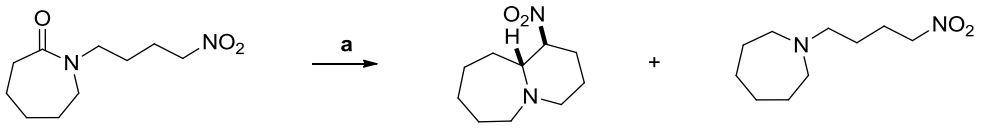
Scheme 51: Synthesis of aldehydes *via* an iminium/enamine reaction. **(a)** Ti(O*i*Pr)$_4$, Ph_2SiH_2, 20 ˚C, 5 h; **(b)** H_3O^+, 1 h, 20 ˚C, 50–90%.

In the presence of an appropriately tethered nucleophilic trap, it was thought that this reaction and alternatives could be applied to the synthesis of ring B of manzamine A and could also be expanded into a general methodology.



Scheme 52: Proposed reaction sequence to form bicycles **363** and **366**. **(a)** Reducing agent. n = 1–4; m = 1, 2; R = alkyl; R^1 = alkyl, H.

The starting materials (Scheme 52, **361** and **364**) were synthesised following work outlined in Scheme 46, employing either *N*- or *C*-alkylation. After initial screening of reagents and conditions, it was found that the Buchwald methodology was adaptable to model systems **361** and **364**. Further successful optimisation of catalyst type and loading, silyl source and loading, solvent, temperature and concentration led to the general conditions which are outlined in Scheme 53.



361a **363a** **367**

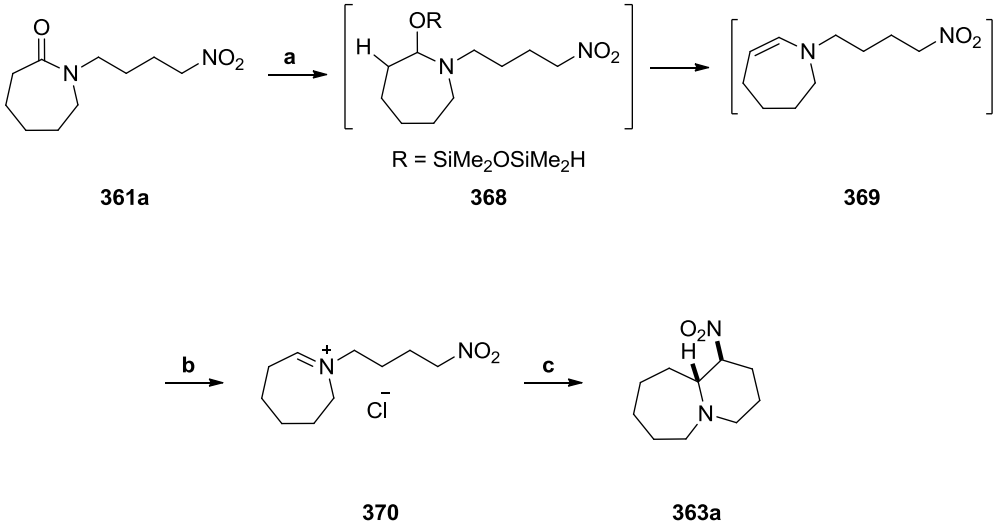
Scheme 53: Synthesis of bicycle **363a**. **(a)** 0.5 mol% $IrCl(CO)(PPh_3)_2$, 2.0 eq TMDS, toluene, RT, 5 min, then 1 M HCl: **363a** 80%, dr: 88:12; **367** 10%.

There were three key points to note about this remarkable, novel reaction. Firstly, the change from stoichiometric Ti(IV) to catalytic Vaska's complex ($IrCl(CO)(PPh_3)_2$). After a wide screen of reducing reagent/catalyst systems, the use of catalytic Vaska's complex with 1,1,3,3-tetramethyldisiloxane (TMDS) (or PMHS; the polymeric version of this reagent) was successful. These conditions were reported by Nagashima *et al.*[130] who converted amides to enamines and with substrate **361a**, 80% yield was achieved with 88:12 dr (Scheme 53). This represented a huge improvement from the starting conditions attempted by Chambers; DIBAL in toluene at room temperature gave **363a** in 11% yield.

The second key point was the speed of reaction; the reaction proceeded very cleanly with high yields and excellent diastereoselectivities in just five minutes.

Thirdly, the acidic work up was crucial. When a basic quench was used, no product was observed. However, using an acidic quench such as silica gel or 1 M HCl and re-basification gave the desired product **363** in excellent yields.

With this knowledge in hand, the mechanism was probed and the hypothesis is outlined in Scheme 54. All intermediates were observed by ^{1}H and ^{13}C NMR spectroscopy throughout the reaction when the reactions were carried out in, and quenched with deuterated solvents.[129] Chambers confirmed that, by isolation and characterisation of intermediates using ^{1}H and ^{13}C NMR spectroscopy, the reaction proceeded *via* enamine intermediate **369** which upon acidic treatment, was converted to iminium **370** before subsequent cyclisation gave desired bicycle **363**.



Scheme 54: Synthesis of bicycle **363a**. **(a)** 0.5 mol% $IrCl(CO)(PPh_3)_2$, TMDS, RT, toluene, 5 min; **(b)** 1 M HCl; **(c)** K_2CO_3, 80%, 88:12 dr.

The substrate scope was wide, and a number of fused ring sizes were accessed (Figure 28).[x] The *C*-alkylated series gave lower yields (Figure 28, **366a** and **366b**), presumably because enamine formation was less favourable. Furthermore, one major limitation with the methodology is that no reactivity was observed with α-carbonyl quaternary centres; no enamine could form, which inhibited the reaction, but does give weight to the proposed mechanism (Scheme 54).

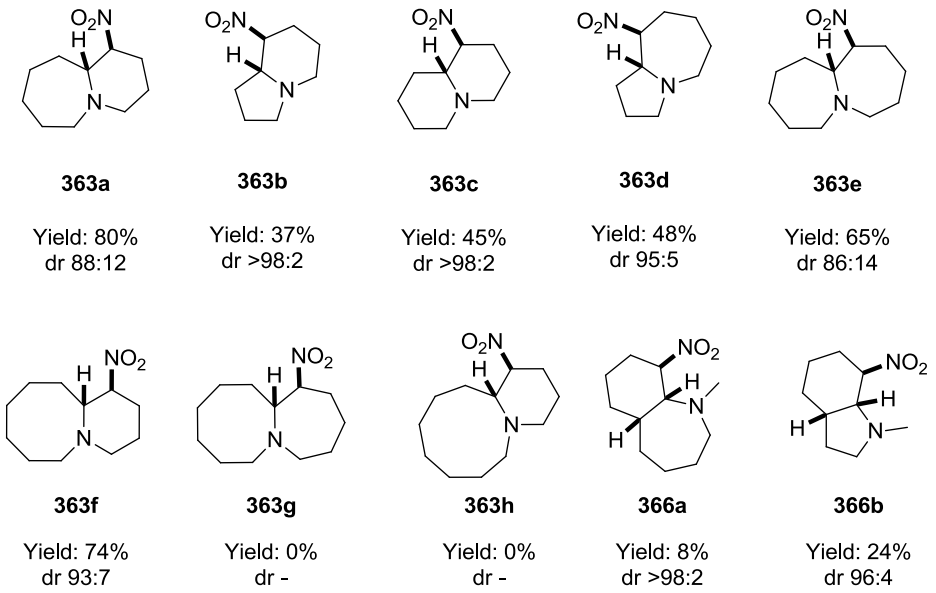


Figure 28: Substrate scope of the intramolecular nitro-Mannich cascade.

[x] For all characterisation details, please see ref 130.

In summary, a new reaction cascade was developed which activated a classically stable, but extremely prevalent amide bond to form a range of bicyclic structures, common in many natural product and drug targets. Of particular note was the highly-controlled partial reduction of the amide bond with successful trapping of the *in situ* formed iminium species by an intramolecular nucleophilic nitroalkane moiety. All intermediates and products could be isolated and characterised by standard methods. In addition, the chemoselectivity was impressive; no reduction of the nitro group was observed. To summarise, it was established that a nitro group was required for the potential construction of ring B.

2.4.5 Application to the Synthesis of Manzamine A

During the course of this research, a second route to manzamine A was in progress (see Chapter 1) which was carried out by Dr Pavol Jakubec (Figure 29).[xi]

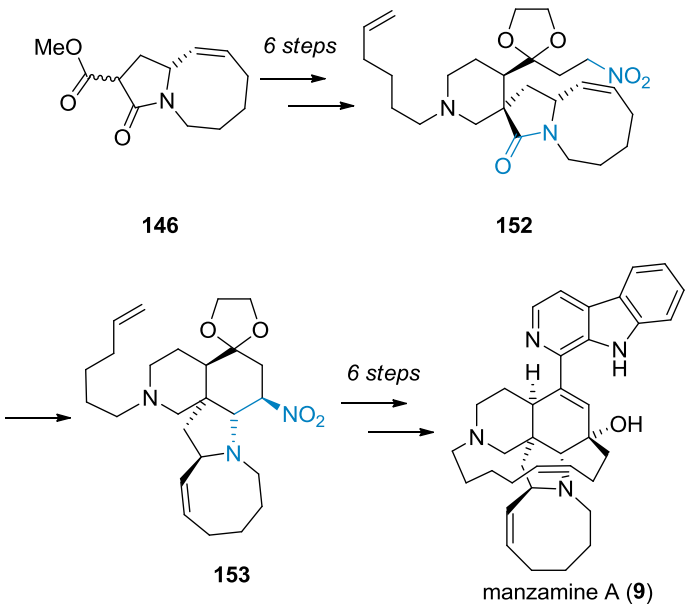


Figure 29: Condensed synthetic route to manzamine A.

Application of the Chambers conditions were trialled on nitro-acetal **152** but were not successful. This result was not unexpected in light of Chambers' results, due to the

[xi] Two parallel routes to manzamine A were ongoing during my DPhil. studies. The work carried out by Dr Jakubec, with whom I worked closely, is again included for continuity and background purposes.

spirocyclic core of **152** which would inhibit enamine formation. However, after a systematic screening of different reagents and conditions, it was found that the original Buchwald methodology with minor modifications (increased equivalents of Ti(IV) and Ph_2SiH_2) was the most successful, yielding **153** in 81% yield, dr 83:17, epimeric at the carbon bearing the nitro. The proposed mechanism is outlined in Figure 30.

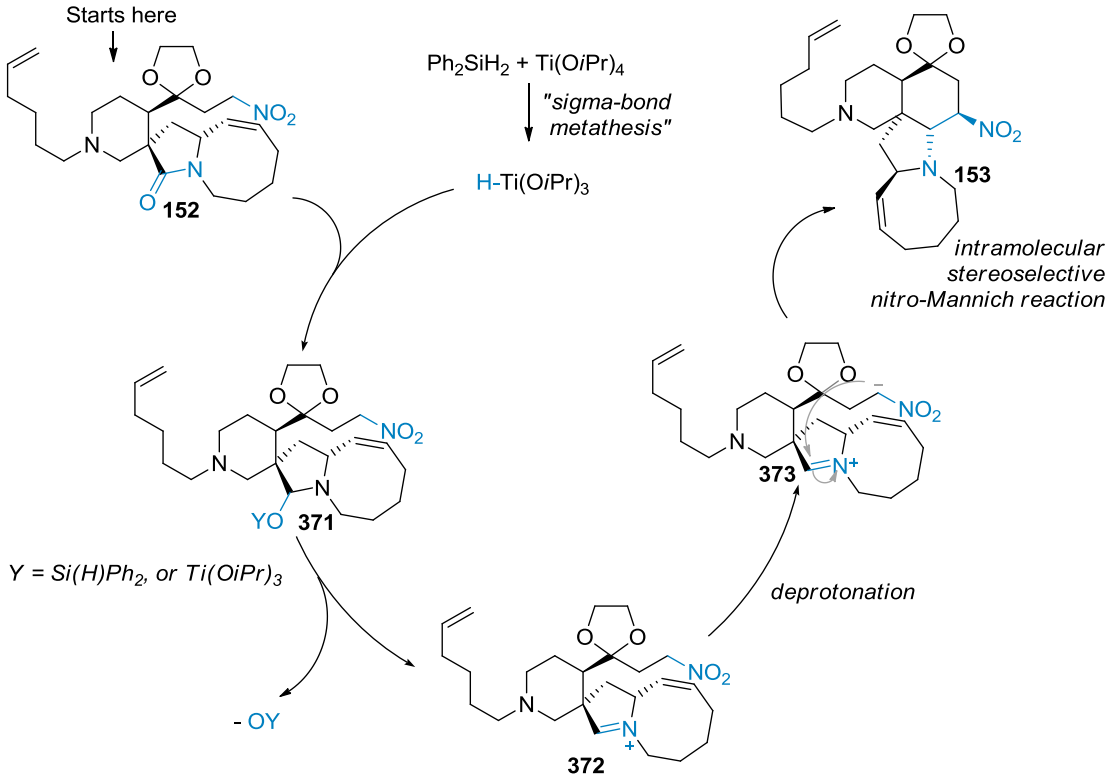


Figure 30: Reaction mechanism for intramolecular nitro-Mannich cascade.[xii]

This reaction was mild and highly selective, and was successful in forming ring B on a densely functionalised substrate. The route to tetracycle **153** was ultimately successful in completing the total synthesis of manzamine A[12] (Chapter 1). Therefore, incorporation of the nitromethylene moiety into the product from the palladium-catalysed arylative spirocyclisation cascade *via* homologation of **263a** was desired.

[xii] The reaction is not catalytic, but is presented in this way for clarity.

2.5 Homologation Studies

The aim was to incorporate an extra CH_2NO_2 to the vinyl β-carboline system (Figure 31), a transformation that was completely unprecedented in the literature, as was any nucleophilic addition to a vinyl β-carboline system.

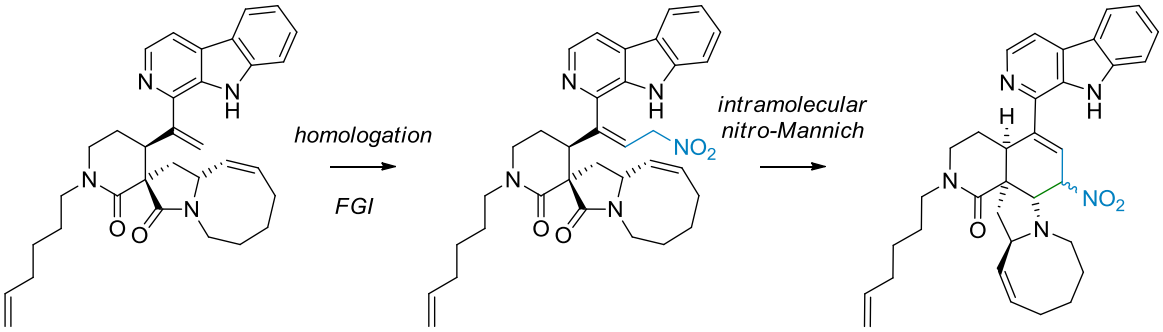


Figure 31: Synthetic plan for 1st generation synthesis.

Accordingly, a model system was sought (Figure 32) in order to validate the chemistry before application to the real system **263a**. The model system **376** would be synthesised *via* a Suzuki cross-coupling reaction between known triflate **377**[131] and known boronic ester **378**.[132]

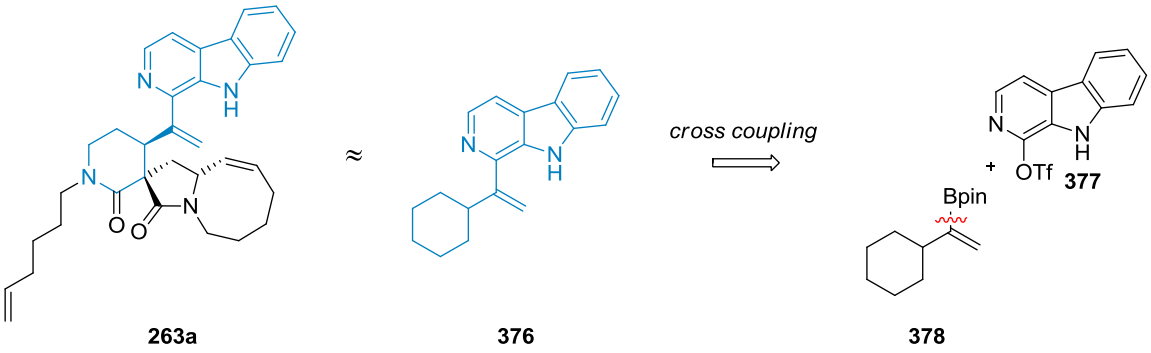


Figure 32: Model system design and retrosynthesis.

The β-carboline possessed a pyridyl moiety, which was electron-withdrawing. It also possessed an indole nitrogen, which could donate electrons into the system. The aim was to exploit the electronics of the system in order to provide reactivity towards nucleophiles, electrophiles, or free radical intermediates (Figure 33).

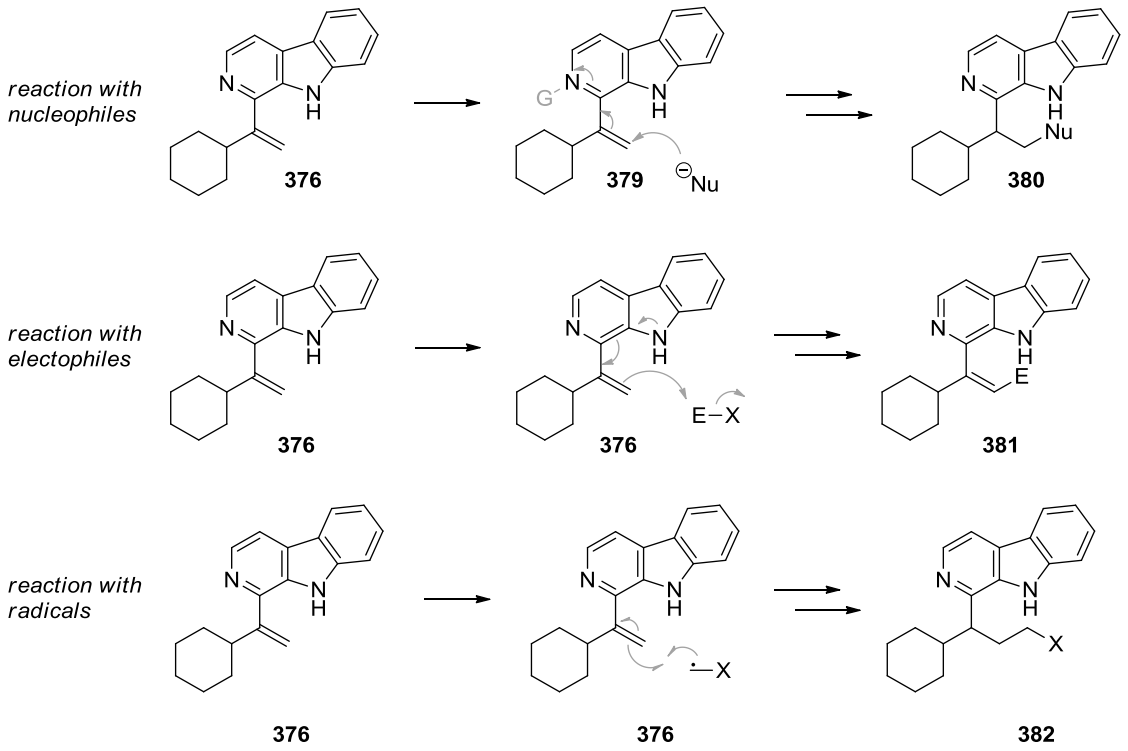


Figure 33: Potential reactivity of the β-carboline system. G = activating group, Nu = nucleophile, E = electrophile, X = leaving group or functionality.

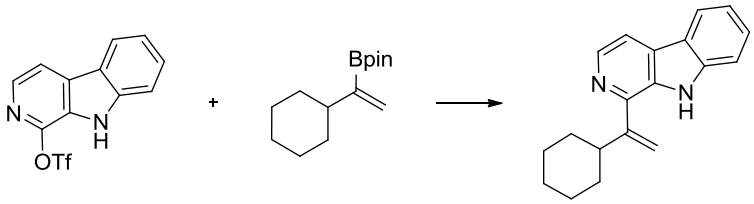
If **376** would react with nucleophiles, we envisaged using an activating species, G, to make the entire system more electron-deficient (Figure 33, **379**). This could be a Lewis acid, *N*-alkylating reagent, or a metal ion. The nucleophile could then attack the electron deficient system (1,4-addition) to form the saturated system **380**. On the other hand, using a suitable electrophile, it was hoped that electrons would be donated in to the system from the indole nitrogen to create an electron-rich double bond which would react with an electrophile (Figure 33). We also hoped that the system could react with either electrophilic or nucleophilic radicals (Figure 33). This would yield the saturated system **382**, and the double bond would be re-introduced later.

*2.5.1 Synthesis of Model System **376***

The synthesis of triflate **377** and boronic ester **378** was carried out according to literature procedures and occurred without incident.[131,132] The Suzuki cross-coupling reaction[133] proceeded after some minor optimisation (Table 7). For this system, the use of 1,4-dioxane with saturated aqueous $NaHCO_3$ was crucial. When $Pd(PPh_3)_4$ was used, model system **376**

was obtained in 42% yield (Table 7, entry 1). When the catalyst was changed to Pd(dppf)Cl_2, **376** was isolated in an increased 51% yield (Table 7, entry 3), which on larger scale (430 mg compared to 50 mg) was significantly improved to 79% yield (Table 7, entry 5). Other solvent systems and bases precedented in the literature with aryl triflates were unsuccessful, some of which are shown in Table 7 (entries 2 and 4).[134,135]

Table 7: Suzuki reaction optimisation .



377 **378** **376**

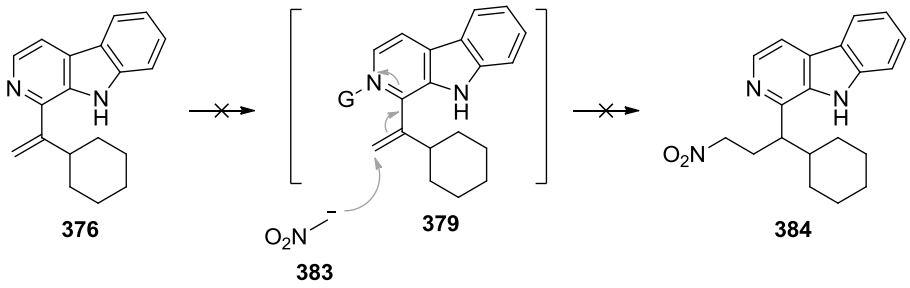
Entry	Catalyst	Base	Solvent	Temp/˚C	Time/h	Yield/%
1	$Pd(PPh_3)_4$	$NaHCO_3$ (sat. aq)	1,4-dioxane	90	12	42
2	$Pd_2(dba)_3$, SPHOS	$NaHCO_3$ (sat. aq)	toluene	90	12	0
3	Pd(dppf)Cl_2	$NaHCO_3$ (sat. aq)	1,4-dioxane	90	12	51
4	Pd(dppf)Cl_2	DIPA	1,4-dioxane	90	12	0
5	Pd(dppf)Cl_2	$NaHCO_3$ (sat. aq)	1,4-dioxane	90	12	79

With **376** in hand, homologation studies could commence. All reactions were carried out with the eventual aim of introducing the all-important nitro group on both the model and real system, either *via* functional group interconversion or direct addition of nitromethane.

2.5.2 Reactions with Nucleophiles

The aim was to activate the pyridine ring with a Lewis acid before the addition of a nitronate anion derived from nitromethane. The results are outlined in Table 8. Initially, activation using palladium(II) was attempted. It was hoped that palladium would coordinate to the alkene and/or pyridyl nitrogen sufficiently for nitronate anion **383** to add into the electrophilic system. However, all attempts failed; different catalyst systems were employed with (Table 8, entries 1 and 2) or without (Table 8, entry 3) Lewis acids in DMSO or toluene but no reaction was observed.

Table 8: Results using a pyridyl Lewis acid and nitronate anion. G = activating group.

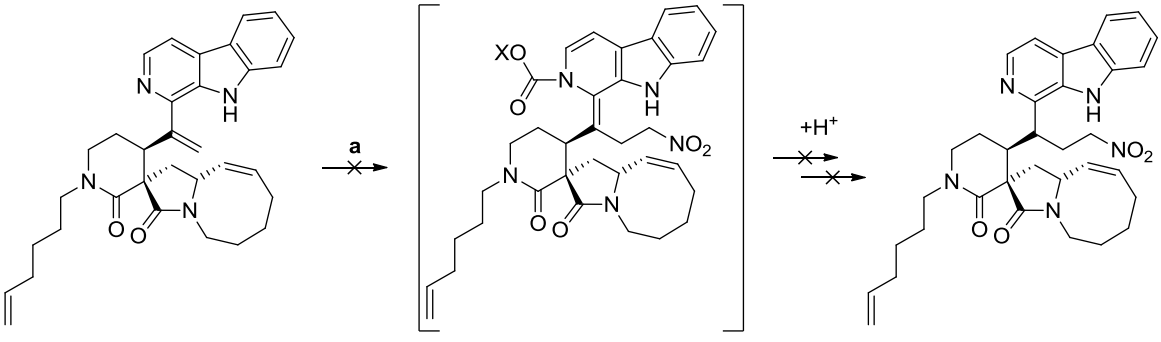


376 379 383 384

Entry	Activating agent/G	Base	Solvent	Temp/˚C	Comments
1	$Pd_2(dba)_3/PPh_3$	NaOMe	DMSO or toluene	22–50	No reaction
2	$Pd(OAc)_2/PPh_3$	NaOMe	DMSO or toluene	22–50	No reaction
3	$Pd_2(dba)_3/PPh_3/ BF_3•OEt_2$	NaOMe	DMSO or toluene	22–50	No reaction
4	$BF_3•OEt_2$	NaOEt	toluene	60	No reaction
5	$BF_3•OEt_2$	DIPA	toluene	90	No reaction
6	$Cu(OTf)_2$	Et_3N	toluene	22–90	No reaction

Classic Lewis acids for pyridyl moieties (Table 8, entries 4–6[136,137]) were used and a variety of bases were employed for deprotonation of nitromethane, however no reactivity was observed and only starting material was recovered.

Activation towards homologation of the real system using either Boc anhydride or ethyl chloroformate was trialled. It was hoped that the system would be sufficiently activated to react with the nitronate anion (Scheme 55).



263a X = Et (**385**) or *t*Bu (**386**) **387**

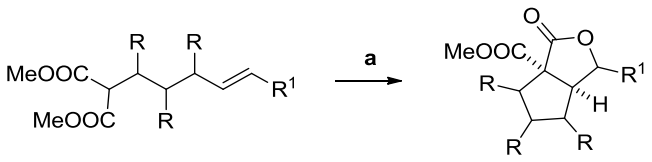
Scheme 55: Activation of **263a** using an acetoxy group. **(a)** $(Boc)_2O$ **388** or ClC(O)OEt **389**, NO_2Me, TMG, RT to 50 ˚C, 16 h.

However, both attempts were unsuccessful presumably due to the low reactivity of the β-carboline system; although the pyridyl nitrogen was electron-withdrawing, activation was

diminished by the electron-donating indole nitrogen. Therefore it was decided to move on to an alternative method, as the system was less reactive to nucleophiles than was originally anticipated.

2.5.3 Reactions with Radicals

Burton *et al.*[138] reported the use of Mn(III) and Cu(II) to synthesise the malonate radical, which then reacted with an alkene or allenic functionality to form a range of γ-lactones **389** (Scheme 56).



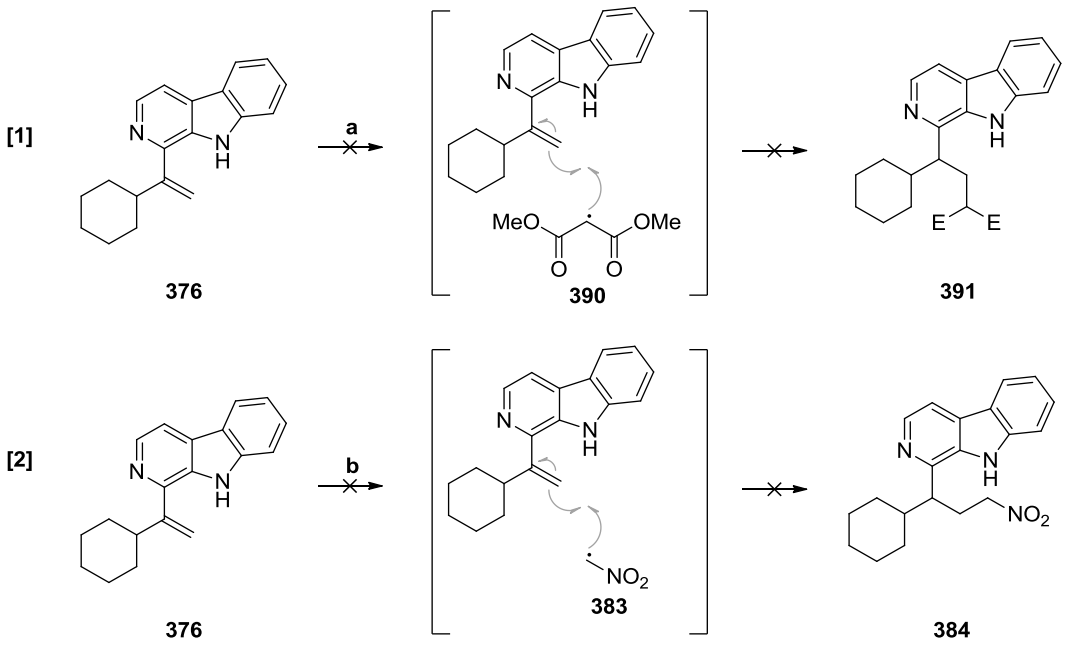
388 **389**

Scheme 56: Synthesis of γ-lactones **389**. **(a)** $Mn(OAc)_3 \bullet 2H_2O$, $Cu(OTf)_2$, MeCN, 80 ˚C, 24 h, 55–92%, dr 1:1–1:0. R = $CH_2OTBDPS$, H; R^1 = C_4H_9, CH_2CH_2OH, $CH_2CH_2OTBDPS$, -$(Me)_2$, C_5H_{11}.

Accordingly, the vinyl β-carboline was treated with dimethyl malonate, Mn(III) and Cu(II). $Mn(OAc)_3 \bullet 2H_2O$ that had been washed with AcOH in diethyl ether was used[xiii] in degassed MeCN, and **376** was subjected to the reaction conditions outlined in Scheme 57. However, no reactivity was observed by TLC analysis, mass spectrometry or crude ^{1}H NMR spectroscopy and all starting material could be recovered (Scheme 57, **[1]**).

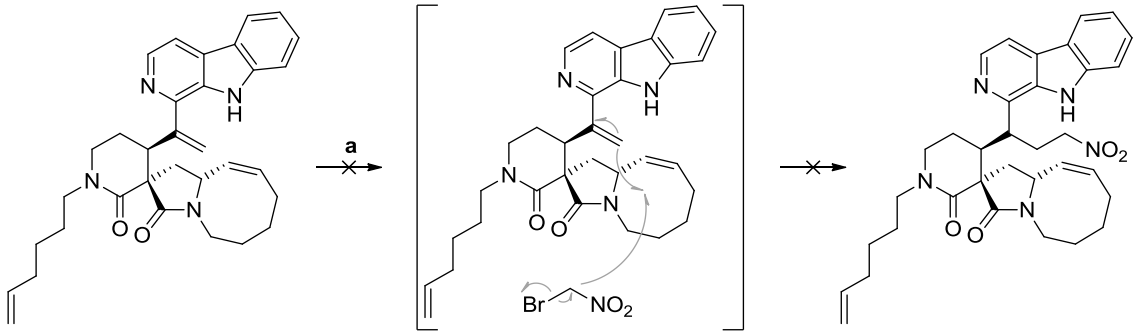
The same reaction was performed to attempt to incorporate a nitromethane radical (Scheme 57, **[2]**). However, no reactivity was observed by TLC analysis, mass spectrometry or crude ^{1}H NMR spectroscopy and only starting material was isolated.

[xiii] This procedure was performed until the filtrate ran clear, and removed any Mn(II) and Mn(IV) that may have been present.



Scheme 57: Radical addition to **376**. **(a)** $Mn(OAc)_3 \bullet 2H_2O$, $Cu(OTf)_2$, MeCN, 55 ˚C, 24 h; **(b)** $Mn(OAc)_3 \bullet 2H_2O$, $Cu(OTf)_2$, NO_2Me, MeCN, 55 ˚C, 24 h. E = COOMe.

Two reactions using the real system **263a** were trialled using classical methods to synthesise radicals: Bu_3SnH/AIBN or SmI_2 (Scheme 58) in degassed toluene or tetrahydrofuran respectively.[139] Bromo-nitromethane was used with each reagent and it was hoped that the nitromethane radical would form and add in to the vinyl β-carboline system. However, no addition into the conjugated double bond was observed with either reagent even after prolonged heating.



Scheme 58: Radical addition to **263a**. **(a)** $BrCH_2NO_2$ **(i)** Bu_3SnH, AIBN, toluene, 110 ˚C, 16 h or **(ii)** SmI_2, THF, RT to reflux.

The radical chemistry was unsuccessful on our system. Therefore, attention turned to C-H functionalisation.

2.5.4 C-H Functionalisation

Over the last 20 years, there has been an explosive growth in the development of C-H bond functionalisation methodology which is based on the concept of converting an unactivated C-H bond to a C-X bond, where X = Ar, Het, O, C, N, etc.).[140] Early work often required very harsh reaction conditions and stoichiometric reagents. However, over the years catalytic methods have been developed, which employ milder reaction conditions, such as lower temperatures with no requirement for inert atmospheres. Work originally was directed towards activation of (hetero)aryl sp^2 C-H bonds but recent developments have included the introduction of almost any functionality such as amines,[141] boronic esters,[142,143] esters,[144] alcohols and ethers,[145] and acetates[146] with any hybridisation[147] (sp, sp^2, sp^3) and with a variety of transition metal catalysts.[148]

Thus, studies into the use of C-H functionalisation as a direct way of introducing the appropriate functionality began. After examination of the literature, systems such as those outlined in Figure 34, which shared chemical similarities with our system, were investigated.

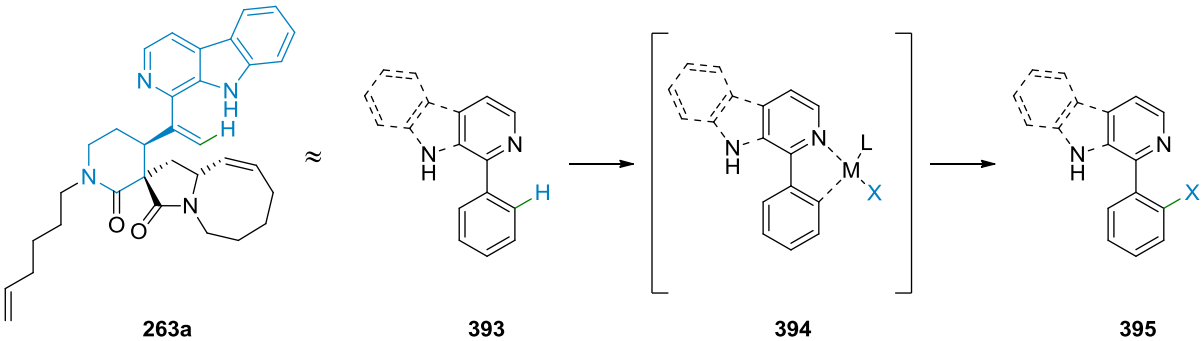


Figure 34: Possible application of C-H functionalisation to our system.

Yu *et al.*[149] utilised $Cu(OAc)_2$ in air with a nucleophilic anion source and strong heating to access a variety of functionalised bi-aryl systems **395** and the yields of the isolated products ranged from 55–93% (Figure 35). Their proposed single electron transfer mechanism is outlined in Figure 35 for which some reasoning was given; no isotope effect was observed

when one unfunctionalised H was exchanged for D, the chlorination reaction was found to be first order when using both $Cu(OAc)_2$ and $CuCl_2$ and electron-withdrawing groups decreased the reaction rates, so the attack to the cationic radical was slower.

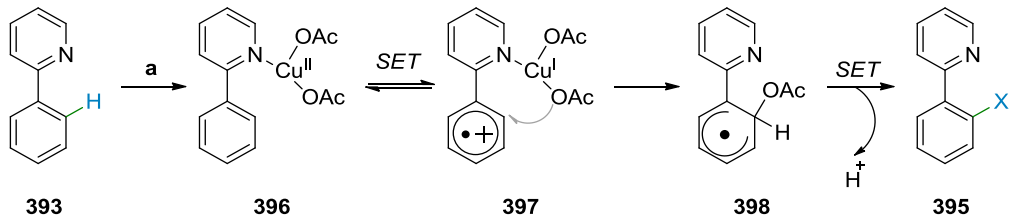
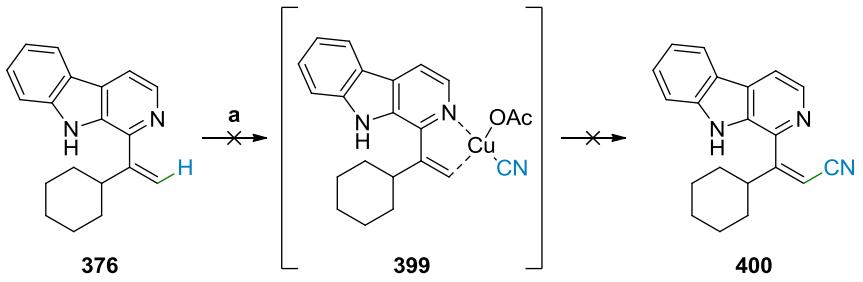


Figure 35: C-H functionalisation using Cu(II) and proposed single electron transfer mechanism. **(a)** $Cu(OAc)_2$ (1 eq), MeCN, air, 130 ˚C, 24 h, 55–93%. X = OAc. If nucleophilic ions are added, X = Br, I, CN, TsNH, *p*-CN-PhO, PhS, MeS, OH.

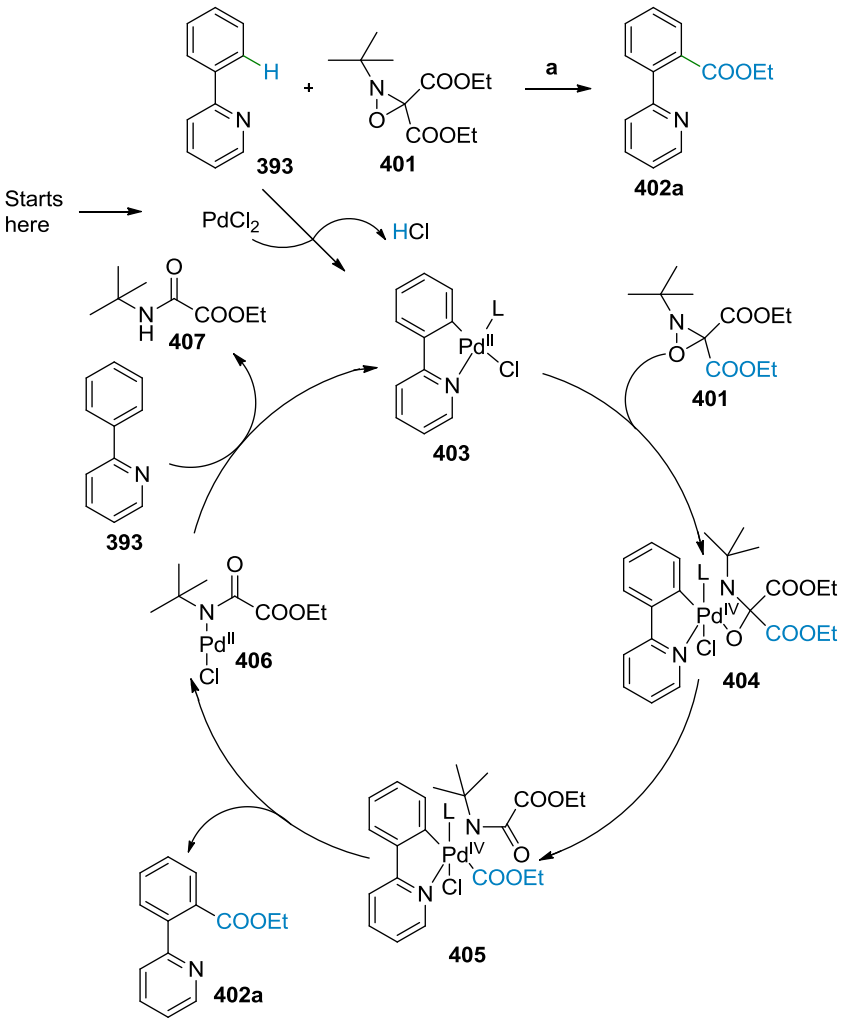
On model system **376**, introduction of a nitrile functionality was attempted as nitrile **400** could then undergo a series of reactions to give the desired nitro group (Scheme 59).



Scheme 59: Attempted C-H functionalisation of **376**. **(a)** $Cu(OAc)_2$ (1 eq), TMSCN, MeCN, air, 130 ˚C, 24 h.

However, on exposure of model system **376** to the reaction conditions outlined in Scheme 59, no reactivity was observed and only starting material was recovered.

Shi *et al.*[150] reported a palladium(II)-catalysed C-H ethoxy-carbonylation which employed oxaziridine **401** to deliver an ethoxyester moiety to pyridyl-phenyl system **393** (Scheme 60). The methodology proved to be very general: ester groups were introduced to a wide range of substituted bi-aryl systems: electron-withdrawing groups (halogens) as well as aryl ureas and fused tricyclic ring systems were tolerated and yields of the isolated products **402** ranged from 50–94%.

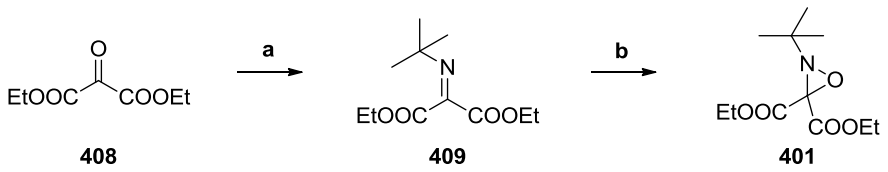


Scheme 60: Proposed catalytic cycle using bi-aryl **393** with $PdCl_2$. **(a)** 10 mol% $PdCl_2$, $CHCl_3$, 100 ˚C, 24 h, 94%.

The mechanism was tentatively suggested (Scheme 60) and involved a Pd(IV) complex; $PdCl_2$ reacted with **393** to generate Pd(II) complex **403** *via* C-H activation. An oxidative insertion into the relatively weak N-O bond (222 kJ/mol compared to 347 kJ/mol for C-C bond) of the oxaziridine gave Pd(IV) species **404** which rearranged and shifted a COOEt group from the carbon to the palladium, instigating breaking of a C-C bond. Reductive elimination gave the functionalised bi-aryl compound **402a** and the formation of amide **407** released the Pd(II) catalyst. However, this mechanism was only postulated, and further investigation of the mechanism was reported to be ongoing.[150]

It was hoped that this methodology could be used on model system **376**. Accordingly, oxaziridine **401** was synthesised according to literature procedures (Scheme 61):[150] imine

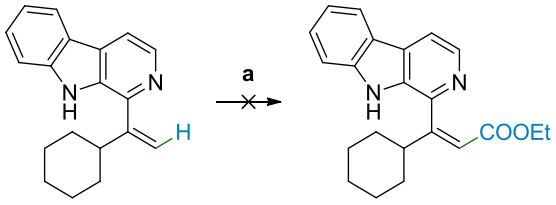
409 was formed when the corresponding amine and ketone **408** were employed in the presence of titanium tetrachloride. Oxaziridine **401** was in turn accessed *via* *m*CPBA oxidation of crude imine **409** which proceeded under basic conditions to avoid any potential hydrolysis of the ester moieties by the *meta*-chlorobenzoic acid generated in the reaction.



408 **409** **401**

Scheme 61: Synthesis of oxaziridine **401**. **(a)** *tert*-butylamine, $TiCl_4$, Et_2O, 0 ˚C to RT, 24 h; **(b)** *m*CPBA, $NaHCO_3$, DCM, 0 ˚C to RT, 24 h, 70% over two steps.

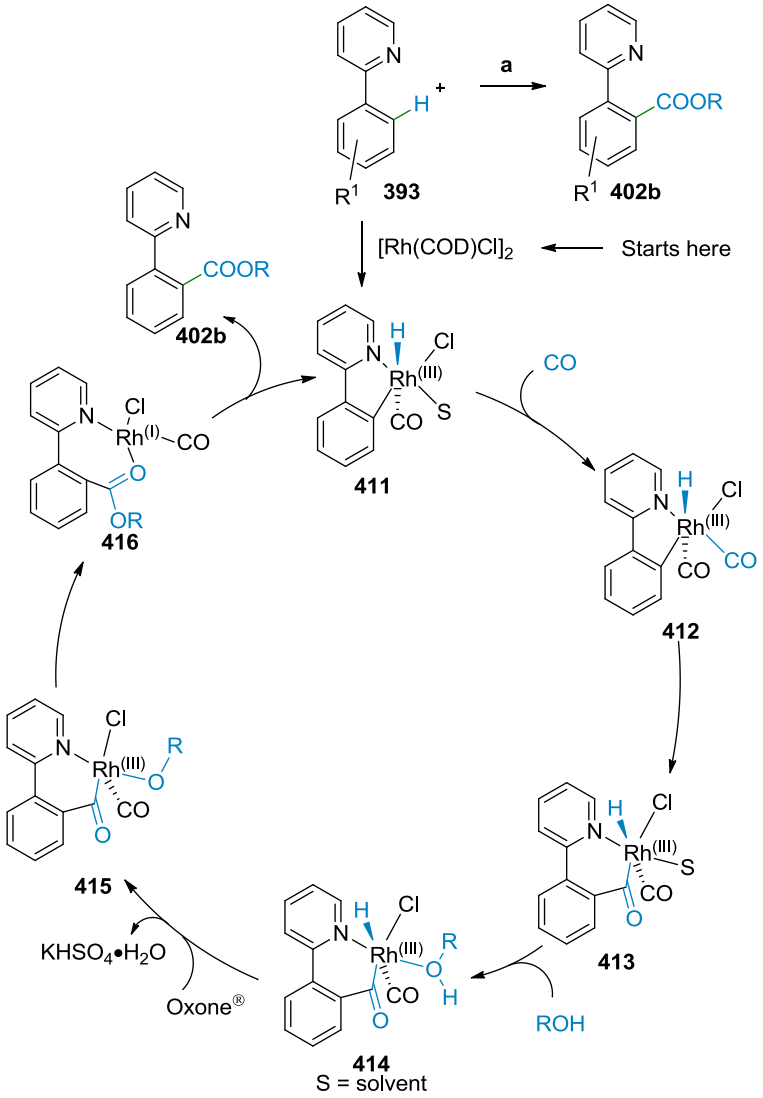
The oxaziridine was employed in the homologation of model substrate **376**, in an attempt to introduce the ethoxy ester moiety. However, on exposure to conditions outlined in the original paper,[150] no reactivity was observed and only starting material was recovered (Scheme 62).



376 **410a**

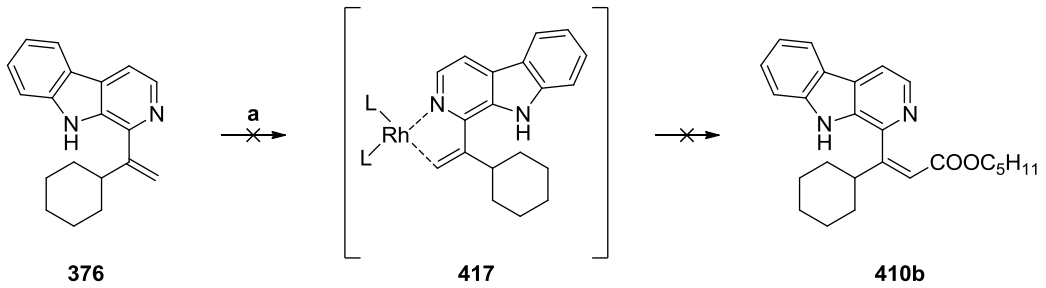
Scheme 62: Attempt to synthesise **410**. **(a) 401**, 10 mol% $PdCl_2$, $CHCl_3$, 100 ˚C, 24 h.

Lastly, it was attempted to follow work published by Zhang *et al.*[151] who reported a protocol for rhodium-catalysed oxidative carbonylation for aryl C-H bond functionalisation, using CO and an alcohol (Scheme 63). Very broad scope was reported; electron-withdrawing and heteroaryl groups fared well (45–90% yield of ester **402** isolated). Electron-donating (OMe) and *ortho*-trifluoromethane groups were also tolerated but with lower isolated yields of ester **402** observed (60–63% and 38% respectively). Zhang postulated two mechanisms of which the more likely route is outlined in Scheme 63, based on their observations and those of others.[151,152,153,154]



Scheme 63: Proposed catalytic cycle using bi-aryl **393** and $[Rh(COD)Cl]_2$. **(a)** $[Rh(COD)Cl]_2$, ROH, Oxone®, CO, toluene, 85 ˚C, 8 h, 38–90%. R = C_5H_{11}; R^1 = H, *p*/*m*/*o*-Me, *p*/*o*-OMe, *p*/*o*-CF_3, *p*/*m*/*o*-F, napthyl.

Zhang postulated that coordination of the *ortho*-directing group (pyridyl moiety), oxidative addition into the C-H bond by Rh^{I} and coordination of a CO molecule gave Rh^{III} complex **411**. Coordination of a further CO molecule to give **412** followed by insertion of CO into the C-Rh bond could give species **413**. The solvent molecule could be replaced by the alcohol to give **414**. Oxidation of the alcohol with Oxone® would give **415** which then could undergo a rearrangement to **416**. Reductive elimination would give functionalised product **402b** and would regenerate the active catalyst species.



376 417 410b

Scheme 64: Attempt to functionalise substrate **376**. **(a)** $[Rh(COD)Cl]_2$, $C_5H_{11}OH$, Oxone®, CO, toluene, 85 ˚C, 8 h.

However, on application to model system **376** (Scheme 64), no reactivity was observed and starting material was recovered even after prolonged heating at high temperatures. The C-H functionalisation attempted so far had not been successful with our substrate. Although this would be an elegant way of introducing the desired functionalised methylene unit, it appeared that the relevant examples published so far in the literature were specific only to pyridyl-phenyl system **393**. It may be that the related model system **376** was too unreactive, or the examples in literature were not transferable to other systems.

2.6 Summary

The new palladium-catalysed reaction was successfully applied to the total synthesis of manzamine A to form separable diastereomers **263a** and **263b**, of which **263a** was desired (Figure 36). Efforts to synthesise ring B were not successful. An intermolecular cyanide addition on related substrate **314** was performed, but gave the undesired stereochemistry after nOe experiments were carried out on advanced intermediate **316**. Therefore an intramolecular cyclisation was sought, after the success in the total synthesis of nakadomarin A. Approaches to introduce a functionalised methylene unit to both a model system and the real system were unsuccessful. A wide variety of chemistry was used including nucleophilic addition, radical addition and C-H activation. However, it seemed that the β-carboline unit was considerably less reactive than was anticipated. Therefore, despite significant effort, a new route was planned introducing the extra CH_2X from the beginning.

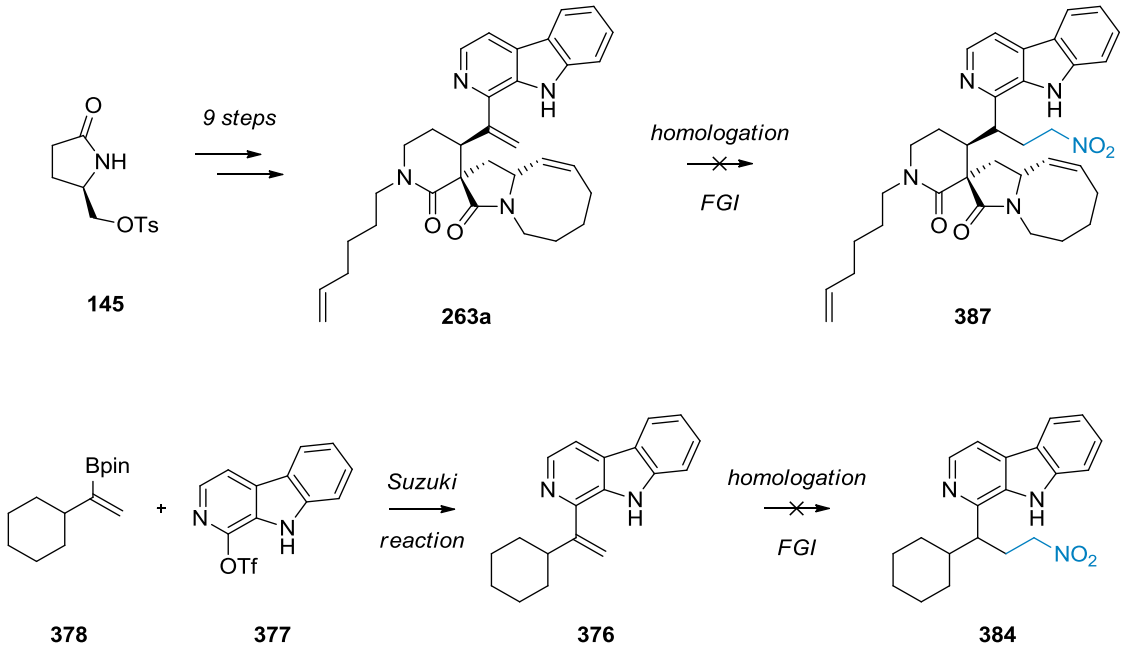


Figure 36: Summary of the synthesis of **263a** and homologation studies.

Chapter 3
2nd Generation: Use of Non-Terminal Allenes in the Synthesis of Manzamine A

3.1 Introduction

In Chapter 2 it was shown that attempts to progress the synthesis from **263a** *via* introduction of the required CH_2-NO_2 (see Section 2.5) failed. A number of methods including nucleophilic attack, radical chemistry and C-H functionalisation (Figure 37) were employed without success.

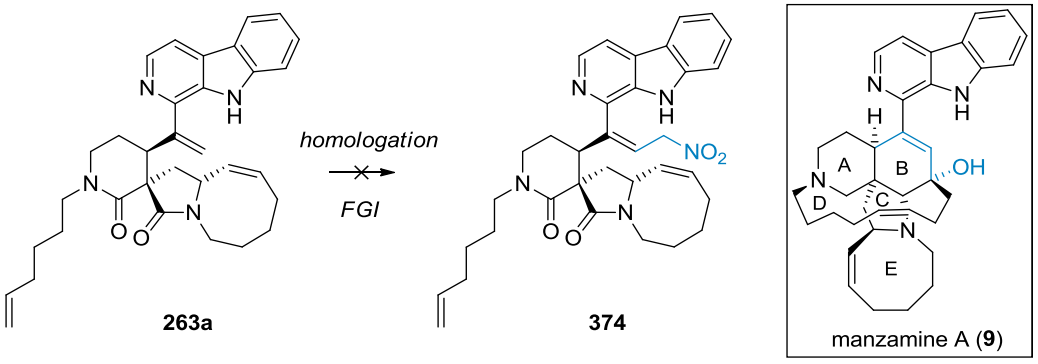


Figure 37: Summary of failed homologation studies in Chapter 2.

Therefore, a new approach was planned that would incorporate the extra CH_2-R (where R was functionality that could be converted to a nitro group) earlier in the synthesis and thus, homologated derivative **374** would be accessed using a modified palladium-catalysed spirocyclisation cascade.

3.1.1 Retrosynthetic Analysis

The retrosynthesis was designed around the first generation route (Chapter 2) and is outlined in Figure 38. The last two steps would be identical; a stereoselective organometallic olefin addition followed by a ring-closing metathesis would give manzamine A (**9**). However, a new primary amine **418** would be synthesised incorporating the homologated allenic system. The desired secondary amine **419** would be accessed by a reductive amination between primary amine **418** and aldehyde **291**.

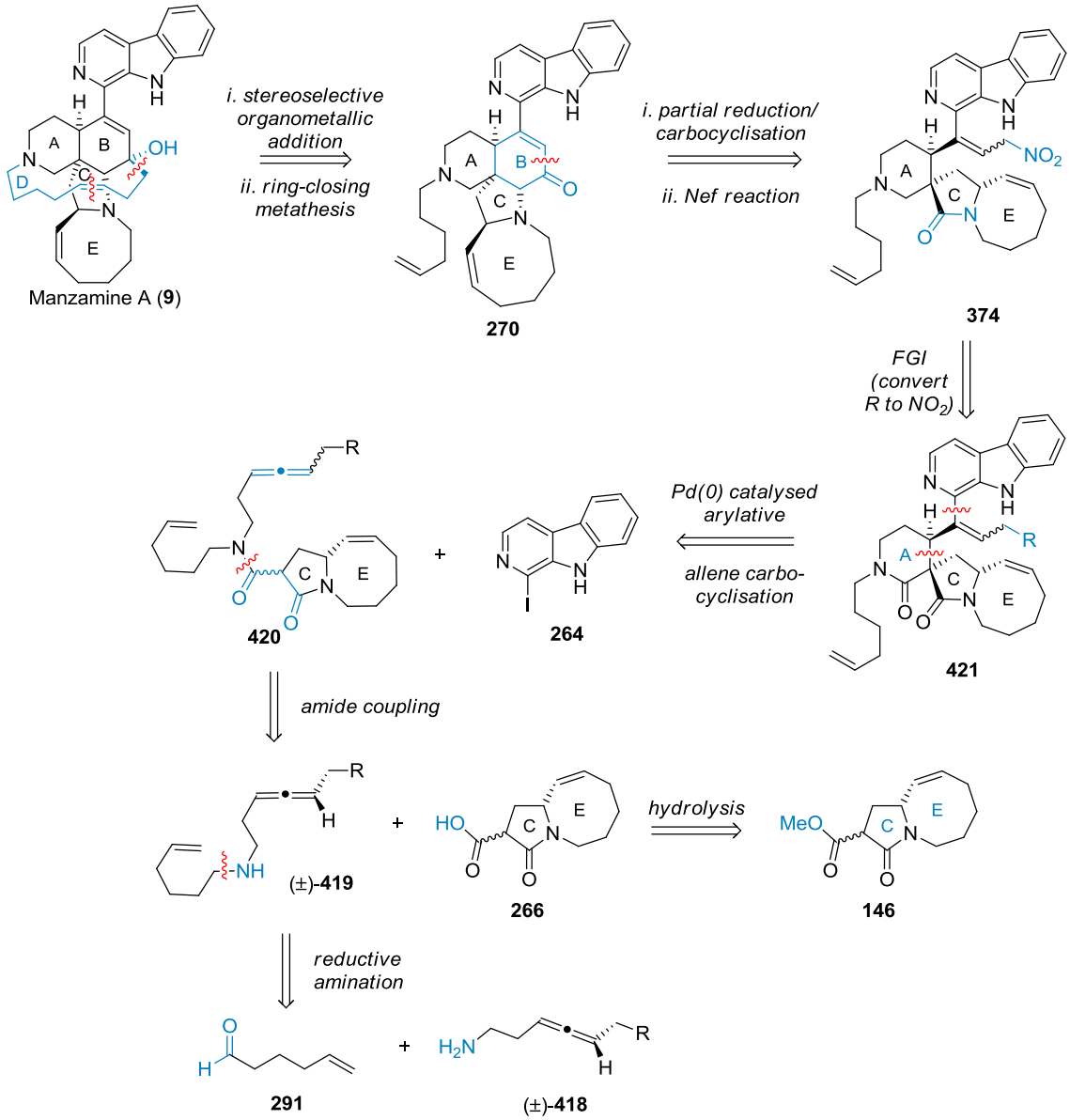
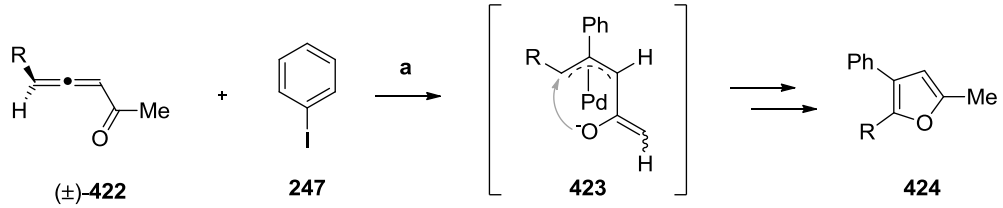


Figure 38: Second generation retrosynthesis. R = functional group that can be converted to a nitro group.

The amide coupling conditions developed in Chapter 2 could be used to afford pro-nucleophile **420**. The palladium-catalysed arylative allene spirocyclisation cascade would introduce ring A to give spirocycle **421** (rings ACE). It was more than likely that some re-optimisation would be required in this step due to any potential reactivity differences between the terminal and non-terminal allene moiety. With the desired CH_2-R in place, R would be converted to a nitro group through functional group interconversion. The partial reduction of the pyrrolidinone carbonyl followed by an intramolecular nitro-Mannich cyclisation reaction would introduce ring B, and a Nef reaction would convert the nitro group to a carbonyl to give tetracycle **270**. A stereoselective organometallic addition followed by a ring-closing metathesis would give manzamine A (**9**).

3.2 Palladium-Catalysed Reactions of Non-Terminal Allenes

In contrast to the large volume of literature available about terminal allenes and their chemistry, there is very little on palladium-catalysed reactions of non-terminal allenes. In 2000, Ma reported a palladium-catalysed cyclisation reaction of aryl or alk-1-enyl halides with 1,2-dienylketones to access highly functionalised furan derivatives **424** (Scheme 65).[155]

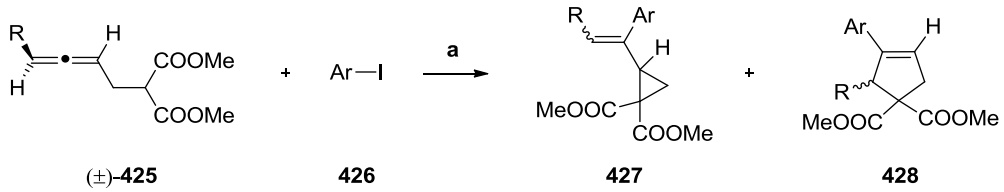


Scheme 65: Synthesis of tri-substituted furans **424**. **(a)** 5 mol% $Pd(PPh_3)_4$, Et_3N, 10 mol% Ag_2CO_3, toluene, 80 ˚C, 9–13 h, 51–92%. R = H, Bu, Ph, $C_{12}H_{15}$.

After initial screening it was found that using $Pd(PPh_3)_4$ and Et_3N with catalytic Ag_2CO_3 in toluene at 80 ˚C, yields of up to 92% of tri-substituted furans **424** were obtained. The Ag(I) was crucial to reactivity, but no reason was given. Indeed, in the full paper, a mechanism was suggested but there was no further mention of the role of Ag(I).[156] Elsewhere, it has been reported that Ag(I) salts can activate allenes (as well as alkynes and alkenes) towards

O-centred nucleophilic attack and this is likely to be the case for this system.[157] A range of different aryl iodides were employed: electron-withdrawing groups such as *p*-nitro, electron-donating groups such as *p*-methoxy and heterocycles were all tolerated. R was also varied; proton, butyl, phenyl and longer alkane chains were tolerated, and the furan products were obtained in yields ranging from 51–92%.

In 2001, Ma reported a study of the regioselectivity observed in a palladium-catalysed cyclisation reaction using 2,3-allenylmalonates (Scheme 66).

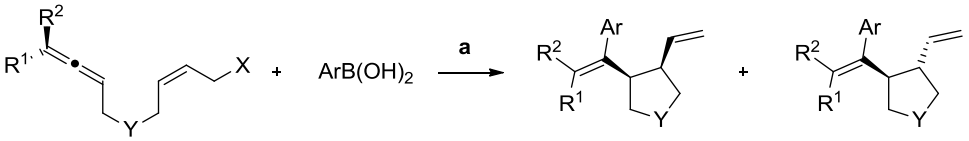


(±)-**425** **426** **427** **428**

Scheme 66: Synthesis of cyclopropane- and cyclopentane-derivatives **427** and **428**. **(a)** 5 mol% $Pd(PPh_3)_4$, K_2CO_3, $nBu_4N^+Br^-$, MeCN, reflux, 12 h, **427**: 57–88%, **428**: 4–9%. Ar = Ph, *p*-OMe, *p*-COOMe, het, vinyl; R = H, Me, nC_6H_{13}, nC_3H_7.

When non-terminal allenes **425** were employed, cyclopropyl derivatives **427** dominated and only trace amounts of cyclopentyl derivatives **428** were isolated. The regioselectivity could be reversed if NaH and DMSO at 85 ˚C were used but no reason was given.

In 2004, Zhang reported a *cis*-selective tandem cyclisation/Suzuki reaction to form pyrrolidines, tetrahydrofurans and cyclopentanes (Scheme 67).[158]



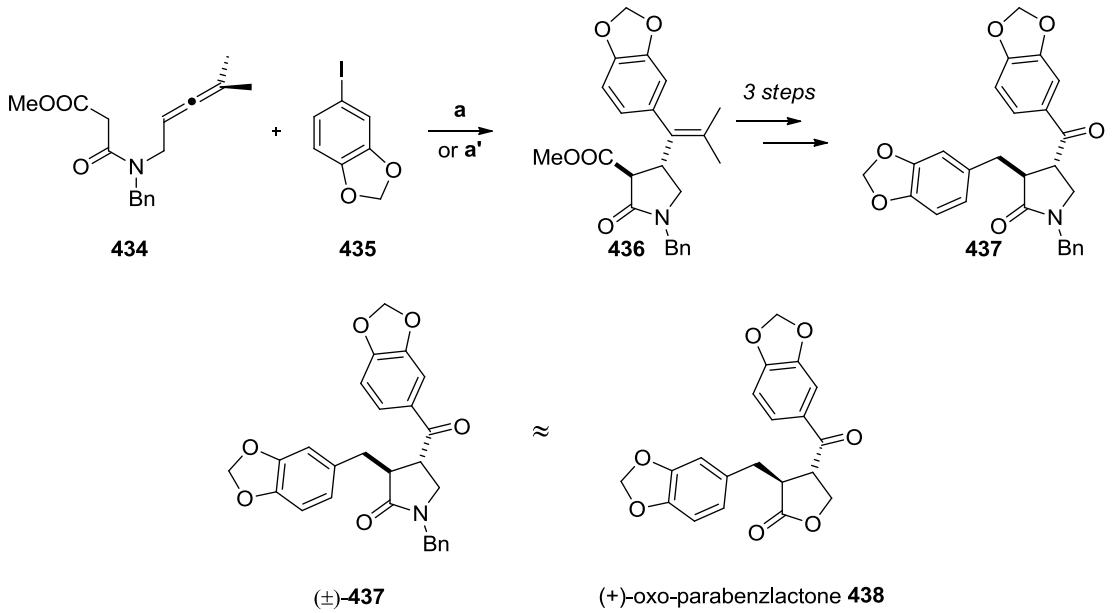
(±)-**429** **430** Y = NTs **431a** = O **432a** = C **433a** Y = NTs **431b** = O **432b** = C **433b**

Scheme 67: Synthesis of *N*-Ts pyrrolidines **431**, tetrahydrofurans **432** and cyclopentanes **433**. **(a)** $K_3PO_4 \bullet 3H_2O$, 5 mol% $Pd(PPh_3)_4$, toluene, 50 ˚C, 42–95%, *cis*/*trans* 4:1–1:0. Y = $C(CO_2Me)_2$, NTs or O; R^1 = H, *n*Pr, *i*Pr or cyclohexyl; R^2 = H or cyclohexyl; Ar = C_6H_5, *p*-OMe-C_6H_4, *p*-Cl-C_6H_4.

The authors suggested that the palladium oxidatively inserted into the allyl-X bond (X = Cl, Br, OCO_2Me) before insertion into the proximal allene bond. Subsequent trapping of the palladium intermediate by an aryl boronic acid **430** followed by reductive elimination gave

the desired product and regenerated the palladium catalyst. The authors postulated that the formation of the major *cis* isomer **431**–**433a** was due to favourable conformations in the transition states. A range of substrates underwent the reaction and the yields of isolated five-membered rings **431**–**433** ranged from 42–95% (Scheme 67). When Y = NTs or O, only the *cis* isomer was observed, which the authors ascribed to the presence of a tethered heteroatom which favoured the intramolecular cyclisation process with high stereoselectivity.

In 2009, Poli reported a phosphine free palladium-catalysed allene carbopalladation sequence to access pyrrolidinones of type **436** (Scheme 68).[159] Initially, to test the reactivity of the system, $Pd(OAc)_2$ with a phosphine ligand (dppf) afforded the *trans* isomer in 38% yield after 5 h (65% conversion). In accordance with Ma and Zhao,[160] addition of TBAB led to a faster rate (1 h) and 64% yield of the isolated lactam **436**. A range of solvents were screened and it was found that DMSO gave the best yield; 88% (100% conversion) when $Pd(OAc)_2$ and the dppf ligand were used (Scheme 68, conditions **(a)**).



Scheme 68: Synthesis of *rac*-aza-parabenzlactone (±)-**437**. **(a)** 10 mol% $Pd(OAc)_2$, 20 mol% dppf, NaH, 20 mol% nBu$_4$N$^+$Br$^-$, DMSO, 55 ˚C, 5 h, 88%; or **(a')** 10 mol% $[PdCl_2(CH_3CN)_2]$, 20 mol% nBuLi, NaH, 20 mol% nBu$_4$N$^+$Br$^-$, DMSO, 55 ˚C, 1.5 h, 67–88%.

However, it was then postulated that DMSO could act as both a solvent and a ligand, as it is known that DMSO can coordinate to transition metals.[161] Therefore using 10 mol% [$PdCl_2(CH_3CN)_2$] and 20 mol% *n*BuLi which reduced Pd(II) to Pd(0),[162,163] lactams of type **436** were obtained 61–88% yield (Scheme 68, conditions **(a')**). Significant reduction in yield was observed if *n*BuLi (64%) or TBAB (62%) were omitted. Poli applied this methodology to a wide range of aryl iodides: electron-withdrawing groups (*p*-CF_3-C_6H_4, *p*-NO_2-C_6H_4), electron-donating groups (*p*-alkyl-C_6H_4, *p*-OMe-C_6H_4) and heterocycles (thiophene and pyridine) were all tolerated (Scheme 68).

Poli then applied this methodology to the synthesis of a *rac*-aza-analogue of (+)-oxo-parabenzlactone **438**, an anti-oxidant lignan natural product found in plants (Scheme 68).[164] Three steps were required from lactam **436**: demethoxycarbonylation followed by deprotonation and quench with piperonyl bromide, then subsequent oxidation of the double bond using $RuCl_3 \bullet (H_2O)_n$ and $NaIO_4$ in $CH_3CN/CCl_4/H_2O$ gave the desired natural product (±)-**437** in 52% yield over three steps (Scheme 68).

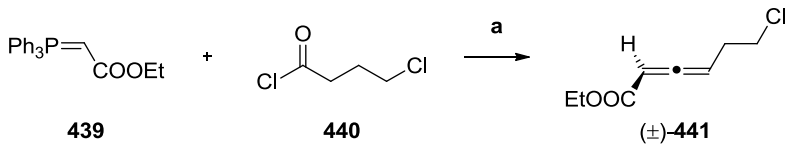
With precedent in the literature for the use of non-terminal allenes under palladium-catalysed conditions, we believed the second generation route would give the desired homologated spirocyclic ACE core of manzamine A.

3.3 Synthesis of the Starting Materials

*3.3.1 Synthesis of Secondary Amine **449***

The synthesis of the desired secondary amine was carried out using similar chemistry to that detailed in Chapter 2, however there were some modifications due to reactivity and stability differences of the internal allene.

The allenic functionality was introduced using a Wittig olefination (Chapter 2, Section 2.1.1.1) following the work of Ma *et al.*[165] and ester **441** was obtained in 95% yield (Scheme 69).



439 **440** (±)-**441**

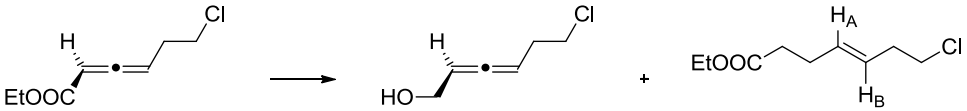
Scheme 69: Synthesis of ester **441**. **(a)** Et_3N, DCM, 10 ˚C to RT, 16 h, 95%.

The reduction to alcohol **442** was somewhat capricious and demanded extensive optimisation (Table 9). One of the possible reasons was that alcohol **442** was volatile, so solvent choice was important to aid isolation. Initially, dichloromethane was chosen as the solvent because there was literature precedent on similar substrates[166] and it has a low boiling point, thus avoiding any potential volatility issues (Table 9, entries 1 and 2).

When dichloromethane was used, low yields (18–20%) were obtained of the desired product. This was not unexpected because all but one paper[166] that published reductions of allenic esters to allenic alcohols reported low yields (13–25%).[167,168] Multiple attempts to isolate side products were carried out but were unsuccessful. In diethyl ether (Table 9, entry 3), complete reduction occurred and analysis of the crude material by ^{1}H NMR spectroscopy showed disappearance of allene signals and the ester moiety. In THF at −78 ˚C (Table 9, entry 4), no reaction was observed and ^{1}H NMR spectroscopy of the crude material showed only ester **441**. In hexane (Table 9, entry 5), the ^{1}H NMR spectrum of the

crude material showed a 2:1 **441**:**442** ratio. No attempts were made to purify the crude material because full conversion had already been observed in entries 1 and 2.

Table 9: Studies towards reduction of ester **441**.



(±)-**441** (±)-**442** **443**

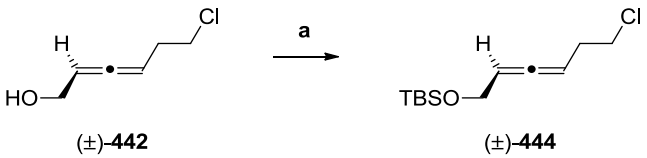
Entry	Solvent	Reducing agent/eq	Temp/˚C	Yield 442
1	DCM	DIBAL (2.1)	−78 to RT	18
2	DCM	DIBAL (5.0)	−78 to RT	20
3	Et_2O	DIBAL (5.0)	−78	0
4	THF	DIBAL (5.0)	−78	**441** only
5	hexane	DIBAL (5.0)	−78	2:1 **441**:**442**
6	toluene	DIBAL (2.1)	−78	0
7	THF	DIBAL (2.0)	−20	0
8	THF	DIBAL (2.0)	0	0
9	DCM	DIBAL (2.01+0.85)	−78	24
10	DCM	DIBAL (2.5)	−78	21
11	EtOH	$NaBH_4$ (3.0)	0	0
12	DCM	DIBAL (2.01)[xiv]	−78	30
13	DCM	DIBAL (2.01)[xv]	−78	35

Ma[167] used toluene as solvent to effect the reduction of allenic esters with DIBAL. However in our case, the volatile nature of alcohol **442** meant that no product could be isolated from the reaction solvent (Table 9, entry 6). Oh *et al.*[168] reported the use of tetrahydrofuran at an elevated temperature. Thus, after we had observed no reactivity at −78 ˚C (Table 9, entry 4), the temperature of the reaction mixture was raised. This proved to be detrimental with our substrate and extensive decomposition occurred (Table 9, entries 7–8). Better yields (21–24%) were obtained when dichloromethane was used as the solvent and the reaction mixture was quenched at −78 ˚C (Table 9, entries 9 and 10). When sodium borohydride in ethanol was used, no product was observed by ^{1}H NMR spectroscopy of the crude material; partial reduction of the allene was observed, which formed **443** where H_A and H_B were *trans*

[xiv] 6 g scale.
[xv] 16 g scale.

to each other (J = 15.0 Hz) (**441**:**443** = 1:1). All the reactions so far were carried out using between 0.2–1 g of ester **441**. Scaling up the reaction using the original conditions (Table 1, entry 9) to 6 g and then 16 g resulted in improved yields of 30% and 35% respectively (Table 9, entries 16 and 17). No further optimisation was performed; the yields obtained matched literature yields and sufficient quantities of alcohol **442** were synthesised for the following steps.

Protection of the alcohol was performed which gave silyl ether **444** (Scheme 70). A silyl group protection was chosen; the protecting group could be introduced and removed under mild conditions that would not be detrimental to other functional groups present in our compound.

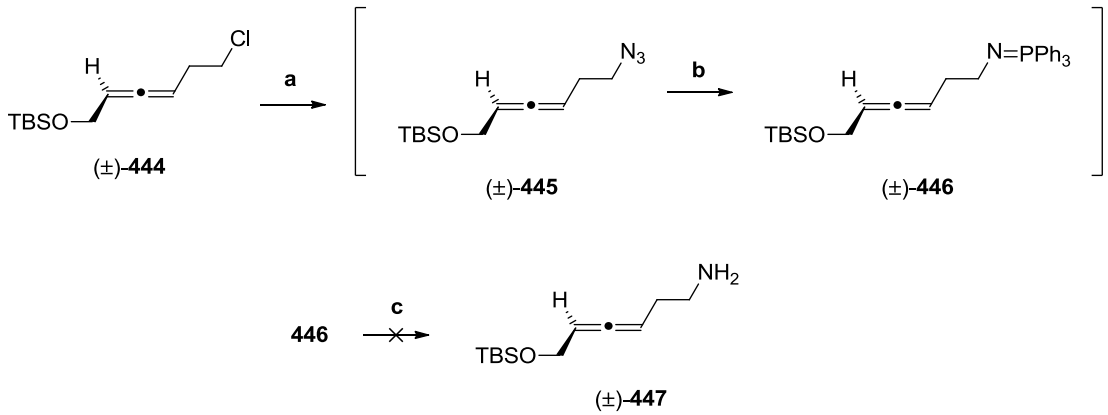


(±)-**442** (±)-**444**

Scheme 70: Silyl protection of **442**. **(a)** TBSCl, DMAP, Et_3N, DCM, RT, 16 h, 86%.

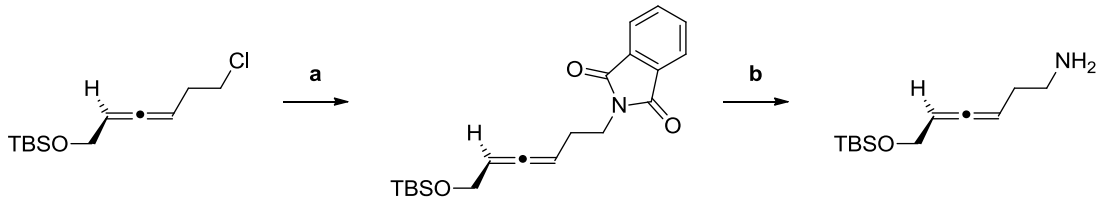
Specifically, a *tert*-butyldimethyl silane-protecting group was chosen. It was stable to subsequent reaction conditions without being too sterically demanding in the impending palladium-catalysed spirocyclisation reaction. The reaction proceeded without issue and silyl ether **444** was obtained in an average yield of 86%.

After silyl-protection, chloride **444** needed to be converted to primary amine **447** (Scheme 71). Unlike in Chapter 2, the hydrolysis of the iminophosphorane was unsuccessful on this substrate.



Scheme 71: Attempt to synthesise primary amine **447**. **(a)** NaN_3, TBAI, DMSO, 50 ˚C, 16 h; **(b)** PPh_3, Et_2O, RT, 16 h; **(c)** H_2O, Et_2O, RT to 40 ˚C, 32 h, or HCl (1 M), Et_2O, RT to 40 ˚C, 48 h.

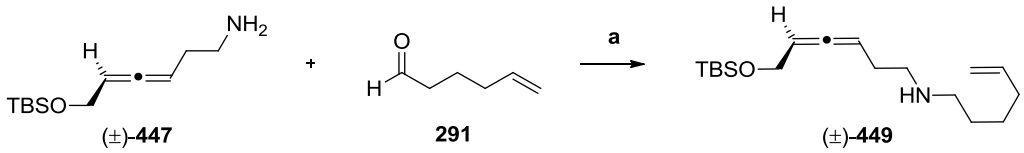
Azide formation was observed by IR spectroscopy (peak at 2100 cm^{-1}) and ^1H NMR spectroscopy (triplet at 3.4 ppm) on the addition of NaN_3. After the addition of triphenylphosphine to azide **445**, iminophosphorane **446** was observed by ^1H, ^{13}C and ^{31}P NMR spectroscopy (16.4 ppm, N=*P*Ph_3). However, hydrolysis of the iminophosphorane with both water[169] or hydrochloric acid (1 M, Scheme 71) failed even after prolonged stirring at room temperature and elevated temperatures.[170] Furthermore, the disappearance of allene signals was observed in the ^1H NMR spectrum of the isolated material. Therefore, to synthesise primary amine **447**, a modified Gabriel reaction was employed.[119]



(±)-444 (±)-**448** (±)-**447**

Scheme 72: Synthesis of primary amine **447**. **(a)** phthalamide, NaI, K_2CO_3, DMF, 60 ˚C, 3 h, 89%; **(b)** H_2NNH_2, EtOH, reflux, 1 h, 88%.

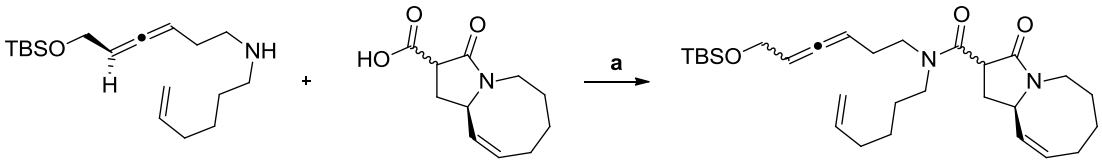
Thus, chloride **444** was converted to phthalamide **448** in 89% yield, which upon hydrazinolysis gave primary amine **447** in 88% yield (Scheme 72). No problems were encountered in separating amine **447** from the phthalamide side products. Finally, the reductive amination to give secondary amine **449** and the yields of the isolated amine ranged from 54–73% (Scheme 73).



Scheme 73: Synthesis of secondary amine **449**. **(a)** $NaBH_4$, EtOH, 0 ˚C to RT, 2 h, 54–73%.

*3.3.2 Synthesis of Spirocyclisation Pro-Nucleophile **450***

With amine **449** and acid **266** in hand, the coupling was carried out using the same conditions outlined in Chapter 2, Section 2.3.3 and the reaction proceeded in 67% yield (Scheme 74).



(±)-**449** **266** **450**

Scheme 74: Synthesis of pro-nucleophile **450**. **(a)** CDI, THF, RT, 16 h, 67%, dr 1:1 **450a**/**450a'**:**450b**/**450b'**.

Although the ^{1}H NMR spectrum showed the presence of only two diastereomers, the ^{13}C NMR spectrum clearly showed four diastereomers (see Appendix 2 for details).

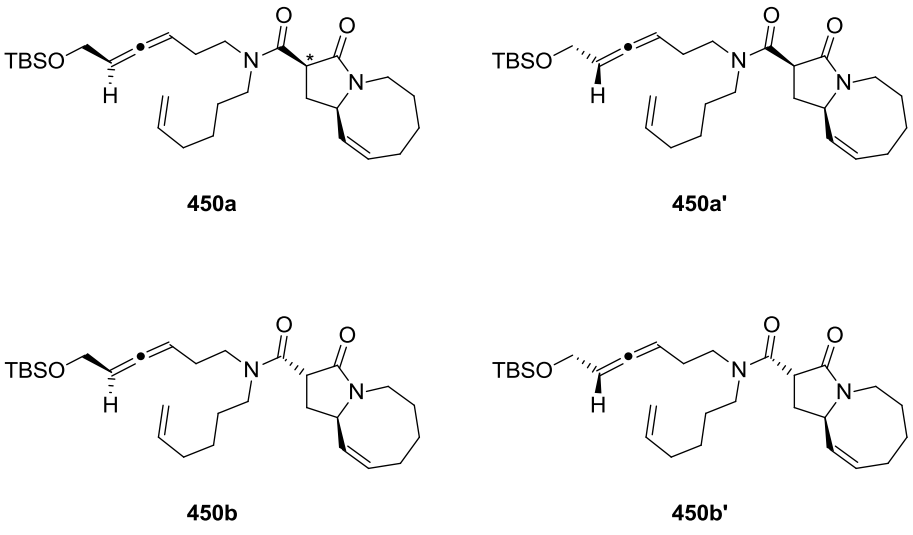


Figure 39: Four diastereomers, two pairs **450a**/**450a'** and **450b**/**450b'**.

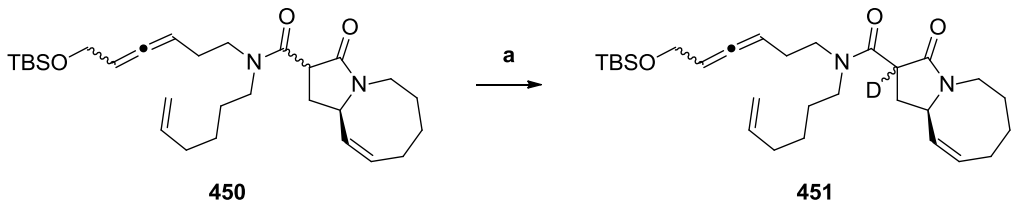
It was deduced that there were two pairs of diastereomers (**450a**/**450a'** and **450b**/**450b'**), where each diastereomer within the pair had identical ^{1}H NMR spectra but different ^{13}C

NMR spectra. The four diastereomers were inseparable by common analytical methods. The pairs were diastereomeric at the methine carbon (Figure 39, C*), and the difference within the pairs arose from the non-terminal allene diastereomers; in the ^{1}H NMR spectra of ester **146** and terminal allene pro-nucleophile **265**, the proton at the known stereocentre (8,5-fused ring junction) shifted by up to 0.3 ppm for the two diastereomers. This was observed for non-terminal allene pro-nucleophile **450** as well (4.35 ppm compared to 4.51 ppm), therefore by analogy, the two pairs were established to be diastereomeric at C*.

3.4 Palladium-Catalysed Arylative Allene Spirocyclisation Studies

3.4.1 Validation of Pro-Nucleophile *450*

Deprotonation of pro-nucleophile **450** using LHMDS followed by a deuterated acetic acid quench showed 100% deuterium incorporation which was observed by ^{1}H NMR spectroscopy and mass spectrometry of the crude reaction material (Scheme 75). This confirmed the enolate could form, and that the difference in allene had minimal effect on the acidity of the methine proton.



450 **451**

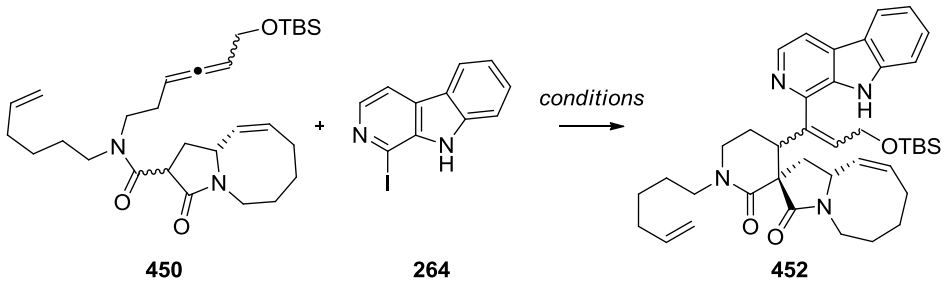
Scheme 75: Synthesis of deuterated derivative **451**. **(a)** LHMDS, CD_3COOD, 1,4-dioxane, RT, 20 min.

3.4.2 Metal-Catalysed Arylative Allene Spirocyclisation

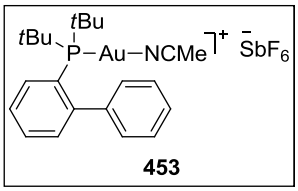
3.4.2.1 Reactions with β-Carboline *264*

The palladium-catalysed reaction was attempted with β-carboline **264** which had previously been successful in the spirocyclisation cascade, and would introduce the required aryl group (analogous to Chapter 2). The conditions that were screened and the results obtained are outlined in Table 10. The original reaction conditions from Chapter 2 were trialled (Table 10, entry 1) but only starting materials were recovered. When the standard conditions (Table 10, entry 2), as well as additives known to activate allenes such as the Echavarren Au(I) catalyst **453** (Table 10, entry 3)[171] or copper iodide (Table 10, entries 1 and 4)[123] were used, no desired product was isolated.

Table 10: Screening of conditions for the palladium catalysed reaction between pro-nucleophile **450** and aryl iodide **264**.



450 **264** **452**



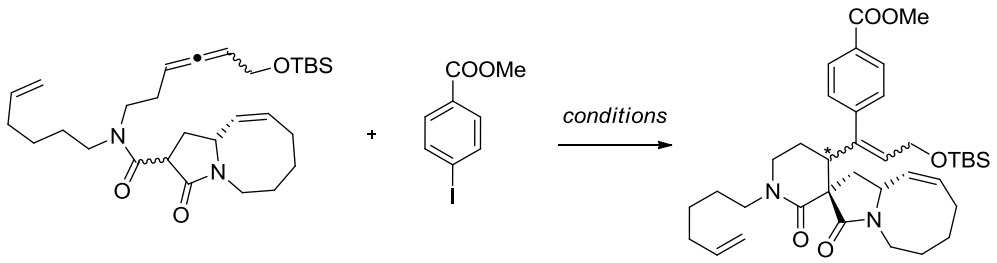
Entry	Solvent	Base	Temp/˚C	PdL_n	Additives	Yield/%
1	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	CuI	0
2	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	---	0
3	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	**453**	0
4	1,4-dioxane	KHMDS	95	$Pd(dppf)Cl_2$	CuI	0

It was ambitious to use the same β-carboline with the new non-terminal allene pro-nucleophile **450** before any validation of **450** had been carried out. Therefore, our attention turned to using model aryl iodide **260** to test the reactivity of the new pro-nucleophile and to save β-carboline **264** material. Aryl iodide **260** was accessed in one step from cheap starting materials using known literature procedures.[172]

*3.4.2.2 Reactions with Model Aryl Iodide **260***

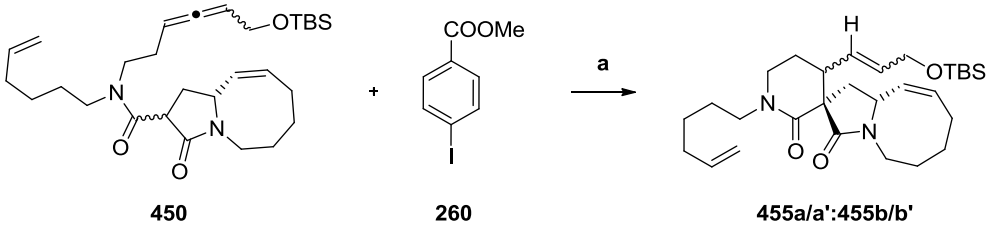
Work began with the simpler aryl iodide **260** which was used for the original validation of the spirocyclisation cascade in Chapter 2. The results are outlined in Table 11. When one equivalent of aryl iodide was used (relative to **450**), 10% yield of **454** was obtained, which was encouraging as proof of principle (Table 11, entry 1). Increasing the amount of **260** to 1.2 equivalents improved the isolated yield of **454** to 22% (Table 11, entry 2), but further increases to 1.5 equivalents of **260** gave only minor improvements in the isolated yield of **454** (Table 11, entry 3, 24% yield).

Table 11: Screening of conditions for pro-nucleophile **450** and model aryl iodide **260**.



Entry	Solvent	260/eq	Base	Temp/˚C	PdL_n	Additives	Yield 454/% dr 454a:b[xvi]	
1	1,4-dioxane	1.0	LHMDS	95	$Pd(dppf)Cl_2$	CuI	10	2:1
2	1,4-dioxane	1.2	LHMDS	95	$Pd(dppf)Cl_2$	CuI	22	2:1
3	1,4-dioxane	1.5	LHMDS	95	$Pd(dppf)Cl_2$	CuI	24	1:1
4	1,4-dioxane	1.2	KHMDS	95	$Pd(dppf)Cl_2$	---	0	---
5	1,4-dioxane	1.2	KHMDS	95	$Pd(dppf)Cl_2$	18-crown-6	0	---
6	1,4-dioxane	1.2	LHMDS	95	$Pd(dppf)Cl_2$	HMPA	0	---

Interestingly, when KHMDS was used (Table 11, entry 4), only cyclised derivative **455** was formed in 78% yield (Scheme 76). The difference in reactivity when using KHMDS compared to LHMDS had previously been observed in our research group.[173]



Scheme 76: Synthesis of spirocycle **455**. **(a)** KHMDS, 10 mol% $Pd(dppf)Cl_2$, 1,4-dioxane, 95 ˚C, 16 h, 78%, dr **455a/a':455b/b'** 2:1.

It was hoped that 18-crown-6 would chelate the potassium ions and further increase the reactivity of enolate **450** but the yield of **455** dropped to 63% (Table 11, entry 5). It was postulated that oligomeric enolates were forming which would decrease reactivity. Therefore, HMPA was added to the reaction mixture in the hope that it would chelate the

[xvi] Diastereomeric at C* as observed by ^{1}H NMR spectroscopy and NMR techniques therein. Configuration of the double bond was not able to be determined using NMR spectroscopy techniques.

potassium ions and disrupt the oligomeric enolates (Table 11, entry 6). However, only decomposition of starting materials was observed.

After the successful formation of spirocycles **454a** and **454b** (Table 11, entry 2), the diastereomers were separated by preparative HPLC, and NOESY experiments indicated the stereochemistry for each diastereomer (Figure 40). In **454a**, strong interactions were observed between H–8 and H–9 and also between H–9 and H–11 which was analogous to the stereochemistry observed in Chapter 2 for **263a**. The stereochemistry at C–7 was known, so it was deduced that H–8, H–9 and H–11 were on the same face, which gave the desired stereochemistry for manzamine A. Conversely, in **454b** strong interactions were observed between H–8 and H–9 and between H–10 and H–11. In this case, H–11 was on the opposite face to H–9 and H–8, and therefore, **454b** possessed the wrong stereochemistry for manzamine A.

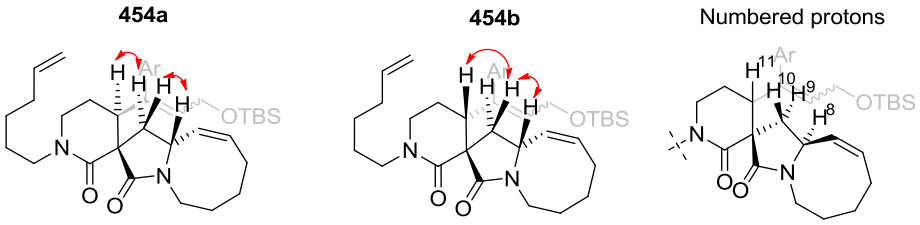
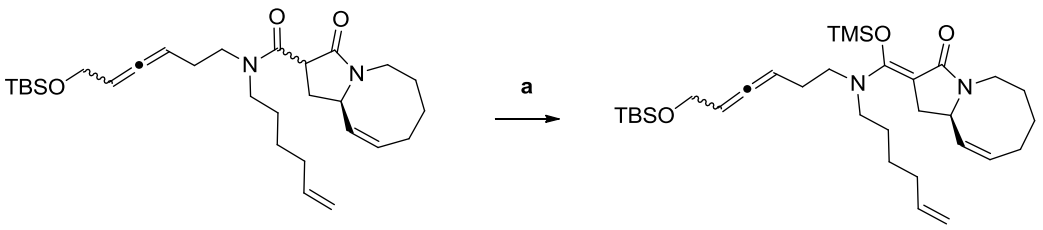


Figure 40: NOESY experimental data for **454a** and **454b**. The red arrow shows strong interactions.

From the results outlined in Table 11, it was clear that non-terminal allene **450** was significantly less reactive under the palladium-catalysed spirocyclisation reaction conditions than the corresponding terminal allene substrate **265**. No reactivity was observed with the β-carboline, and only low reactivity was observed with the model aryl iodide. The reactivity of the carbon nucleophile needed to be increased to compensate for the less reactive non-terminal allene. Thus, our attentions turned to employing a silyl enol ether.

3.4.2.3 Synthesis of Silyl Enol Ether **456**

Increasing the reactivity of an enolate was reported by Mukaiyama in 1973 during the development of the Mukaiyama aldol reaction[174] and was achieved by synthesising a silyl enol ether. Accordingly, pro-nucleophile **450** was subjected to deprotonation by LHMDS and the enolate was subsequently trapped using TMSCl (Scheme 77).[xvii]



450 **456**

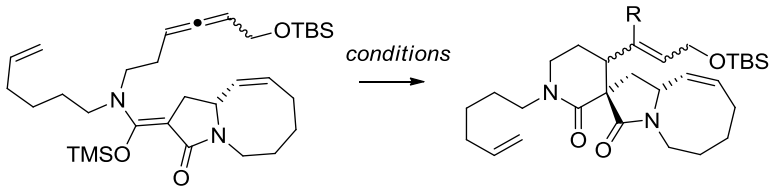
Scheme 77: Synthesis of silyl enol ether **456**. **(a)** LHMDS, TMSCl, 1,4-dioxane, 0 ˚C to RT, 4 h, 100% mass return.

The silyl enol ether **456** was used crude as any form of column chromatography (alumina, silica gel) hydrolysed **456** to give starting material, **450**.

Silyl enol ether **456** was subjected to the standard reaction conditions ($Pd(dppf)Cl_2$, 1,4-dioxane, 95 ˚C), with or without model aryl iodide **260** (Table 12, entries 1 and 2). However, no cyclisation was observed and only de-silylated starting material was recovered. Au(I) can catalyse the addition of nucleophiles onto allenes,[171] so both Echavarren's catalyst[175] (Table 12, entry 3) and $AuPPh_3Cl$/AgOTf (Table 12, entry 4) were employed. No reactivity was seen when either gold catalyst was employed and again, only de-silylated starting material **450** was isolated.

[xvii] The silyl enol ether **456** was isolated as a 4:1 mixture of isomers. The TMS group is positioned as shown, and not on the pyrrolidinone carbonyl (no shift in NC*H* proton).

Table 12: Attempted cyclisation of silyl enol ether **456**.



456

R = Ar **454**
R = H **455**

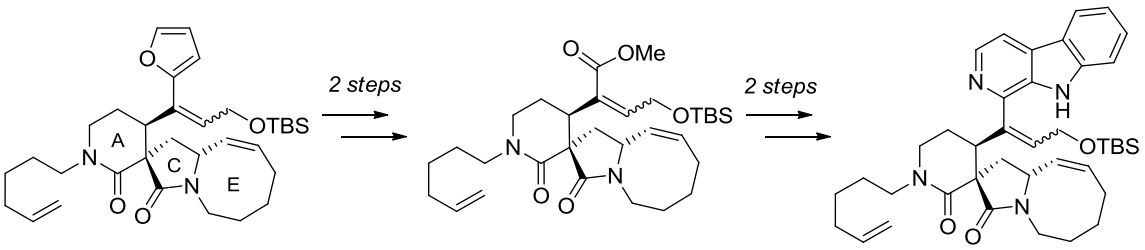
Entry	Solvent	Temp/˚C	Catalyst	Additives	R	Yield 454 or 455/%
1	1,4-dioxane	95	$Pd(dppf)Cl_2$	---	H	0[xviii]
2	1,4-dioxane	95	$Pd(dppf)Cl_2$	**260**	*p*-COOMe-C_6H_4-	0
3	1,4-dioxane	65	**453**	---	H	0
4	1,4-dioxane	65	$AuPPh_3Cl$, AgOTf	---	H	**0**

Success had been achieved in the spirocyclisation reaction when model aryl iodide **260** was used with pro-nucleophile **450** (Section 3.4.2.2), albeit in low yields. Therefore, the use of a different aryl iodide that could be converted to the β-carboline later in the synthesis was investigated.

*3.4.2.4 Reactions with β-Carboline Substitute **459***

Iodo-furan **459** would be employed because it could be transformed into a β-carboline using literature procedures (Scheme 78).[176,8] Oxidation of furan derivative **457**[176] followed by esterification of the subsequent acid would give ester **458**. The ester could then undergo partial reduction to the aldehyde which, using literature precedented reactions, could be converted to the desired β-carboline (see Chapter 1).[8]

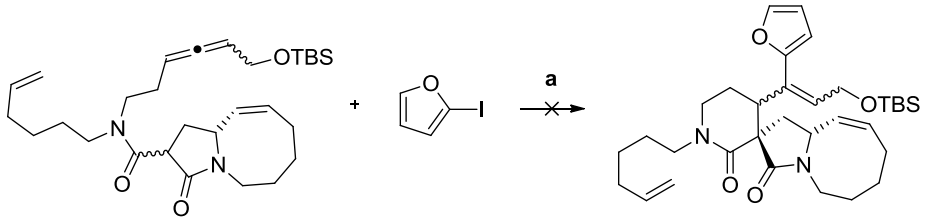
[xviii] Only de-silylated product **450** was obtained.



457a **458** **452**

Scheme 78: Conversion of furan derivative **457a** to β-carboline derivative **452**.

The most successful conditions from the original methodology (Chapter 2) were utilised: LHMDS with Pd(dppf)Cl_2 in 1,4-dioxane at 95 ˚C (Scheme 79). However, only decomposition of 2-iodo-furan **459** was observed, presumably due to the sluggish reactivity of pro-nucleophile **450** and elevated reaction temperatures.



450 **459** **457a,b**

Scheme 79: Synthesis of furyl derivative **457**. **(a)** LHMDS, Pd(dppf)Cl_2, 1,4-dioxane, 95 ˚C.

3.4.3 Summary

The use of the non-terminal allene in the palladium-catalysed arylative allene spirocyclisation cascade as the key step towards the synthesis of manzamine A was not as successful as hoped (Figure 41). Deuterium labelling showed that the enolate had formed, but when the desired β-carboline was used in the spirocyclisation reaction, no product was observed when a range of conditions were used. When model aryl iodide **260** was employed, 24% yield of spirocycle **454** was obtained which was encouraging. There was proof that the desired cyclisation could occur, observed when KHMDS was used instead of LHMDS; 78% yield of cyclised derivative **455** was obtained, but with no incorporation of the aryl iodide. This may have been due to increased unfavourable steric hindrance around the

palladium catalyst during the reaction. When β-carboline substitute, 2-iodo-furan was used, no reactivity was observed when the standard successful conditions were employed.

It was postulated that the problem with the second generation route was the lower reactivity of the non-terminal allene. This was the only difference to the system as β-carboline **264** and model aryl iodide **260** were successfully employed in Chapter 2 with the terminal allene pro-nucleophile **265**. The idea of using a substitute for the β-carboline in the spirocyclisation had not been considered previously and was encouraging. Even though no reactivity was observed on the non-terminal allene substrate, it was likely that the furan would be successful with the terminal allene pro-nucleophile, analogous to the success with β-carboline **264** and model aryl iodide **260**. This would give the furan derivative of **263a** which, using the chemistry outlined in Scheme 78 (on the terminal allene system) could be transformed into an α,β-unsaturated ester. A 1,4-Michael addition could then be carried out to introduce the CH_2-NO_2. This new route is discussed in Chapter 4.

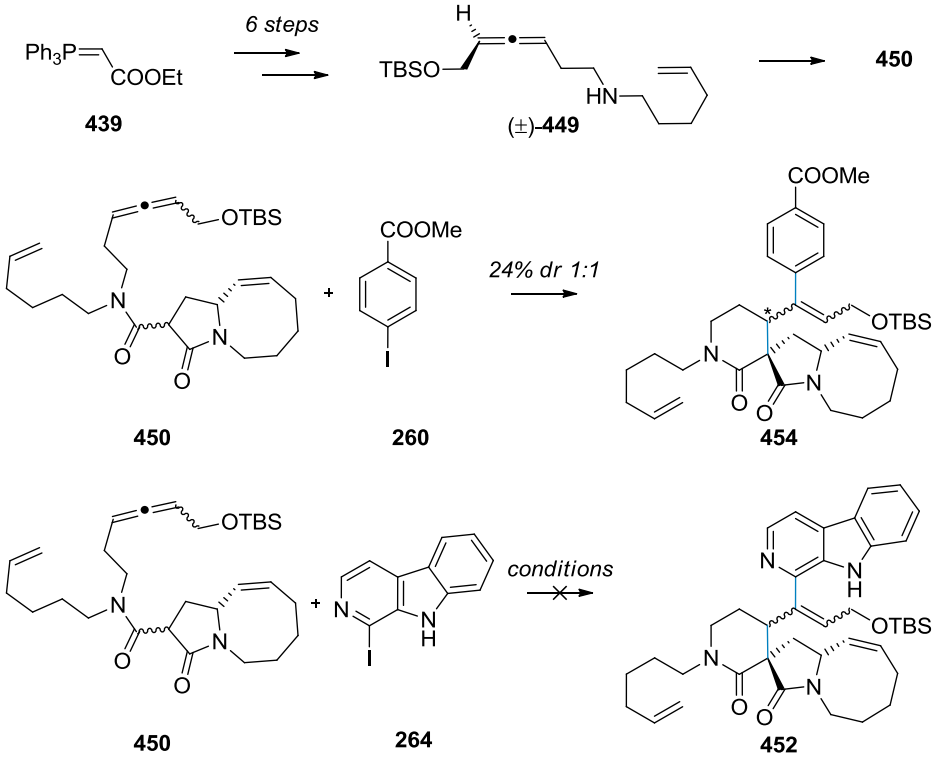


Figure 41: Summary of non-terminal allene substrate in the palladium-catalysed arylative allene spirocyclisation.

Chapter 4
3rd Generation: Homologation of an α,β-Unsaturated Ester

4.1 Introduction

In Chapters 2 and 3, two routes towards the synthesis of manzamine A were discussed and were based on a palladium-catalysed arylative allene spirocyclisation cascade. However, these two routes failed to progress to manzamine A and a new route was sought. The first generation (Chapter 2) relied on the homologation of a vinyl β-carboline system, to ultimately introduce a nitromethylene unit (CH_2-NO_2) (Figure 42, **[1]**), which would provide a functionalised one-carbon extension required for ring B construction. However, using a range of methodologies, no progress from **263a** was made (Chapter 2).

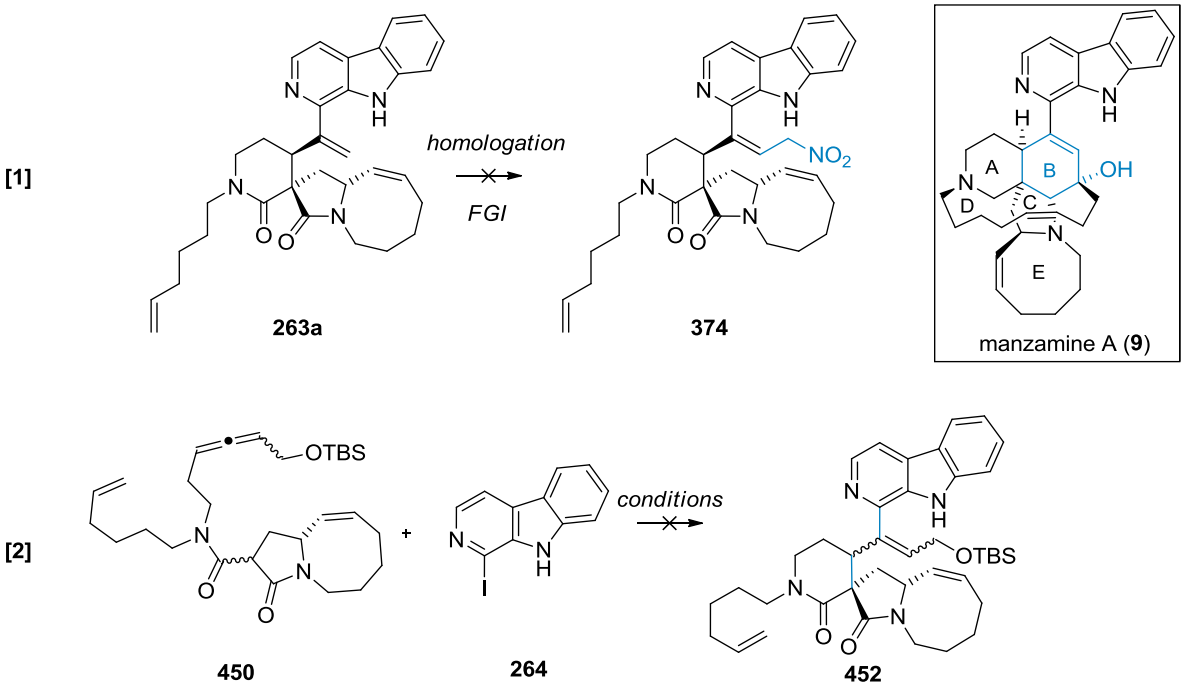


Figure 42: Unsuccessful first and second generation routes.

The second generation (Chapter 3) outlined the use of non-terminal allene **450** (Figure 42, **[2]**). It was hoped that this approach would allow the early incorporation of the crucial functionalised methylene unit, and then, that pro-nucleophile **450** would undergo the palladium-catalysed arylative allene spirocyclisation reaction. As such, the homologated allene pro-nucleophile **450** was synthesised incorporating functionality that could be converted to a nitro group later in the synthesis. However, the use of non-terminal allenes was not successful; only low yields were obtained in the palladium-catalysed spirocyclisation with a reactive model aryl iodide and none of spirocycle **452** was isolated using iodo-β-carboline **264** (Chapter 3). However, in our studies towards using the non-terminal allene pro-nucleophile, a substitute for the β-carboline was used, 2-iodo-furan. Although unsuccessful with the non-terminal allene, we believed we could incorporate its use into the synthesis of manzamine A (**9**).

4.1.1 Retrosynthetic Analysis

For the third generation, the key target molecule was α,β-unsaturated ester **465** (Figure 43). The vinyl-ester would be much more reactive compared to the vinyl β-carboline and thus lend itself to functionalisation *via* a Michael addition reaction. The β-carboline would be introduced in the final steps from **460**, in a similar fashion to other routes previously published (Chapter 1). The heavily decorated pentacycle **460** would be accessed *via* a stereoselective organometallic olefin addition (**461**) to ketone **462** followed by a ring-closing metathesis thus constructing ring D. Ketone **462** would be synthesised from nitro-derivative **463** *via* a Nef reaction and a dehydrogenation. Using an intramolecular nitro-Mannich reaction (Chapter 2), ring B could be synthesised from homologated nitro derivative **464**. Nitro-ester **464** would be obtained directly from a 1,4-Michael addition to ester **465** with the nitromethane anion. Ester **465** would be accessed from furan **466** *via* an oxidation and esterification of the subsequent acid that forms. Furan derivative **466** would be synthesised using the palladium-catalysed spirocyclisation methodology developed in

Chapter 2, using 2-iodo-furan **459** and terminal allene pro-nucleophile **264** which in turn would be synthesised *via* an amide coupling (Chapter 2).

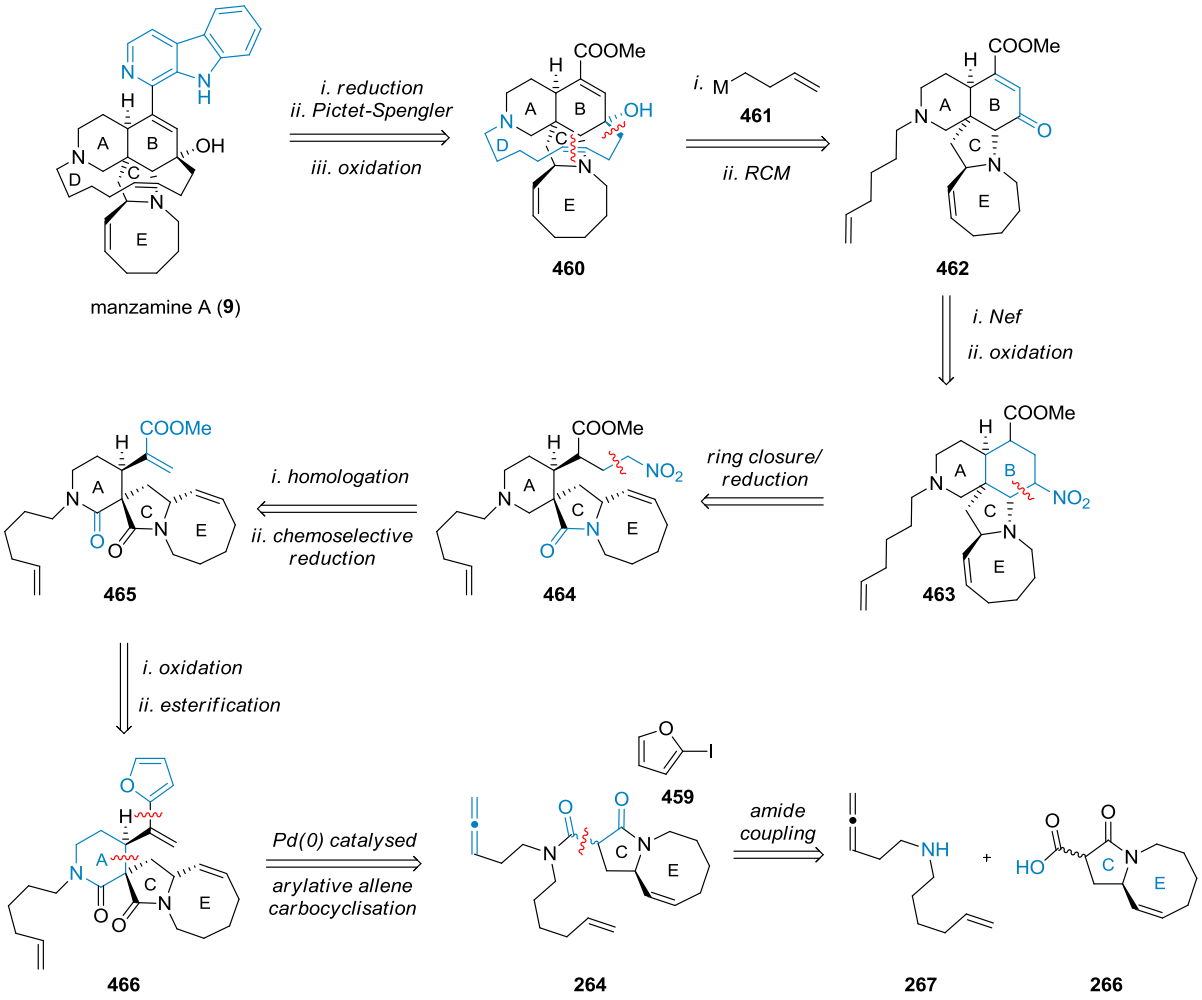
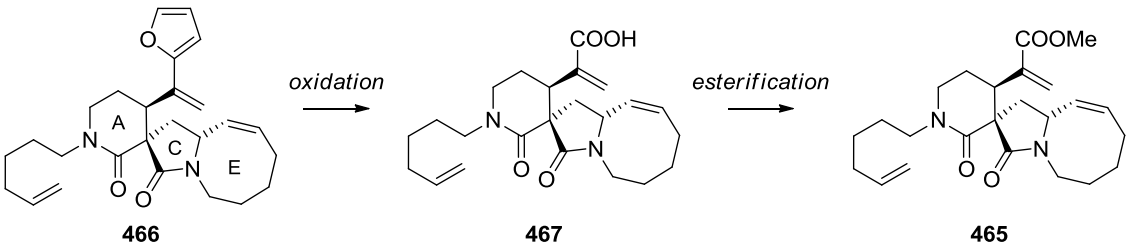


Figure 43: Retrosynthesis of manzamine A (**9**) using a 3rd generation route.

4.1.2 Route I: Using 2-iodo-furan

We wanted to incorporate the furan moiety because potentially, it could be converted to the target ester **465** *via* oxidation and esterification (Scheme 80). Ester **465** in turn could be converted to the desired β-carboline system using literature procedures.[12]

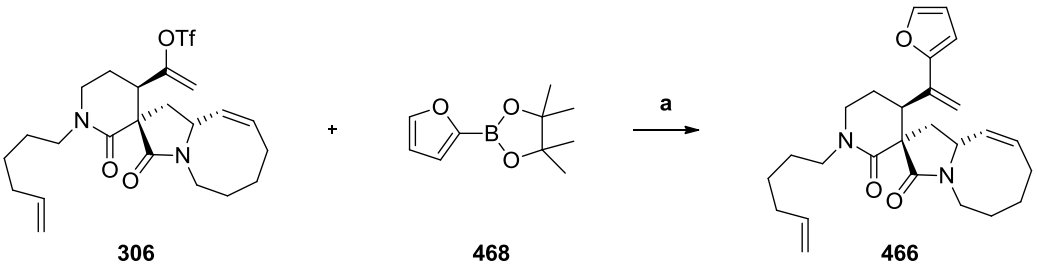


Scheme 80: Planned conversion of furan **466** to ester **465**.

The use of 2-iodo-furan in the palladium-catalysed spirocyclisation cascade was considered, but extensive optimisation to obtain the correct diastereomer in good yield was envisaged. Therefore, in order to rapidly access furan **466** as a single diastereomer to test the subsequent steps, a Suzuki cross-coupling reaction[133] was carried out between triflate **306** (the synthesis is described in Section 4.2.7) and known furan-boronic ester **468**.[177]

*4.1.2.1 Suzuki Reaction to Access Single Diastereomer **466***

A Suzuki cross-coupling reaction was performed between triflate **306** and boronic ester **468** (synthesised following a literature procedure[177]) which gave furan derivative **466** as a single diastereomer in 75% yield (Scheme 81). The product stereochemistry was confirmed by nOe experiments and the stereochemistry of a precursor to triflate **306** was established by single crystal X-ray diffraction (see Section 4.2.3).



306 **468** **466**

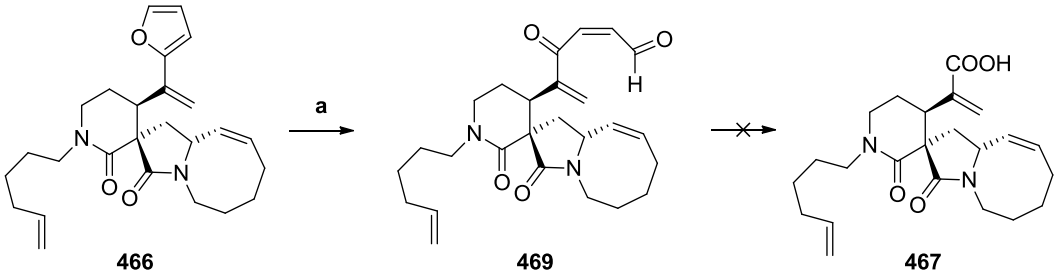
Scheme 81: Suzuki coupling between triflate **306** and boronic ester **468**. **(a)** 10 mol% $Pd(PPh_3)_4$, Cs_2CO_3, DME, H_2O, 75 ˚C, 4 h, 75%.

With furan derivative **466** in hand and before optimisation of the palladium-catalysed arylative allene spirocyclisation cascade was carried out, we needed to confirm the following points:

1. Could the furan be oxidised to the corresponding carboxylic acid **467**?
2. Could the acid be converted to the desired ester intermediate **465**?
3. Could the ester be homologated?
4. Would the previously successful[12] partial reduction/cyclisation cascade to form ring B translate to this substrate?

4.1.2.2 Oxidation of Furan Derivative **466**

The oxidation of the furan was investigated using spirocycle **466** (Scheme 82). Using literature conditions,[176] furan **466** was exposed to catalytic $RuCl_3 \bullet xH_2O$ (10 wt%) and a stoichiometric amount of oxidant $NaIO_4$ in a mixture of MeCN:CCl_4:H_2O (1:1:1.5).



Scheme 82: Oxidation of furan derivative **466**. **(a)** MeCN, CCl_4, $RuCl_3 \bullet xH_2O$, $NaIO_4$, H_2O, RT to 40 ˚C, 24 h, 39% **469**.

However, even with prolonged stirring at RT and heating to 40 ˚C, only intermediate aldehyde **469** was isolated, in 39% yield. The reaction conditions were harsh, and it was possible that the starting material decomposed. Re-exposure of pure aldehyde **469** to the reaction conditions outlined in Scheme 83, gave no further reaction and acid **467** was not isolated. A range of conditions were employed to no avail; when oxidant systems such as $KMnO_4$/*t*BuOH/NaH_2PO_4 or $RuO_2 \bullet H_2O$/$NaIO_4$ were used, no reaction was observed. Therefore, due to time-constraints, this route was not pursued further.

All attempts to make the acid failed, thus the synthesis of ester **465** from acid **467** was not performed. Therefore, a new route was sought to rapidly access ester **465**, and investigations into whether ester **465** would lead to manzamine A (**9**) could begin.

4.1.3 Route II: Alternative Synthesis of Ester **465**

The second route to ester **465** was developed based around the successful strategy used in the Dixon group to complete the total synthesis of ircinal A, a common precursor to manzamine A.[12] The route would allow access to the desired α,β-unsaturated ester **465** (Figure 44) *via* carbonylation of triflate **306**.

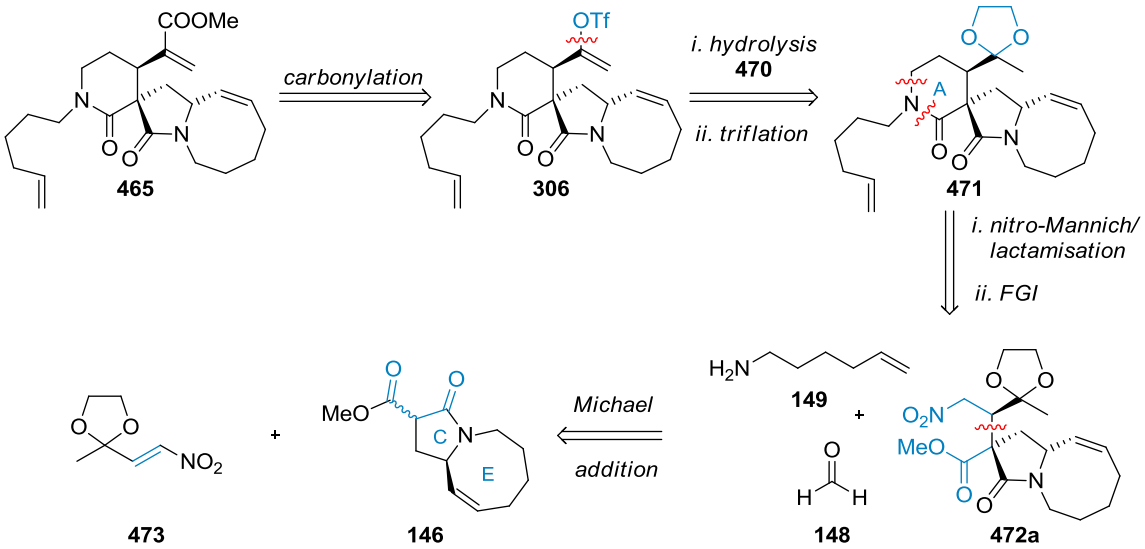


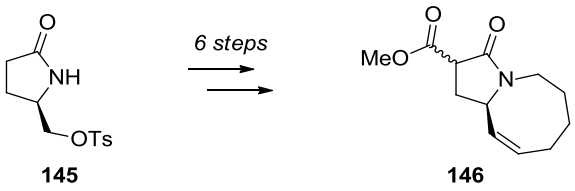
Figure 44: Retrosynthesis of **465** *via* route II.

Triflate **306** would in turn be synthesised by triflation under kinetic control of ketone **470**, which would be synthesised from the hydrolysis of acetal **471**. Acetal **471** would be formed *via* a nitro-Mannich/lactamisation cascade between nitro-acetal **472a**, amine **149** and *para*-formaldehyde **148**, a reaction that has been extensively developed within the Dixon group.[178–183] Lastly, a diastereoselective Michael addition between ester **146** and nitro-olefin **473** would give diastereomerically pure nitro-acetal **472a** (Figure 44).

4.2 Synthesis of Starting Materials

4.2.1 Synthesis of Ester **146**

Ester **146** was synthesised according to literature procedures which were outlined in Chapter 2 (Figure 45).

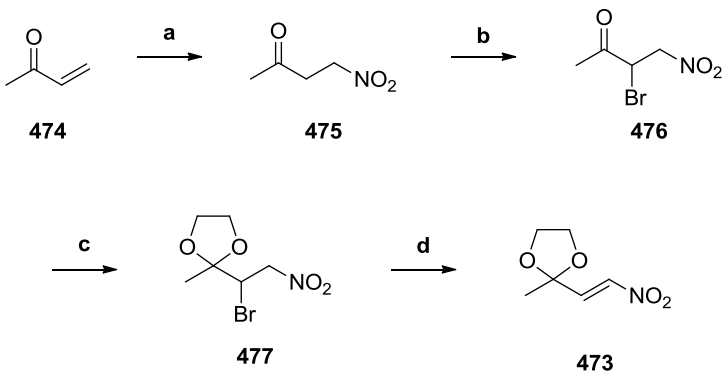


145 **146**

Figure 45: Overview of the synthesis of **146** (see Chapter 2 for details).

4.2.2 Synthesis of Nitro-Olefin **473**

The synthesis of the nitro-olefin was carried out according to literature procedures (Scheme 83).[184] A Michael addition to methyl vinyl ketone **474** (MVK) using sodium nitrite proceeded in 58% yield giving nitro-ketone **475**. Bromination gave α-bromo ketone **476** in 91% yield. Protection of the ketone under Dean-Stark conditions gave acetal **477** which upon treatment with triethylamine gave the desired nitro-olefin **473** in 90% yield over two steps.



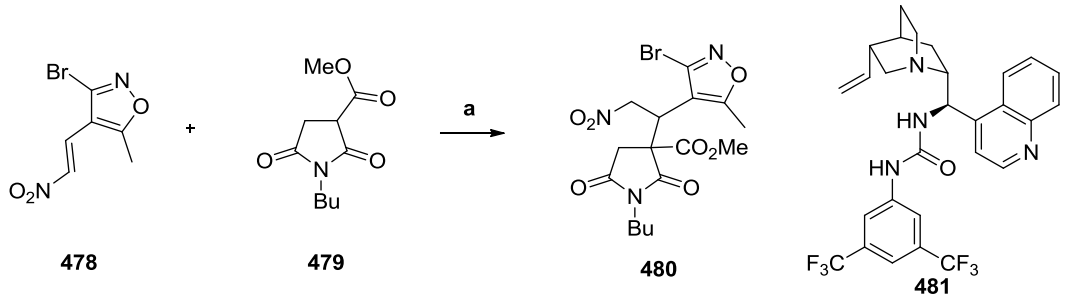
474 **475** **476**

477 **473**

Scheme 83: Synthesis of nitro-olefin **473**. **(a)** $NaNO_2$, THF, HOAc, RT, 24 h, 58%; **(b)** Br_2, *p*TSA•H_2O, DCM, RT, 20 min, 91%; **(c)** $HOCH_2CH_2OH$, *p*TSA•H_2O, benzene, reflux, 16 h, 3:1 **477**:**473**; **(d)** Et_3N, DCM, RT, 30 min, 90% over two steps.

4.2.3 Michael Addition

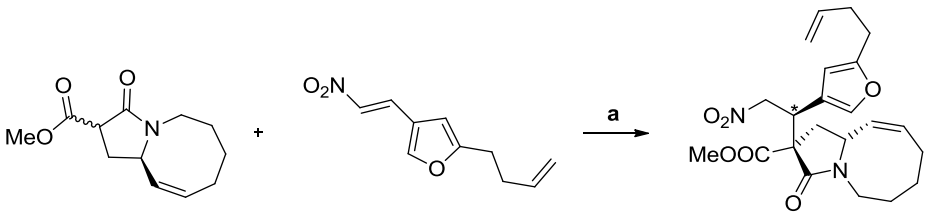
Diastereoselective Michael additions have been used on multiple occasions in the Dixon group for creating stereocentres, especially in the syntheses of complex natural products such as nakadomarin A[17] and manzamine A.[12]



478 479 480 481

Scheme 84: Synthesis of nitro-ester **480** *via* a Michael addition. **(a)** DABCO, THF, 0 ˚C, 97%, dr 1:1.5 or **481**, DCM, 0 ˚C, 100%, dr 1:2, 85% ee. Stereochemistry not given.

Dr Wolfgang Felzmann carried out the first investigations in to the Michael addition utilising nitro-olefin **478** and pro-nucleophile **479** (Scheme 84).[xix] This reaction was then successfully employed in the Dixon group total synthesis of nakadomarin A (Scheme 85).[17] Dixon used substituted furyl-electrophile **482** and organocatalyst **481** (15 mol%) in toluene at 30 °C which afforded the desired compound **483** in 57% yield, 91:9 dr.[17]



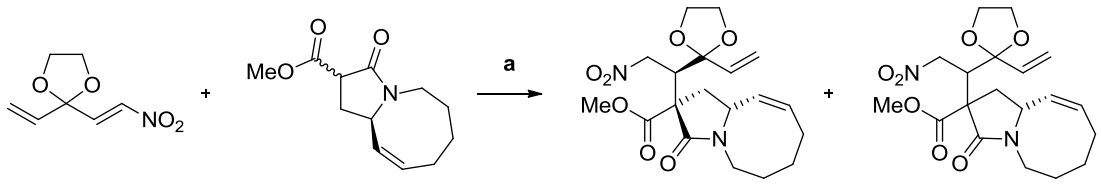
146 482 483

Scheme 85: Michael addition between pro-nucleophile **146** and functionalised nitro-olefin **482**. **(a)** 15 mol% **481**, toluene, 30 ˚C, 8 d, 57%, dr 91:9. Diastereomeric at C*.

Both the synthesis of **480** and **483** employed an organocatalyst. However, the reaction times were lengthy - a major drawback in a natural product synthesis. It was found that in our total synthesis of manzamine A (see Chapter 1) with a different nitro-olefin, a strong

[xix] Unpublished work by Dr Felzmann.

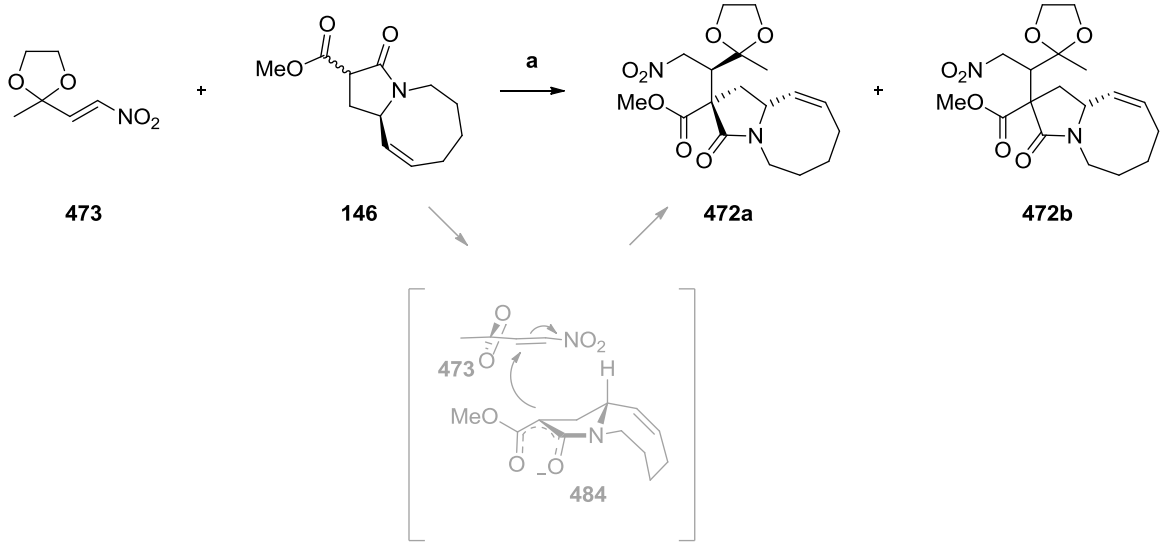
base was required (Scheme 86); no reaction was observed with any organocatalyst.[xx] This was likely due to the increased steric bulk of the acetal and the de-conjugated double bond; the system was less reactive.



144 **146** **147a** **147b**

Scheme 86: Synthesis of nitro-esters **147a** and **147b**. **(a)** KHMDS, 18-crown-6, THF, -94 °C, 1 h, crude dr 3:1, **147a** 65%, **147b** 21%.

Using the conditions described in Scheme 86, on exposure of nitro-olefin **473** to the enolate of ester **146** (Scheme 87, **484**), a highly diastereoselective Michael addition occurred. Initially, the reaction was carried out at −78 ˚C (dr 3:1). However, it was found that the diastereoselectivity was influenced by decreasing the reaction temperature from −78 ˚C to −94 ˚C resulting in an increased diastereomeric ratio, from 3:1 to 5:1 (**472a**:**b**), as observed in the crude ^{1}H NMR spectra.

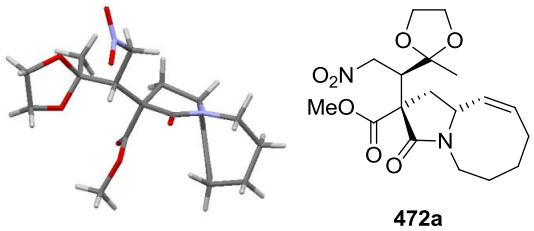


Scheme 87: Synthesis of nitro-esters **472a** and **472b**. **(a)** KHMDS, 18-crown-6, THF, −94 ˚C, 30 min, 94%, dr 5:1, **472a** 81%, **472b** 13%.

At −94 ˚C, the desired diastereomer **472a** was isolated in 81% yield, and second diastereomer **472b** was isolated in 13% yield. The diastereoselectivity at the newly formed

[xx] Unpublished work carried out by Dr Pavol Jakubec.

quaternary centre was controlled by the 8,5-fused stereocentre. Addition of the nitro-olefin to the convex face of the enolised pro-nucleophile gave Michael addition product **472a**: the concave face was blocked by the 8-membered ring (Scheme 87, **484**). Attempts were made to prove the absolute stereochemistry of minor diastereomer **472b**, by further derivatisation in order to synthesise a crystal for single crystal X-ray diffraction. While all attempts to prove the absolute chemical structure of the minor diastereomer failed, the stereochemistry of the major diastereomer **472a** was determined unambiguously by single crystal X-ray diffraction (Figure 46).

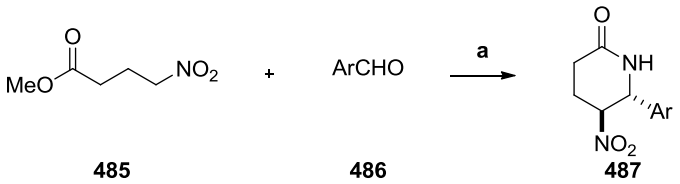


472a

Figure 46: X-ray structure of **472a**.

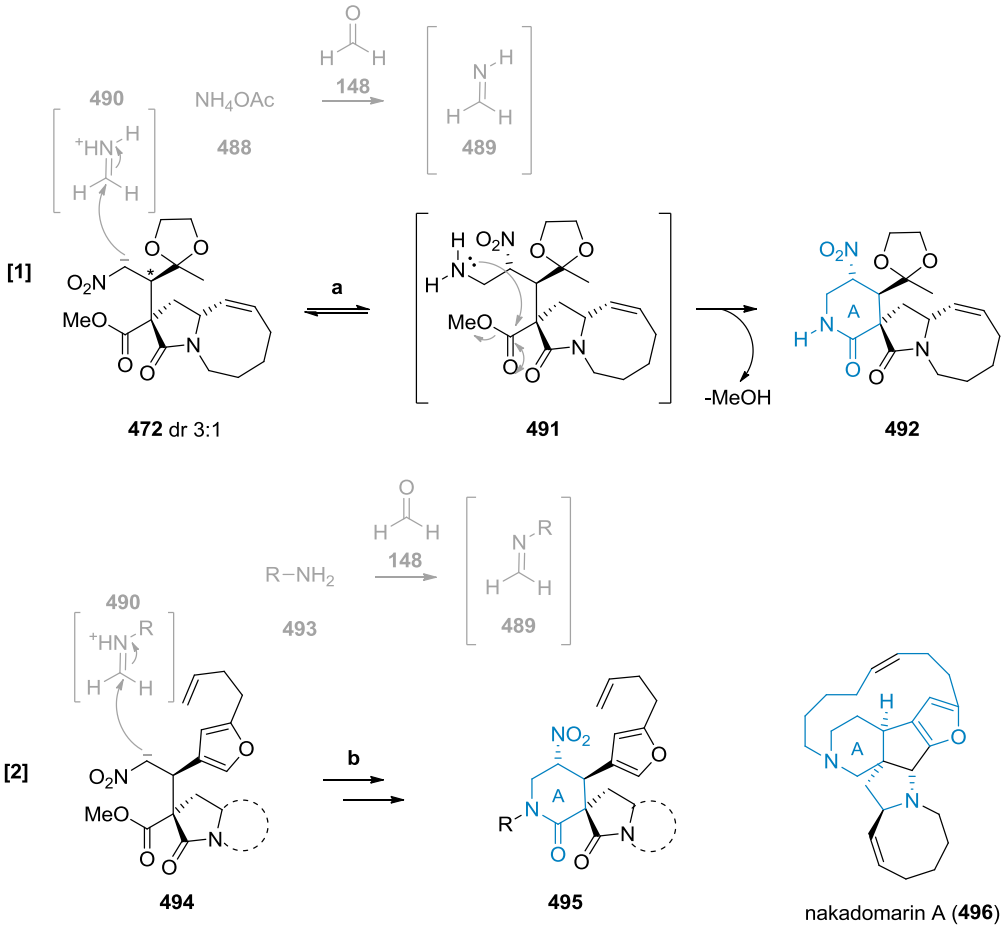
4.2.4 Nitro-Mannich/Lactamisation

Nitro-Mannich/lactamisation reactions were first reported independently by Mühlstädt in 1975 and Jain in 1976 as a method of synthesising 6-aryl-substituted 5-nitropiperidin-2-ones (Scheme 88).[185,186] Jain highlighted the *trans* relationship between the nitro and aryl groups. A wide range of aryl groups were employed; electron-withdrawing groups such as *p*-NO_2-C_6H_4- and electron-donating groups such as *p*-OMe-C_6H_4- were well tolerated in this reaction and piperidinones **487** were isolated in up to 95% yield. However, it wasn't until the early 1990s when the synthetic value of this reaction was fully realised and since then, a plethora of papers has been published, including multiple reports from the Dixon group.[178–183]



Scheme 88: Mühlstädt's and Jain's synthesis of nitro-piperidin-2-ones **487**. **(a)** NH_4OAc, EtOH, reflux, 12 h, up to 95%. Ar = Ph, *p*-Me-, *p*-MeO-, *p*-Cl-, *p*-Me_2N-, *p*-Et_2N-, *p*-NO_2-, *p*-CN-, *p*-Br-, *p*-Me_2CH-, *p*-OH-, *p*-COOH-, *p*-AcN-, *o*-Cl- and *m*-NO_2-C_6H_4-.

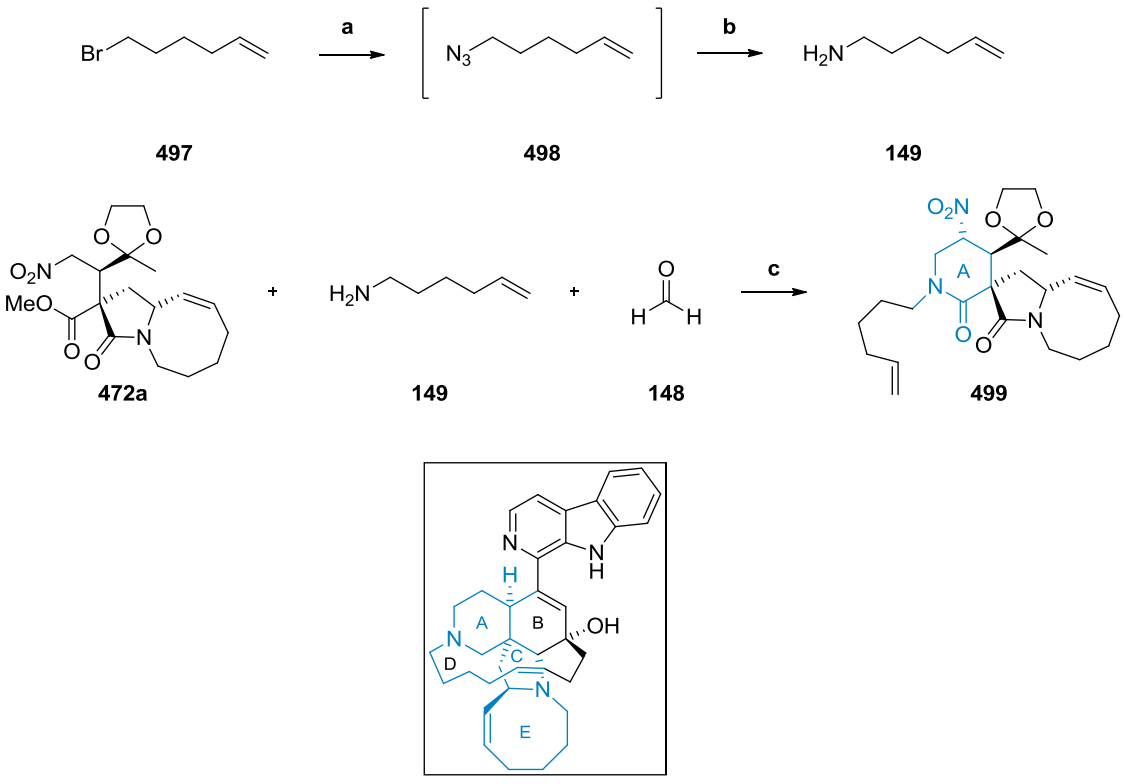
The nitro-Mannich/lactamisation reaction was developed on a manzamine A-type system by Dr Pavol Jakubec (Scheme 89, **[1]**), which introduced a one-carbon homologation whilst forming the piperidinone ring in **492**. Following work by Mühlstädt and Jain, NH_4OAc **488** with *para*-formaldehyde **148** formed imine **489** which on exposure to a 3:1 diastereomeric mixture of nitro-ester **472,** underwent the nitro-Mannich/lactamisation cascade to give piperidinone **492** in 69% yield.



Scheme 89: Application of the nitro-Mannich/lactamisation cascade to form **492** and **495**. **(a)** $(HCHO)_n$, NH_4OAc, EtOH, 150 ˚C in sealed tube, 69%; **(b)** appropriate amine, CH_2=O, MeOH, reflux, 3 h, 52–68%. R = H or alkyl.

A possible mechanism is outlined in Scheme 89, **[1]**: the *in situ* formed imine **489** ($pKa_H \approx 11$) is sufficiently basic to deprotonate the α-nitro carbon (pKa ≈ 10), thus forming iminium ion **490**. Recent reports from our research group indicate that the subsequent nitro-Mannich reaction is reversible and only one of the potential diastereomers undergoes the irreversible lactamisation to form ring A **492**.[179]

The reaction was further extended within the Dixon research group to form a range of heterocycles, with excellent diastereo- and enantiocontrol.[178–183] This versatile reaction was also applied by Dixon to the total synthesis of nakadomarin A (Scheme 89, **[2]**)[17,187,188] the recently reported total synthesis of manzamine A[12] (see Chapter 1) and in this synthesis of manzamine A (Scheme 90).



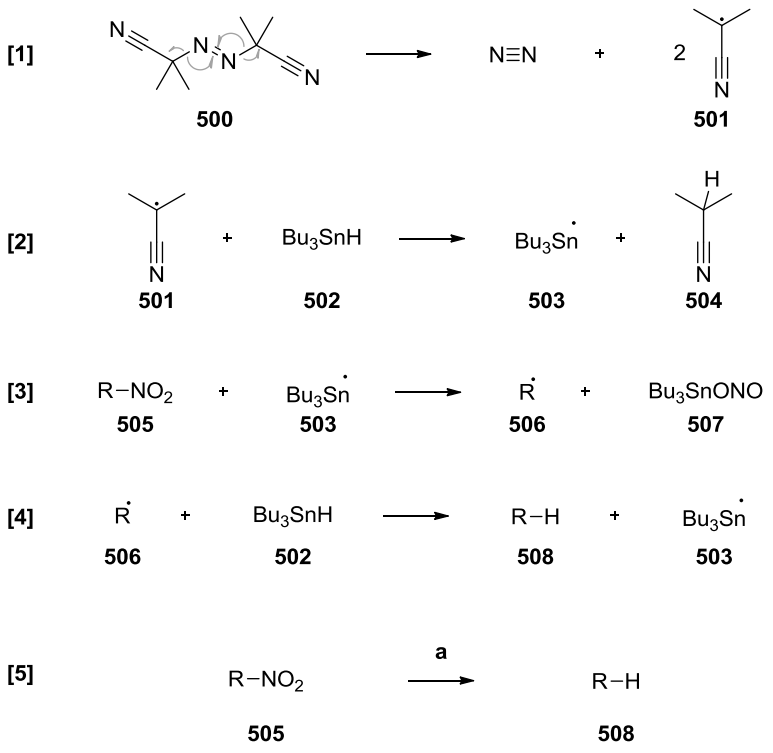
Scheme 90: Synthesis of primary amine **149** and nitro-acetal **499**. **(a)** NaN_3, DMSO, 50 °C, 2 h; **(b)** H_2O, PPh_3, Et_2O, RT, 16 h, 49% over two steps; **(c)** MeOH, reflux, 3 h, 91%.

Amine **149** was synthesised in 49% yield over two steps from commercially available bromide **497**. The addition of amine **149** and *para*-formaldehyde (**148**) to nitro-ester **472a**

in methanol was carried out and the reaction mixture was heated at reflux to give the desired nitro-acetal **499** in 91% yield.

4.2.5 Nitro Group Removal

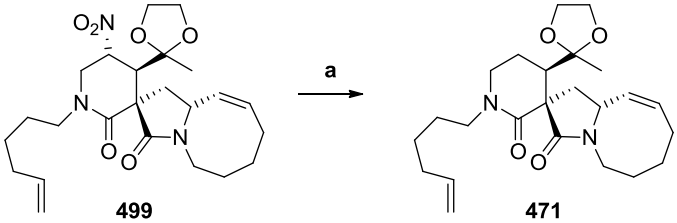
The removal of a nitro group under radical conditions was first reported in 1985 by Ono *et al.* (Scheme 91).[189] Substoichiometric AIBN **500** was used as a radical initiator as it readily undergoes thermal decomposition to form nitrogen and *iso*-propylnitrile radical **501** (Scheme 91, **[1]**). Radical **501** reacted with Bu_3SnH **502** in an initiation step to form the tri-butyl tin radical **503** (Scheme 91, **[2]**) which was free to propagate and react with the nitro group (Scheme 91, **[3]**). Radical **506** was synthesised which reacted with **502** to form **508** with concomitant regeneration of **503** (Scheme 91, **[4]**).[189]



Scheme 91: AIBN and Bu_3SnH radical mechanism,[189] and application to **505**. **(a)** AIBN (0.25 eq), Bu_3SnH (1.2 eq), benzene, 80 ˚C, 1–2 h, 26–94%. R = *t*Bu, Ph, *p*-CN-, *p*-MeO-, $-CH_2CH(Ph)SPh$, $-(CH_2)_2COO(CH_2)_2Br$.

Ono applied this methodology to tertiary and secondary nitro-alkanes in the presence of a variety of other functional groups; ester, nitrile, methoxy, sulfide, ketone and halogen groups were all tolerated in yields ranging from 26–94% (Scheme 91, **[5]**). Since then, very

few changes have been made to the original reaction conditions, and the reaction has proved very useful for selectively removing a nitro group, even on complex, functionalised compounds. Indeed, this method of removing a nitro group was used in all of the Dixon total syntheses of nakadomarin A,[17,187,188] and in the total synthesis of manzamine A,[12] where functional groups such as amides, alkynes, alkenes, furans and acetals were all tolerated.

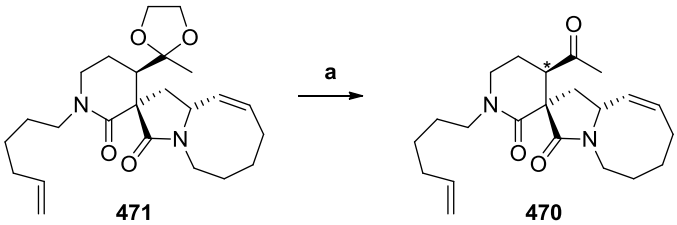


Scheme 92: Proto-denitration of **499**. **(a)** AIBN (0.2 eq), Bu_3SnH (5.0 eq), toluene, reflux, 3 h, 71%.

Accordingly, nitro-acetal **499** was exposed to AIBN and Bu_3SnH under a nitrogen atmosphere, using toluene in place of benzene, and proto-denitrated derivative **471** was obtained in 71% yield (Scheme 92).

4.2.6 Hydrolysis

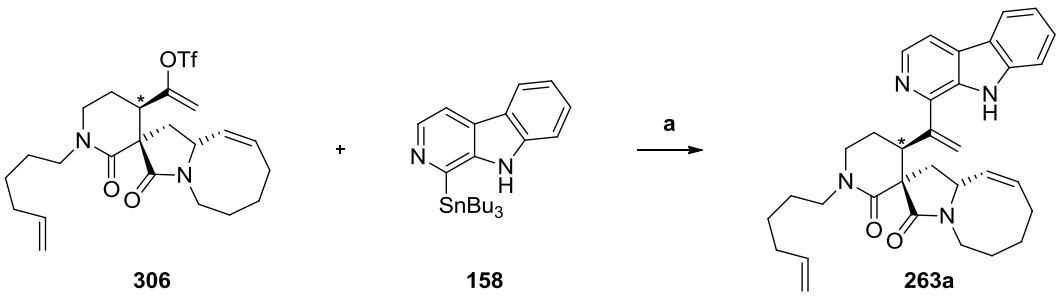
The acidic hydrolysis of acetals is well known and a robust reaction. One concern about acetal **471** was epimerisation of C* once ketone **470** had formed *via* acidic keto-enol tautomerisation. However, no epimerisation was observed by ^1H NMR spectroscopy and the reaction proceeded in 89% yield on up to 2 g scale (Scheme 93).



Scheme 93: Hydrolysis of acetal **471**. **(a)** HCl (1 M), THF, RT, 16 h, 89%.

The lack of epimerisation of C* (Scheme 93) was confirmed by coupling triflate derivative **306** (access by the same route, see Section 4.2.9) with stannane **158** (Scheme 94).

A Stille coupling was performed and spirocycle **263a** was isolated, contaminated with residual tin-derived side-products. However, the majority of the peaks were not overlapping with impurities and the ^{1}H NMR spectra of **263a** synthesised *via* the cross-coupling, and **263a** synthesised in the palladium-catalysed cascade (stereochemistry confirmed by NOESY experiments), were identical.

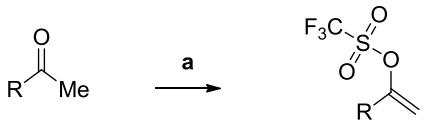


306 **158** **263a**

Scheme 94: Synthesis of **263a** *via* a Stille cross-coupling. **(a)** 15 mol% $Pd(PPh_3)_4$, DMF, 60 ˚C, 18 h, 94% (~50% purity).

4.2.7 Triflation

The conversion of a ketone to a vinyl-triflate was first reported in 1969 independently by Stang[190] and Jones.[191] Dueber developed the methodology in 1970 and used trifluoromethanesulfonic (triflic) anhydride in dichloromethane or pentane with a basic quench to form vinyl-triflates from the corresponding ketone or aldehyde (Scheme 95).[192]

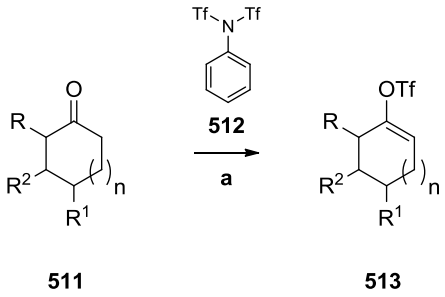


509 **510**

Scheme 95: Formation of vinyl-triflates **510**. **(a)** triflic anhydride, Na_2CO_3, CH_2Cl_2 or pentane, −70 ˚C to −10 ˚C, 30 min to 14 days, 18–50%. R = C_6H_5, *i*Pr, $(Ph)_2CH$.

Vinyl-triflates are used as an alternative to halides in cross-coupling reactions and therefore are important moieties to easily access. This reaction has enabled direct transformation of a ketone or aldehyde into a synthetically valuable derivative for coupling reactions. In the 1980s McMurry *et al.* reported the use of *N*-(2-phenyl)triflimide **512** as an alternative to

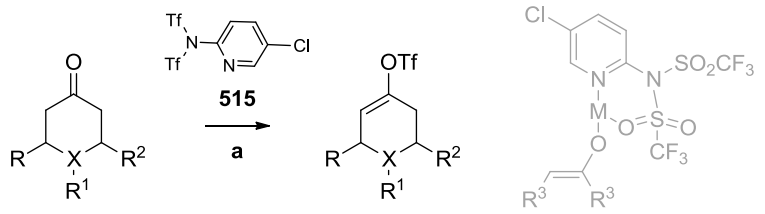
triflic anhydride (Scheme 96); it is an air stable solid compared to an unstable, fuming liquid and regioselectively affords the least-substituted enol triflate. Furthermore, when triflic anhydride was unsuccessful for McMurry, triflating agent **512** prevailed. In all cases, kinetic regioselective enolisation occurred and the enolate was trapped with the triflating electrophile **512** with no rearrangement of the double bond, which had occasionally been observed when using triflic anhydride. However, long reaction times (> 9 h) at 0 ˚C were required for full conversion to occur and it was possible for some enolates to be unstable or epimerise under these conditions.



511 **513**

Scheme 96: Triflation of ketones **511**. **(a) 512**, LDA, dimethoxyethane, –78 ˚C to 0 ˚C, 65–82%. R = H or Me; R^1 = *t*Bu, R^2 = H or R^1 = R^2 = -$(CH_2)_4$-; n = 1 or 3.

Further progress was made with the introduction of Comins' reagent. In 1992, Comins reported the use of *N*-(5-chloro-2-pyridyl)triflimide, a colourless crystalline solid (Scheme 97, **515**).[76] The phenyl ring in McMurry's reagent was replaced with an electron-deficient 5-chloro-pyridyl ring in the hope that this would make the triflimide groups more electrophilic, thus more susceptible to nucleophilic attack by the enolate.



514 **516** **517**

Scheme 97: Triflation of ketones **514**. **(a) 515**, LDA or NHMDS, THF, −78 ˚C, 2–12h, 73–92%. X = N or C; R = H, Me, *n*Pr, Ph; R^1 = H, Ph, *t*Bu, Bn, CO_2Bn (when X = N); R^2 = Me, H; R^3 = alkyl.

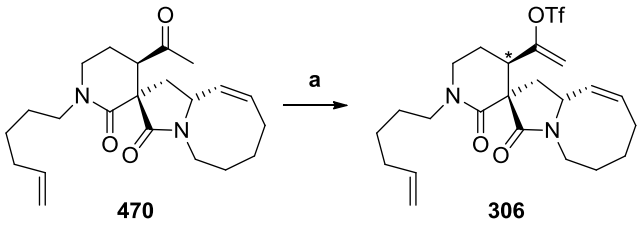
Comins also postulated that the pyridyl nitrogen could chelate the metallo-enolate **517**, which may also be beneficial.

It was found that when strong bases such as LDA or NHMDS at −78 ˚C were used for a relatively short reaction time (usually 2 h), the triflation proceeded in yields ranging from 73–92%. A variety of substituted, nitrogen-containing and/or 2,3-unsaturated cyclohexanones were used, including amide functionality which did not interfere with the triflation reaction.

Accordingly, the three methods outlined above to introduce the triflate moiety were investigated. Some optimisation had been carried out on manzamine A-type substrates by Dr Jakubec in the total synthesis of manzamine A.[12] When triflic anhydride or McMurray's reagent was used, no reactivity was observed. Comins' reagent was the most successful in the total synthesis of manzamine A (Chapter 1). It was crucial to have the Comins' reagent in the reaction mixture before the addition of the base otherwise poor conversion (35–75% starter recovered) was observed, even after prolonged reaction times. It was also found that an excess of reagents were required; 2.4 eq of Comins' reagent and 3.4 eq of KHMDS.

Ketone **470** was subjected to the conditions found optimal by Dr Jakubec and further results are outlined in Table 13. The standard method to perform this reaction was as follows: ketone **470** was dissolved in tetrahydrofuran and Comins' reagent was added at room temperature. The reaction mixture was cooled to −78 ˚C and KHMDS was added dropwise slowly. The reaction was monitored by TLC analysis. If starting material was still present after 5 min, a further equivalent of base was added and the reaction continued to be monitored by TLC analysis. When the reaction was deemed complete by TLC analysis, the reaction mixture was partially concentrated under reduced pressure rapidly, before being loaded on to a silica gel column for purification.

Table 13: Results of triflation optimisation. **(a)** KHMDS, Comins' reagent, THF, −78 ˚C, 5–60 min.



470 **306**

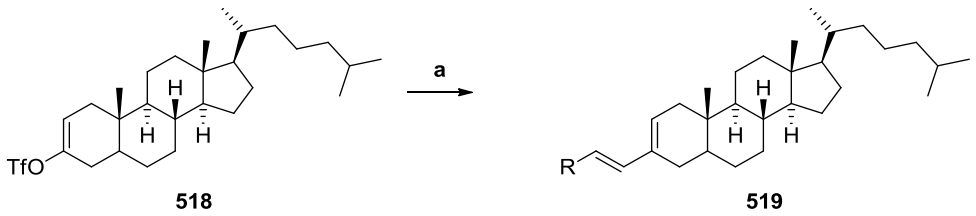
Entry	Scale/mg	KHMDS/eq	Comins/eq	Temp/˚C	Work-up	Yield/%
1	20	3.4 + 1	2.4	−78	silica gel	70
2	40	3.4	2.4	−78	silica gel	72
3	90	3.4	2.4	−78	silica gel	74
4	110	3.4	2.4	−78	silica gel	58
5	150	3.4	2.4	−78	silica gel	26

On 20 mg scale, triflate **306** was isolated in 70% yield (Table 13, entry 1). On scale up to 40 mg and 90 mg, yields of 72% and 74% were achieved respectively (Table 13, entries 2 and 3). However, the reaction was less successful on larger scale; on further scale up to 100 mg and 150 mg, the yield decreased to 58% and 26% respectively (Table 13, entries 4 and 5). This may be attributed to the work-up; the solvent was concentrated under reduced pressure before being directly loaded on to a silica gel column. On larger scale, this may result in decomposition due to residual KHMDS present. Therefore, the reaction mixture was quenched with saturated aqueous NH_4Cl at −78 ˚C before warming to room temperature. However, this often led to observation of an unknown compound that was chromatographically inseparable from the desired product **306** and was tentatively assigned as a diastereomer epimeric at C*; the characteristic difference in the ^1H NMR spectrum was the shift of the NC*H* proton which was indicative of diastereomers. However, sufficient quantities of triflate **306** were synthesised to test the following steps.

Future work needs to be carried out on this step for the triflation reaction to be of use in the total synthesis of manzamine A. On small scale, the yields were acceptable, but it was not possible to scale-up and maintain a good yield. However, due to reasons discussed in Section 4.2.11, further optimisation using ketone **470** was not required.

4.2.8 Alkoxycarbonylation

The alkoxycarbonylation of enol triflates was first reported in the mid-1980s by Cacchi *et al.* after their discovery that palladium(0) can oxidatively add into enol triflates and that the subsequent palladium(II) complex can insert into olefins (Scheme 98).[193,194]

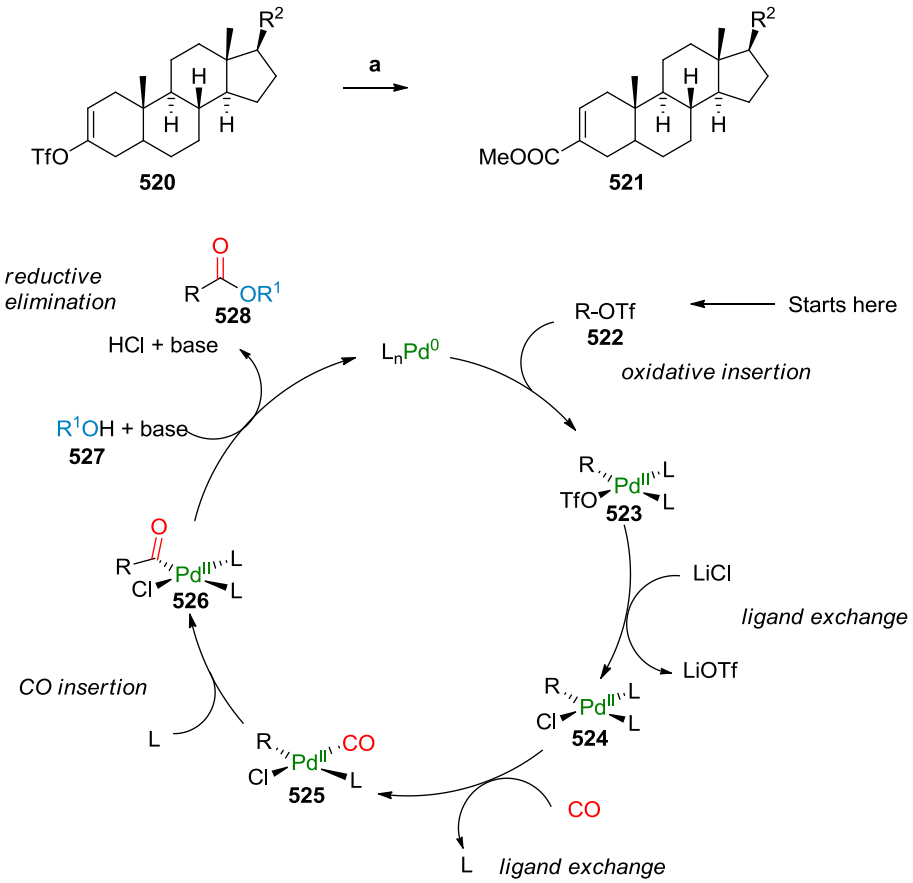


518 **519**

Scheme 98: Heck-type coupling of polycyclic triflate **518**. **(a)** RCH=CH_2, Et_3N, 20 mol% $Pd(OAc)_2$, 40 mol% PPh_3, DMF, 60 ˚C, 5 h, 20–86%. R = COOMe, acetyl, CH_2OH, Ph, nC_8H_{17}.

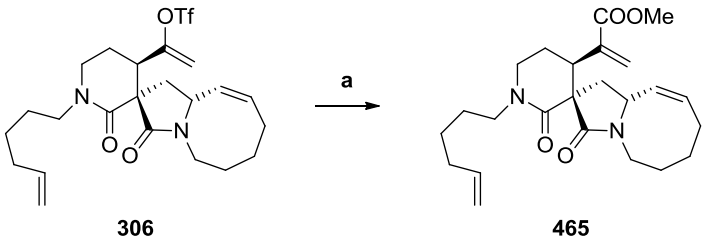
The methodology was extended to the insertion of CO into Ar-X or vinyl-X bonds (where X = halogen or OTf) to afford α,β-unsaturated esters. A combination of palladium acetate and triphenyl phosphine in the presence of triethylamine using a 2:1 DMF:MeOH solvent system in a CO atmosphere produced α,β-unsaturated ester **521** in yields ranging from 69–90% (Scheme 99).[194]

Scheme 99 outlines a possible mechanism for the carbonylation reaction. The addition of LiCl to the reaction mixture leads to the formation of stabilised square-planar intermediate **524**.[195] In this cross-coupling reaction, the first step is oxidative addition of palladium(0) into the aryl-OTf or vinyl-OTf bond in **522** to form the palladium(II) complex **523**. If lithium chloride is present, ligand exchange between the OTf group and the chloride ion occurs and forms complex **524** which can then undergo further ligand exchange with CO to give complex **525**. CO inserts into the Pd-R bond (**526**, R = aryl or vinyl) and on addition of the desired alcohol (or amine) **527** in the presence of base, a reductive elimination occurs to give the ester (or amide) **528** and regenerates the Pd(0) catalyst.



Scheme 99: Alkoxycarbonylation of triflate **520** and generic alkoxycarbonylation mechanism. **(a)** Et_3N, 30 mol% $Pd(OAc)_2$, 60 mol% PPh_3, MeOH, DMF, CO, RT, 1.5 h, 69–90%. R = Ar or vinyl; R^1 = alkyl; R^2 = alkyl, OAc.

The methoxycarbonylation of triflate **306** would allow us to access our target α,β-unsaturated ester that was our key chemical precursor to the crucial homologation step.

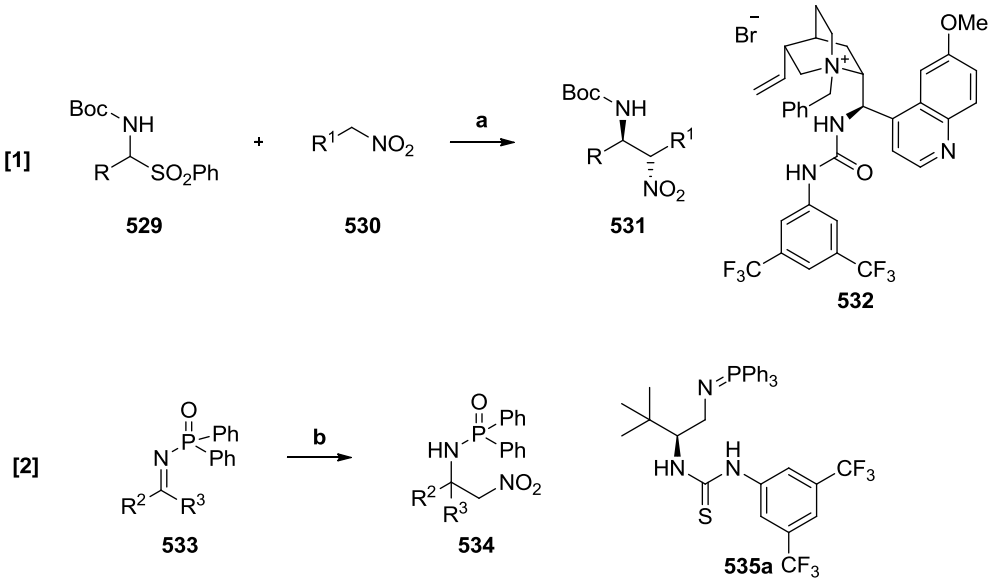


Scheme 100: Methoxycarbonylation of **306**. **(a)** Et_3N, 20 mol% $Pd(OAc)_2$, 40 mol% PPh_3, LiCl, MeOH:MeCN 1:2, CO, RT, 16 h, 75–86%.

The methoxycarbonylation was carried out following work by McBriar.[196] Triflate **306** was exposed to the conditions outlined in Scheme 100 and ester **465** was isolated in yields ranging from 75–86%.

4.2.9 Nitromethane Addition

The Dixon group has a strong interest in the enantioselective addition of nitromethane and other nitroalkane derivatives into electrophilic centres using bifunctional catalysts (Scheme 101, **532** and **535a**).[197,198] Both catalysts **532** and **535a** promote the addition of nitroalkanes into imines with excellent enantioselectivities (84–95% for **532**, 76–95% for **535a**) and, where relevant, a diastereomeric ratio of 6:1–24:1. When cinchonidine-derived ammonium catalyst **532** was used (Scheme 101, **[1]**), a range of amido-sulfones were tolerated and nitroamines **531** were isolated in yields ranging from 62–97%. Electron-withdrawing aryl moieties such as *p*-CF_3-C_6H_4, electron-donating aryl moieties such as *p*-OMe-C_6H_4, heteroaryl (3-pyridyl) and cyclohexyl groups were tolerated. R^1 was a proton or alkyl groups, and bulkier groups gave a higher level of enantiomeric control.[197]

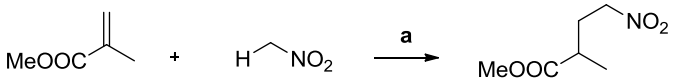


Scheme 101: Enantioselective nitroalkane addition to **532** and **535a**. **(a)** 5 mol**% 532**, KOH, TBME, −20 ˚C, 12 h, 63–100%, dr 6:1–24:1, 84–95% ee; **(b)** 10 mol% **535a**, $MeNO_2$, −15 ˚C or 0 ˚C, 20–96 h, 62–97%, 76–95% ee. R = aryl, heteroaryl, cyclohexyl, *i*Bu; R^1 = H, Me, Et; R^2 = aryl, heteroaryl; R^3 = Me, Et.

The second catalyst, iminophosphorane **535a** (Scheme 101, **[2]**) could also be employed with a wide range of substituted imines to give nitroamines **534** in yields ranging from 62–97% and enantioselectivities ranging from 76–95% ee. R^2 tended to be a substituted aryl group: electron-withdrawing groups such as *p*-NO_2-C_6H_4, electron-donating groups such as

p/*m*/*o*-OMe-C_6H_4 and *p*-Me-C_6H_4, as well as heteroaryls such as 2-furyl and 3-pyridyl and halogenated aryls such as *p*/*o* or *m*-F/Cl or Br-C_6H_4 were all tolerated.[198]

There are relatively few examples in the literature of nitromethane addition into α,β-unsaturated esters. The reaction was first reported in 1949 by Leonard and Shoemaker (Scheme 102).[199] It was common to use organic bases for the reaction; TMG (pKa_H = 23.3 in MeCN)[200] and Et_2HN (pKa_H = 18.9 in MeCN)[201] have both been used.



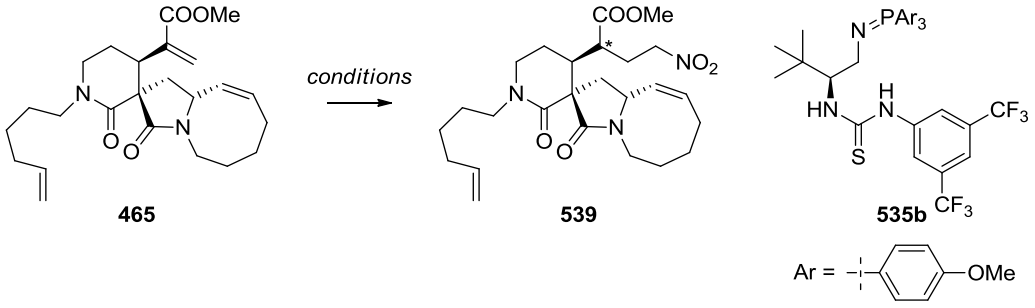
536 **537** **538**

Scheme 102: Nitromethane addition into α,β-unsaturated ester **536**. **(a)** Et_2HN, RT, 14 d, 45%. No further details given.

With the key α,β-unsaturated ester **465** in hand, the 1,4-Michael addition was investigated and results are outlined in Table 14.

Initial results on small scale showed that the nitromethane addition to the α,β-unsaturated ester **465** proceeded in moderate yields and **539** was isolated as a single diastereomer. For example, when 20 equivalents of nitromethane and 30 mol% TMG were used, 27% yield of nitro-ester **539** was obtained after 16 h (Table 14, entry 1). When dichloromethane with 30 mol% BEMP was used, no improvement was observed (Table 14, entry 2) and after 48 h, 24% yield of nitro-ester **539** was obtained. Switching to the use of nitromethane as solvent (0.18 M) proved beneficial: when 30 mol% BEMP or 10 mol% TBD was employed (Table 14, entries 3 and 5), yields of 53% and 56% of nitro-ester **539** were achieved respectively.

Table 14: Nitromethane addition into α,β-unsaturated ester **464**. Single diastereomer observed at C*.



Entry	Scale/mg	$MeNO_2$	Base/eq	Time/h	Yield 539/%
1	10	20 eq	TMG/0.3	16	27
2	11	20 eq/CH_2Cl_2 1:1 vol.	BEMP/0.3	48	24
3	15	0.18 M	BEMP/0.3	16	53
4	15	0.18 M	**535b**/0.1	48	64
5	25	0.18 M	TBD/0.1	48	56
6	35	0.18 M	**535b**/0.2	24	62

During the course of the studies in to catalyst **535b** by Dixon *et al.*, it was found that the pKa_H was in the same region as TMG (pKa_H TMG = 23.3 in MeCN, pKa_H **535b** = 22.7 in MeCN).[xxi] It was also observed that **535b** gave much shorter reaction times and higher yields than its counterparts, such as catalyst **481**. When catalyst **535b** was used in this reaction, nitro-ester **439** was isolated in 62% and 64% yield (Table 14, entries 4 and 6).

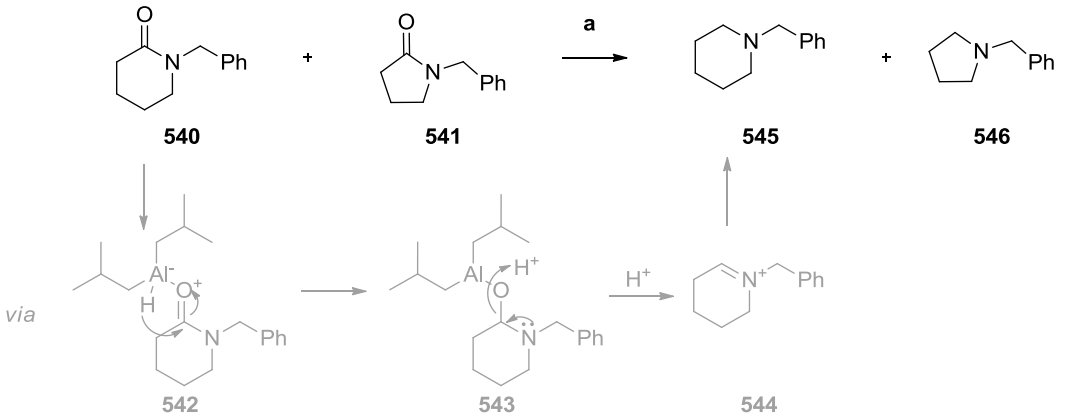
4.2.10 Chemoselective Reduction

With homologated ester **539** in hand, the chemoselective reduction of the piperidinone carbonyl was attempted. Chemoselective reduction of a piperidinone carbonyl bond in spirocyclic piperidinone/pyrrolidinone systems in manzamine family alkaloids has been reported.[12,17]

At time of publication, no reasons were given for this notable reactivity difference. We wanted to investigate this further through a combined empirical and theoretical approach, and we wanted to prove that the reactivity difference was general, and not just specific to complex spiro-compounds (Scheme 103).

[xxi] Unpublished work by Dr M. García and A. Farley.

Therefore, six separate reactions were set up with a 1:1 mixture of piperidinone **540** and pyrrolidinone **541** in toluene (Scheme 103). Six equivalents of DIBAL were added at −78 ˚C and the separate reactions were quenched at different time intervals (Chart 1, 1–10 min).



Scheme 103: Chemoselective reduction of lactams **540** and **541**. **(a)** DIBAL (6 eq), toluene, −78 ˚C, 1–10 min, then MeOH, −78 ˚C to RT, Na_2SO_4•$10H_2O$, Et_2O, 30 min.

After work-up, the crude material was analysed by ^{1}H NMR spectroscopy: conversion of **540** and **541** to **545** and **546** was measured against an internal standard (mesitylene) that was added to the deuterated chloroform. The characteristic benzylic protons of all species could be integrated against the internal standard.

Even after 1 minute at −78 ˚C, over 80% of *N*-methyl-piperidinone **540** had reacted. In contrast, less than 5% of *N*-methyl-pyrrolidinone **541** had reacted, further demonstrating the significant reactivity difference.

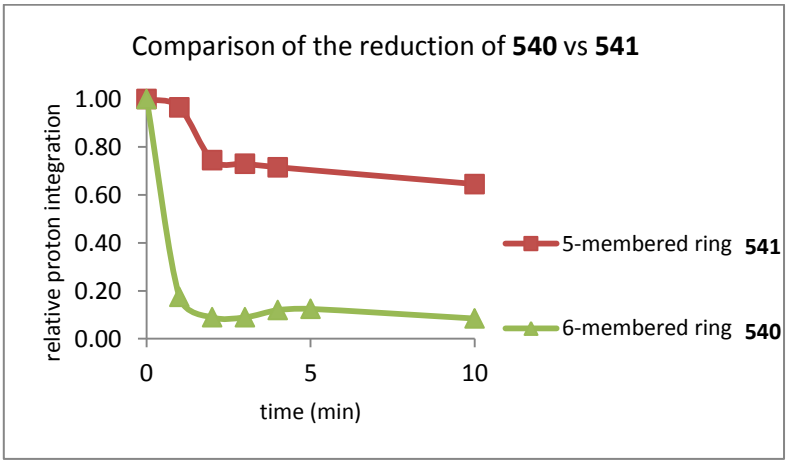


Chart 1: Investigation of *N*-methyl-piperidinone reduction.

Initial results established that the piperidinone carbonyl reduction was significantly faster than the pyrrolidinone carbonyl, and at first glance there is seemingly no reason for this.

In collaboration with Dr Rob Paton at the University of Oxford, the following results were obtained. For piperidinone **547** (Figure 47, **[1]**), during reduction there was minimal torsional strain around the ring; ΔG_{act} is relatively low (**548**) and ΔG_{rxn} was thermodynamically favourable (**549**). However, in the case of pyrrolidinone **327** (Figure 47, **[2]**), during reduction there was a build up of torsional strain: hydrogens on C–3 and C–4 were eclipsed leading to a higher ΔG_{act} and ΔG_{rxn} (**550** and **552**). This made the reduction of the pyrrolidinone carbonyl less favourable than the reduction of the piperidinone carbonyl, supporting the reactivity difference observed in our more complex, spirocyclic system.

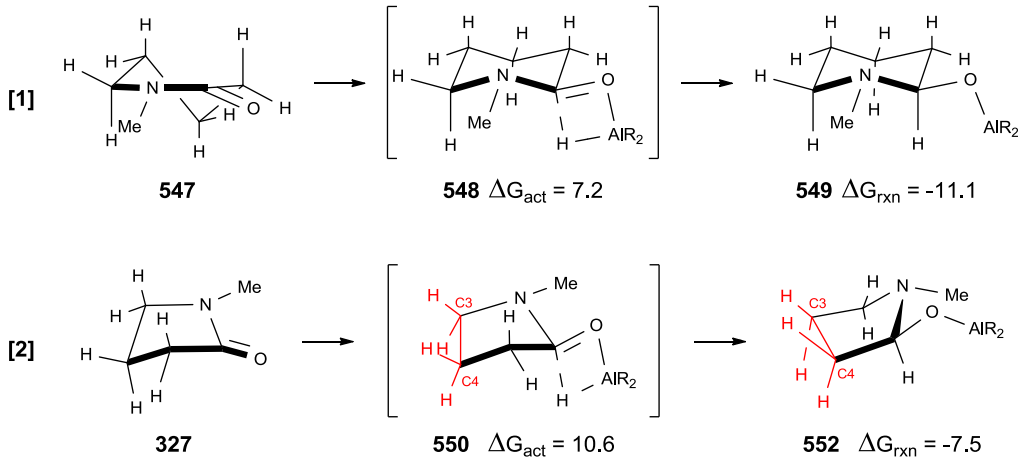
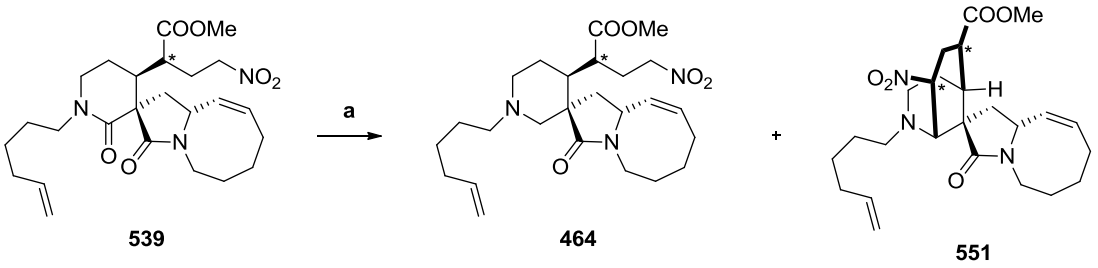


Figure 47: *N*-methyl piperidinone **547** *vs*. *N*-methyl pyrrolidinone **327** ring reduction using aluminium based reducing reagents. R = alkyl or H. DFT measurements were used to calcuate ΔG values.

In summary, both the experimental and computational data were in excellent agreement and offered an explanation for the reactivity differences observed in both simple and complex systems, such as in the total syntheses of both manzamine A and nakadomarin A.[12,17] We believed that this reaction was general and would be a useful synthetic tool within organic chemistry.

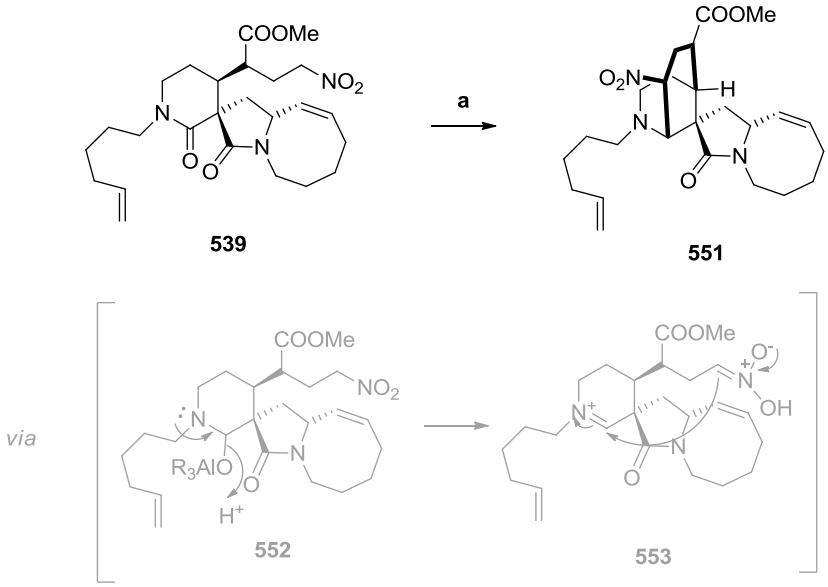
With ester **539**, the added concern was the potential reduction of the ester moiety, compared to the acetal or furan moieties which were present previously. It is well-known

that esters can be reduced with $MHAl(R)_3$ reducing agents (where M is a metal and R is an alkyl, proton or alkoxy group) at −78 ˚C.



Scheme 104: Chemoselective reduction of amide **539**. **(a)** DIBAL, THF, −78 ˚C to −20 ˚C then MeOH, −20 ˚C to RT, Na_2SO_4•$10H_2O$, Et_2O, 16 h, **464**: 40%, **551**: 28%. Stereochemistry of **551** at C* unable to be determined by NMR techniques or single crystal X-ray diffraction.

Thus, following previously successful conditions,[12] nitro-ester **539** was exposed to three equivalents of DIBAL at −78 ˚C and the reaction mixture was warmed to −20 ˚C. The reaction was monitored by mass spectrometry and TLC analysis. When no starting material was observed by TLC analysis, the reaction mixture was quenched (MeOH and Na_2SO_4•$10H_2O$ followed by Et_2O) and the crude material was subjected to column chromatography. The desired piperidine **464** was isolated in 40% yield (Scheme 104) and no reduction of the ester was observed. Interestingly, significant quantities (28% yield) of tetracycle **551** were isolated (Scheme 105).

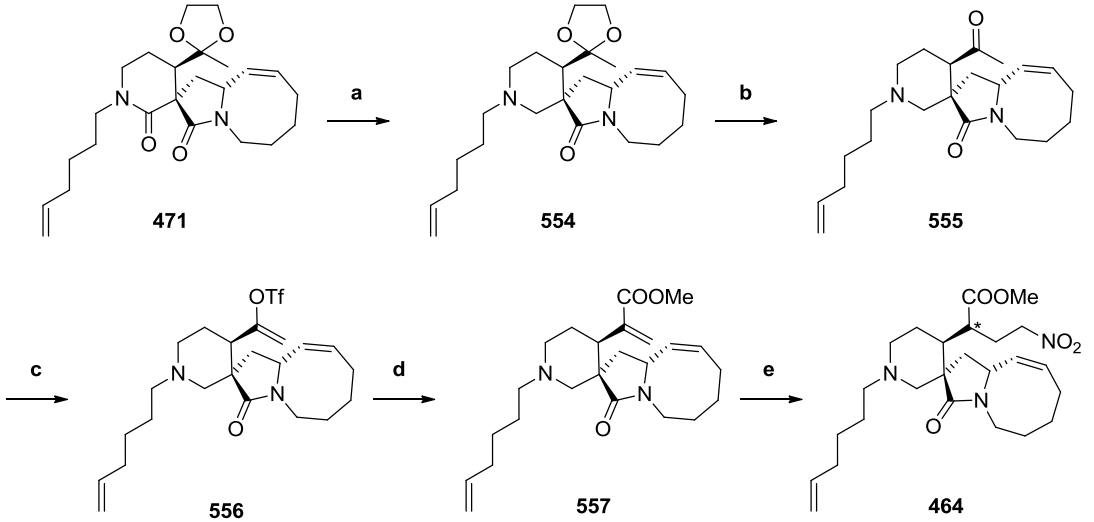


Scheme 105: Cyclisation of **539** with proposed mechanism. **(a)** DIBAL, THF, −78 ˚C to −20 ˚C, then MeOH, −20 ˚C to RT, then Na_2SO_4•$10H_2O$, Et_2O, 16 h, 28%.

This was a very encouraging result and was observed presumably due to attack of the α-nitro carbanion onto the iminium ion intermediate **553** that formed during the DIBAL reduction (Scheme 105), in a similar fashion to the mechanism proposed by Chambers (described in Section 2.4.4).

At this stage in the synthesis it was unacceptable to continue with such a low yield (40%) of piperidinone **464**. The side product, although interesting, was isolated multiple times and was a persistent unwanted reaction. The cyclisation was not desired and was consuming large quantities of front-line material. Due to material constraints, it was impractical to continue with this route as the cyclisation problem was unable to be overcome sufficiently. At this late stage, it would be more efficient to reconfigure the route and carry out the chemoselective reduction earlier in the synthesis, in order to rapidly access the desired tetracyclic intermediate **463**. It was known from the parallel route to manzamine A that the chemoselective reduction could proceed smoothly when an acetal, not ester, functionality was present. Thus, a reconfigured route was investigated.

4.2.11 Reconfiguring the Route

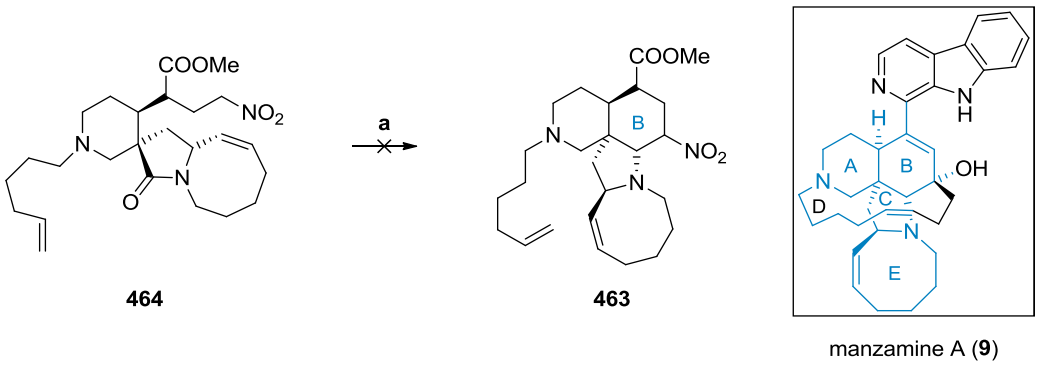


Scheme 106: Synthetic route from acetal **471** to nitro-ester **464**. **(a)** $LiAlH_4$, HCOOH, toluene, −78 ˚C to −20 ˚C, 1 h, then Rochelle salt (20 wt% in water), 85–94%; **(b)** HCl (1 M), THF, RT, 16 h, 95%; **(c)** KHMDS, Comins' reagent, THF, −78 ˚C, 10 min, 42%; **(d)** Et_3N, 20 mol% $Pd(OAc)_2$, 40 mol% PPh_3, LiCl, MeOH, MeCN, CO, 48 h, 85%; **(e)** 30 mol% TBD, NO_2Me, RT, 48 h, 54%. Stereochemistry at C* undefined due to signals overlapping in the ^1H NMR spectrum.

In an effort to overcome the reduction/cyclisation problem, the reduction of the piperidinone was carried out on acetal **471** using lithium aluminium hydride with a formic acid quench (Scheme 106). Piperidine **554** was obtained in yields ranging from 85–94%. Subsequent hydrolysis of acetal **554** proceeded without issue and afforded ketone **555** in up to 98% isolated yield. The triflation was once again capricious and the best yield achieved was 42% of triflate **556** although the yields of **556** were generally in the range of 25–34%. The triflate **556** was chromatographically similar to residual Comins' reagent. However, one benefit of having the tertiary amine present was that an acid/base work-up[xxii] could be performed which removed all traces of Comins' reagent, a problem observed in Section 4.2.7. The key carbonylation of triflate **556** gave ester **557** in yields ranging from 73–85% and the nitromethane addition into ester **557** with 30 mol% TBD proceeded in 54% yield to give nitro-ester **464**.

4.2.12 Cyclisation

With nitro-ester **464** in hand, studies towards the cyclisation to form tetracycle **463** could begin. Due to time constraints, only one set of reaction conditions were trialled on 8 mg scale (Scheme 107).



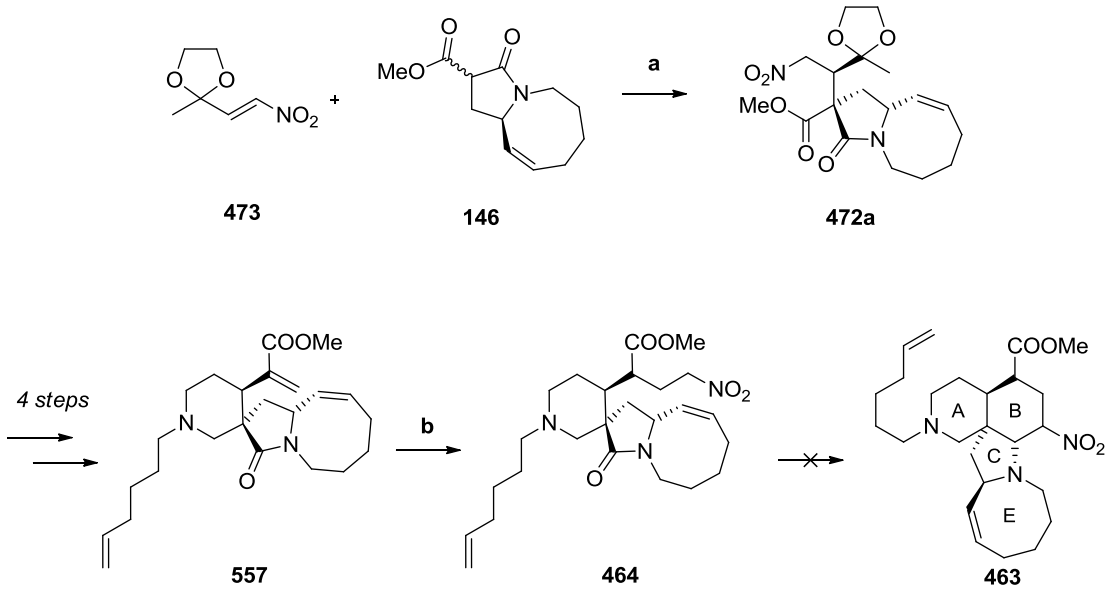
Scheme 107: Attempted cyclisation of **464**. **(a)** Ph_2SiH_2 (9 eq), $Ti(OiPr)_4$ (5 eq), hexane, 0 ˚C, 3 h.

[xxii] This involved addition 1 M HCl to the triflate which was dissolved in diethyl ether. The acidic aqueous washings containing the ammonium salt of **556** were extracted with diethyl ether before being re-basified using solid NaOH to pH > 10. The basic aqueous layer was extracted with diethyl ether to give pure **556**.

Using the previously successful conditions,[12] nitro-ester **464** was exposed to Ph_2SiH_2 and $Ti(OiPr)_4$ in hexane at 0 ˚C. Monitoring by usual methods for this reaction (mass spectrometry and TLC analysis) was not successful. Upon work-up, only substantial quantities of silane and baseline spots were observed by TLC analysis, and mass spectrometry did not show product or starting material. After direct purification by flash column chromatography, 7 mg of material were recovered which were silane residues. After an acid/base work-up to attempt to remove the silane residues and recover any possible product-related material, only a complex ^{1}H NMR spectrum was obtained. However, with further optimisation it should be possible for the cyclisation to be successful.

4.3 Summary

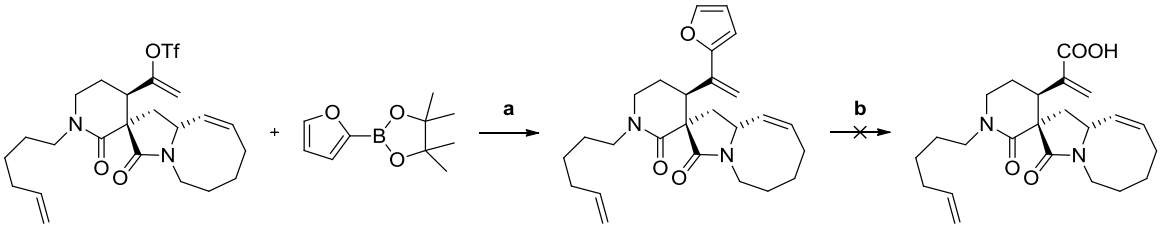
In summary, a third generation route of the core of manzamine A was developed that centred on a diastereoselective Michael addition which installed the α-quaternary stereocentre that had previously been problematic and **472a** was isolated as a single diastereomer (Scheme 108).



Scheme 108: Summary of 3rd generation route. **(a)** KHMDS, 18-crown-6, THF, −94 ˚C, 30 min, 94%, dr 5:1; **(b)** 30 mol% TBD, $MeNO_2$, RT, 48 h, 54%.

In addition, homologation of the vinyl-ester **557** was successful, directly introducing the extra CH_2-NO_2 in one step, overcoming the problems outlined in Chapters 2 and 3. Due to time constraints, only one attempt was made to synthesise advanced tetracyclic intermediate **463**, which unfortunately was not successful. However, with further optimisation, the reaction should proceed, analogous to the first Dixon group total synthesis of manzamine A.[12]

Linking the palladium-catalysed spirocyclisation cascade with the route outlined in Scheme 108 was desired and so a β-carboline aryl-surrogate was used. Furan boronic ester **468** was employed in a Suzuki cross-coupling reaction with triflate **306** which gave diastereomerically pure furan derivative **466** in 75% yield (Scheme 109).



306 **468** **466** **467**

Scheme 109: Attempted synthesis of **467** *via* a cross-coupling reaction and oxidation. **(a)** 10 mol% $Pd(PPh_3)_4$, Cs_2CO_3, DME, H_2O, 75 ˚C, 4 h, 75%; **(b)** MeCN, CCl_4, $RuCl_3 \bullet xH_2O$, $NaIO_4$, H_2O, RT, 48 h.

Oxidation of furyl-derivative **466** was not successful using classic oxidation conditions and only the aldehyde intermediate was isolated. However, with further investigation, this reaction should proceed. Subsequent esterification would give α,β-unsaturated ester **465** which would link the two routes together.

4.4 Conclusions

In conclusion, two routes have been developed to access three advanced cores of manzamine A.

The first generation (Chapter 2) used a terminal allene pro-nucleophile in the presence of base with an iodo-β-carboline under palladium-catalysed conditions to access the densely functionalised ACE spirocyclic core of manzamine A, introducing two new carbon-carbon bonds and two new stereocentres in a single step (Figure 48, **[1]**). However, it was not possible to introduce the functionalised methylene unit needed for construction of ring B and therefore, a new route was sought.

The second generation (Chapter 3) was also based on the palladium-catalysed arylative allene spirocyclisation cascade and had the desired functionalised methylene unit incorporated which created a non-terminal allene pro-nucleophile (Figure 48, **[2]**). Reactivity of the non-terminal allene substrate was diminished relative to the terminal allene substrate; very low yields were obtained of the desired spirocyclic products when using a model aryl-iodide. When the desired iodo-β-carboline was used, no trace of spirocyclic product was observed.

The third generation (Chapter 4) was concerned with synthesising the α,β-unsaturated ester derivative of the ACE spirocyclic core of manzamine A. The α,β-unsaturated ester was much more reactive than the corresponding vinyl β-carboline system towards homologation. It was planned to be accessed *via* two routes. The first was based on the palladium-catalysed arylative allene spirocyclisation cascade using 2-iodo-furan that would act as a substitute for the β-carboline. Before optimisation of the palladium-catalysed spirocyclisation, the diastereomerically pure furyl derivative was synthesised *via* a Suzuki cross-coupling reaction. However, the oxidation of the desired single diastereomer was not successful.

Attention turned to using a different route altogether which would allow rapid access to the desired α,β-unsaturated ester (Figure 48, **[3]**). This was based on a diastereoselective Michael addition to construct two stereocentres and the stereochemistry was confirmed by single crystal X-ray diffraction studies. Four further steps were required to access the desired α,β-unsaturated ester, which underwent homologation with nitromethane under base-catalysed conditions. Initial attempts to form the ABCE tetracyclic core failed, however, with optimisation, this reaction should proceed, based on parallel work carried out within the Dixon research group.

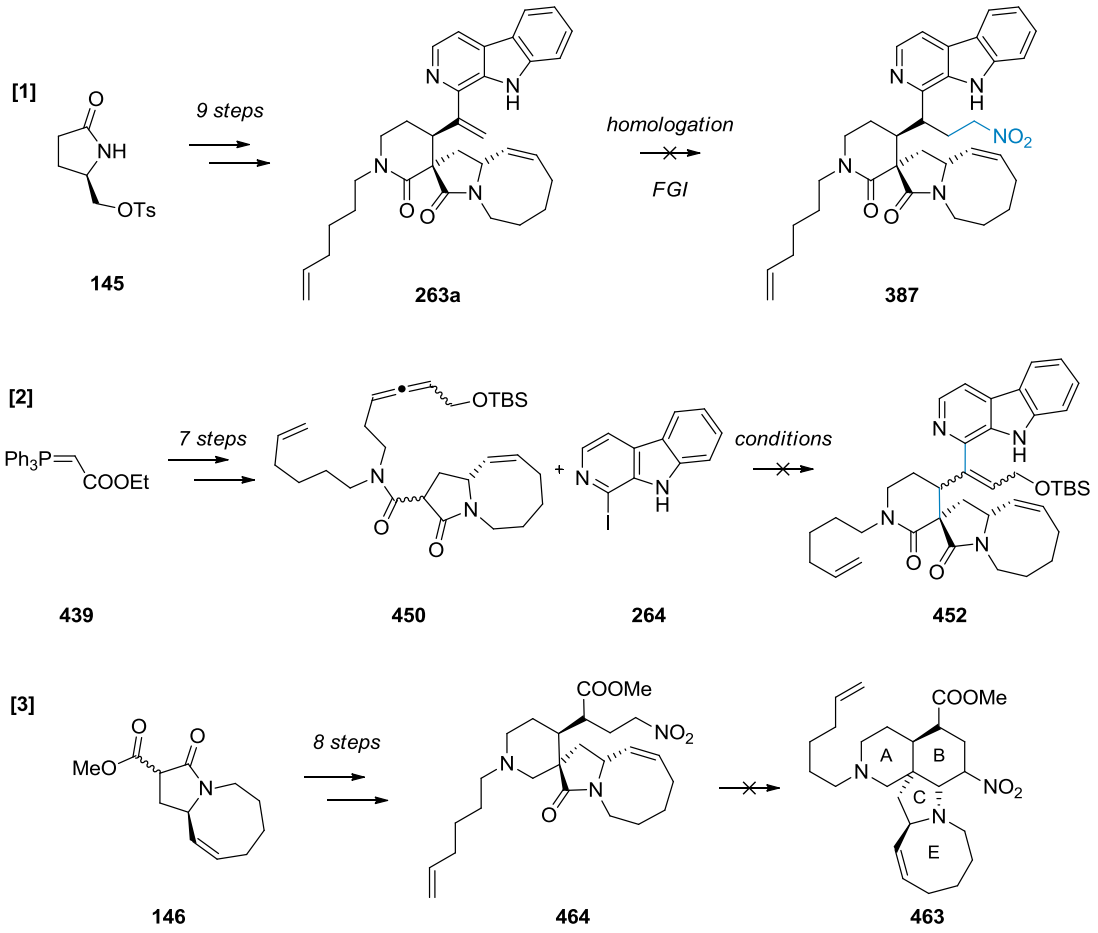
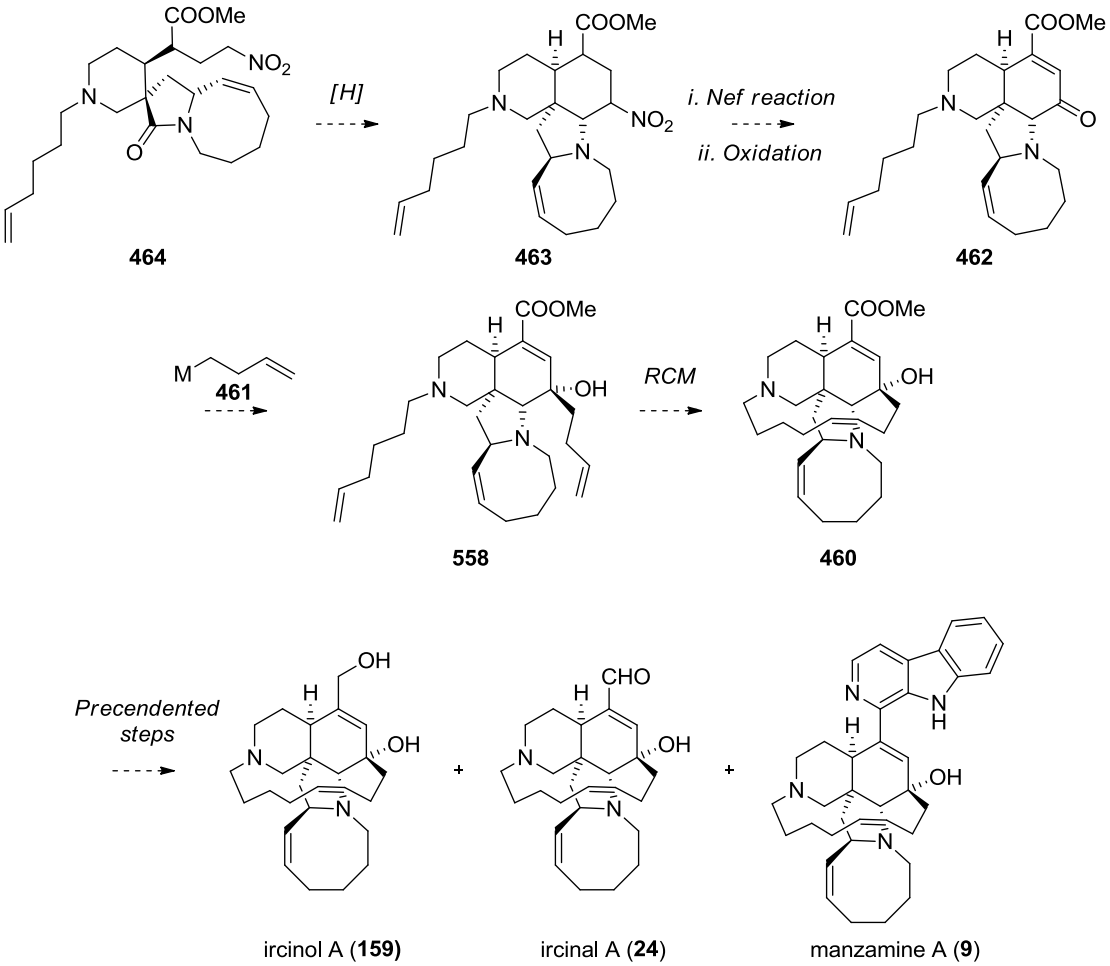


Figure 48: Summary of Chapters 2–4.

4.5 Future Work

The planned route to complete the synthesis is outlined in Scheme 110. From nitro-ester **464** the reductive cyclisation would be carried out to give tetracycle **463**. A precedented[12] Nef reaction would convert the nitro group to a carbonyl moiety, and a dehydrogenation would re-introduce the double bond to give ester **462**. A precedented stereoselective[12] organometallic addition would give alcohol **558** which would be followed by a ring-closing metathesis, in which the Dixon group has considerable experience.[12,17,187,202] Decorated pentacycle **460** could then give three related alkaloids of the manzamine family: ircinol A (**159**), ircinal A (**24**) and manzamine A (**9**).



Scheme 110: Planned synthetic route to synthesise manzamine A and related alkaloids, ircinol A and ircinal A.

Further work would also include linking the palladium-catalysed spirocyclisation route (Chapter 2) with the Michael addition route (Chapter 4) as it would be a novel way of

accessing manzamine A with respect to the recently published Dixon group total synthesis.[12] The oxidation of furan derivative and esterification should be relatively straightforward, and this would link the two routes together.

It should also be possible to make some analogues of manzamine A, either by condensing different amines to ircinal A (**24**) or by performing the Suzuki cross-coupling with triflate **306** with other aryl groups, and these analogues of manzamine A may also possess interesting biological properties.

Chapter 5
Experimental

1.1. General Experimental Techniques

For reactions requiring anhydrous conditions, glassware was dried in an oven at 100 °C and reactions were carried out under a nitrogen atmosphere. Room temperature (RT) refers to 20–25 °C. Temperatures of 0 °C, −20 °C, −50 °C, −78 °C and −94 °C were achieved using an ice-bath or dry ice in acetone or liquid nitrogen/acetone.

1.2. Solvents and Reagents

Bulk solutions were concentrated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or provided by the communal stills of the Chemistry Research Laboratory, Oxford unless otherwise stated. Petroleum ether (PE) refers to distilled light petroleum with boiling points in the range of either 30−40 °C or 40−60 °C. For reactions requiring dry conditions, triethylamine and diisopropylamine were distilled from calcium hydride and stored over solid KOH. Commercially available reagents were used as received unless otherwise stated. Formaldehyde was used as a 37 wt. % in water.

1.3. Chromatography

All reactions were monitored by thin-layer chromatography (TLC) where appropriate using Merck Kieselgel 60 F_{254} (230-400 mesh) silica plates which were visualised by UV-light (250 nm) or by staining using aqueous potassium permanganate solutions where appropriate. Column chromatography was carried out using Merck Kieselgel 60 silica gel (230-400 mesh) unless otherwise stated.

1.4. Spectroscopy

Proton NMR data in this thesis is reported *as observed* on a given spectrometer at a specified frequency, and not as theoretically predicted by a coupling environment.

All ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were collected on either a Bruker DPX400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker AVC400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker AVC500 (500 MHz ^{1}H, 125 MHz ^{13}C) or Bruker AVC700 (700 MHz ^{1}H, 175 MHz ^{13}C) and in the deuterated solvent stated. Chemical shift values (δ) are reported relative to the solvent residual as an internal reference and are quoted in parts per million (ppm ± 0.01 ppm). Assignments were aided by COSY, DEPT, HMQC, HMBC and TOCSY experiments. The abbreviations s, d, t, q, quin., sept., br. and m denote singlet, doublet, triplet, quartet, quintet, septet, broad and multiplet respectively. Line broadening was ±0.3 Hz, therefore all coupling constants, *J*, are quoted in Hertz (Hz ± 0.5 Hz), as stated. The assignment "Ar*C*" refers to an aromatic carbon bonded to a proton and "ArC_{quat}" refers to a quaternary aromatic carbon.

Low resolution mass spectrometric (*m/z*) data was acquired by electrospray ionisation (ESI) on an LCT Premier Open Access instrument. High resolution mass spectrometric data was acquired using the University of Oxford mass spectrometry service on a Bruker Microtof (ES) mass spectrometer.

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer deposited as a thin film, with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). Only diagnostic absorbances are reported.

X-ray Crystallographic Data was collected on a Nonius Kappa CCD diffractometer. Structure refinement and analysis was carried out using CRYSTALS software package.

Optical rotations were recorded using an Optical Activity AA-1000 polarimeter at room temperature; $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is given in g/100 mL at 589 nm.

Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

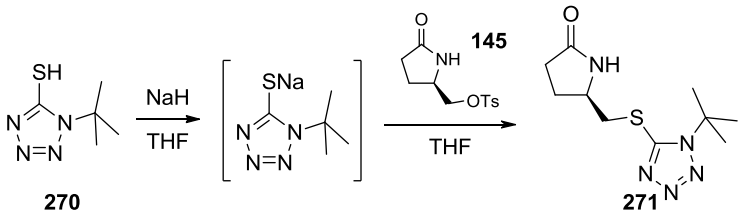
1.5 Naming of Compounds

Compound names are those generated by ACD LABS 12.0 following IUPAC nomenclature.

1.6 Starting Materials

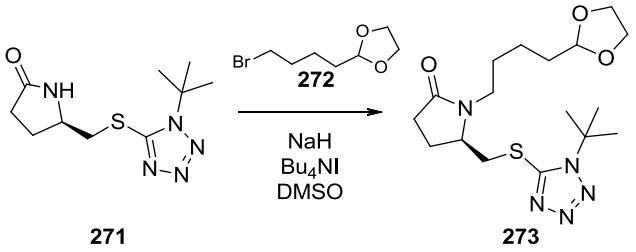
The following compounds are commercially available: 1-*tert*-butyl-1H-tetrazole-5-thiol **270**, [(2*R*)-5-oxopyrrolidin-2-yl]methyl 4-methylbenzenesulfonate **145** (but these can be made according to literature procedures[203,204]), 2-(4-bromobutyl)-1,3-dioxolane **272**, but-3-yn-1-yl 4-methylbenzenesulfonate **268**, hex-5-en-1-amine **149** and *tert*-butyl hex-5-en-1-ylcarbamate **282**. Amide **303** was synthesised by Dr Meiling Li.

(5*R*)-5-{[(1-*tert*-Butyl-1H-tetrazol-5-yl)sulfanyl]methyl}pyrrolidin-2-one (271)



A solution of tetrazole **270** (1.5 eq, 66.8 mmol, 10.5 g) in tetrahydrofuran (0.37 mL/mmol **270**, 25 mL) was added dropwise to a suspension of NaH (1.5 eq, 66.8 mmol, 60% dispersion in mineral oil, 2.66 g) in tetrahydrofuran (1.3 mL/mmol NaH, 87 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C. A suspension of tosylate **145** (1.0 eq, 44.5 mmol, 12.0 g) in tetrahydrofuran (4.63 mL/mmol **145**, 206 mL) was added over 5 min. The resulting mixture was stirred at reflux for 14.5 h, cooled to RT and quenched by the dropwise addition of ammonium chloride (saturated aqueous, 128 mL). The organic phase was separated and the aqueous layer was extracted (EtOAc, 3 × 60 mL). The combined organic extracts were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc → 1:5 MeOH:EtOAc) to yield the title compound **271** (10.8 g, 95%) as a colourless solid. **m.p.** 116 – 117 °C (lit.[17] 114 – 116 °C); $\mathbf{[\alpha]_D^{24}}$ = −71.3 (c = 0.53, $CHCl_3$; lit.[17] $[\alpha]_D^{24}$ = −68.0, c = 2.46, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.73 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.91 - 2.00 (m, 1 H, COCH$_2$C$\underline{H}_A$H$_B$), 2.33 - 2.50 (m, 3 H, COCH$_2$CH$_A\underline{H}_B$, COC$\underline{H}_2$), 3.35 (dd, 1 H, *J* = 14.0, 7.0 Hz, SC$\underline{H}_A$H$_B$), 3.70 (dd, 1 H, *J* = 14.0, 5.0 Hz, SCH$_A\underline{H}_B$), 4.18 - 4.24 (m, 1 H, NC$\underline{H}$), 6.29 (br. s, 1 H, NH); ***m/z*** (ESI$^+$) 278 (35%, $[M+H]^+$), 533 (100, $[2M+Na]^+$). Data are in agreement with literature.[17]

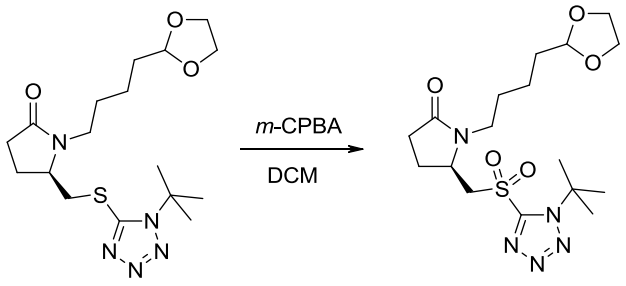
(5*R*)-1-[4-(1,3-Dioxolan-2-yl)butyl]-5-{[(1-*tert*-butyl-1H-tetrazol-5-yl)sulfanyl]methyl} pyrrolidin-2-one (273)



271 273

A solution of lactam **271** (1.0 eq, 17.1 mmol, 4.36 g) in DMSO (0.88 mL/mmol **271**, 15 mL) was added to a slurry of NaH (1.2 eq, 20.5 mmol, 60% dispersion in mineral oil, 0.820 g) in DMSO (1.41 mL/mmol NaH, 29 mL). The mixture was stirred for 10 min at RT before the addition of Bu_4NI (0.2 eq, 3.4 mmol, 1.25 g) followed by the dropwise addition of neat acetal **272** (1.5 eq, 25.6 mmol, 5.35 g). The reaction mixture was stirred for 14 h at RT after which ammonium chloride (saturated aqueous, 25 mL) was added. The organic phase was separated and the aqueous layer was extracted (Et_2O, 4 × 20 mL). The combined organic extracts were washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc → 1:5 MeOH:EtOAc) to yield the title compound **273** (4.66 g, 71%) as a pale yellow oil. $\mathbf{[\alpha]_D^{24}}$ = +42.7 (c = 0.71, $CHCl_3$; lit.[17] $[\alpha]_D^{24}$ = +40.3, c = 2.97, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.39 - 1.46 (m, 2 H, $NCH_2CH_2C\underline{H}_2$), 1.52 - 1.62 (m, 2 H, $NCH_2C\underline{H}_2$), 1.73 (m, 11 H, $C(C\underline{H}_3)_3$, $OCHC\underline{H}_2$), 1.85 - 1.96 (m, 1 H, $COCH_2C\underline{H}_AH_B$), 2.19 - 2.53 (m, 3 H, $COCH_2CH_A\underline{H}_B$, $COC\underline{H}_2$), 2.99 - 3.10 (m, 1 H, $NC\underline{H}_AH_B$), 3.28 (dd, 1 H, *J* = 13.5, 8.0 Hz, $SC\underline{H}_AH_B$), 3.67 - 3.76 (m, 1 H, $NCH_A\underline{H}_B$), 3.80 - 3.99 (m, 5 H, $SCH_A\underline{H}_B$, $OC\underline{H}_2C\underline{H}_2O$), 4.07 - 4.18 (m, 1 H, $NC\underline{H}$), 4.81 - 4.88 (m, 1 H, $CH_2C\underline{H}O$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.3 ($NCH_2CH_2\underline{C}H_2$), 23.5 ($COCH_2\underline{C}H_2$), 27.3 ($NCH_2\underline{C}H_2$), 28.7 ($C(\underline{C}H_3)_3$), 29.7 ($CO\underline{C}H_2$), 33.3 ($OCH\underline{C}H_2$), 36.5 ($S\underline{C}H_2$), 40.6 ($N\underline{C}H_2$), 56.2 ($N\underline{C}H$), 61.2 ($\underline{C}(CH_3)_3$), 64.8 ($O\underline{C}H_2\underline{C}H_2O$), 104.3 ($CH_2\underline{C}HO$), 151.7 ($S\underline{C}N_2$), 174.8 ($N\underline{C}O$); ***m/z*** ($ESI^+$) 406 (28%, $[M+H]^+$), 789 (100, $[2M+Na]^+$). Data are in agreement with literature.[17]

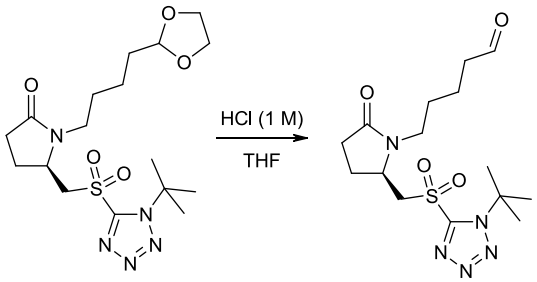
(5*R*)-5-{[(1-*tert*-Butyl-1H-tetrazol-5-yl)sulfonyl]methyl}-1-[4-(1,3-dioxolan-2-yl)butyl] pyrrolidin-2-one (274)



273 **274**

To a stirred solution of sulfide **273** (1.0 eq, 2.19 mmol, 0.840 g) in CH_2Cl_2 (13.7 mL) was added *m*-CPBA (4.0 eq, 8.77 mmol, 70–73% in water, 2.06 g). The aqueous phase was separated, Na_2SO_4 (0.95 g) was added to the organic phase and the reaction mixture was stirred for 14 h at RT. The insoluble solids were filtered and washed with CH_2Cl_2 (30 mL) and the filtrate was carefully concentrated *in vacuo* to give a slurry. The residue was immediately purified by flash column chromatography (Et_2O → 1:20 MeOH:Et_2O → 1:10 MeOH:Et_2O) to yield the title compound **274** (0.710 g, 78%) as a colourless oil. **$[\alpha]_D^{24}$** = +18.1 (c = 1.03, $CHCl_3$; lit.[17] $[\alpha]_D^{24}$ = +16.8, c = 3.58, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.49 (quin., 2 H, *J* = 8.0 Hz, $NCH_2CH_2C\underline{H}_2$), 1.55 - 1.78 (m, 4 H, $NCH_2C\underline{H}_2$, $OCHC\underline{H}_2$), 1.86 (s, 9 H, $C(C\underline{H}_3)_3$), 2.24 - 2.59 (m, 4 H, $C(O)C\underline{H}_2C\underline{H}_2CH$), 3.00 - 3.09 (m, 1 H, $NC\underline{H}_AH_B$), 3.68 - 3.81 (m, 2 H, $NCH_A\underline{H}_B$, $SO_2C\underline{H}_AH_B$), 3.82 - 3.88 (m, 2 H, $OC\underline{H}_2CH_2O$), 3.94 - 3.99 (m, 2 H, $OCH_2C\underline{H}_2O$), 4.31 - 4.38 (m, 2 H, $NC\underline{H}$, $SO_2CH_A\underline{H}_B$), 4.83 - 4.89 (t, 1 H, *J* = 4.5 Hz, $CH_2C\underline{H}O$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.1 ($NCH_2CH_2\underline{C}H_2$), 24.8 ($COCH_2\underline{C}H_2$), 27.1 ($NCH_2\underline{C}H_2$), 29.0 ($CO\underline{C}H_2$), 29.7 ($C(\underline{C}H_3)_3$), 33.2 ($OCH\underline{C}H_2$), 40.5 ($N\underline{C}H_2$), 52.6 ($N\underline{C}H$), 58.3 ($SO_2\underline{C}H_2$), 64.8 ($O\underline{C}H_2\underline{C}H_2O$), 65.7 ($\underline{C}(CH_3)_3$), 104.3 ($CH_2\underline{C}HO$), 154.1 ($S\underline{C}N_2$), 174.5 ($N\underline{C}O$); ***m/z*** ($ESI^+$) 853 (100%, $[2M+Na]^+$). Data are in agreement with literature.[17]

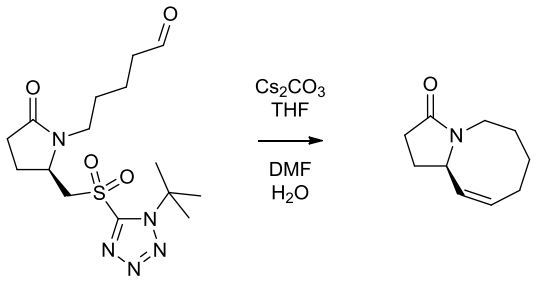
5-[(2*R*)-2-{[(1-*tert*-Butyl-1H-tetrazol-5-yl)sulfonyl]methyl}-5-oxopyrrolidin-1-yl]pentanal (275)



274 **275**

To a solution of sulfone **274** (1.0 eq, 11.8 mmol, 4.91 g) in tetrahydrofuran (4.0 mL/mmol **274**, 47 mL) was added HCl (1 M, 189 mL) and the reaction mixture was stirred for 3 h at RT. The mixture was adjusted to pH 8 using solid K_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic extracts were washed (brine, 40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the crude title compound **275** (4.03 g, 92%) as a colourless oil which was used without further purification. $\mathbf{[\alpha]_D^{24}}$ = +20.1 (c = 0.68, $CHCl_3$; lit.[17] $[\alpha]_D^{24}$ = +22.3, c = 1.75, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.55 - 1.72 (m, 4 H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.86 (s, 9 H, $C(C\underline{H}_3)_3$), 2.22 - 2.31 (m, 1 H, $COCH_2C\underline{H}_AH_B$), 2.35 - 2.57 (m, 5 H, $COC\underline{H}_2CH_A\underline{H}_B$, $HCOC\underline{H}_2$), 3.00 - 3.10 (m, 1 H, $NC\underline{H}_AH_B$), 3.65 - 3.85 (m, 2 H, $NCH_A\underline{H}_B$, $SO_2C\underline{H}_AH_B$), 4.30 - 4.39 (m, 2 H, $NC\underline{H}$, $SO_2CH_A\underline{H}_B$), 9.78 (s, 1 H, $CO\underline{H}$); ***m/z*** (ESI^+) 767 (100%, $[2M+Na]^+$). Data are in agreement with literature.[17]

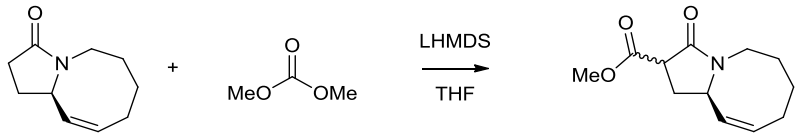
(9*Z*,10a*R*)-1,5,6,7,8,10a-Hexahydropyrrolo[1,2-*a*]azocin-3(2H)-one (276)



275 **276**

A solution of aldehyde **275** (1.0 eq, 1.8 mmol, 0.66 g) in THF (2.8 mL/mmol **275**, 5.0 mL) and DMF (0.56 mL/mmol **275**, 1.0 mL) was added to a suspension of Cs_2CO_3 (3 eq, 5.3 mmol, 1.7 g) in THF (11 mL/mmol **275**, 20 mL), DMF (4.8 mL/mmol **275**, 8.6 mL) and H_2O (0.09 mL/mmol **275**, 0.16 mL) at 70 °C dropwise over 10 h *via* syringe pump. The reaction mixture was cooled to RT and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 (50 mL), filtered through Celite® eluting with CH_2Cl_2 (3 × 20 mL) and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc) to yield the title compound **276** (0.16 g, 54%) as a pale yellow oil. $\mathbf{[\alpha]_D^{24}}$ = −85.4 (c = 0.93, $CHCl_3$; lit.[17] $[\alpha]_D^{25}$ = −87.1, c = 3.44, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.54 - 1.75 (m, 3 H, 3 H of $NCH_2C\underline{H_2}C\underline{H_2}C\underline{H_2}$), 1.78 - 1.91 (m, 2 H, $COCH_2C\underline{H_2}$), 2.14 - 2.53 (m, 5 H, $COC\underline{H_2}CH_2$, 3 H of $NCH_2C\underline{H_2}C\underline{H_2}C\underline{H_2}$), 3.48 - 3.50 (m, 2 H, $NC\underline{H_2}CH_2$), 4.35 (q, 1 H, *J* = 6.0 Hz, $NC\underline{H}CH{=}CH$), 5.49 (dd, 1 H, *J* = 11.0, 6.0 Hz, $NCHC\underline{H}{=}CH$), 5.83 - 5.90 (m, 1 H, $HCHC{=}C\underline{H}$); ***m/z*** (ESI^+) 188 (35%, $[M+Na]^+$), 353 (100, $[2M+Na]^+$). Data are in agreement with literature.[17]

Methyl(2*R*,*S*,9*Z*,10a*R*)-3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylate (146)

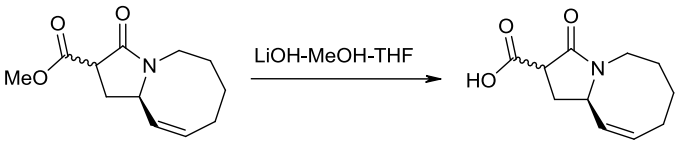


276 **559** **146**

A solution of bicycle **276** (1.0 eq, 2.1 mmol, 0.34 g) and dimethylcarbonate **559** (1.3 eq, 2.7 mmol, 0.22 mL) in THF (4.4 mL/mmol **276**, 9.0 mL) was added dropwise to LHMDS (2.2 eq, 4.5 mmol, 0.9 M soln. in hexanes, 5.0 mL) at −78 °C over 5 min. The resulting mixture was stirred for 30 min at −78 °C before being warmed to 0 °C over 2 h. Glacial acetic acid (5.4 eq, 11 mmol, 0.66 mL) was added dropwise at 0 °C followed by the addition of Et_2O (10 mL) and the reaction mixture was stirred vigorously for 5 min at RT. The insoluble solids were filtered off, washed with Et_2O (2 × 5 mL) and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Et_2O) to yield the title compound **146** (0.39 g, 86%, dr 1:1) as a pale yellow oil. **$[\alpha]_D^{24}$ =** −94.5 (c = 1.4, $CHCl_3$; lit.[17] $[\alpha]_D^{24}$ = −96.0, c = 2.05, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.41 - 2.09 (m, 9 H, 5 H of diastereomer 1 (DS1): $NCH_2C\underline{H_2}C\underline{H_2}$, $NCHC\underline{H_A}H_B$, 4 H of diastereomer 2 (DS2): $NCH_2C\underline{H_2}C\underline{H_2}$), 2.11 - 2.38 (m, 5 H, 2 H DS1: $N(CH_2)_3C\underline{H_2}$, 3 H DS2: $N(CH_2)_3C\underline{H_2}$, $NCHC\underline{H_A}H_B$), 2.51 - 2.56 (m, 1 H, $NCHCH_A\underline{H_B}$ DS2), 2.57 - 2.66 (m, 1 H, $NCHCH_A\underline{H_B}$ DS1), 3.20 - 3.28 (m, 1 H, $NC\underline{H_A}H_B$ DS2), 3.45 - 3.53 (m, 4 H, 3 H DS1: $COC\underline{H}CH_2$, $NC\underline{H_2}$, 1 H DS2: $COC\underline{H}CH_2$), 3.63 - 3.70 (m, 1 H, $NCH_A\underline{H_B}$ DS2), 3.79 (s, 6 H, $OC\underline{H_3}$ of both DS), 4.35 (q, 1 H, *J* = 7.5 Hz, $NC\underline{H}CH$ DS2), 4.46 (q, 1 H, *J* = 6.5 Hz, $NC\underline{H}CH$ DS1), 5.40 - 5.50 (m, 2 H, $NCHC\underline{H}$ of both DS), 5.86 (dt, 1 H, *J* = 11.0, 8.5 Hz, $CHCH=C\underline{H}$ DS1), 5.96 (dt, 1 H, *J* = 11.0, 8.5 Hz, $CHCH=C\underline{H}$ DS2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.1, 25.5, 26.0, 26.9, 27.3, 28.2 ($NCH_2\underline{C}H_2\underline{C}H_2\underline{C}H_2$ of both DS), 30.1 ($NCH\underline{C}H_2$ DS2), 30.6 ($NCH\underline{C}H_2$ DS1) 41.2 ($N\underline{C}H_2CH_2$ DS2), 41.6 ($N\underline{C}H_2CH_2$ DS1), 48.3 ($CO\underline{C}HCH_2$ DS2) 48.8 ($CO\underline{C}HCH_2$ DS1), 52.6 ($COO\underline{C}H_3$ of both DS), 54.3 ($N\underline{C}HCH_2$ DS1), 55.3 ($N\underline{C}HCH_2$ DS2), 128.8 ($NCH\underline{C}H=CH$ DS2), 129.7 ($NCH\underline{C}H=CH$ DS1),

132.5 (NCHCH=<u>C</u>H DS1), 134.5 (NCHCH=<u>C</u>H DS2), [169.1, 169.2, 170.6, 170.7] (N<u>C</u>=O, <u>C</u>OOMe of both DS). Data are in agreement with literature.[17]

(2*R*,*S*,9*Z*,10a*R*)-3-Oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylic acid (266)

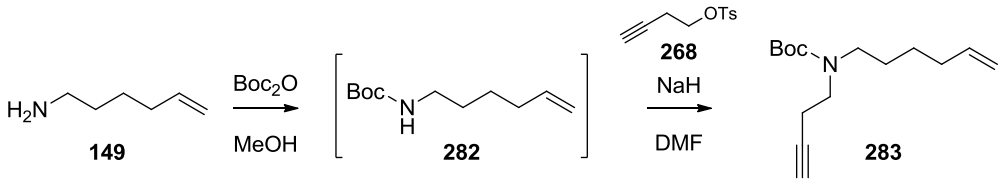


146 **266**

A solution of bicycle **146** (1.0 eq, 2.4 mmol, 0.54 g) in aqueous LiOH (4.5 mL/mmol **146**, 1.0 M, 11 mL), MeOH (1.1 mL/mmol **146**, 2.7 mL) and THF (4.5 mL/mmol **146**, 11 mL) was stirred at RT for 2 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The pH of the aqueous layer was adjusted to 1 (1 M HCl) and extracted with CH_2Cl_2 (6 × 20 mL). The combined organics were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the title compound **266** (0.52 g, ~100%, dr 9:5) as a pale brown solid which was used without further purification. **m.p.** 107 – 110 °C; **$[\alpha]_D^{24}$** = −100.9 (c = 0.57, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 3016 (OH), 1735 (C=O), 1647 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.44 - 1.85 (m, 4 H, 2 H of diastereomer 1 (DS1, major): $NCH_2CH_2C\underline{H}_2$, 2 H of diastereomer 2 (DS2, minor): $NCH_2CH_2C\underline{H}_2$), 1.97 - 2.05 (m, 1 H, $NCHC\underline{H}_AH_B$ DS2), 2.08 - 2.30 (m, 5 H, 3 H DS1: $N(CH_2)_3C\underline{H}_2$, $NCHC\underline{H}_AH_B$, 2 H DS2: $N(CH_2)_3C\underline{H}_2$), 2.50 - 2.57 (m, 1 H, $NCHCH_A\underline{H}_B$ DS1), 2.64 - 2.71 (m, 1 H, $NCHCH_A\underline{H}_B$ DS2), 3.05 - 3.10 (m, 2 H, $NCH_2C\underline{H}_2$ DS2), 3.26 - 3.31 (m, 2 H, $NCH_2C\underline{H}_2$ DS1), 3.44 - 3.49 (m, 2 H, COC<u>H</u>CO of both DS), 3.69 - 3.76 (m, 2 H, $NC\underline{H}_2$ DS1), 3.81 - 3.87 (m, 2 H, $NC\underline{H}_2$ DS2), 4.30 - 4.48 (m, 2 H, $NC\underline{H}CH_2$ of both DS), 5.36 (dd, 1 H, *J* = 11.0, 5.0 Hz, NCHC<u>H</u>=CH DS2), 5.50 (dd, 1 H, *J* = 11.0, 5.0 Hz, NCHC<u>H</u>=CH DS1), 5.77 (dt, 1 H, *J* = 9.0, 9.5 Hz, NCHCH=C<u>H</u> DS1), 6.04 (dt, 1 H, *J* = 9.0, 9.5 Hz, NCHCH=C<u>H</u> DS2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 23.9, 24.1, 26.5, 26.8, 27.3, 27.8 ($NCH_2\underline{C}H_2\underline{C}H_2\underline{C}H_2$ of both DS), 29.2 ($NCH\underline{C}H_2$ of both DS), 41.0 ($N\underline{C}H_2CH_2$ DS2), 42.6 ($N\underline{C}H_2CH_2$ DS1), 45.7 (CO<u>C</u>HCO of DS2), 46.6 (CO<u>C</u>HCO of DS1), 55.6 ($N\underline{C}HCH_2$ DS2), 56.1 ($N\underline{C}HCH_2$ DS1), 127.3 ($NCH\underline{C}H$=CH DS2), 129.8

(NCH<u>C</u>H=CH DS1), 130.8 (NCHCH=<u>C</u>H DS1), 133.5 (NCHCH=<u>C</u>H DS2), 169.7, 169.9, 171.1, 171.7 (N<u>C</u>=O, <u>C</u>OOH of both DS); ***m/z*** (ESI^+) 232 (60%, $[M+Na]^+$), 441 (70%, $[2M+Na]^+$); **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{15}NO_3Na$) requires *m/z* 232.0944, found *m/z* 232.0947.

***tert*-Butyl but-3-yn-1-yl(hex-5-en-1-yl)carbamate (283)**

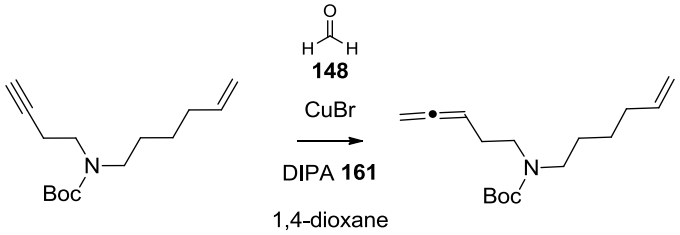


To amine **149** (1.0 eq, 1.01 mmol, 100 mg) in MeOH (1 mL/mmol **149**, 1 mL) was added di-*tert*-butyl dicarbonate (1.0 eq, 1.01 mmol, 220 mg) and the reaction was stirred at RT. After 3 h, the reaction mixture was concentrated *in vacuo* and the crude product was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.23 - 1.49 (m, 13 H, C(C<u>H</u>$_3$)$_3$, NCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.92 - 2.00 (m, 2 H, CH$_2$=CHC<u>H</u>$_2$), 2.85 - 3.02 (m, 2 H, NC<u>H</u>$_2$), 4.70 (br. s, 1 H, N<u>H</u>), 4.81 - 4.99 (m, 2 H, C<u>H</u>$_2$=CH), 5.70 (ddt, 1 H, *J* = 17.0, 10.0, 6.5 Hz, CH$_2$=C<u>H</u>); ***m/z*** (ESI^+) 200 (100%, $[M+H]^+$), 222 (70%, $[M+Na]^+$).

To crude Boc-protected amine **282** (1.0 eq, 0.96 mmol, 190 mg) in dimethylformamide (5.2 mL/mmol **282**, 5 mL) was added NaH (1.1 eq, 1.06 mmol, 42 mg) at RT and the reaction mixture was stirred for 30 min. Tosylate **268** (1.1 eq, 1.06 mmol, 240 mg) was added neat and the reaction mixture was stirred for 23 h at RT. Water (2 mL) was carefully added to the reaction mixture followed by diethyl ether (5 mL). The organic and aqueous layers were separated and the aqueous layer was extracted (Et_2O, 3 × 5 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc → 1:4 MeOH:EtOAc) to yield title compound **283** (210 mg, 88%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2929 (C-H), 2126 (C≡C), 1681 (C=O), 1640 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$, rotameric) δ_H 1.33 - 1.42 (m, 2 H, CH$_2$=CHCH$_2$C<u>H</u>$_2$), 1.55 -

1.57 (m, 11 H, CH_2=CH(CH_2)$_2$C$\underline{H}_2$, C(C$\underline{H}_3$)$_3$), 1.96 (s, 1 H, C≡C$\underline{H}$), 2.08 (q, 2 H, *J* = 7.0 Hz, CH_2=CHC$\underline{H}_2$), 2.34 - 2.42 (m, 2 H, $\underline{H}_2$CC≡CH), 3.20 - 3.41 (m, 4 H, 2 × NC$\underline{H}_2$), 4.97 (dd, 2 H, *J* = 17.0, 6.5 Hz, C$\underline{H}_2$=CH), 5.78 (ddt, 1 H, *J* = 17.0, 10.0, 6.5 Hz, CH_2=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.8 (NCH$_2$CH$_2$$\underline{C}H_2$), 29.1 (C($\underline{C}H_3$)$_3$), 29.0 (NCH$_2$$\underline{C}H_2C_{quat}$), 28.7 (NCH$_2$$\underline{C}H_2CH_2$), 33.7 ($\underline{C}H_2$CH=CH$_2$), 49.9 (N$\underline{C}H_2CH_2C_{quat}$), 51.1 (N$\underline{C}H_2$(CH$_2$)$_3$), 70.2 (H$_2$CC≡$\underline{C}$H), 81.4 (H$_2C\underline{C}$≡CH), 83.1 ($\underline{C}$(CH$_3$)$_3$), 113.4 ($\underline{C}H_2$=CH), 138.6 (CH$_2$=$\underline{C}$H), 172.1 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 252 (100%, [M+H]$^+$), 274 (50%, [M+Na]$^+$); **HRMS** (TOF MS FI$^+$) exact mass calculated for [M+H]$^+$ ($C_{15}H_{26}NO_2$) requires *m/z* 252.1958, found *m/z* 252.1954.

tert-Butyl hex-5-en-1-yl(penta-3,4-dien-1-yl)carbamate (284)

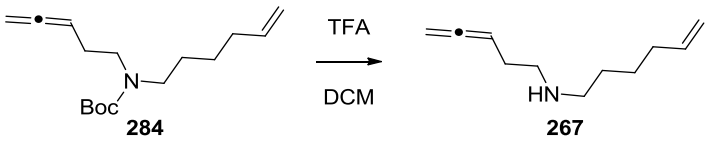


283 **284**

According to literature procedure,[115] to alkyne **283** (1.0 eq, 6.8 mmol, 1.7 g) in 1,4-dioxane (6.8 mL) was added formaldehyde **148** (2.5 eq, 17 mmol, 37% soln. in water, 1.2 mL), CuBr (0.5 eq, 3.4 mmol, 0.49 g) and diisopropylamine **161** (2.0 eq, 14 mmol, 1.8 mL) and the reaction mixture was stirred at reflux for 16 h. The reaction was cooled to RT and partitioned between water (10 mL) and EtOAc (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted (EtOAc, 3 × 10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (petroleum ether) to yield title compound **284** (0.76 g, 56%) as a yellow oil. **IR** ν_{max}(film)/ cm^{-1} 2931 (C-H), 1958 (C=C=C), 1680 (C=O), 1646 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$, rotameric) δ_H 1.12 - 1.63 (m, 13 H, C(C$\underline{H}_3$)$_3$, NCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 2.12 (q, *J* = 7.5 Hz, 2 H, C=CHC$\underline{H}_2$), 2.20 - 2.31 (m, 2 H, CH$_2$=CHC$\underline{H}_2$), 3.24 (m, 4 H, 2 × NC$\underline{H}_2$), 4.68 - 4.77 (m, 2 H, C$\underline{H}_2$=C=CH), 4.94 - 5.16 (m, 3 H, C$\underline{H}_2$=CH, CH$_2$=C=C$\underline{H}$), 5.84 (ddt, *J* = 17.0,

10.0, 6.5 Hz, 1 H, CH_2=C<u>*H*</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 26.9 ($NCH_2CH_2\underline{C}H_2$), 28.4 ($C(\underline{C}H_3)_3$), 29.0 ($NCH_2\underline{C}H_2CH$), 29.5 ($NCH_2\underline{C}H_2CH_2$), 34.2 ($\underline{C}H_2CH{=}CH_2$), 49.4 ($N\underline{C}H_2CH_2CH$), 50.7 ($N\underline{C}H_2(CH_2)_3$), 74.3 ($\underline{C}H_2{=}C_{quat}$), 82.5 ($\underline{C}(CH_3)_3$), 89.1 ($CH_2{=}C{=}\underline{C}H$), 113.8 ($\underline{C}H_2{=}CH$), 138.9 ($CH_2{=}\underline{C}H$), 171.5 (<u>*C*</u>=O), 207.6 ($CH_2\underline{C}CH$); ***m/z*** (ESI^+) 266 (100%, $[M+H]^+$), 288 (60%, $[M+Na]^+$); **HRMS** (TOF MS FI^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{28}NO_2$) requires *m/z* 266.2115, found *m/z* 266.2120.

***N*-(Penta-3,4-dien-1-yl)hex-5-en-1-amine (267)**

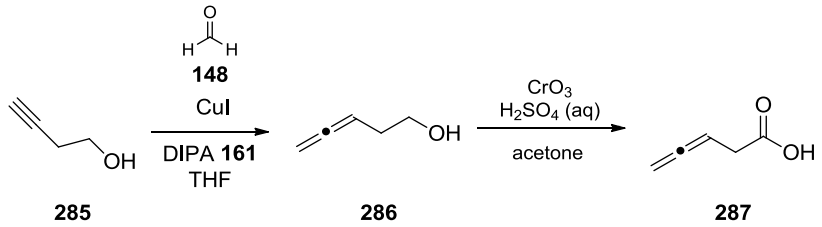


284 **267**

To Boc-protected amine **284** (1.0 eq, 0.19 mmol, 50 mg) in dichloromethane (80 µL) was added TFA (6.0 eq, 1.1 mmol, 80 µL) at 0 ˚C. The reaction mixture was warmed to RT and was stirred for 4 h. The trifluoroacetic acid and dichloromethane were removed *in vacuo* and the TFA salt was redissolved in dichloromethane (0.5 mL) and washed with a solution of K_2CO_3 (10 wt% in water, 3 × 1 mL). The aqueous layer was extracted (CH_2Cl_2, 2 mL) and the organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield crude title compound **267** as a yellow oil (20 mg, 63% mass return).

See page 175 for full characterisation of **267**.

Penta-3,4-dienoic acid (287)



285 286 287

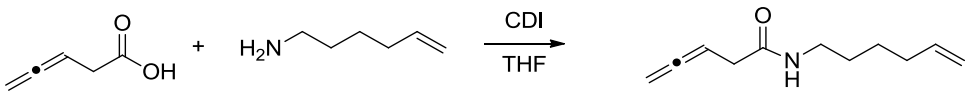
According to modified literature procedure,[203] to a solution of but-3-yn-1-ol **285** (1.0 eq, 0.35 mol, 27 mL) in tetrahydrofuran (690 mL) was added diisopropylamine **161** (2.0 eq, 0.71 mol, 99 mL), *para*-formaldehyde **148** (2.5 eq, 0.89 mol, 27 g) and CuI (0.5 eq, 0.19 mol, 35 g) at RT and the reaction mixture was heated at reflux for 17 h. The reaction mixture was cooled to RT and poured onto aqueous HCl (3 M, 2 mL/mmol **285**, 700 mL) and Et_2O (300 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (4 × 100 mL). The combined organic extracts were washed (brine, 150 mL), dried (Na_2SO_4) and filtered. The solvent was removed under a stream of nitrogen and the crude product was distilled at reduced pressure to yield compound **286** (7.73 g, 26%) as a colourless oil. **b.p.** 80 °C, 20 mbar; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.30 - 2.36 (m, 2 H, C$\underline{H_2}$CH$_2$OH), 3.78 (t, 2 H, *J* = 6.5 Hz, C$\underline{H_2}$OH), 4.77 - 4.80 (m, 2 H, C$\underline{H_2}$=C=CH), 5.15 - 5.22 (m, 1 H, CH$_2$=C=C$\underline{H}$). Data are in agreement with literature.[203]

Jones reagent was freshly prepared. To CrO_3 (1.37 g) in a 5 mL volumetric flask was added water (2.00 mL). The mixture was placed in a sonicator for 1 min before being cooled using an ice-bath. H_2SO_4 (95–97%, 1.15 mL) was added. The mixture was diluted with water to give a total volume of 5 mL.

According to literature procedure,[204] to a solution of allene-alcohol **286** (1.2 mmol, 0.10 g) in acetone (1.7 mL/mmol **286**, 2.0 mL) was added Jones' reagent dropwise (10 mL/g **268**, 1 mL) at 0 °C over 5 min and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was concentrated *in vacuo*, H_2O (2 mL) was added and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were extracted with aqueous

KOH solution (1 M, 2 × 5 mL) and the pH of the aqueous layer was adjusted to 1 (HCl, 12 M). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 → 1:10 MeOH:CH_2Cl_2) to yield title compound **287** (0.078 g, 67%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.16 - 3.19 (m, 2 H, HOOCC$\underline{H}_2$), 4.83 - 4.87 (m, 2 H, C$\underline{H}_2$=C=CH), 5.28 - 5.35 (m, 1 H, CH_2=C=C$\underline{H}$); **HRMS** (TOF MS FI$^+$) exact mass calculated for $[M]^+$ ($C_5H_6O_2$) requires *m/z* 98.0368, found *m/z* 98.0372. Data are in agreement with literature.[204]

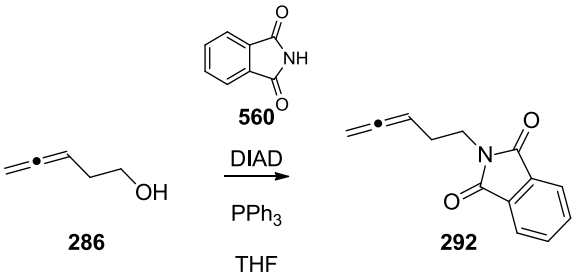
***N*-(Hex-5-en-1-yl)penta-3,4-dienamide (288)**



287 **149** **288**

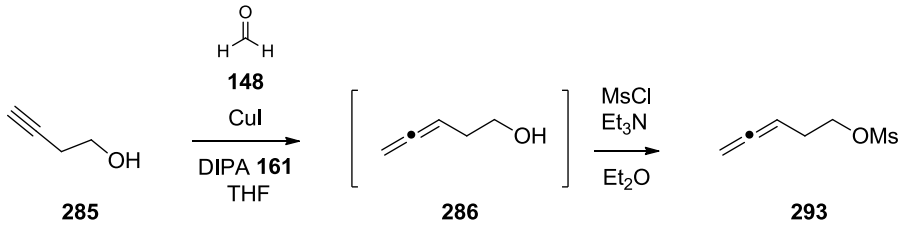
To a solution of acid **2879** (1.0 eq, 1.0 mmol, 0.10 g) in THF (1.9 mL/mmol **287**, 2.0 mL) was added CDI (1.1 eq, 1.1 mmol, 0.11 g). After stirring for 5 min, amine **149** (1.0 eq, 1.0 mmol, 0.17 g) was added. After 1 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc → 1:10 MeOH:EtOAc) to yield the title compound **288** (0.13 g, 71%) as a yellow oil. **IR** (film)/cm^{-1} 1941 (C=C=C), 1685 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.39 - 1.47 (m, 2 H, $NCH_2C\underline{H}_2$), 1.49 - 1.58 (m, 2 H, $NCH_2CH_2C\underline{H}_2$), 2.07 (q, 2 H, *J* = 7.0 Hz, CH_2=CHC$\underline{H}_2$), 2.92 - 2.99 (m, 2 H, NCOC$\underline{H}_2$), 3.24 - 3.32 (m, 2 H, NC$\underline{H}_2$), 4.75 - 4.84 (m, 2 H, C$\underline{H}_2$CCH), 4.93 - 5.08 (m, 2 H, C$\underline{H}_2$=CH), 5.21 - 5.30 (m, 1 H, CH_2CC$\underline{H}$), 5.62 - 5.75 (m, 1 H, CH_2=C$\underline{H}$), 6.32 (br. s, 1 H, N$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 26.1 ($NCH_2CH_2\underline{C}H_2$), 28.9 ($NCH_2\underline{C}H_2$), 33.2 ($CH_2$=CH$\underline{C}H_2$), 36.2 (CO$\underline{C}H_2$), 39.5 (N$\underline{C}H_2$), 75.6 ($\underline{C}H_2$=C=CH), 84.3 ($CH_2$=C=$\underline{C}$H), 114.7 ($\underline{C}H_2$=CH), 138.3 ($CH_2$=$\underline{C}$H), 170.5 ($\underline{C}$=O), 209.6 ($CH_2$=$\underline{C}$=CH); ***m/z*** (ESI$^+$) 202 (100%, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{17}NNaO$) requires *m/z* 202.1202, found *m/z* 202.1197.

2-(Penta-3,4-dien-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (292)



To a solution of alcohol **286** (1.0 eq, 5.6 mmol, 0.50 g), phthalimide **560** (1.1 eq, 6.5 mmol, 0.95 g) and PPh_3 (1.08 eq, 6.4 mmol, 1.7 g) in tetrahydrofuran (4.2 mL/mmol **286**, 25 mL) was added DIAD (1.2 eq, 7.1 mmol, 1.4 mL) at 0 ˚C and the reaction mixture was warmed to RT. After 18 h, the reaction mixture was partitioned between water (10 mL) and EtOAc (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted (EtOAc, 3 × 10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (petroleum ether) to yield title compound **292** (1.0 g, 80%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 1955 (C=C=C), 1661 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.38 - 2.49 (m, 2 H, $NCH_2C\underline{H}_2$), 3.83 (t, *J* = 7.5 Hz, 2 H, $NC\underline{H}_2$), 4.62 - 4.73 (m, 2 H, $C\underline{H}_2$=C=CH), 5.16 (quin., *J* = 7.0 Hz, 1 H, CH_2=C=C$\underline{H}$), 7.74 - 7.82 (m, 2 H, Ar$\underline{H}$), 7.85 - 7.96 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 27.6 ($CH\underline{C}H_2CH_2N$), 37.4 ($N\underline{C}H_2$), 74.7 ($\underline{C}H_2$=C=CH), 85.6 (CH_2=C=$\underline{C}$H), 124.1 (Ar$\underline{C}$), 132.3 (Ar$\underline{C}_{quat}$), 134.5 (Ar$\underline{C}$), 169.2 ($\underline{C}$=O), 205.3 (HC=$\underline{C}$=CH); **HRMS** (TOF MS FI$^+$) exact mass calculated for $[M]^+$ ($C_{13}H_{11}NO_2$) requires *m/z* 213.0790, found *m/z* 213.0790.

Penta-3,4-dien-1-yl methanesulfonate (293)

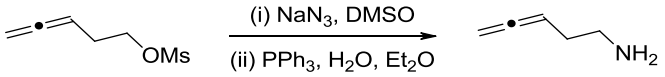


According to literature procedure,[203] to a solution of but-3-yn-1-ol **285** (1.0 eq, 0.29 mol, 22 mL) in tetrahydrofuran (1.9 mL/mmol **285**, 550 mL) was added diisopropylamine **161** (2.0 eq, 0.57 mol, 80 mL), paraformaldehyde **148** (2.5 eq, 0.71 mol, 21 g) and CuI (0.5 eq, 0.14 mol, 27 g) at RT and the reaction mixture was heated at reflux for 17 h. The reaction mixture was cooled to RT and poured onto aqueous HCl (3 M, 500 mL) and Et_2O (200 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (4 × 75 mL). The combined organic extracts were washed (brine, 100 mL), dried (Na_2SO_4) and filtered affording a solution of penta-3,4-dien-1-ol **286** in diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.30 - 2.36 (m, 2 H, C$\underline{H}_2$CH$_2$OH), 3.78 (t, 2 H, *J* = 6.5 Hz, C$\underline{H}_2$OH), 4.77 - 4.80 (m, 2 H, C$\underline{H}_2$=C=CH), 5.18 (quin., *J* = 7.0 Hz, 1 H, CH$_2$=C=C$\underline{H}$).

According to a modified literature procedure,[177] to the combined organic extracts was added Et_3N (0.30 mL/mmol **285**, 88 mL) and methanesulfonyl chloride (0.12 mL/mmol **285**, 36 mL) dropwise at 0 °C. After 2 h the reaction mixture was concentrated *in vacuo*, redissolved in CH_2Cl_2 (100 mL) and H_2O (50 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:10 EtOAc:PE → 1:1 EtOAc:PE) to yield the title compound **293** (13 g, 27% over two steps) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1957 (C=C=C), 1351 (S=O), 1173 (S=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.38 - 2.46 (m, 2 H, C$\underline{H}_2$CH), 2.99 (s, 3 H, C$\underline{H}_3$), 4.24 (t, 2 H, *J* = 7.0 Hz, C$\underline{H}_2$O), 4.72 - 4.75 (m, 2 H, C$\underline{H}_2$=C$_{quat}$), 5.10 (quin., 1 H, *J* = 7.0 Hz, C$\underline{H}$CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 28.0 (CH$\underline{C}$H$_2$),

37.4 (<u>C</u>H_3), 68.9 (<u>C</u>H_2O), 76.1 (<u>C</u>H_2=C), 84.9 (<u>C</u>H), 209.1 (CH_2<u>C</u>CH); **HRMS** (TOF MS FI^+) exact mass calculated for $[M]^+$ ($C_6H_{10}SO_3$) requires *m/z* 162.0351, found *m/z* 162.0354. Data are in agreement with literature.[177]

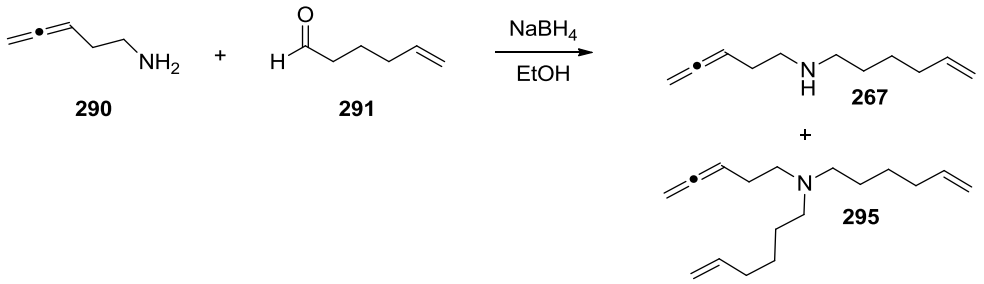
Penta-3,4-dien-1-amine (290)



293 **290**

To a solution of mesylate **293** (1.0 eq, 28.3 mmol, 4.59 g) in DMSO (1.17 mL/mmol **293**, 33.1 mL) was added NaN_3 (1.5 eq, 42.5 mmol, 2.76 g) at RT. The reaction mixture was heated at 50 °C. After 5 h, the reaction mixture was cooled to RT and Et_2O (20 mL) and H_2O (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 50 mL). The combined organics were washed (brine, 50 mL) and dried (Na_2SO_4). To the organic layer was added H_2O (5.0 eq, 142 mmol, 2.55 mL) and triphenylphosphine (2.0 eq, 56.7 mmol, 14.9 g) portionwise over 10 min. After 24 h, the pH of the reaction mixture was adjusted to 1 by the addition of aqueous HCl solution (1 M). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The pH of the aqueous layer was adjusted to >10 by the addition of solid NaOH. The aqueous layer was extracted with Et_2O (5 × 20 mL) and the combined organic extracts were washed (brine, 50 mL), dried (Na_2SO_4), filtered and the solvent was removed using a stream of nitrogen to give the title compound **290** (2.48 g, quant.) as a yellow oil. **b.p.** 44 °C at 50 mbar; **IR** ν_{max}(film)/cm^{-1} 3364 (N-H), 1947 (C=C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.10 - 2.20 (m, 2 H, $NCH_2C\underline{H_2}$), 2.77 (t, 2 H, *J* = 6.5 Hz, $NC\underline{H_2}$), 4.62 - 4.73 (m, 2 H, $C\underline{H_2}$=C=CH), 5.08 (quin., 1 H, *J* = 7.0 Hz, C=C<u>H</u>CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 32.6 ($NCH_2\underline{C}H_2$), 41.5 ($N\underline{C}H_2$), 74.8 (<u>C</u>H_2=C), 87.5 (C=<u>C</u>H), 208.9 (CH_2=<u>C</u>=CH); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ (C_5H_9NNa) requires *m/z* 83.0735, found *m/z* 83.0736.

***N*-(Penta-3,4-dien-1-yl)hex-5-en-1-amine (267)** and ***N*,*N*-di(penta-3,4-dien-1-yl)hex-5-en-1-amine (295)**



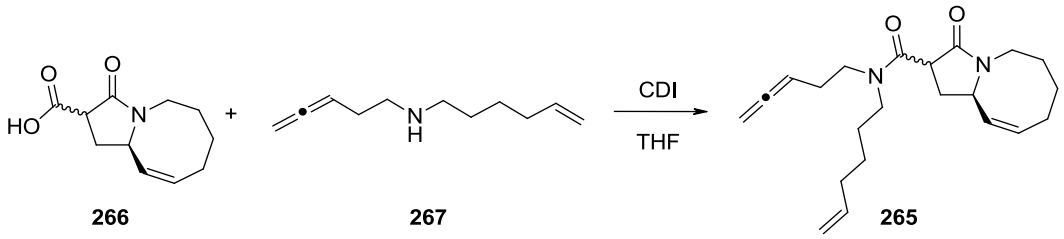
290 **291** **267** **295**

267: To a solution of amine **290** (1.5 eq, 6.0 mmol, 0.50 g) in EtOH (0.60 mL/mmol **290**, 3.6 mL) was added aldehyde **291** (1.0 eq, 4.0 mmol, 0.39 g) at RT. After 2 h, the reaction mixture was cooled to 0 °C and $NaBH_4$ (1.0 eq, 4.0 mmol, 0.15 g) was added as a single portion. After 4 h, Et_2O (20 mL) and H_2O (10 mL) were added. The organic layer was separated and the aqueous layer was extracted (Et_2O, 2 × 10 mL). The combined organic extracts were washed (brine, 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:10 MeOH:EtOAc → 1:5 MeOH:EtOAc) to yield title compound **267** (0.58 g, 88%) as a pale yellow oil.

267: IR ν_{max}(film)/cm^{-1} 3215 (N-H), 2904 (C-H), 1956 (C=C=C), 1680 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.38 - 1.43 (m, 2 H, CH_2=CHCH$_2$C$\underline{H_2}$), 1.45 - 1.52 (m, 2 H, NCH$_2$C$\underline{H_2}$CH$_2$), 2.04 - 2.08 (m, 2 H, CH_2=CHC$\underline{H_2}$), 2.15 - 2.20 (m, 2 H, NCH$_2$C$\underline{H_2}$CH), 2.59 (t, 2 H, *J* = 7.0 Hz, NC$\underline{H_2}$(CH$_2$)$_3$), 2.69 (t, 2 H, *J* = 7.0 Hz, NC$\underline{H_2}$CH$_2$CH), 4.65 - 4.68 (m, 2 H, C$\underline{H_2}$=C=CH), 4.91 - 5.01 (m, 2 H, C$\underline{H_2}$=CHCH$_2$), 5.08 (quin., 1 H, *J* = 7.0 Hz, C=C$\underline{H}$), 5.73 - 5.84 (m, 1 H, CH_2=C$\underline{H}$CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 26.6 (NCH$_2$CH$_2$$\underline{C}H_2$), 28.7 (NCH$_2$$\underline{C}H_2$CH), 29.5 (NCH$_2$$\underline{C}H_2CH_2$), 33.6 ($\underline{C}H_2$CH=CH$_2$), 49.0 (N$\underline{C}H_2CH_2$CH), 50.5 (N$\underline{C}H_2$(CH$_2$)$_3$), 74.8 ($\underline{C}H_2$=C=CH), 88.5 (CH$_2$=C=$\underline{C}$H), 114.4 ($\underline{C}H_2$=CH), 138.9 (CH$_2$=$\underline{C}$H), 208.8 (CH$_2$$\underline{C}$CH); ***m/z*** (ESI$^+$) 166 (100%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{11}H_{20}N$) requires *m/z* 166.1596, found *m/z* 166.1590.

295: To a solution of crude amine **290** (3.0 eq, 2.4 mmol, 0.20 g) in EtOH (0.60 mL/mmol **290**, 1.4 mL) was added aldehyde **291** (1.0 eq, 0.80 mmol, 0.078 g) at RT. After 2 h, the reaction mixture was cooled to 0 °C and $NaBH_4$ (1.0 eq, 0.80 mmol, 0.030 g) was added as a single portion. After 4 h, Et_2O (5 mL) and H_2O (5 mL) were added. The organic layer was separated and the aqueous layer was extracted (Et_2O, 2 × 5 mL). The combined organic extracts were washed (brine, 5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:10 MeOH:EtOAc → 1:5 MeOH:EtOAc) to yield amine **267** (0.079 g, 60%) and title compound **295** (0.067 g, 34%) as pale yellow oils. **IR** ν_{max}(film)/cm^{-1} 2928 (C-H), 1956 (C=C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.29 - 1.74 (m, 8 H, 2 × $NCH_2C\underline{H_2}C\underline{H_2}$), 1.95 - 2.21 (m, 6 H, 2 × CH_2=$CHC\underline{H_2}$, CH_2=C=$CHC\underline{H_2}$), 3.60 - 3.71 (m, 6 H, 3 × $NC\underline{H_2}$), 4.60 - 4.79 (m, 2 H, $C\underline{H_2}$=C=CH), 4.91 - 5.19 (m, 5 H, 2 × $C\underline{H_2}$=$CHCH_2$, CH_2=C=C$\underline{H}$), 5.71 - 5.89 (m, 2 H, 2 × CH_2=C$\underline{H}CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.2 ($NCH_2CH_2\underline{C}H_2$), 25.8 ($NCH_2CH_2\underline{C}H_2$), 31.5 ($NCH_2\underline{C}H_2CH$), 32.1 ($NCH_2\underline{C}H_2CH_2$), 32.8 ($\underline{C}H_2CH$=$CH_2$), 33.9 ($\underline{C}H_2CH$=$CH_2$), 54.8, 55.2, 57.8 (3 × $N\underline{C}H_2$), 74.6 ($\underline{C}H_2$=C), 87.4 ($CH_2C\underline{C}H$), 114.2 ($\underline{C}H_2$=CH), 114.5 ($\underline{C}H_2$=CH), 130.7 (2 × CH_2=$\underline{C}$H), 208.8 ($CH_2\underline{C}CH$); ***m/z*** (ESI$^+$) 248 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{29}N$) requires *m/z* 248.2373, found *m/z* 248.2378.

(2*R*,*S*,9*Z*,10a*R*)-*N*-(Hex-5-en-1-yl)-3-oxo-*N*-(penta-3,4-dien-1-yl)-1,2,3,5,6,7,8,10a-octahydropyrrolo [1,2-*a*]azocine-2-carboxamide (265)



266 **267** **265**

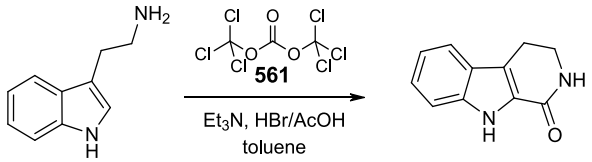
To a solution of acid **266** (1.0 eq, 0.51 mmol, 0.10 g) in tetrahydrofuran (1.4 mL/mmol **266**, 0.70 mL) was added CDI (1.1 eq, 0.56 mmol, 0.091 g) and the resulting mixture was stirred for 10 min at RT after which amine **267** (1.1 eq, 0.56 mmol, 0.092 g) in tetrahydrofuran (1.2 mL/mmol **267**, 0.68 mL) was added to the reaction mixture. After 16 h, Et_2O (5 mL) and H_2O (5 mL) were added and the organic layer was separated. The aqueous layer was extracted (Et_2O, 2 × 10 mL) and the combined organic extracts were washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 EtOAc:PE) to yield the title compound **265** (0.15 g, 81%, dr 9:4) as a pale yellow oil. The diastereomers were characterised as a mixture. $\mathbf{[\alpha]_D^{24}}$ = -31.9 (c = 0.86, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 3074 (C-H), 2929 (C-H), 1955 (C=C=C), 1685 (C=O), 1641 (C=C); ***m/z*** (ESI^+) 357 (50%, $[M+H]^+$), 379 (100, $[M+Na]^+$) 735, (100, $[2M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{32}N_2NaO_2$) requires *m/z* 379.2356, found *m/z* 379.2353.

Diastereomer 1, major: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28 - 1.70 (m, 6 H, CH_2=CHCH$_2$C$\underline{H_2}$C$\underline{H_2}$, CH=CHCH$_2$C$\underline{H_2}$), 1.71 - 1.94 (m, 1 H, NCHC$\underline{H_A}$H$_B$), 1.98 - 2.07 (m, 2 H, CH_2=CHC$\underline{H_2}$), 2.09 - 2.24 (m, 4 H, CH=CHC$\underline{H_2}$, C=CHC$\underline{H_2}$), 2.63 - 2.73 (m, 1 H, NCHCH$_A$$\underline{H_B}$), 3.01 - 3.34 (m, 6 H, NC$\underline{H_2}$CH$_2$CH=C, CH_2=CH(CH$_2$)$_3$C$\underline{H_2}$, CHNCH$_2$C$\underline{H_2}$), 3.57 - 3.75 (m, 1 H, COC$\underline{H}$CO), 3.74 - 3.91 (m, 2 H, CHNC$\underline{H_2}$), 4.51 - 4.58 (m, 1 H, NC$\underline{H}$), 4.66 - 4.76 (m, 2 H, C$\underline{H_2}$=C=CH), 4.91 - 5.10 (m, 2 H, C$\underline{H_2}$=CH), 5.10 - 5.16 (m, 1 H, CH_2=C=C$\underline{H}$), 5.40 - 5.45 (m, 1 H, CHC$\underline{H}$=CH), 5.72 - 5.89 (m, 2 H, CHCH=C$\underline{H}$, CH_2=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.7, 26.2, 27.0, 27.3, 28.3 (C$\underline{H_2}$C$\underline{H_2}$CH=CHCH, C$\underline{H_2}$C$\underline{H_2}$CH$_2$CH=CH$_2$, NCH$_2$C$\underline{H_2}$CH=C$_{quat}$), 31.4 (NCH$\underline{C}$H$_2$), 33.7

(CH_2=CH<u>C</u>H_2), 41.3 (CH_2=CH(CH_2)$_3$<u>C</u>H_2), 45.6 (CO<u>C</u>HCO), 46.7, 46.8 (CHNCH$_2$<u>C</u>H_2, N<u>C</u>H_2CH$_2$CH=C), 47.8 (CHN<u>C</u>H_2), 55.8 (N<u>C</u>H), 75.4 (<u>C</u>H_2=C=CH), 86.7 (CH_2=C=<u>C</u>H), 114.9 (<u>C</u>H_2=CH), 129.5, (NCH<u>C</u>H=CH), 132.9 (NCHCH=<u>C</u>H), 138.5 (CH_2=<u>C</u>H), 169.1, 170.8 (2 × <u>C</u>=O), 209.23 (CH_2=<u>C</u>=CH).

Diastereomer 2, minor: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.28 - 1.70 (m, 6 H, CH_2=CHCH$_2$C<u>H$_2$</u>C<u>H$_2$</u>, CH=CHCH$_2$C<u>H$_2$</u>), 1.98 - 2.07 (m, 2 H, CH_2=CHC<u>H$_2$</u>), 2.09 - 2.24 (m, 4 H, CH=CHC<u>H$_2$</u>, C=CHC<u>H$_2$</u>), 2.26 - 2.34 (m, 1 H, NCHC<u>H$_A$</u>H$_B$), 2.35 - 2.46 (m, 1 H, NCHCH$_A$<u>H$_B$</u>), 3.01 - 3.34 (m, 2 H, CHNCH$_2$C<u>H$_2$</u>), 3.39 - 3.55 (m, 4 H, N(C<u>H$_2$</u>)(C<u>H$_2$</u>)), 3.57 - 3.75 (m, 1 H, COC<u>H</u>CO), 3.74 - 3.91 (m, 2 H, CHNC<u>H$_2$</u>), 4.33 (q, 1 H, *J* = 7.5 Hz, NC<u>H</u>), 4.66 - 4.76 (m, 2 H, C<u>H$_2$</u>=C=CH), 4.91 - 5.10 (m, 2 H, C<u>H$_2$</u>=CH), 5.10 - 5.16 (m, 1 H, CH_2=C=C<u>H</u>), 5.49 - 5.56 (m, 1 H, CHC<u>H</u>=CH), 5.72 - 5.89 (m, 1 H, CH_2=C<u>H</u>), 5.91 - 5.99 (m, 1 H, CHCH=C<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.9, 26.9, 27.2, 27.5, 28.4 (CHN(CH_2)$_2$<u>C</u>H$_2$<u>C</u>H$_2$, CH_2NCH$_2$<u>C</u>H$_2$<u>C</u>H$_2$, NCH$_2$<u>C</u>H$_2$CH=C), 30.2 (NCH<u>C</u>H$_2$), 33.7 (CH_2=CH<u>C</u>H$_2$), 41.8 (CH_2=CH(CH_2)$_3$<u>C</u>H$_2$), 46.1 (COC<u>H</u>CO), 46.7, 46.9 (CHNCH$_2$<u>C</u>H$_2$, N<u>C</u>H$_2$CH$_2$CH=C), 48.6 (CHN<u>C</u>H$_2$), 54.2 (N<u>C</u>H), 76.0 (<u>C</u>H$_2$=C=CH), 87.4 (CH_2=C=<u>C</u>H), 115.3 (<u>C</u>H$_2$=CH), 130.6 (NCH<u>C</u>H=CH), 135.0 (NCHCH=<u>C</u>H), 139.0 (CH_2=<u>C</u>H), 170.5, 171.3 (2 × <u>C</u>=O), 209.23 (CH_2=<u>C</u>=CH).

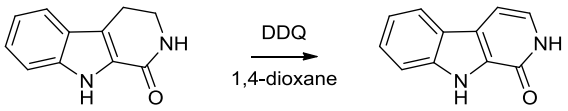
2,3,4,9-Tetrahydro-1*H*-β-carbolin-1-one (297)



296 **297**

To a warmed (50 °C) solution of tryptamine **296** (1.0 eq, 3.1 mmol, 0.50 g) in toluene (14 mL/mmol **296**, 44 mL) was added Et_3N (2.4 eq, 7.6 mmol, 1.1 mL). After 30 min, the reaction mixture was cooled to RT and triphosgene **561** (0.4 eq, 1.3 mmol, 0.37 g) in toluene (1.5 mL/mmol **296**, 1.9 mL) was added dropwise. After 20 min, HBr (0.23 mL/mmol **296**, 33% soln. in AcOH, 0.72 mL) was added slowly to the reaction mixture which was then heated at reflux. After 30 min, the reaction mixture was cooled to RT followed by the addition of ethyl acetate (40 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted (EtOAc, 3 × 30 mL). The combined organic extracts were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc) to yield the title compound **297** (0.23 g, 40%) as a colourless solid. **m.p.** 185 – 187 °C (lit. 188 – 189 °C[120]); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.09 (t, 2 H, *J* = 7.0 Hz, $NCH_2C\underline{H_2}$), 3.73 (td, 2 H, *J* = 7.0, 2.0 Hz, $NC\underline{H_2}CH_2$), 5.72 (br. s, 1 H, CON*H*), 7.11 - 7.20 (m, 1 H, Ar*H*), 7.34 (td, 1 H, *J* = 8.0 Hz, 1.0 Hz, Ar*H*), 7.45 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.60 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 9.11 (br. s, 1 H, N*H*); ***m/z*** (ESI^+) 209 (35%, $[M+Na]^+$). Data are in agreement with literature.[120]

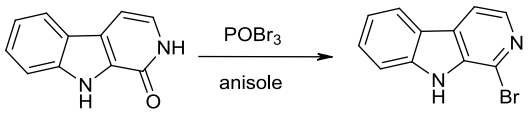
2,9-Dihydro-1*H*-β-carbolin-1-one (298)



297 **298**

To a solution of heterocycle **297** (1.0 eq, 0.54 mmol, 0.10 g) in 1,4-dioxane (17 mL/mmol **297**, 9.3 mL) was added DDQ (3.1 eq, 1.7 mmol, 0.38 g) at RT. The solution turned from yellow to black immediately. After 4 h, 1,4-dioxane was removed *in vacuo*. The residue was dissolved in 10% aqueous NaOH (60 mL) and the resulting solution was extracted (EtOAc, 4 × 20 mL). The combined organic extracts were washed (brine, 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc → 1:10 MeOH:EtOAc) to yield the title compound **298** (0.072 g, 72%) as a pale yellow solid. **m.p.** 250 – 253 °C (lit. 251 – 256 °C[120]); **^{1}H NMR** (400 MHz, D_6MSO) δ_H 7.00 (d, 1 H, *J* = 7.0 Hz, ArH), 7.10 (d, 1 H, *J* = 7.0 Hz, Ar*H*), 7.17 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.38 - 7.43 (m, 1 H, Ar*H*), 7.52 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 8.03 (d, 1 H, *J* = 8.0 Hz, Ar*H*); ***m/z*** $(ESI)^+$ 243 (100%, $[M+MeCN+NH_3]^+$). Data are in agreement with literature.[120]

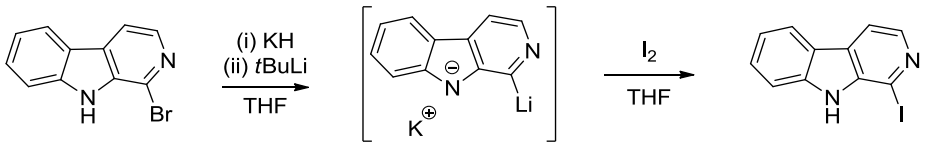
1-Bromo-9*H*-β-carboline (299)



298 **299**

To a solution of β-carboline **298** (1.0 eq, 1.09 mmol, 0.200 g) in anisole (2 mL/mmol **298**, 2.18 mL) was added $POBr_3$ (7.0 eq, 7.61 mmol, 2.18 g) and the resulting mixture was heated at 120 °C. After 4 h, the reaction mixture was cooled to RT and poured on to a saturated solution of Na_2CO_3 (200 mL) which was extracted (EtOAc, 3 × 25 mL). The combined organics were washed (H_2O, 2 × 50 mL then brine, 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:10 EtOAc:PE → 1:3 EtOAc:PE) to yield title compound **299** (0.140 g, 51%) as a pale yellow solid. **m.p.** 151 – 153 °C (lit. 152 °C[121]); **^{1}H NMR** (400 MHz, D_6MSO) δ_H 7.29 (t, 1 H, *J* = 7.0 Hz, Ar*H*), 7.58 (m, 1 H, Ar*H*), 7.65 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 8.14 (m, 1 H, Ar*H*), 8.20 (d, 1 H, *J* = 5.5 Hz, Ar*H*), 8.24 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 11.80 (br. s, 1 H, N*H*); ***m/z*** (ESI$^-$) ^{79}Br 245 (100%, $[M-H]^-$), ^{81}Br 247 (100%, $[M-H]^-$). Data are in agreement with literature.[121]

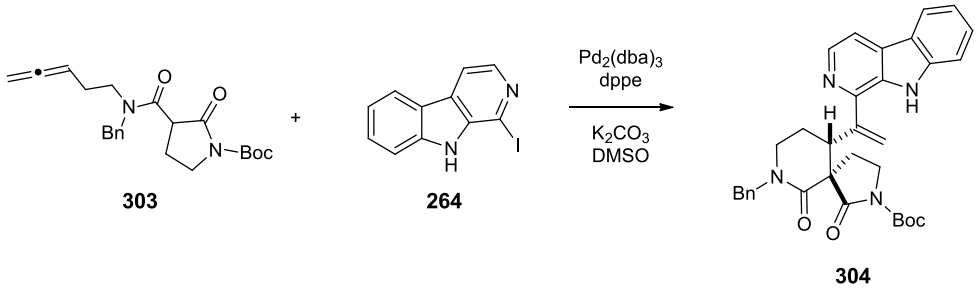
1-Iodo-9*H*-β-carboline (264)



299 **300** **264**

To a slurried mixture of KH (1.0 eq, 0.73 mmol, 30% dispersion in mineral oil, 0.098 g) in freshly distilled tetrahydrofuran (1.1 mL/mmol **299**, 0.77 mL) was added bromo-β-carboline **299** (1.0 eq, 0.73 mmol, 0.18 g) in tetrahydrofuran (4.2 mL/mmol **299**, 3.1 mL) at 0 °C. After 40 min, the mixture was cooled to −78 °C and *t*BuLi (2.0 eq, 1.5 mmol, 1.7 M in pentane, 0.85 mL) was added dropwise. After 20 min, I_2 (1.0 eq, 0.73 mmol, 0.18 g) in tetrahydrofuran (0.68 mL/mmol iodine, 0.50 mL) was added slowly to the dark red solution and the mixture was warmed to room temperature. EtOAc (5 mL) and $NaHCO_3$ (saturated aqueous, 5 mL) was added. The aqueous layer was extracted (EtOAc, 3 × 5 mL) and the combined organic extracts were washed (brine, 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc:PE) to yield title compound **264** (0.16 g, 75%) as a yellow solid. **m.p.** 88 – 90 °C; **IR** ν_{max}(film)/cm^{-1} 3351 (N-H), 2985 (C-H); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.31 (ddd, 1 H, *J* = 8.0, 6.5, 1.5 Hz, Ar*H*), 7.54 - 7.59 (m, 2 H, Ar*H*), 7.86 (d, 1 H, *J* = 5.0 Hz, Ar*H*), 8.07 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 8.23 (d, 1 H, *J* = 5.0 Hz, Ar*H*), 8.73 (br. s, 1 H, N*H*); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 100.9 (*C*-I), 111.9 (Ar*C*), 114.7 (NCH*C*H), 120.8 (Ar*C*), 122.2 (Ar*C*), 122.3 (NHCC_{quat}), 128.2 (NHCC_{quat}), 129.0 (Ar*C*), 138.7 (NHC_{quat}), 139.4 (N*C*H=CH), 140.2 (N*C*H=CH); ***m/z*** (ESI$^+$) 295 (100%, $[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{11}H_8IN_2$) requires *m/z* 294.9581, found *m/z* 294.9574.

***rac-tert*-Butyl-(5*R*)-7-benzyl-10-[1-(9*H*-β-carbolin-1-yl)vinyl]-1,6-dioxo-2,7-diazaspiro [4.5]decane-2-carboxylate (304)**



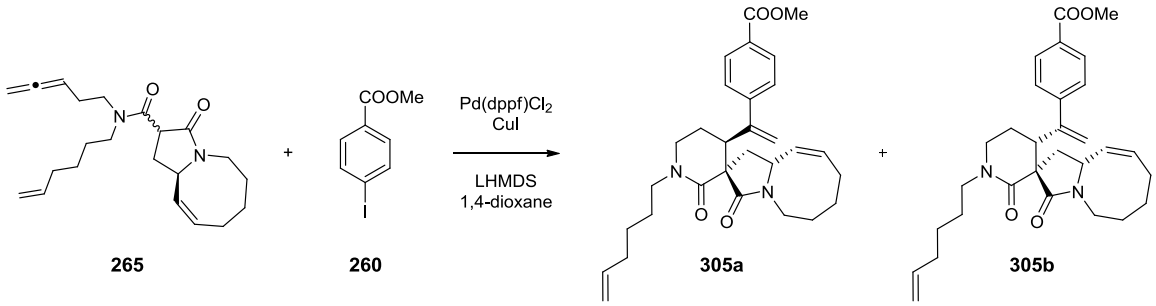
303 **264** **304**

$Pd_2(dba)_3$ (5 mol%, 0.004 mmol, 4 mg) and dppe (10 mol%, 0.008 mmol, 3 mg) in dimethylsulfoxide (1.7 mL/mmol **303**, 0.2 mL) were stirred at RT for 30 min. To the reaction mixture was added a suspension of amide **303** (1.0 eq, 0.08 mmol, 32 mg), β-carboline **264** (1.5 eq, 0.12 mmol, 35 mg) and potassium carbonate (2.0 eq, 0.16 mmol, 22 mg) in dimethylsulfoxide (1.7 mL/mmol **303**, 0.2 mL) and the resulting suspension was stirred at 70 °C in a sealed vial. After 16 h, the reaction mixture was cooled to room temperature and partitioned between diethyl ether (1 mL) and water (1 mL). The organics were separated and the aqueous was extracted with diethyl ether (3 × 2 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (PE → 1:1 EtOAc:PE → EtOAc → 1:10 MeOH:EtOAc) to yield the title compound **304** (4 mg, 18%) as an orange oil. **IR** ν_{max}(film)/cm^{-1} 2979 (C-H), 1776 (2 × C=O), 1628 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.39 (s, 9 H, (C$\underline{H}_3$)$_3$), 1.71 - 1.81 (m, 1 H, CHC$\underline{H}_A$H$_B$), 2.34 - 2.43 (m, 1 H, CC$\underline{H}_A$H$_B$), 2.60 - 2.72 (m, 2 H, CHCH$_A\underline{H}_B$, CCH$_A\underline{H}_B$), 3.26 - 3.44 (m, 2 H, CHCH$_2$C$\underline{H}_2$), 3.57 - 3.65 (m, 1 H, (CO)$_2$NC$\underline{H}_A$H$_B$), 3.86 - 3.92 (m, 1 H, (CO)$_2$NCH$_A\underline{H}_B$), 4.09 - 4.13 (m, 1 H, C_{quat}C$\underline{H}$), 4.55 (d, *J* = 14.5 Hz, 1 H, NC$\underline{H}_A$H$_B$Ph), 4.75 (d, *J* = 14.5 Hz, 1 H, NCH$_A\underline{H}_B$Ph), 5.51 (br. s, 1 H, C=C$\underline{H}_A$H$_B$), 5.77 (br. s, 1 H, C=CCH$_A\underline{H}_B$), 7.28 - 7.40 (m, 6 H, Ar$\underline{H}$), 7.48 - 7.58 (m, 2 H, Ar$\underline{H}$), 7.86 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$), 8.11 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 8.27 (s, 1 H, N$\underline{H}$), 8.43 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 23.2 (CH$\underline{C}$H$_2$), 26.5 (C$\underline{C}$H$_2$), 27.8 (C($\underline{C}$H$_3$)$_3$), 43.3 (C$\underline{C}$HC), 44.3 (CCH$_2\underline{C}$H$_2$), 45.0 (BnN$\underline{C}$H$_2$), 50.8 (N$\underline{C}$H$_2$Ph), 57.1 ((CO)$_2\underline{C}$CH$_2$), 82.7 ($\underline{C}$(CH$_3$)$_3$), 111.5 (Ar$\underline{C}$), 114.1 (Ar$\underline{C}$), 117.8 (C=$\underline{C}$H$_2$), 120.4 (Ar$\underline{C}$), 121.7 (Ar$\underline{C}$), 121.9 (Ar$\underline{C}$),

127.5 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 128.7 (Ar*C*), 129.6 (ArC_{quat}), 133.5 (ArC_{quat}), 136.7 (ArC_{quat}), 138.7 (Ar*C*), 139.9 (ArC_{quat}), 142.8 (ArC_{quat}), 146.4 (ArC_{quat}), 149.7 (ArC_{quat}), 169.4 (*C*=O), 171.1 (*C*=O), 172.8 (*C*=O); ***m/z*** (ESI$^+$) 551 (100%, $[M+H]^+$), 573 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{33}H_{35}N_4O_4$) requires *m/z* 551.2653, found *m/z* 551.2650.

Methyl 4-{1-[(3*R*,4*S*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]vinyl}benzoate (305a)

Methyl 4-{1-[(3*R*,4*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]vinyl}benzoate (305b)



265 **260** **305a** **305b**

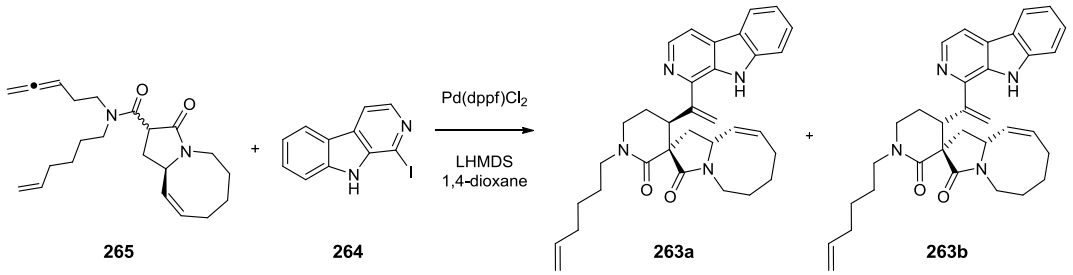
To amide **265** (1.0 eq, 0.14 mmol, 50 mg) was added LHMDS (1.0 eq, 0.14 mmol, 1.0 M soln. in hexanes, 0.14 mL) dropwise and the resulting mixture was stirred for 5 min. To the solution was added a suspension of $Pd(dppf)Cl_2$ (2.5 mol%, 0.035 mmol, 3.0 mg) and aryl iodide **260** (1.5 eq, 0.21 mmol, 55 mg) in 1,4-dioxane (1.5 mL/mmol **265**, 0.31 mL) and the resulting mixture was stirred at 95 °C. After 16 h, the reaction mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc) to yield the separated diastereomers **350a** (0.015 mg, 22%) and **305b** (0.016 mg, 23%) as yellow oils. **305a: $[\alpha]_D^{24}$** = −24.0 (c = 0.30, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2979 (C-H), 1776 (C=O), 1628 (C=C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.22 - 1.32 (m, 1 H, $CHNCH_2C\underline{H}_AH_B$), 1.35 - 1.47 (m, 4 H, $H_2C{=}CHCH_2CH_2C\underline{H}_AH_B$, $H_2C{=}CHCH_2C\underline{H}_2$, $CHNCH_2CH_A\underline{H}_B$), 1.63 - 1.71 (m, 2 H, $NCHC\underline{H}_AH_B$, $H_2C{=}CHCH_2CH_2CH_A\underline{H}_B$), 1.80 - 1.90 (m, 1 H, $NCH_2C\underline{H}_AH_BCH$), 2.00 - 2.10 (m, 5 H, $CH{=}CHC\underline{H}_AH_B$, $CH{=}CHCH_2C\underline{H}_2$, $H_2C{=}CHC\underline{H}_2$), 2.23 - 2.39 (m, 1 H, $CH{=}CHCH_A\underline{H}_B$), 2.67 - 2.75 (m, 1 H, $NCHCH_A\underline{H}_B$), 2.91 - 3.05 (m, 1 H, $CHNC\underline{H}_AH_B$), 3.15 - 3.24 (m, 2 H, $NCH_2CH_2C\underline{H}$, $NCH_2CH_A\underline{H}_BCH$), 3.35 - 3.61 (m, 4 H, 2 × $NC\underline{H}_2$), 3.65 - 3.79 (m, 1 H, $CHNCH_A\underline{H}_B$), 3.83 - 3.97 (m, 4 H, $COOC\underline{H}_3$, $NC\underline{H}CH{=}CH$), 4.89 - 5.06 (m, 2 H, $\underline{H}_2C{=}CH$), 5.28 - 5.37 (m, 1 H, $NCHC\underline{H}{=}CH$), 5.43 (br. s, 1 H, $C{=}C\underline{H}_AH_B$), 5.53 (br. s, 1 H, $C{=}CH_A\underline{H}_B$), 5.73 - 5.90 (m, 2 H, $NCHCH{=}C\underline{H}$, $H_2C{=}C\underline{H}CH_2$), 7.49 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}$), 8.04 (d, *J* = 8.5 Hz, 2 H, $Ar\underline{H}$); **^{13}C**

NMR (125 MHz, $CDCl_3$) δ_C 26.1 (CCH$\underline{C}H_2$), 26.3 (H_2C=CH(CH_2)$_2\underline{C}H_2$), 26.4 (NCHCH=CH$\underline{C}H_2$), 26.6 (CH_2=CHC$H_2\underline{C}H_2$), 27.6 (CH=CHC$H_2\underline{C}H_2$), 29.7 (CHNC$H_2\underline{C}H_2$), 33.4 (H_2C=CH$\underline{C}H_2$), 36.1 (NCH$\underline{C}H_2$), 40.8 (CHN$\underline{C}H_2$), 46.1 (C$\underline{C}$HCH_2), 47.6 (N$\underline{C}H_2CH_2CH$), 48.5 (N$\underline{C}H_2$(CH_2)$_3$CH=CH_2), 52.2 (COO$\underline{C}H_3$), 52.8 (N$\underline{C}$HCH=CH), 57.5 (NC(O)$\underline{C}$C(O)N), 114.6 ($H_2\underline{C}$=CH), 118.5 (C=$\underline{C}H_2$), 125.9 (Ar$\underline{C}$), 129.5 (CH$\underline{C}$=CH_2), 129.6 (NCH$\underline{C}$H=CH), 129.9 (Ar$\underline{C}$), 134.3 (NCHCH=$\underline{C}$H), 138.6 (H_2C=$\underline{C}$H), 147.5 (Ar$\underline{C}_{quat}$), 147.7 (Ar$\underline{C}_{quat}$), 166.6 ($\underline{C}$=O), 169.5 ($\underline{C}$=O), 171.2 ($\underline{C}$=O); ***m/z*** (ESI^+) 491 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{30}H_{39}N_2O_4$) requires *m/z* 490.2832, found *m/z* 490.2833.

305b: $[\alpha]_D^{24}$ = −16.4 (c = 0.22, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2979 (C-H), 1777 (C=O), 1625 (C=C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 0.93 - 1.04 (m, 1 H, CHCH=CHCH_2C$\underline{H}_A$$H_B$), 1.37 - 1.46 (m, 3 H, CH_2=CHCH_2C$\underline{H}_2$, CHCH=CHCH_2C$H_A\underline{H}_B$), 1.51 - 1.72 (m, 4 H, CH_2=CH(CH_2)$_2$C$\underline{H}_2$, CHNCH_2C$\underline{H}_2$), 1.81 - 1.95 (m, 1 H, NCH_2C$\underline{H}_A$$H_B$CH), 1.96 - 2.12 (m, 3 H, CHCH=CHC$\underline{H}_A$$H_B$, CH_2=CHC$\underline{H}_2$), 2.14 - 2.22 (m, 2 H, NCH_2C$H_A\underline{H}_B$CH, NCHC$\underline{H}_A$$H_B$), 2.42 - 2.52 (m, 2 H, NCHC$H_A\underline{H}_B$, CHCH=CHC$H_A\underline{H}_B$), 2.53 - 2.68 (m, 1 H, CHNC$\underline{H}_A$$H_B$), 3.33 - 3.46 (m, 4 H, CH_2=CH(CH_2)$_3$C$\underline{H}_2$, NC$\underline{H}_A$$H_B$$CH_2$CH, CHNC$H_A\underline{H}_B$), 3.59 (ddd, *J* = 11.5, 11.5, 4.0 Hz, 1 H, NC$H_A\underline{H}_B$$CH_2$CH), 3.73 (dd, *J* = 11.5, 1.5 Hz, 1 H, C_{quat}C$\underline{H}$), 3.84 (q, *J* = 7.5 Hz, 1 H, NC$\underline{H}$), 3.91 (s, 3 H, COOC$\underline{H}_3$), 4.92 - 5.05 (m, 2 H, C$\underline{H}_2$=CH), 5.22 (s, 1 H, C_{quat}=C$\underline{H}_A$$H_B$), 5.41 - 5.50 (m, 1 H, NCHC$\underline{H}$=CH), 5.54 (s, 1 H, C_{quat}=C$H_A\underline{H}_B$), 5.71 - 5.87 (m, 2 H, NCHCH=C$\underline{H}$, CH_2=C$\underline{H}$), 7.45 - 7.51 (m, 2 H, Ar$\underline{H}$), 7.99 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 25.5 (CHCH=CH$\underline{C}H_2$, NC$H_2\underline{C}H_2$CH), 25.6 (CHNC$H_2\underline{C}H_2$), 26.1 (CH_2=CHC$H_2\underline{C}H_2$), 26.3 (CH_2=CH(CH_2)$_2\underline{C}H_2$), 27.1 (CHNCH_2C$H_2\underline{C}H_2$), 33.4 (CH_2=CH$\underline{C}H_2$), 34.8 (NCH$\underline{C}H_2$), 41.5 ($C_{quat}\underline{C}$H), 41.6 (CHN$\underline{C}H_2$), 46.4 (N$\underline{C}H_2CH_2CH$), 47.9 (CH_2=CH(CH_2)$_3\underline{C}H_2$), 52.1 (COO$\underline{C}H_3$), 55.0 (N$\underline{C}$H), 57.3 ($\underline{C}_{quat}$CH), 114.6 ($\underline{C}H_2$=CH), 117.5 (C=$\underline{C}H_2$), 126.6 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$, NCH$\underline{C}$H=CH), 133.3 (NCHCH=$\underline{C}$H), 138.6 (CH_2=$\underline{C}$H), 144.5 (Ar$\underline{C}_{quat}$), 148.3 (Ar$\underline{C}_{quat}$), 166.7 ($\underline{C}$OOMe), 170.7 (N$\underline{C}$=O), 172.4 (N$\underline{C}$=O); ***m/z*** (ESI^+) 491 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{33}H_{39}N_4O_2$) requires *m/z* 490.2832, found *m/z* 490.2833.

(3*R*,4*S*,9'*Z*,10a'*R*)-4-[1-(9*H*-β-Carbolin-1-yl)vinyl]-1-(hex-5-en-1-yl)-1',5',6',7',8',10a'-hexahydro-2H-spiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocine]-2,3'-dione (263a)

(3*R*,4*R*,9'*Z*,10a'*R*)-4-[1-(9*H*-β-Carbolin-1-yl)vinyl]-1-(hex-5-en-1-yl)-1',5',6',7',8',10a'-hexahydro-2H-spiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocine]-2,3'-dione (263b)



265 **264** **263a** **263b**

To amide **265** (1.5 eq, 0.14 mmol, 50 mg) was added LHMDS (1.5 eq, 0.14 mmol, 0.9 M soln. in hexanes, 0.15 mL) dropwise and the resulting mixture was stirred for 5 min. To the solution was added a suspension of $Pd(dppf)Cl_2$ (10 mol%, 0.009 mmol, 7 mg) and β-carboline **264** (1.0 eq, 0.093 mmol, 27 mg) in 1,4-dioxane (1.5 mL/mmol **265**, 0.31 mL) and the resulting mixture was stirred at 95 °C. After 16 h, the reaction mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc) to yield the title compound **263** (30 mg, 62%, dr 3:2 **263a**:**263b**) as a yellow oil. The two diastereomers were separated by preparative HPLC (AGILENT reverse phase Kromasil 100-3.5C18 150 × 4.6 mm ramp mode of eluent MeCN:MeOH:H_2O 38:38:24 to MeCN:MeOH 50:50, wavelength 254 nm, flow 1.0 mL/min) to yield **263a** and **263b** in 37% and 25% respectively as white solids.

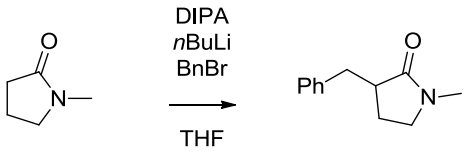
263a: **m.p.** 82 – 84 °C; $[\alpha]_D^{24}$ = −24.1 (c = 0.40, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2929 (C-H), 2858 (C-H), 1662 (C=O), 1625 (C=C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.04 - 1.14 (m, 1 H, $HCNCH_2CH_2C\underline{H}_AH_B$), 1.25 - 1.34 (m, 1 H, $HCNCH_2C\underline{H}_AH_B$), 1.35 - 1.49 (m, 3 H, $HCNCH_2CH_A\underline{H}_B$, CH_2=$CHCH_2C\underline{H}_2$), 1.50 - 1.65 (m, 3 H, CH_2=$CH(CH_2)_2C\underline{H}_2$, CH=$CHC\underline{H}_AH_B$), 1.88 - 1.94 (m, 2 H, $NCH_2C\underline{H}_AH_BCH$, $HCNCH_2CH_2CH_A\underline{H}_B$), 2.01 - 2.13 (m, 4 H, $C_{quat}C\underline{H}_AH_BCH$, CH=$CHCH_A\underline{H}_B$, CH_2=$CHC\underline{H}_2$), 2.50 (dd, *J* = 13.0, 6.5 Hz, 1 H, $C_{quat}CH_A\underline{H}_BCH$), 2.98 - 3.08 (m, 1 H, $HCNC\underline{H}_AH_B$), 3.05 - 3.87 (m, 1 H, $NCH_2CH_A\underline{H}_BCH$), 3.25 - 3.33 (m, 1 H, CH_2=$CH(CH_2)_3C\underline{H}_AH_B$), 3.36 - 3.45 (m,

1 H, NC$\underline{H}_A$H$_B$CH$_2$CH), 3.46 - 3.59 (m, 3 H, NC$\underline{H}$CH=CH, NCH$_A\underline{H}_B$CH$_2$CH, CH$_2$=CH(CH$_2$)$_3$CH$_A\underline{H}_B$), 3.60 - 3.69 (m, 1 H, CHNCH$_A\underline{H}_B$), 3.89 (dd, *J* = 13.0, 2.5 Hz, 1 H, CC$\underline{H}$C), 4.92 - 5.04 (m, 2 H, CH$_2$CH=C$\underline{H}_2$), 5.29 (dd, *J* = 10.0, 8.0 Hz, 1 H, NCHC$\underline{H}$=CH), 5.70 (d, *J* = 10.0 Hz, 1 H, NCHCH=C$\underline{H}$), 5.75 - 5.84 (m, 1 H, CH$_2$C$\underline{H}$=CH$_2$), 5.87 (br. s, 1 H, CHC=C$\underline{H}_A$H$_B$), 5.89 (br. s, 1 H, CHC=CH$_A\underline{H}_B$), 7.32 (t, *J* = 7.5 Hz, 1 H, Ar$\underline{H}$), 7.49 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 7.55 - 7.60 (m, 1 H, Ar$\underline{H}$), 7.91 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$), 8.15 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 8.48 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$), 8.73 (br. s, 1 H, N$\underline{H}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 25.5 (NCH$_2\underline{C}$H$_2$CH), 26.1 (NCHCH=CH$\underline{C}$H$_2$), 26.4 (CH$_2$=CH(CH$_2$)$_2\underline{C}$H$_2$), 27.1 (HCNCH$_2$CH$_2\underline{C}$H$_2$), 28.2 (HCNCH$_2\underline{C}$H$_2$), 33.4 (CH$_2$=CH$\underline{C}$H$_2$), 37.1 (C$\underline{C}$H$_2$CH), 40.7 (CHN$\underline{C}$H$_2$), 44.3 (C$\underline{C}$HC), 47.3 (N$\underline{C}$H$_2$CH$_2$CH), 48.4 (CH$_2$=CH(CH$_2$)$_3\underline{C}$H$_2$), 52.8 (N$\underline{C}$H), 56.7 ($\underline{C}_{quat}$CH), 111.4 (Ar$\underline{C}$), 113.8 (Ar$\underline{C}$), 114.7 ($\underline{C}$H$_2$=CH), 118.7 ($\underline{C}$H$_2$=C$_{quat}$), 120.1 (Ar$\underline{C}$), 128.6 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$), 129.7 (Ar$\underline{C}$), 129.9 (NCH$\underline{C}$H=CH), 133.7 (NCHCH=$\underline{C}$H), 138.5 (Ar$\underline{C}$), 138.6 (CH$_2$=$\underline{C}$H), 140.3 (Ar$\underline{C}$), 143.8 (Ar$\underline{C}_{quat}$), 147.2 (CH$_2$=$\underline{C}$CH), 170.5 ($\underline{C}$=O), 172.3 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 523 (100%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{33}H_{39}N_4O_2$) requires *m/z* 523.3068, found *m/z* 523.3075.

263b: **m.p.** 79 – 81 °C; **[α]$_D^{24}$** = −4.7 (c = 0.70, CHCl$_3$); **IR** ν_{max}(film)/cm^{-1} 2929 (C-H), 2858 (C-H), 1662 (C=O), 1625 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 1.04 - 1.14 (m, 1 H, HCNCH$_2$C$\underline{H}_A$H$_B$), 1.19 (dd, *J* = 13.0, 8.0 Hz, 1 H, C$_{quat}$C$\underline{H}_A$CH$_B$CH), 1.35 - 1.51 (m, 3 H, CH$_2$=CHCH$_2$C$\underline{H}_2$, CHNCH$_2$CH$_2$C$\underline{H}_A$H$_B$), 1.52 - 1.68 (m, 4 H, HCNCH$_2$C$\underline{H}_2$, CH$_2$=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.77 - 1.87 (m, 1 H, CHNCH$_2$CH$_2$CH$_A$C$\underline{H}_B$), 1.93 - 2.11 (m, 5 H, NCH$_2$C$\underline{H}_A$H$_B$CH, CH$_2$=CHC$\underline{H}_2$, CH=CHCH$_2$), 2.32 (dd, *J* = 13.0, 7.5 Hz, 1 H, C$_{quat}$CH$_A$C$\underline{H}_B$CH), 2.57 - 2.59 (m, 1 H, CHNC$\underline{H}_A$H$_B$), 3.14 - 3.24 (m, 2 H, NCH$_2$CH$_A\underline{H}_B$, NC$\underline{H}_A$CH$_B$CH$_2$CH), 3.46 - 3.62 (m, 3 H, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_2$, NCH$_A$C$\underline{H}_B$CH$_2$CH), 3.68 (dd, *J* = 13.0, 2.5 Hz, 1 H, C$_{quat}$C$\underline{H}$), 3.76 (dd, *J* = 9.0, 9.0 Hz, 1 H, NCHC$\underline{H}$=CH), 3.93 (dd, *J* = 13.5, 9.0 H, 1 H, CHNCH$_A\underline{H}_B$), 4.46 (q, *J* = 8.0 Hz, 1 H, NC$\underline{H}$CH=CH), 4.93 - 5.04 (m, 2 H, CH=C$\underline{H}_2$), 5.25 - 5.33 (m, 1 H, NCHCH=C$\underline{H}$), 5.75 - 5.84 (m, 2 H, C$_{quat}$=C$\underline{H}_A$H$_B$, C$\underline{H}$=CH$_2$), 5.91 (br. s, 1 H, C$_{quat}$=CH$_A\underline{H}_B$), 7.30 (t, *J* = 7.5 Hz, 1 H, Ar$\underline{H}$), 7.45 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 7.53 - 7.58 (m, 1 H, Ar$\underline{H}$), 7.89 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$), 8.13 (d, *J* = 8.0 Hz, 1

H, Ar*H*), 8.46 (d, *J* = 5.5 Hz, 1 H, Ar*H*), 8.66 (br. s, 1 H, N*H*); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 25.7 ($NCH_2\underline{C}H_2CH$), 25.9 (CH_2=$CHCH_2\underline{C}H_2$), 26.1 (CH_2=$CH(CH_2)_2\underline{C}H_2$), 26.4 (NCHCH=$CH\underline{C}H_2$), 27.1 ($HCNCH_2CH_2\underline{C}H_2$), 28.1 ($HCNCH_2\underline{C}H_2$), 33.4 ($CH_2$=$CH\underline{C}H_2$), 36.7 ($C\underline{C}H_2CH$), 40.9 ($CHN\underline{C}H_2$), 44.3 ($C\underline{C}HC$), 47.9 ($N\underline{C}H_2CH_2CH$), 48.5 ($CH_2$=$CH(CH_2)_3\underline{C}H_2$), 52.8 ($N\underline{C}H$), 57.6 ($\underline{C}_{quat}CH$), 111.4 (Ar*C*), 114.0 (Ar*C*), 114.6 ($\underline{C}H_2$=CH), 118.6 (Ar*C*), 120.4 (Ar*C*), 121.8 (Ar*C*), 128.8 (NCH*C*H=CH), 129.5 (Ar*C*), 129.7 (Ar*C*), 129.8 (Ar*C*), 133.4 (Ar*C*), 133.7 (NCHCH=*C*H), 138.6 (Ar*C*), 138.6 (CH_2=*C*H), 139.9 (Ar*C*), 145.1 ($Ar\underline{C}_{quat}$), 146.4 (CH_2=*C*CH), 170.1 (*C*=O), 172.2 (*C*=O); ***m/z*** (ESI^+) 523 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{33}H_{39}N_4O_2$) requires *m/z* 523.3068, found *m/z* 523.3075.

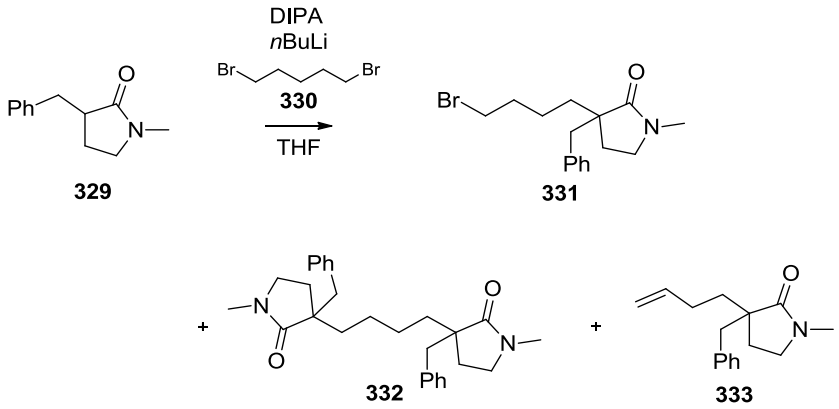
3-Benzyl-1-methylpyrrolidin-2-one (329)



327 **329**

To diisopropylamine (1.05 eq, 53.0 mmol, 7.44 mL) in tetrahydrofuran (270 mL) was added *n*BuLi (1.05 eq, 53.0 mmol, 1.6 M in hexanes, 33.0 mL) slowly *via* syringe pump over 1.5 h at −78 ˚C. The reaction mixture was warmed to 0 ˚C and stirred for 15 min before being cooled to −78 ˚C. *N*-methyl pyrrolidinone **327** (1.00 eq, 50.5 mmol, 4.86 mL) was added at −78 ˚C followed by the addition of benzyl bromide after 1 h (1.01 eq, 51.0 mmol, 6.10 mL). The reaction mixture was warmed to RT and stirred for 16 h. The tetrahydrofuran was removed under reduced pressure and the crude reaction mixture was redissolved in dichloromethane (200 mL). Ammonium chloride (saturated aqueous, 100 mL) was added and the organic and aqueous layers were separated. The aqueous layer was extracted (dichloromethane, 3 × 50 mL) and the combined organics were washed (brine, 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc → 1:10 MeOH:EtOAc) to yield the title compound **329** (8.41 g, 88%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 3026 (C-H), 2923 (C-H), 1684 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.64 - 1.76 (m, 1 H, $NCH_2C\underline{H}_AH_B$), 1.92 - 2.06 (m, 1 H, $NCH_2CH_A\underline{H}_B$), 2.59 - 2.73 (m, 2 H, C*H*, $PhC\underline{H}_AH_B$), 2.79 (s, 3 H, $NC\underline{H}_3$), 3.01 - 3.10 (m, 1 H, $NC\underline{H}_AH_B$), 3.12 - 3.23 (m, 2 H, $NCH_A\underline{H}_B$, $CHCH_A\underline{H}_B$), 7.12 - 7.30 (m, 5 H, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.4 ($NCH_2\underline{C}H_2$), 30.1 ($N\underline{C}H_3$), 37.5 ($Ph\underline{C}H_2$), 43.8 ($\underline{C}H$), 47.9 ($N\underline{C}H_2$), 126.6 (Ar*C*), 128.7 (Ar*C*), 129.3 (Ar*C*), 139.8 ($Ar\underline{C}_{quat}$), 176.2 (*C*=O); ***m/z*** (ESI$^+$) 190 (50%, $[M+H]^+$), 212 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{15}NNaO$) requires *m/z* 212.1046, found *m/z* 212.1046. Data are in agreement with literature.[205]

3-Benzyl-3-(4-bromobutyl)-1-methylpyrrolidin-2-one (331), **3,3'-butane-1,4-diylbis(3-benzyl-1-methyl pyrrolidin-2-one) (332)** and **3-benzyl-3-(but-3-en-1-yl)-1-methylpyrrolidin-2-one (333)**



To lithium bis(trimethylsilyl)amide (1.2 eq, 19.3 mmol, 1.0 M in THF, 19.3 mL) was added lactam **329** (1.0 eq, 16.1 mmol, 3.04 g) in tetrahydrofuran (0.95 mL/mmol **329**, 15.2 mL) dropwise at −78 ˚C. After 1 h, 1,4-dibromobutane **330** (2.0 eq, 32.2 mmol, 3.84 mL) was added in one portion and the reaction mixture was warmed to RT. Ethyl acetate (30 mL) and water (40 mL) were added and the layers were separated. The aqueous layer was extracted (EtOAc, 2 × 30 mL) and the combined organics were washed (brine, 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc → 1:10 MeOH:EtOAc) to yield the title compound **331** (1.45 g, 30%), **332** (2.43 g, 35%), and **333** (0.39 g, 10%) as pale yellow oils.

331: **IR** ν_{max}(film)/cm^{-1} 3061 (C-H), 2974 (C-H), 1663 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.30 - 1.42 (m, 1 H, $BrCH_2CH_2C\underline{H}_AH_B$), 1.49 - 1.68 (m, 3 H, $BrCH_2CH_2CH_A\underline{H}_B$, $BrCH_2C\underline{H}_2$), 1.81 - 2.01 (m, 4 H, $NCH_2C\underline{H}_2$, $CC\underline{H}_2(CH_2)_3$), 2.18 (td, *J* = 8.5, 8.0 Hz, 1 H, $NC\underline{H}_AH_B$), 2.58 (d, *J* = 13.0 Hz, 1 H, $C\underline{H}_AH_BPh$), 2.65 (s, 3 H, $NC\underline{H}_3$), 2.85 - 3.06 (m, 2 H, $CH_A\underline{H}_BPh$, $NCH_A\underline{H}_B$), 3.33 - 3.49 (m, 2 H, $BrC\underline{H}_2$), 7.11 - 7.25 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 23.0 ($Br(CH_2)_2\underline{C}H_2$), 26.8 ($C\underline{C}H_2(CH_2)_3$), 29.6 ($N\underline{C}H_3$), 33.0 ($NCH_2\underline{C}H_2$), 33.7 ($Br\underline{C}H_2$), 37.1 ($BrCH_2\underline{C}H_2$), 43.5 ($\underline{C}H_2Ph$), 46.4 ($N\underline{C}H_2$), 49.3 ($\underline{C}_{quat}$), 126.6 (Ar$\underline{C}$), 128.0 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$), 137.6 (Ar$\underline{C}_{quat}$), 177.3 ($\underline{C}O$); ***m/z*** ($ESI^+$) 324 (30%, $[M+H]^+$), 346 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for

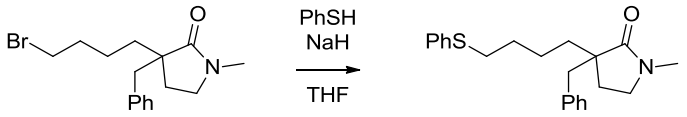
$[M+Na]^+$ ($C_{16}H_{22}BrNNaO$) requires *m/z* 346.0777 and 348.0757, found *m/z* 346.0778 and 348.0756.

332: IR ν_{max}(film)/cm^{-1} 2935 (C-H), 1672 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.22 (dd, *J* = 7.0 Hz, 3.5 Hz, 2 H, 2 × $CCH_2C\underline{H}_AH_B$), 1.35 (dd, *J* = 7.0, 3.5 Hz, 2 H, 2 × $CCH_2CH_A\underline{H}_B$), 1.50 - 1.55 (m, 2 H, 2 × $CC\underline{H}_AH_BCH_2$), 1.57 - 1.61 (m, 2 H, 2 × $CCH_A\underline{H}_BCH_2$), 1.79 - 1.97 (m, 4 H, 2 × $NCH_2C\underline{H}_2$), 2.16 - 2.28 (m, 2 H, 2 × $NC\underline{H}_AH_B$), 2.54 (d, *J* = 13.0 Hz, 2 H, 2 × $C\underline{H}_AH_BPh$) 2.65 (s, 6 H, 2 × $NC\underline{H}_3$), 2.85 - 3.02 (m, 4 H, 2 × $CH_A\underline{H}_BPh$, 2 × $NCH_A\underline{H}_B$), 7.09 - 7.30 (m, 10 H, Ar<u>*H*</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.9 (2 × $CCH_2\underline{C}H_2$), 26.6 (2 × $NCH_2\underline{C}H_2$), 29.5 (2 × $N\underline{C}H_3$), 38.2 (2 × $C\underline{C}H_2CH_2$), 43.8 (2 × $\underline{C}H_2Ph$), 46.5 (2 × $N\underline{C}H_2$), 49.4 (2 × $\underline{C}CH_2$), 126.5 (2 × Ar<u>*C*</u>), 127.9 (2 × Ar<u>*C*</u>), 129.9 (4 × Ar<u>*C*</u>), 137.8 (2 × Ar$\underline{C}_{quat}$), 177.6 (2 × $\underline{C}$=O);[xxiii] ***m/z*** (ESI^+) 433 (50%, $[M+H]^+$), 455 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{28}H_{37}N_2O_2$) requires *m/z* 433.2850, found *m/z* 433.2835.

333: IR ν_{max}(film)/cm^{-1} 3063 (C-H), 2919 (C-H), 1677 (C=O), 1603 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.59 - 1.68 (m, 1 H, $CC\underline{H}_AH_BCH_2$), 1.72 - 1.82 (m, 1 H, $CCH_A\underline{H}_BCH_2$), 1.84 - 1.93 (m, 1 H, $(H_3C)NCH_2C\underline{H}_AH_B$), 1.96 (dd, *J* = 9.0, 4.0 Hz, 1 H, $NCH_2CH_A\underline{H}_B$), 1.98 - 2.18 (m, 2 H, CH_2=$CHC\underline{H}_2$), 2.19 - 2.28 (m, 1 H, $NC\underline{H}_AH_B$), 2.60 (d, *J* = 13.0 Hz, 1 H, $C\underline{H}_AH_BPh$), 2.66 (s, 3 H, $NC\underline{H}_3$), 2.94 (td, *J* = 9.0, 4.0 Hz, 1 H, $NCH_A\underline{H}_B$), 3.01 (d, *J* = 13.0 Hz, 1 H, $CH_A\underline{H}_BPh$), 4.92 - 5.08 (m, 2 H, $C\underline{H}_2$=CH), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1 H, CH_2=$C\underline{H}$), 7.13 - 7.28 (m, 5 H, Ar<u>*H*</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 26.8 ($NCH_2\underline{C}H_2$), 28.8 (CH_2=$CH\underline{C}H_2$), 29.6 ($N\underline{C}H_3$), 37.3 ($C\underline{C}H_2CH_2$), 43.5 ($\underline{C}H_2Ph$), 46.4 ($N\underline{C}H_2$), 49.2 ($\underline{C}(CH_2)_2$), 114.6 ($\underline{C}H_2$=CH), 126.6 (Ar<u>*C*</u>), 128.0 (Ar<u>*C*</u>), 129.9 (Ar<u>*C*</u>), 137.7 (Ar$\underline{C}_{quat}$), 138.3 (CH_2=$\underline{C}$H), 177.4 ($\underline{C}$=O); ***m/z*** (ESI+) 244 (50%, $[M+H]^+$), 266 (90, $[M+Na]^+$); HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}NO$) requires m/z 244.1696, found m/z 244.1697.

[xxiii] The inconsistency in style is due to the symmetric nature of compound **332**.

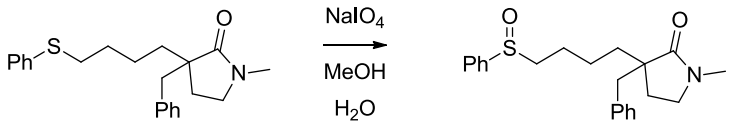
3-Benzyl-1-methyl-3-[4-(phenylthio)butyl]pyrrolidin-2-one (334)



331 **334**

To a slurry of sodium hydride (1.1 eq, 0.51 mmol, 60% dispersion in mineral oil, 0.020 g) in tetrahydrofuran (2.6 mL/mmol bromide **331**, 1.2 mL) was added thiophenol (1.1 eq, 0.51 mmol, 0.05 mL) dropwise at 0 ˚C. After 30 min, bromide **331** (1.0 eq, 0.46 mmol, 0.15 g) in tetrahydrofuran (1.1 mL/mmol **331**, 0.50 mL) was added and the reaction mixture was stirred for 7 h at RT. Water (10 mL) was added slowly followed by ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted (EtOAc, 2 × 15 mL). The combined organics were washed (brine, 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:3 EtOAc:PE → 1:1 EtOAc:PE) to yield the title compound **334** (0.13 mg, 91%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 3059 (C-H), 2935 (C-H), 1683 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.30 - 1.40 (m, 1 H, $PhSCH_2CH_2C\underline{H}_A\underline{H}_B$), 1.46 - 1.75 (m, 5 H, $C_{quat}C\underline{H}_2$, $PhSCH_2C\underline{H}_2CH_A\underline{H}_B$), 1.81 - 1.89 (m, 1 H, $NCH_2C\underline{H}_A\underline{H}_B$), 1.91 - 1.99 (m, 1 H, $NCH_2CH_A\underline{H}_B$), 2.18 - 2.25 (m, 1 H, $NC\underline{H}_A\underline{H}_B$), 2.58 (d, *J* = 13.0 Hz, 1 H, $C\underline{H}_A\underline{H}_BPh$), 2.66 (s, 3 H, $NC\underline{H}_3$), 2.86 - 3.02 (m, 4 H, $PhSC\underline{H}_2$, $CH_A\underline{H}_BPh$, $NCH_A\underline{H}_B$), 7.10 - 7.36 (m, 10 H, $Ar\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 23.6 ($C_{quat}CH_2\underline{C}H_2$), 26.8 ($NCH_2\underline{C}H_2$), 29.6 ($C_{quat}\underline{C}H_2(CH_2)_3$, $N\underline{C}H_3$), 33.4 ($\underline{C}H_2SPh$), 37.6 ($PhSCH_2\underline{C}H_2$), 43.5 ($\underline{C}H_2Ph$), 46.4 ($N\underline{C}H_2$), 49.3 ($\underline{C}_{quat}$), 125.7 ($Ar\underline{C}$), 126.5 ($Ar\underline{C}$), 128.0 ($Ar\underline{C}$), 128.8 ($Ar\underline{C}$), 129.0 ($Ar\underline{C}$), 129.9 ($Ar\underline{C}$), 136.7 ($Ar\underline{C}_{quat}$), 137.7 ($Ar\underline{C}_{quat}$), 177.5 ($\underline{C}$=O); m/z (ESI+) 354 (50%, $[M+H]^+$), 376 (100, $[M+Na]^+$); HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{27}NSONa$) requires m/z 376.1706, found m/z 376.1701.

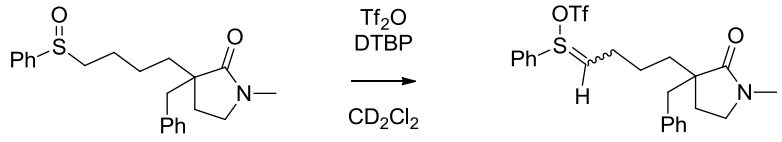
3-Benzyl-1-methyl-3-[4-(phenylsulfinyl)butyl]pyrrolidin-2-one (335)



334 **335**

To a solution of $NaIO_4$ (1.1 eq, 1.4 mmol, 0.29 g) in H_2O (1.5 mL/mmol **334**, 1.8 mL) was added a solution of sulfide **334** (1.0 eq, 1.2 mmol, 0.43 g) in methanol (4.1 mL/mmol **334**, 5.0 mL) dropwise at 0 ˚C. After 6 h, the colourless solid was filtered and washed with ethyl acetate (30 mL). The colourless solid was stirred in ethyl acetate (15 mL) for 15 min, filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:10 MeOH:EtOAc) to yield the title compound **335** (0.42 g, 93%, dr 1:1) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 2921 (C-H), 1672 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.25 - 1.39 (m, 1 H, S(O)$(CH_2)_2$C$\underline{H}_A$H$_B$), 1.41 - 1.66 (m, 4 H, C_{quat}C$\underline{H}_A$H$_B$, S(O)CH_2C$\underline{H}_2$, S(O)$(CH_2)_2$C$H_A\underline{H}_B$), 1.69 - 1.85 (m, 2 H, $C_{quat}CH_A\underline{H}_B$, NCH_2C$\underline{H}_AH_B$), 1.87 - 1.98 (m, 1 H, $NCH_2CH_A\underline{H}_B$), 2.09 - 2.20 (m, 1 H, NC$\underline{H}_A$H$_B$), 2.51 (d, *J* = 13.0 Hz, 1 H, C$\underline{H}_A$H$_B$Ph) 2.60 (s, 3 H, C$\underline{H}_3$ DS1), 2.61 (s, 3 H, C$\underline{H}_3$ DS2), 2.71 - 2.98 (m, 4 H, $CH_A\underline{H}_B$Ph, $NCH_A\underline{H}_B$, C$\underline{H}_2$S(O)Ph), 7.07 - 7.24 (m, 5 H, Ar$\underline{H}$), 7.41 - 7.67 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 22.7 ($C_{quat}CH_2\underline{C}H_2$ DS1), 23.0 ($C_{quat}CH_2\underline{C}H_2$ DS2), 23.8 ($C_{quat}\underline{C}H_2$ DS1), 24.0 ($C_{quat}\underline{C}H_2$ DS2), 27.1 ($NCH_2\underline{C}H_2$ DS1), 27.3 ($NCH_2\underline{C}H_2$ DS2), 30.0 (N$\underline{C}H_3$ both DS), 37.9 ($C_{quat}CH_2CH_2\underline{C}H_2$ DS1), 38.0 ($C_{quat}CH_2CH_2\underline{C}H_2$ DS2), 43.8 ($C_{quat}\underline{C}H_2$Ph DS1), 44.1 ($C_{quat}\underline{C}H_2$Ph DS2), 46.8 (N$\underline{C}H_2$ both DS), 49.6 ($\underline{C}_{quat}CH_2$ of both DS), 57.2 ($\underline{C}H_2$SOPh DS1), 57.3 ($\underline{C}H_2$SOPh DS2), 124.4 (Ar$\underline{C}$), 127.0 (Ar$\underline{C}$), 128.4 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$), 130.2 (Ar$\underline{C}$), 131.3 (Ar$\underline{C}$), 137.9 (Ar$\underline{C}_{quat}$), 144.2 (Ar$\underline{C}_{quat}$ DS1), 144.3 (Ar$\underline{C}_{quat}$ DS2), 177.7 ($\underline{C}$=O of both DS); ***m/z*** (ESI$^+$) 370 (15%, $[M+H]^+$), 392 (100, $[M+Na]^+$) 761, (100, $[2M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{27}NNaSO_2$) requires *m/z* 392.1655, found *m/z* 392.1651.

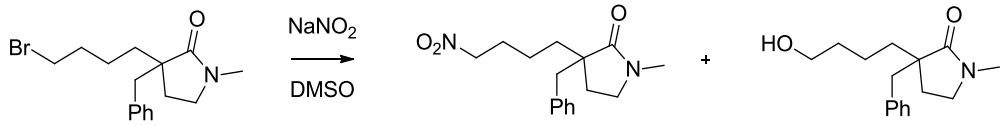
3-Benzyl-3-{(4*Z*)-4-[3,3-dioxido-1-phenyl-3-(trifluoromethyl)-1λ^4,3λ^6-dithioxan-1-ylidene] butyl}-1-methylpyrrolidin-2-one (348)



335 **348**

To sulfone **335** (1.0 eq, 0.14 mmol, 50 mg) in CD_2Cl_2 (10 mL/g **335**, 0.50 mL) was added 2,6-di-*tert*-butylpyridine (1.2 eq, 0.16 mmol, 36 µL) and trifluoromethanesulfonic anhydride (1.2 eq, 0.16 mmol, 28 µL) at −78 ˚C. After 2 h, the reaction mixture was analysed by ^{1}H NMR spectroscopy and full conversion to the product **348** as a 1:1 mixture of *E*/*Z* isomers was observed. **IR** ν_{max}(film)/cm^{-1} 2974 (C-H), 1777 (C=O), 1663 (C=C); **^{1}H NMR** (400 MHz, CD_2Cl_2) δ_H 1.36 - 1.71 (m, 4 H, $C_{quat}CH_2C\underline{H}_2$, $C_{quat}C\underline{H}_2CH_2$), 1.82 - 2.05 (m, 4 H, $CHC\underline{H}_2$, $NCH_2C\underline{H}_2$), 2.26 (dt, *J* = 15.5, 8.0 Hz, 1 H, $NC\underline{H}_AH_B$), 2.61 (d, *J* = 13.0 Hz, 1 H, $C_{quat}C\underline{H}_AH_BPh$), 2.67 (s, 3 H, $NC\underline{H}_3$), 2.93 - 3.01 (m, 2 H, $NCH_A\underline{H}_B$, $C_{quat}CH_A\underline{H}_BPh$), 6.23 (q, *J* = 7.0 Hz, 1 H, TfOS=C$\underline{H}$), 7.16 - 7.21 (m, 1 H, Ar$\underline{H}$), 7.24 - 7.31 (m, 2 H, Ar$\underline{H}$), 7.36 - 7.49 (m, 4 H, Ar$\underline{H}$), 7.54 - 7.58 (m, 2 H, Ar$\underline{H}$), 7.93 (t, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ_C 20.9 ($C_{quat}CH_2\underline{C}H_2$ DS1), 21.0 ($C_{quat}CH_2\underline{C}H_2$ DS2), 27.1 ($CH\underline{C}H_2$ DS1), 27.2 ($CH\underline{C}H_2$ DS2), 29.8 ($N\underline{C}H_3$ both DS), 34.6 ($NCH_2\underline{C}H_2$ both DS), 37.7 ($C_{quat}\underline{C}H_2$ both DS), 43.6 ($\underline{C}H_2Ph$ DS1), 43.7 ($\underline{C}H_2Ph$ DS2), 46.9 ($N\underline{C}H_2$ both DS), 49.7 ($\underline{C}_{quat}CH_2$ DS1), 49.8 ($\underline{C}_{quat}CH_2$ DS2), 85.9 (S=$\underline{C}$H DS1), 86.0 (S=$\underline{C}$H DS2), 118.5 (Ar$\underline{C}$), 127.0 (Ar$\underline{C}$), 128.4 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$), 129.7 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$), 130.2 (Ar$\underline{C}$), 135.2 (Ar$\underline{C}$), 135.3 (Ar$\underline{C}$), 137.9 (Ar$\underline{C}_{quat}$), 141.2 (Ar$\underline{C}_{quat}$), 177.7 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 370 (50%, [M-OTf+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{23}H_{27}F_3NO_4S_2$) requires *m/z* 502.1328, found *m/z* 502.1333.

3-Benzyl-1-methyl-3-(4-nitrobutyl)pyrrolidin-2-one (336) and **3-Benzyl-3-(4-hydroxy butyl)-1-methylpyrrolidin-2-one (337)**



331 **336** **337**

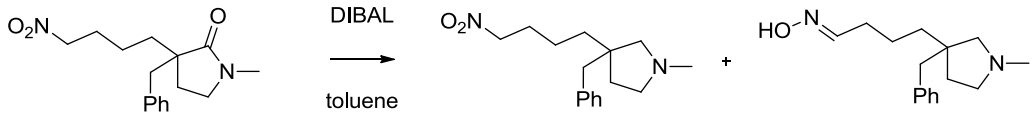
To a solution of bromide **331** (1.0 eq, 4.47 mmol, 1.45 g) in dimethylsulfoxide (1.5 mL/mmol **331**, 6.7 mL) was added sodium nitrate (2.0 eq, 8.95 mmol, 0.61 g) at RT. After 2 h, the reaction mixture was partitioned between ethyl acetate (30 mL) and water (60 mL). The aqueous layer was extracted (EtOAc, 3 × 30 mL) and the combined organics were washed (water, 2 × 30 mL then brine, 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc → 1:10 MeOH:EtOAc) to yield compounds **336** and **337** in 54% and 32% respectively as pale yellow oils.

336: IR ν_{max}(film)/cm^{-1} 2915 (C-H), 1678 (C=O), 1549 (NO_2), 1333 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.27 - 1.40 (m, 1 H, $CCH_2C\underline{H}_AH_B$), 1.42 - 1.52 (m, 1 H, $CCH_2CH_A\underline{H}_B$), 1.52 - 1.62 (m, 1 H, $CC\underline{H}_AH_B$), 1.65 - 1.74 (m, 1 H, $CCH_A\underline{H}_B$), 1.77 - 1.88 (m, 1 H, $NCH_2C\underline{H}_AH_B$), 1.91 - 2.06 (m, 3 H, $NCH_2CH_A\underline{H}_B$, $NO_2CH_2C\underline{H}_2$), 2.13 - 2.21 (m, 1 H, $NC\underline{H}_AH_B$), 2.55 (d, *J* = 13.0 Hz, 1 H, $C\underline{H}_AH_BPh$), 2.64 (s, 3 H, $NC\underline{H}_3$), 2.86 - 2.91 (td, *J* = 9.0, 3.0 Hz, 1 H, $NCH_A\underline{H}_B$), 2.97 (d, *J* = 13.0 Hz, 1 H, $CH_A\underline{H}_BPh$), 4.32 - 4.45 (m, 2 H, $NO_2C\underline{H}_2$), 7.11 - 7.17 (m, 2 H, Ar$\underline{H}$), 7.19 - 7.29 (m, 3 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.3 ($CCH_2\underline{C}H_2$), 26.7 ($NCH_2\underline{C}H_2$), 27.7 ($NO_2CH_2\underline{C}H_2$), 29.6 ($N\underline{C}H_3$), 37.2 ($C\underline{C}H_2$), 43.6 ($\underline{C}H_2Ph$), 46.3 ($N\underline{C}H_2$), 49.2 ($\underline{C}_{quat}$), 75.4 ($NO_2\underline{C}H_2$), 126.7 (Ar$\underline{C}$), 128.0 (Ar$\underline{C}$), 129.8 (Ar$\underline{C}$), 137.4 (Ar$\underline{C}_{quat}$), 177.1 ($\underline{C}$=O); ***m/z*** (ESI^+) 291 (40%, $[M+H]^+$), 313 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}N_2NaO_3$) requires *m/z* 313.1523, found *m/z* 313.1515.

337: IR ν_{max}(film)/cm^{-1} 3430 (O-H, broad), 2940 (C-H), 1681 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.23 - 1.36 (m, 1 H, $CCH_2C\underline{H}_AH_B$), 1.40 - 1.50 (m, 1 H, $CCH_2CH_A\underline{H}_B$), 1.52 - 1.61 (m, 1 H, $CC\underline{H}_AH_B$), 1.63 - 1.78 (m, 3 H, $CCH_A\underline{H}_B$, $HOCH_2C\underline{H}_2$), 1.79 - 1.88 (m, 1 H, $NCH_2C\underline{H}_AH_B$), 1.90 -

1.98 (m, 1 H, $NCH_2CH_A\underline{H}_B$), 2.12 - 2.21 (m, 1 H, $NC\underline{H}_AH_B$), 2.55 (d, *J* = 13.0 Hz, 1 H, $C\underline{H}_AH_BPh$), 2.63 (s, 3 H, $NC\underline{H}_3$), 2.90 (td, *J* = 9.5, 3.5 Hz, 1 H, $NCH_A\underline{H}_B$), 2.97 (d, *J* = 13.0 Hz, 1 H, $CH_A\underline{H}_BPh$), 4.69 (br. s, 2 H, $HOC\underline{H}_2$), 7.10 - 7.15 (m, 2 H, Ar*H*), 7.17 - 7.26 (m, 3 H, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 20.8 ($CCH_2\underline{C}H_2$), 26.7 ($NCH_2\underline{C}H_2$), 29.4 ($N\underline{C}H_3$), 29.6 ($HOCH_2\underline{C}H_2$), 37.6 ($C\underline{C}H_2$), 43.6 ($\underline{C}H_2Ph$), 46.4 ($N\underline{C}H_2$), 49.4 (C_{quat}), 67.9 ($\underline{C}H_2OH$), 126.6 (Ar*C*), 128.0 (Ar*C*), 129.8 (Ar*C*), 137.5 ($Ar\underline{C}_{quat}$), 177.4 ($\underline{C}$=O); ***m/z*** (ESI^+) 284 (60%, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{23}NNaO_2$) requires *m/z* 284.1621, found *m/z* 284.1614.

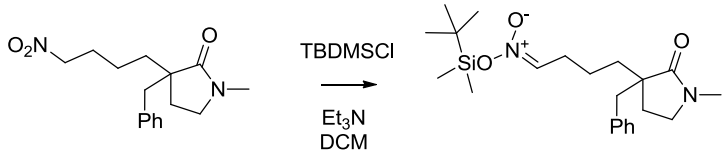
3-Benzyl-1-methyl-3-(4-nitrobutyl)pyrrolidine (353)



336 **353** **354**

To amide **336** (1 eq, 0.12 mmol, 43 mg) in toluene (20 mL/mmol **336**, 2.3 mL) was added DIBAL (1.45 eq, 0.23 mmol, 1.0 M in cyclohexanes, 0.23 mL) dropwise at −20 ˚C. After 45 min, methanol (0.5 mL) was added and the reaction was warmed to RT. After 20 min, $NaSO_4 \bullet 10H_2O$ (0.5 g) and diethyl ether (5 mL) were added to the reaction mixture at RT. After 1 h, the colourless solids were filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:4 EtOAc:PE → 1:1 EtOAc:PE → EtOAc → 1:5 MeOH:EtOAc) to yield starting material (11 mg, 35%) and a 3:1 mixture of **353** and **354** (15 mg, 45%) as pale yellow oils. **IR** ν_{max}(film)/cm^{-1} 2924 (C-H), 1543 (NO_2), 1336 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.23 - 1.35 (m, 2 H, $C_{quat}C\underline{H_2}CH_2CH_2$), 1.38 - 1.68 (m, 3 H, $C_{quat}CH_2C\underline{H_2}CH_2$, $NCH_2C\underline{H_A}H_B$), 1.83 (ddd, *J* = 13.0, 7.5, 6.0 Hz, 1 H, $NCH_2CH_A\underline{H_B}$), 1.91 - 2.05 (m, 2 H, $NO_2CH_2C\underline{H_2}$), 2.37 (s, 3 H, $NC\underline{H_3}$), 2.38 - 2.45 (m, 1 H, $NC\underline{H_A}H_BC_{quat}$), 2.53 - 2.76 (m, 5 H, $NCH_A\underline{H_B}C_{quat}$, $C\underline{H_2}Ph$, $NC\underline{H_2}CH_2$), 4.40 (t, *J* = 7.0 Hz, 2 H, $C\underline{H_2}NO_2$), 6.73 (t, *J* = 5.5 Hz, 1 H, N=C$\underline{H}$ of oxime), 6.86 (br. s, 1 H, OH of oxime), 7.07 - 7.33 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.5 ($C_{quat}CH_2\underline{C}H_2CH_2$), 27.8 ($NO_2CH_2\underline{C}H_2$), 29.7 ($C_{quat}\underline{C}H_2(CH_2)_2$), 36.4 ($NCH_2\underline{C}H_2$), 42.4 ($N\underline{C}H_3$), 44.0 ($\underline{C}H_2Ph$), 45.9 ($\underline{C}_{quat}$), 55.8 ($N\underline{C}H_2CH_2$), 66.6 ($N\underline{C}H_2C_{quat}$), 75.5 ($NO_2C\underline{H_2}$), 128.0 (Ar$\underline{C}$), 130.2 (Ar$\underline{C}$), 138.6 (Ar$\underline{C}_{quat}$), 152.5 (N=$\underline{C}$H of oxime); ***m/z*** (ESI$^+$) 277 (100%, $[M+H]^+$), 299 (40, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}N_2O_2$) requires *m/z* 277.1911, found *m/z* 277.1916. Compounds **353** and **354** characterised as a mixture.

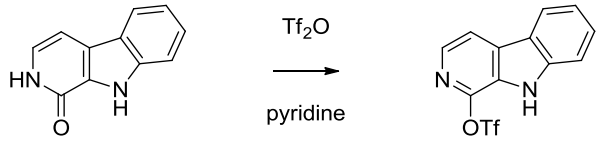
tert-Butyl(dimethyl)silyl [(1*E*)-4-(3-benzyl-1-methyl-2-oxopyrrolidin-3-yl)butylidene] azinate (355)



336 **355**

To nitro **336** (1.0 eq, 0.17 mmol, 50 mg) in dichloromethane (3 mL/mmol **336**, 0.51 mL) at −78 ˚C was added *tert*-butyldimethylsilyl chloride (1.5 eq, 0.26 mmol, 39 mg) followed by triethylamine (1.2 eq, 0.21 mmol, 29 µL). The reaction mixture was warmed to RT, filtered through Celite® and the filtrate was concentrated *in vacuo*. Crude NMR spectroscopy showed 5:1 **355**:**336** material which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.32 (s, 6 H, 2 × SiC$\underline{H}_3$), 0.96 (s, 9 H, Si(C(C$\underline{H}_3$)$_3$)), 1.15 - 1.75 (m, 4 H, $C_{quat}C\underline{H}_2C\underline{H}_2$), 1.77 - 2.10 (m, 2 H, $NCH_2C\underline{H}_2$), 2.15 - 2.36 (m, 2 H, C$\underline{H}_A$H$_B$Ph, NC$\underline{H}_A$H$_B$), 2.53 - 2.71 (m, 4 H, NC$\underline{H}_3$, N=CHC$\underline{H}_A$H$_B$), 2.86 - 3.00 (m, 2 H, CH$_A\underline{H}_B$Ph, NCH$_A\underline{H}_B$), 3.39 - 3.55 (m, 1 H, N=CHCH$_A\underline{H}_B$), 6.04 - 6.24 (m, 1 H, N=C$\underline{H}$CH$_2$), 7.05 - 7.35 (m, 5 H, Ar$\underline{H}$); ***m/z*** (ESI$^+$) 290 (60%, [M-TBDMS]$^+$), 405 (100, [M+H]$^+$), 427 (40, [M+Na]$^+$).

9*H*-β-Carbolin-1-yl trifluoromethanesulfonate (377)

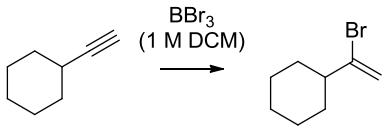


298 **377**

To a solution of β-carboline **298** (1.0 eq, 1.9 mmol, 0.34 g) in pyridine (10 mL/mmol **298**, 19 mL) was added trifluoromethanesulfonic anhydride (1.2 eq, 2.2 mmol, 0.37 mL) at 0 ˚C. The reaction mixture was warmed to RT and after 5 hours, was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (PE → 1:5 EtOAc:PE → 1:1 EtOAc:PE) to afford the title compound **377** (0.39 g, 67%) as a yellow solid. **m.p.** 80 – 82 ˚C (lit. 82 ˚C[131]); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37 (t, *J* = 7.5 Hz, 1 H, Ar$\underline{H}$), 7.54 - 7.67 (m, 2 H, Ar$\underline{H}$), 7.97 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$), 8.11 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 8.15 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$),

8.70 (br. s, 1 H, N<u>*H*</u>); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F -72.46 (C<u>*F*</u>$_3$); ***m/z*** (ESI^+) 317 (50%, $[M+H]^+$), 339 (100, $[M+Na]^+$) 655, (100, $[2M+Na]^+$). Data are in agreement with literature.[131]

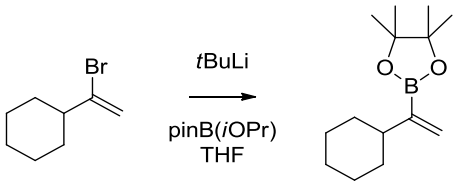
(1-Bromoethenyl)cyclohexane (563)



562 **563**

To boron tribromide (0.50 eq, 4.6 mmol, 1 M in dichloromethane, 4.6 mL) was added ethynylcyclohexane **562** (1.0 eq, 9.3 mmol, 1.2 mL) at −78 ˚C. The reaction mixture was warmed to RT over 3 h. Acetic acid (glacial, 1 mL/mmol **562**, 9.3 mL) was added and the reaction mixture was stirred for 1 h. Water (30 mL) and dichloromethane (20 mL) were added and the organic layer was separated. The aqueous layer was extracted (CH_2Cl_2, 3 × 20 mL) and the combined organics were washed (brine, 30 mL), dried ($MgSO_4$) and filtered. The solvent was carefully removed under a stream of nitrogen to give 1.6 g of crude title compound **563** which was used without purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.05 - 1.38 (m, 5 H, $CHCH_2CH_2C\underline{H}_2$, $CHCH_2C\underline{H}_2$, $CHCH_2C\underline{H}_AH_B$), 1.63 - 1.72 (m, 1 H, $CHCH_2CH_A\underline{H}_B$), 1.75 - 1.83 (m, 2 H, $CHC\underline{H}_2$), 1.87 - 1.95 (m, 2 H, $CHC\underline{H}_2$), 2.09 - 2.23 (m, 1 H, C<u>*H*</u>), 5.37 (d, *J* = 2.0 Hz, 1 H, $C=C\underline{H}_AH_B$), 5.55 (dd, *J* = 2.0, 1.0 Hz, 1 H, $C=CH_A\underline{H}_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.9 ($CHCH_2CH_2\underline{C}H_2$), 26.0 (2 × $CHCH_2\underline{C}H_2$), 32.1 (2 × $CH\underline{C}H_2$), 48.5 (<u>*C*</u>H), 114.1 ($C=\underline{C}H_2$), 141.3 ($\underline{C}=CH_2$). Data are in agreement with literature.[132]

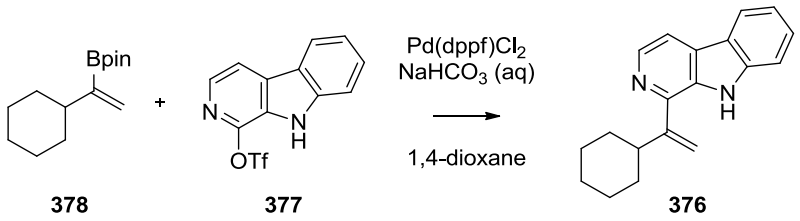
2-(1-Cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (378)



563 **378**

To cyclohexylbromide **563** (1.0 eq, 5.47 mmol, 1.03 g) in tetrahydrofuran (1.64 mL/mmol **563**, 8.97 mL) was added *t*BuLi (2.0 eq, 11.0 mmol, 1.7 M in pentane, 6.44 mL) dropwise at −78 ˚C. The solution turned from pale yellow to dark red. After 1 h, a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 eq, 8.20 mmol, 1.67 mL) in tetrahydrofuran (1.40 mL/mmol of **563**, 11.5 mL) was added and the reaction mixture was warmed to RT. After 3 h, HCl (1 M, 2.19 mL/mmol **563**, 12.0 mL) was added and the clear biphasic mixture was stirred for 30 min. Diethyl ether (40 mL) was added followed by the separation of the organic and aqueous layers. The aqueous layer was extracted (Et_2O, 3 × 20 mL) and the combined organics were washed (brine, 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20:1 PE:EtOAc) to yield the title compound **378** (0.89 g, 69%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 3074 (C-H), 2929 (C-H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.08 - 1.23 (m, 2 H, $CHCH_2CH_2C\underline{H}_2$), 1.25 - 1.38 (m, 16 H, 4 × $C\underline{H}_3$, 2 × $CHCH_2C\underline{H}_2$), 1.62 - 1.79 (m, 4 H, 2 × $CHC\underline{H}_2$), 2.05 - 2.15 (m, 1 H, $C\underline{H}$), 5.55 (d, *J* = 2.5 Hz, 1 H, $C=C\underline{H}_AH_B$), 5.71 (d, *J* = 2.5 Hz, 1 H, $C=CH_A\underline{H}_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.7 (4 × $\underline{C}H_3$), 26.3 ($CHCH_2CH_2\underline{C}H_2$), 26.7 ($CHCH_2\underline{C}H_2CH_2\underline{C}H_2$), 32.5 ($CH(\underline{C}H_2)_2$), 42.8 ($\underline{C}H$), 67.4 ($C_{quat}(CH_3)_2$), 83.1 ($\underline{C}=CH_2$), 125.9 ($C=\underline{C}H_2$); **HRMS** (TOF MS FI+) exact mass calculated for $[M]^+$ ($C_{14}H_{25}BO_2$) requires *m/z* 236.1950, found *m/z* 236.1952. Data are in agreement with literature.[206]

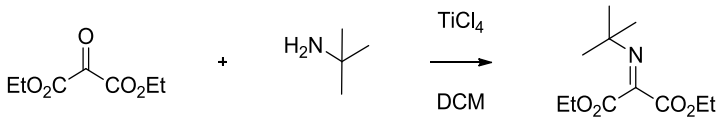
1-(1-Cyclohexylvinyl)-9*H*-β-carboline (376)



378 **377** **376**

To a degassed solution of pinacol ester **378** (1.4 eq, 1.8 mmol, 0.42 g), triflate **377** (1.0 eq, 1.3 mmol, 0.40 g) and sodium bicarbonate (saturated aqueous, 1.3 mL/mmol **378**, 2.2 mL), in 1,4-dioxane (3.8 mL/mmol **378**, 6.6 mL) was added $Pd(dppf)Cl_2$ (0.05 eq, 0.063 mmol, 51 mg) and the reaction mixture was stirred at 80 ˚C. After 2 h, a further portion of $Pd(dppf)Cl_2$ (0.10 eq, 0.12 mmol, 100 mg) was added and the reaction mixture was stirred at 80 ˚C. After 16 h, the reaction mixture was cooled to RT and partitioned between dichloromethane (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted (dichloromethane, 3 × 15 mL). The combined organics were washed (brine, 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 PE:EtOAc → EtOAc → 1:10 MeOH:EtOAc) to yield the title compound **376** (0.27 g, 79%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2924 (C-H), 2854 (C-H), 1626 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.17 - 1.45 (m, 7 H, $CHCH_2CH_2CH\underline{H}_A\underline{H}_B$, $CHC\underline{H}_A\underline{H}_B$, $CHC\underline{H}_A\underline{H}_B$, 2 × $CHCH_2C\underline{H}_2$), 1.63 - 1.86 (m, 3 H, $CHCH_2CH_2CH_A\underline{H}_B$, $CHCH_A\underline{H}_B$, $CHCH_A\underline{H}_B$), 2.98 (t, *J* = 11.5 Hz, 1 H, $C\underline{H}(CH_2)_2$), 5.53 (br. s, 2 H, $C=C\underline{H}_2$), 7.30 (t, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 7.49 - 7.60 (m, 2 H, Ar$\underline{H}$), 7.86 (d, *J* = 5.5 Hz, 1 H, Ar$\underline{H}$), 8.14 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 8.39 (br. s, 1 H, N$\underline{H}$), 8.48 (d, *J* = 5.0 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 26.4 ($CHCH_2\underline{C}H_2CH_2\underline{C}H_2$), 29.6 ($CHCH_2CH_2\underline{C}H_2$), 32.1 ($CH(\underline{C}H_2)_2$), 42.0 ($C\underline{C}H$), 111.3 (Ar$\underline{C}$), 112.7 ($C=\underline{C}H_2$), 113.2 (Ar$\underline{C}$), 120.0 (Ar$\underline{C}$), 121.7 (Ar$\underline{C}$), 122.0 (Ar$\underline{C}_{quat}$), 128.3 (Ar$\underline{C}$), 128.9 (Ar$\underline{C}_{quat}$), 133.8 (Ar$\underline{C}_{quat}$), 138.6 (Ar$\underline{C}$), 139.8 (Ar$\underline{C}_{quat}$), 145.2 (Ar$\underline{C}_{quat}$), 153.4 ($\underline{C}=CH_2$); ***m/z*** ($ESI^-$) 275 (100%, $[M-H]^-$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}N_2$) requires *m/z* 277.1699, found *m/z* 277.1695.

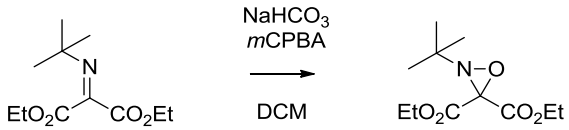
Diethyl (*tert*-butylimino)malonate (409)



408 **564** **409**

To ketone **408** (1.0 eq, 1.1 mmol, 0.17 mL) and amine **564** (4.0 eq, 4.6 mmol, 0.48 mL) in dichloromethane (1.0 mL/mmol **408**, 1.1 mL) was added $TiCl_4$ (0.55 eq, 0.62 mmol, 0.67 mL) dropwise at 0 °C. After 24 h, the reaction mixture was poured on to aqueous sodium hydroxide (1 M, 10 mL). Ethyl acetate (15 mL) was added and the mixture was filtered through Celite®. The organic and aqueous layers were separated and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue (0.15 g) was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.16 - 1.40 (m, 15 H, $(C\underline{H}_3)_3$, 2 × $C\underline{H}_3$), 4.29 (q, *J* = 7.0 Hz, 4 H, 2 × $CH_3C\underline{H}_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 14.1 ($\underline{C}H_3$), 14.4 ($\underline{C}H_3$), 29.7 ($C(\underline{C}H_3)_3$), 59.3 ($\underline{C}(CH_3)_3$), 62.2 ($COO\underline{C}H_2$), 62.7 ($COO\underline{C}H_2$), 149.0 ($\underline{C}$=N), 161.9 ($\underline{C}$=O), 166.1 ($\underline{C}$=O). Data are in agreement with literature.[150]

Diethyl 2-*tert*-butyloxaziridine-3,3-dicarboxylate (401)

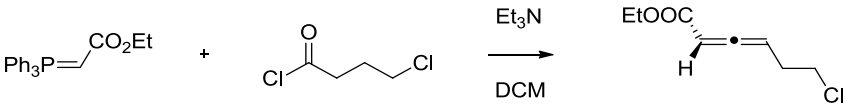


409 **401**

To a solution of imine **409** (1.0 eq, 0.65 mmol, 0.15 g) and $NaHCO_3$ (1.2 eq, 0.78 mmol, 0.065 g) in dichloromethane (1.0 mL/mmol **409**, 0.65 mL) was added a solution of *m*-chloroperoxybenzoic acid (1.18 eq, 0.77 mmol, 0.13 g) and Na_2SO_4 (0.50 g) in dichloromethane (2.0 mL/mmol **409**, 1.3 mL) at 0 °C. After stirring the reaction for 24 h at room temperature, the reaction mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (9:1 PE:EtOAc) to yield the title compound **401** (0.11 g, 70% over two steps) as a pale yellow

oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.22 (s, 9 H, ($C\underline{H}_3)_3$), 1.29 - 1.42 (m, 6 H, 2 × $C\underline{H}_3$), 4.25 - 4.42 (m, 4 H, 2 × $C\underline{H}_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 13.8 (2 × $CH_2\underline{C}H_3$), 25.8 (($\underline{C}H_3)_3$), 60.3 ($\underline{C}_{quat}$(N)(O)), 62.4 ($\underline{C}(CH_3)_3$), 63.1 (2 × $\underline{C}H_2CH_3$), 164.4 ($\underline{C}$=O), 165.0 ($\underline{C}$=O); ***m/z*** (ESI^+) 268 (45%, $[M+Na]^+$), 513 (100, $[2M+Na]^+$). Data are in agreement with literature.[150]

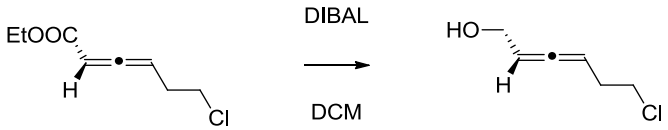
***rac*-Ethyl 6-chlorohexa-2,3-dienoate (441)**



439 **440** (±)-**441**

To a solution of ethyl (triphenylphosphoranylidene)acetate **439** (1.0 eq, 0.130 mol, 46.8 g) in dichloromethane (450 mL) was added triethylamine (1.1 eq, 0.140 mol, 20.8 mL). The resulting mixture was cooled to 0 ˚C and 4-chlorobutanoyl chloride **440** (1.0 eq, 0.130 mol, 15.0 mL) was added dropwise before the reaction mixture was warmed to room temperature. After 12 h, approximately half the volume of dichloromethane was removed *in vacuo* and diethyl ether (250 mL) was added. The white precipitate was removed *via* filtration through Celite® which was washed with diethyl ether (4 × 200 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (1:4 EtOAc:PE) to yield title compound **441** (20.6 g, 91%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 2983 (C-H), 1964 (C=C=C), 1713 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.28 (t, *J* = 7.0 Hz, 3 H, $C\underline{H}_3CH_2$), 2.60 (qd, *J* = 7.0, 3.0 Hz, 2 H, $ClCH_2C\underline{H}_2$), 3.61 (t, *J* = 7.0 Hz, 2 H, $ClC\underline{H}_2$), 4.19 (q, *J* = 7.0 Hz, 2 H, $CH_3C\underline{H}_2$), 5.62 - 5.74 (m, 2 H, $C\underline{H}C\underline{C}\underline{H}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 14.2 ($\underline{C}H_3$), 30.8 ($CH\underline{C}H_2$), 43.0 ($\underline{C}H_2Cl$), 60.9 ($CH_3\underline{C}H_2$), 89.2, 91.9 ($\underline{C}HC\underline{C}H$), 165.7 ($\underline{C}$=O), 212.3 ($CH\underline{C}CH$); ***m/z*** ($ESI^+$) 197 (100%, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{11}ClNaO_2$) requires *m/z* 197.0345, found *m/z* 197.0340.

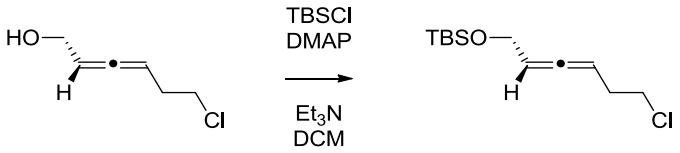
***rac*-6-Chlorohexa-2,3-dien-1-ol (442)**



(±)-**441** (±)-**442**

To a solution of ester **441** (1.0 eq, 0.0920 mol, 16.2 g) in dichloromethane (650 mL) was added DIBAL (2.0 eq, 1 M solution in cyclohexanes, 0.180 mol, 185 mL) dropwise at 0 ˚C. After 2 h, MeOH (1 mL/mmol **441**, 92 mL) was added dropwise and the reaction mixture was warmed to room temperature. After 20 min, $Na_2SO_4 \bullet 10H_2O$ (10.0 g) and diethyl ether (400 mL) were added. After 16 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc → 1:10 MeOH:EtOAc) to yield title compound **442** (4.49 g, 35%) as a pale yellow oil. **IR** ν_{max}(film)/ cm^{-1} 3345 (O-H), 2958 (C-H), 1965 (C=C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.83 (br. s, 1 H, O*H*), 2.49 (qd, *J* = 6.5, 3.0 Hz, 2 H, $ClCH_2CH_2$), 3.55 - 3.63 (m, 2 H, $ClCH_2$), 4.14 (dd, *J* = 5.0, 3.0 Hz, 2 H, CH_2OH), 5.29 - 5.47 (m, 2 H, CHCCH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 31.7 ($CHCH_2$), 43.7 (CH_2Cl), 60.3 (CH_2OH), 90.3, 93.1 ($CHCCH$), 203.6 ($CHCCH$); **HRMS** (TOF MS FI+) exact mass calculated for $[M+H]^+$ ($C_6H_{10}OCl$) requires *m/z* 132.0342, found *m/z* 132.0343.

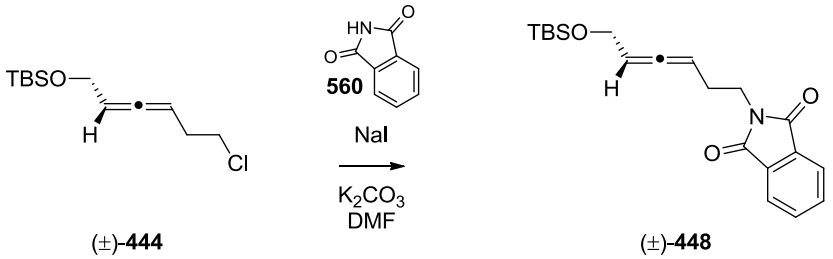
***rac-tert*-Butyl[(6-chlorohexa-2,3-dien-1-yl)oxy]dimethylsilane (444)**



(±)-**442** (±)-**444**

To alcohol **442** (1.0 eq, 20.6 mmol, 3.02 g) in dichloromethane (3 mL/mmol, 62 mL) was added DMAP (0.2 eq, 4.12 mmol, 0.500 g), Et_3N (1.7 eq, 35.0 mmol, 4.90 mL) and TBSCl (1.5 eq, 30.9 mmol, 4.65 g) at RT. After 16 h, water (30 mL) was added and the organic layer was separated. The aqueous layer was extracted (DCM, 3 × 20 mL), the combined organics were washed (water, 30 mL then brine, 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (PE → 9:1 PE:EtOAc) to yield title compound **444** (4.09 g, 86%) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 2929 (C-H), 2016 (C=C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.10 (s, 6 H, 2 × C$\underline{H}_3$), 0.93 (s, 9 H, C(C$\underline{H}_3$)$_3$), 2.43 (qd, *J* = 7.0, 3.0 Hz, 2 H, CHC$\underline{H}_2$CH$_2$Cl), 3.51 (t, *J* = 7.0 Hz, 2 H, ClC$\underline{H}_2$), 4.22 - 4.25 (m, 2 H, C$\underline{H}_2$OSi), 5.22 - 5.30 (m, 2 H, C$\underline{H}$CC$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C -5.4 (Si$\underline{C}$H$_3$), -5.3 (Si$\underline{C}$H$_3$), 19.0 ($\underline{C}$(CH$_3$)$_3$), 25.9 (C($\underline{C}$H$_3$)$_3$), 32.0 (C$\underline{C}$H$_2$CH$_2$Cl), 43.7 ($\underline{C}$H$_2$Cl), 61.5 ($\underline{C}$H$_2$OSi), 88.8, 92.9 (H$\underline{C}$=C=$\underline{C}$H), 204.0 (HC=$\underline{C}$=CH); ***m/z*** (ESI$^+$) 247 (45%, [M+H]$^+$), 269 (55, [M+Na]$^+$); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{12}H_{23}ClNaOSi$) requires *m/z* 269.1099 found *m/z* 269.1099 .

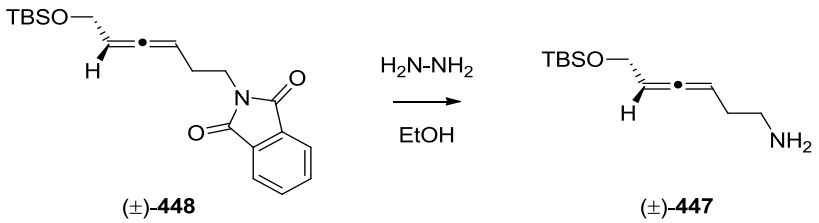
***rac*-2-(5-{[*tert*-Butyl(dimethyl)silyl]oxy}penta-3,4-dien-1-yl)-1 H-isoindole-1,3(2H)-dione (448)**



(±)-**444** (±)-**448**

To chloride **444** (1.0 eq, 2.15 mmol, 0.500 g) in DMF (5 mL/mmol **444**, 10.8 mL) was added K_2CO_3 (1.5 eq, 3.23 mmol, 0.450 g), NaI (1.1 eq, 2.37 mmol, 0.360 g) and phthalamide **560** (1.2 eq, 2.59 mmol, 0.380 g) at RT. The reaction was stirred at 60 ˚C for 3 h before being cooled to RT. Et_2O (50 mL) and water (50 mL) were added and the organic layer was separated. The aqueous layer was extracted (Et_2O, 3 × 20 mL) and the combined organics were washed (water, 50 mL then brine, 40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (9:1 PE:EtOAc → 4:1 PE:EtOAc) to yield title compound **448** (0.69 g, 89%) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 2953 (C-H), 2856 (C-H), 1967 (C=C=C), 1773 (C=O), 1704 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.04 (s, 6 H, 2 × SiC$\underline{H}_3$), 0.87 (s, 9 H, (C$\underline{H}_3$)$_3$), 2.39 - 2.41 (m, 2 H, CH=C=CHC$\underline{H}_2$CH$_2$), 3.77 (t, *J* = 7.5 Hz, 2 H, NC$\underline{H}_2$), 4.06 (ddd, *J* = 7.0, 6.0, 3.0 Hz, 2 H, SiOC$\underline{H}_2$), 5.18 (qq, *J* = 6.0, 3.0 Hz, 2 H, C$\underline{H}$=C=C$\underline{H}$), 7.69 - 7.75 (m, 2 H, Ar$\underline{H}$), 7.85 (dd, *J* = 5.5, 3.0 Hz, 2 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C -5.3 (Si$\underline{C}$H$_3$), -5.1 (Si$\underline{C}$H$_3$), 18.6 ($\underline{C}$(CH$_3$)$_3$), 25.8 (C($\underline{C}$H$_3$)$_3$), 27.6 (CH$\underline{C}$H$_2$CH$_2$N), 37.4 (N$\underline{C}$H$_2$), 61.6 (SiO$\underline{C}$H$_2$), 88.5, 92.4 (H$\underline{C}$=C=$\underline{C}$H), 123.2 (Ar$\underline{C}$), 132.0 (Ar$\underline{C}_{quat}$), 133.9 (Ar$\underline{C}$), 168.2 ($\underline{C}$=O), 204.0 (HC=$\underline{C}$=CH); ***m/z*** (ESI$^+$) 358 (40%, [M+H]$^+$), 380 (100, [M+Na]$^+$); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{20}H_{27}NNaO_3Si$) requires *m/z* 380.1655, found *m/z* 380.1652.

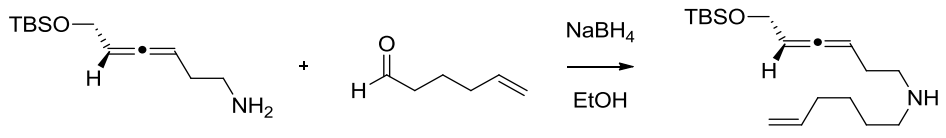
***rac*-5-{[*tert*-Butyl(dimethyl)silyl]oxy}penta-3,4-dien-1-amine (447)**



(±)-**448** (±)-**447**

To phthalamide **448** (1.0 eq, 6.1 mmol, 2.2 g) in EtOH (10 mL/mmol **448**, 61 mL) was added hydrazine (6.8 eq, 41 mmol, 50% soln. in water, 2.6 mL) at RT. The reaction mixture was heated to reflux. After 1 h, the reaction mixture was cooled to RT and the white solid was filtered and washed (DCM, 3 × 50 mL). The filtrate was concentrated *in vacuo* to yield the title compound **447** (1.1 g, 88%) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 2953 (C-H), 2929 (C-H), 1963 (C=C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.06 (s, 6 H, Si(C$\underline{H}_3$)$_2$), 0.88 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.21 (br. s, 2 H, N$\underline{H}_2$), 2.09 - 2.16 (m, 2 H, C$\underline{H}_2$CH$_2$NH$_2$), 2.73 - 2.80 (m, 2 H, C$\underline{H}_2$NH$_2$), 4.13 - 4.20 (m, 2 H, SiOC$\underline{H}_2$), 5.11 - 5.25 (m, 2 H, $\underline{H}$C=C=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C -5.3 (Si$\underline{C}$H$_3$), -5.1 (Si$\underline{C}$H$_3$), 18.3 ($\underline{C}$(CH$_3$)$_3$), 25.9 (C($\underline{C}$H$_3$)$_3$), 33.0 (CH$\underline{C}$H$_2$CH$_2$N), 41.5 (N$\underline{C}$H$_2$), 62.2 (SiO$\underline{C}$H$_2$), 89.9, 91.9 (H$\underline{C}$=C=$\underline{C}$H), 203.8 (HC=$\underline{C}$=CH); ***m/z*** (ESI$^+$) 352 (100%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{12}H_{26}NOSi$) requires *m/z* 352.2091, found *m/z* 352.2085.

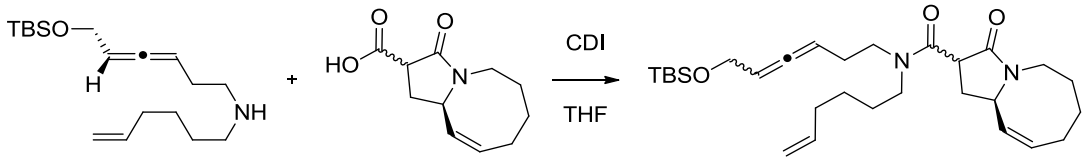
***rac*-*N*-(5-{[*tert*-Butyl(dimethyl)silyl]oxy}penta-3,4-dien-1-yl)hex-5-en-1-amine (449)**



(±)-**447** **291** (±)-**449**

Amine **447** (2.0 eq, 1.0 mmol, 0.23 g) and aldehyde **291** (1.0 eq, 0.50 mmol, 0.049 g) were stirred in EtOH (1 mL/mmol **447**, 1 mL) for 1 h. The reaction mixture was cooled to 0 ˚C and $NaBH_4$ (1.1 eq, 0.55 mmol, 0.020 g) was added. The reaction mixture was warmed to RT. After 1 h, Et_2O (10 mL) and water (3 mL) were added and the organic layer was separated. The aqueous layer was extracted (Et_2O, 3 × 5 mL) and the combined organics were washed (water, 10 mL then brine, 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc → 4:1 EtOAc:MeOH) to yield title compound **449** (0.082 g, 54%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 3077 (C-H), 2953 (C-H), 1964 (C=C=C), 1640 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.06 (s, 6 H, Si(C$\underline{H}_3$)$_2$), 0.88 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.35 - 1.45 (m, 2 H, N(CH$_2$)$_2$C$\underline{H}_2$), 1.46 - 1.55 (m, 2 H, NCH$_2$C$\underline{H}_2$), 2.04 - 2.06 (m, 2 H, CH$_2$=CHC$\underline{H}_2$), 2.20 - 2.24 (m, 2 H, CCHC$\underline{H}_2$CH$_2$), 2.58 - 2.61 (m, 2 H, NC$\underline{H}_2$(CH$_2$)$_3$), 2.71 (t, *J* = 4.0 Hz, 2 H, CCHCH$_2$C$\underline{H}_2$), 4.15 (dd, *J* = 6.0, 3.0 Hz, 2 H, SiOC$\underline{H}_2$), 4.88 - 5.05 (m, 2 H, C$\underline{H}_2$=CH), 5.12 - 5.26 (m, 2 H, $\underline{H}$C=C=C$\underline{H}$), 5.71 - 5.86 (m, 1 H, CH$_2$=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C -5.3 (Si$\underline{C}$H$_3$), -5.1 (Si$\underline{C}$H$_3$), 18.3 ($\underline{C}$(CH$_3$)$_3$), 25.8 (C($\underline{C}$H$_3$)$_3$), 26.6 (N(CH$_2$)$_2\underline{C}$H$_2$), 29.2 (CCH$\underline{C}$H$_2$CH$_2$N), 29.3 (NCH$_2\underline{C}$H$_2$CH$_2$), 33.5 (CH$_2$=CH$\underline{C}$H$_2$), 48.8 (N$\underline{C}$H$_2$CH$_2$CH), 49.4 (N$\underline{C}$H$_{2(}$CH$_2$)$_3$), 61.7 (SiO$\underline{C}$H$_2$), 90.0, 92.2 (H$\underline{C}$=C=$\underline{C}$H), 114.5 ($\underline{C}$H$_2$=CH), 138.6 (CH$_2$=$\underline{C}$H), 203.6 (HC=$\underline{C}$=CH); ***m/z*** (ESI$^+$) 310 (50%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{18}H_{36}NOSi$) requires *m/z* 310.2561, found *m/z* 310.2568.

(9*Z*,10a*R*)-*N*-(5-{[*tert*-Butyl(dimethyl)silyl]oxy}penta-3,4-dien-1-yl)-*N*-(hex-5-en-1-yl)-3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxamide (450)



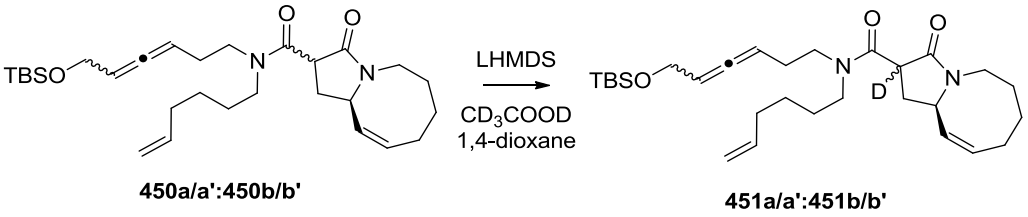
(±)-**449** **266** **450a/a':450b/b'**

To acid **266** (1.0 eq, 1.09 mmol, 0.227 g) in tetrahydrofuran (1.2 mL/mmol **266**, 0.11 mL) was added CDI (1.2 eq, 1.31 mmol, 0.212 g) at RT. After 20 min, amine **449** (1.1 eq, 1.20 mmol, 0.373 g) in tetrahydrofuran (1.40 mL/mmol **449**, 1.68 mL) was added and the reaction mixture was stirred for 16 h. Et_2O (10 mL) and water (10 mL) were added and the organic layer was separated. The aqueous layer was extracted (Et_2O, 3 × 15 mL) and the combined organics were washed (water, 20 mL then brine, 15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (4:1 PE:EtOAc) to yield title compound **450** (0.367 g, 67%, dr 2:1 **450a/a'**:**450b/b'**) as a pale yellow oil. $[\alpha]_D^{24}$ = −13.2 (c = 0.5, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2929 (C-H), 2785 (C-H), 1960 (C=C=C), 1683 (C=O), 1640 (C=O); **^{1}H NMR**[xxiv] (400 MHz, $CDCl_3$) δ_H 0.06 (s, 6 H, Si(C$\underline{H}_3$)$_2$), 0.89 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.29 - 1.75 (m, 7 H, CHNCH$_2$C$\underline{H}_A$H$_B$, CHNCH$_2$CH$_2$C$\underline{H}_2$ of 2 diastereomers, CH$_2$=CHCH$_2$C$\underline{H}_2$, CH$_2$=CHCH$_2$CH$_2$C$\underline{H}_2$), 1.78 - 2.00 (m, 4 H, CHNCH$_2$CH$_2$C$\underline{H}_2$ of 2 diastereomers, CHNCH$_2$CH$_A$$\underline{H}_B$, NCHC$\underline{H}_AH_B$ of 2 diastereomers), 2.07 (dd, *J* = 12.0, 7.0 Hz, 4 H, CH$_2$=CHC$\underline{H}_2$), 2.13 - 2.30 (m, 6 H, CHCH=CHC$\underline{H}_2$, C=CHC$\underline{H}_2$CH$_2$N, NCHC$\underline{H}_A$H$_B$ of 2 diastereomers), 2.41 - 2.53 (m, 2 H, NCHCH$_A$$\underline{H}_B$ of 2 diastereomers), 2.68 - 2.79 (m, 1 H, NCHCH$_A$$\underline{H}_B$ of 2 diastereomers), 3.04 - 3.39 (m, 6 H, CHNC$\underline{H}_A$H$_B$, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_2$, NC$\underline{H}_A$H$_B$CH$_2$CH=C$_{quat}$), 3.41 - 3.62 (m, 1 H, CHNCH$_A$$\underline{H}_B$ of 2 diastereomers), 3.63 - 3.77 (m, 2 H, NCH$_A$$\underline{H}_BCH_2$CH=C$_{quat}$, OCC$\underline{H}$CO), 3.78 - 3.95 (m, 1 H, CHNCH$_A$$\underline{H}_B$ of 2 diastereomers), 4.12 - 4.18 (m, 2 H, SiOC$\underline{H}_2$), 4.30 (q, *J* = 7.5 Hz, 1 H, NC$\underline{H}$CH=CH of 2 diastereomers), 4.53 (q, *J* = 6.5 Hz, 1 H, NC$\underline{H}$CH=CH of

[xxiv] Due to complex nature of spectrum, consisting of four diastereomers and many overlapping signals, only key and correct signals have been assigned. Unless otherwise stated, all assignments are for all diastereomers present.

2 diastereomers), 4.89 - 5.07 (m, 2 H, C<u>*H*</u>$_2$=CH), 5.19 - 5.31 (m, 2 H, <u>*H*</u>C=C=C<u>*H*</u>), 5.37 - 5.46 (m, 1 H, NCHC<u>*H*</u>=CH of 2 diastereomers), 5.51 (dd, *J* = 10.5, 7.5 Hz, 1 H, NCHC<u>*H*</u>=CH of 2 diastereomers), 5.76 - 5.79 (m, 2 H, NCHCH=C<u>*H*</u> of 2 diastereomers, CH_2=C<u>*H*</u>), 5.94 (q, *J* = 10.0 Hz, 1 H, NCHCH=C<u>*H*</u> of 2 diastereomers); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C [-5.3, -5.1, -4.8, -4.7] (Si(<u>*C*</u>H_3)$_2$), [18.8] (<u>*C*</u>$(CH_3)_3$), [25.9, 26.1] (NCHCH=CH<u>*C*</u>H_2 2 DS), [26.3, 26.4] (C(<u>*C*</u>H_3)$_3$), [26.4, 26.5] (CHNCH_2<u>*C*</u>H_2), [26.6, 26.7] (CH_2=CHCH_2<u>*C*</u>H_2), [26.8, 26.8] (NCHCH=CH<u>*C*</u>H_2 2 DS), [27.6, 27.6, 27.6] (CH_2=CH$(CH_2)_2$<u>*C*</u>H_2), [27.7, 27.9, 28.0] (CHNCH_2CH_2<u>*C*</u>H_2), [28.7, 28.7, 28.8, 28.8] (NCH_2<u>*C*</u>H_2C=C_{quat}), [30.3, 30.3, 31.5] (NCH<u>*C*</u>H_2), [33.7, 33.8, 33.9, 33.9] (CH_2=CH<u>*C*</u>H_2), [41.2, 41.4, 41.9, 41.9] (N<u>*C*</u>H_2CH_2CH=C=CH), [46.2, 46.2, 46.3] (<u>*C*</u>H$(CO)_2$), [46.9, 47.1, 48.0, 48.1] (CHN<u>*C*</u>H_2), [48.8] (CH_2=CH$(CH_2)_3$<u>*C*</u>H_2), [54.3, 55.9, 55.9] (N<u>*C*</u>H), [61.9, 62.0, 62.3, 62.3] (<u>*C*</u>H_2OSi), [89.1, 89.2, 89.7, 89.8] (CH=C=<u>*C*</u>HCH_2CH_2), [92.6, 92.7, 93.1, 93.2] (OCH_2<u>*C*</u>H=C), [115.0, 115.0, 115.4, 115.5] (<u>*C*</u>H_2=CH), [129.6, 130.7, 130.7] (NCH<u>*C*</u>H=CH), [133.1, 133.1, 135.2, 135.2] (NCHCH=<u>*C*</u>H), [138.6, 138.6, 139.1, 139.1] (CH_2=<u>*C*</u>H), [169.1, 169.2, 169.6, 169.7] ($(CH_2)_2$N<u>*C*</u>O), [170.5, 170.9, 170.9] (CHN<u>*C*</u>O), [204.2, 204.2, 204.3, 204.4] (HC=<u>*C*</u>=CH); ***m/z*** (ESI$^+$) 501 (50%, $[M+H]^+$), 523 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{29}H_{49}N_2O_3Si$) requires *m/z* 501.3507, found *m/z* 501.3509.

(9*Z*,10a*R*)-*N*-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}hexa-3,4-dien-1-yl)-*N*-(hex-5-en-1-yl)-3-oxo(2-^{2}H)-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxamide (451)

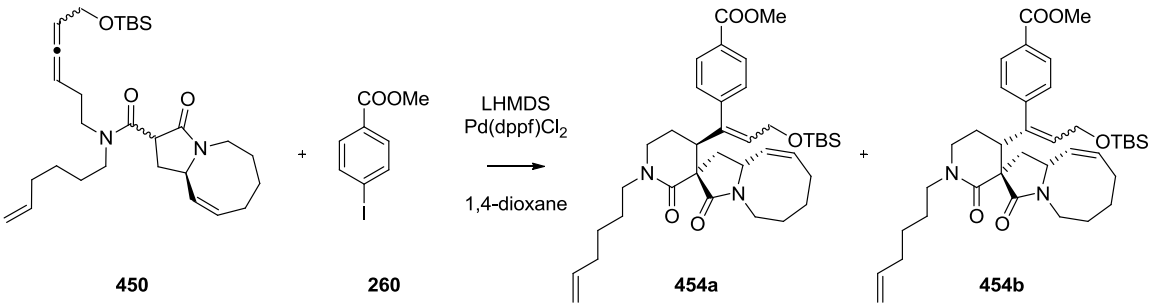


450a/a':450b/b' **451a/a':451b/b'**

To pro-nucleophile **450** (1 eq, 0.024 mmol, 12 mg) in 1,4-dioxane (0.1 mL) was added LHMDS (1.2 eq., 0.028 mmol, 1.0 M in hexanes, 0.028 mL) at RT. After 20 min, CD_3COOD (10 µL) was added and the reaction mixture was concentrated *in vacuo*. The crude residue was analysed by ^{1}H NMR spectroscopy and mass spectrometry (**451a/a'**:**451b/b'**, dr 73:62). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.08 (s, 6 H, Si(C$\underline{H}_3$)$_2$), 0.91 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.13 - 2.54 (m, 16 H, CHNCH$_2$CH$_2$C$\underline{H}_2$, CH$_2$=CHCH$_2$C$\underline{H}_2$, CH$_2$=CHCH$_2$CH$_2$C$\underline{H}_2$ NCHC$\underline{H}_A$H$_B$, CH$_2$=CHC$\underline{H}_2$ CHCH=CHC$\underline{H}_2$, C$_{quat}$=CHC$\underline{H}_2$CH$_2$N, NCHCH$_A$$\underline{H}_B$ of 2 diastereomers, CHNCH$_2$C$\underline{H}_2$), 2.69 - 2.80 (m, 1 H, NCHCH$_A$$\underline{H}_B$ of 2 diastereomers), 3.03 - 4.00 (m, 6 H, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_2$, NC$\underline{H}_2$CH$_2$CH=C$_{quat}$, CHNC$\underline{H}_2$), 4.13 - 4.22 (m, 2 H SiOC$\underline{H}_2$), 4.32 (q, *J* = 7.0 Hz, 1 H, NC$\underline{H}$CH=CH of 2 diastereomers), 4.55 (q, *J* = 7.0 Hz, 1 H, NC$\underline{H}$CH=CH of 2 diastereomers), 4.89 - 5.07 (m, 2 H, C$\underline{H}_2$=CH), 5.11 - 5.32 (m, 2 H, $\underline{H}$C=C=C$\underline{H}$), 5.38 - 5.47 (m, 1 H, NCHC$\underline{H}$=CH of 2 diastereomers), 5.48 - 5.57 (m, 1 H, NCHC$\underline{H}$=CH of 2 diastereomers), 5.72 - 5.90 (m, 2 H, NCHCH=C$\underline{H}$ of 2 diastereomers, CH$_2$=C$\underline{H}$), 5.91 - 6.01 (m, 1 H, NCHCH=C$\underline{H}$ of 2 diastereomers); ***m/z*** (ESI$^+$) 502 (50%, [M+H]$^+$), 524 (100, [M+Na]$^+$).

Methyl 4-{(1*Z*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-[(3*R*,4*S*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]prop-1-en-1-yl}benzoate (454a)

Methyl 4-{(1*Z*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-[(3*R*,4*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]prop-1-en-1-yl}benzoate (454b)



450 **260** **454a** **454b**

To amide **450** (1.5 eq, 0.10 mmol, 50 mg) was added LHMDS (1.5 eq, 0.15 mmol, 1.0 M soln. in hexanes, 0.15 mL) dropwise and the resulting mixture was stirred for 5 min. To the solution was added a suspension of $Pd(dppf)Cl_2$ (10 mol%, 0.01 mmol, 8 mg) and aryl iodide **260** (1.2 eq, 0.12 mmol, 31 mg) in 1,4-dioxane (10 mL/mmol **450**, 1 mL) and the resulting mixture was stirred at 95 °C. After 16 h, the reaction mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc) to yield the title compound **454** (14 mg, 22%, dr 1:1 **454a**:**454b**) as a yellow oil. The two diastereomers were separated by preparative HPLC (AGILENT reverse phase Kromasil 100-3.5C18 150 × 4.6 mm ramp mode of eluent MeCN:MeOH:H_2O 38:38:24 to MeCN:MeOH 50:50, wavelength 254 nm, flow 1.0 mL/min) to yield **454a** and **454b** in 10% and 11% respectively as colourless oils.

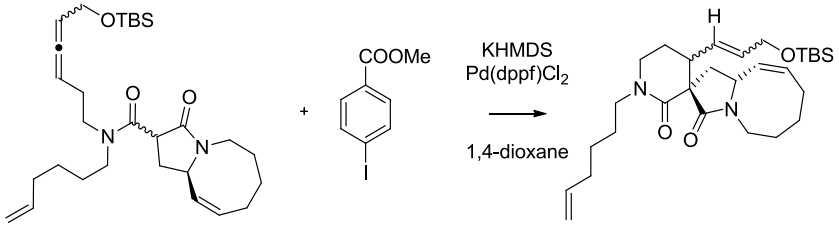
454a: $[\alpha]_D^{24}$ = −14.6 (c = 0.07, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2930 (C-H), 2864 (C-H), 1666 (C=O), 1613 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H -0.90 (s, 6 H, Si(C$\underline{H}_3$)$_2$), 0.85 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.34 - 1.43 (m, 3 H, CHNCH$_2$C$\underline{H}_A$H$_B$, CH$_2$=CHCH$_2$C$\underline{H}_A$H$_B$, CH=CHCH$_2$C$\underline{H}_A$H$_B$), 1.46 - 1.55 (m, 4 H, CCHC$\underline{H}_A$H$_B$, CH$_2$=CHCH$_2$CH$_A\underline{H}_B$ CH$_2$=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.61 - 1.90 (m, 2 H, CCHCH$_A\underline{H}_B$, CH=CHCH$_2$CH$_A\underline{H}_B$), 1.93 - 2.01 (m, 1 H, NCHC$\underline{H}_A$H$_B$), 2.03 - 2.12 (m, 2 H, CH$_2$=CHC$\underline{H}_2$), 2.19 -

2.29 (m, 2 H, CH=CHC$\underline{H}_2$), 2.50 - 2.69 (m, 3 H, NCHCH$_A\underline{H}_B$, CHNCH$_2$CH$_A\underline{H}_B$, NC$\underline{H}_A$H$_B$CH$_2$CHC), 3.19 - 3.29 (m, 1 H, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_A$H$_B$), 3.36 - 3.47 (m, 4 H, CH$_2$=CH(CH$_2$)$_3$CH$_A\underline{H}_B$, NCH$_2$CH$_2$C$\underline{H}$, CHNC$\underline{H}_2$), 3.48 - 3.58 (m, 1 H, NCH$_A\underline{H}_B$CH$_2$CHC), 3.91 - 3.93 (s, 3 H, COOC$\underline{H}_3$), 3.95 (dd, *J* = 12.0, 6.0 Hz, C$\underline{H}_A$H$_B$OSi), 4.03 (dd, *J* = 12.0, 6.5 Hz, 1 H, CH$_A\underline{H}_B$OSi), 4.61 (q, *J* = 7.5 Hz, 1 H, NC$\underline{H}$CH$_2$), 4.91 - 5.04 (m, 2 H, C$\underline{H}_2$=CH), 5.35 (dd, *J* = 10.5, 8.5 Hz, 1 H, NCHC$\underline{H}$=CH), 5.58 (t, *J* = 6.5 Hz, 1 H, C=C$\underline{H}$), 5.73 - 5.85 (m, 1 H, CH$_2$=C$\underline{H}$), 5.94 - 6.04 (m, 1 H, NCHCH=C$\underline{H}$), 7.14 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}$), 7.95 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C -5.3 (Si$\underline{C}$H$_3$), -5.2 (Si$\underline{C}$H$_3$), 18.3 ($\underline{C}$(CH$_3$)$_3$), 23.8 (CHNCH$_2\underline{C}$H$_2$), 25.8 (C($\underline{C}$H$_3$)$_3$), 26.2 (CH$_2$=CH(CH$_2$)$\underline{C}$H$_2$), 26.2 (CH$_2$=CHCH$_2\underline{C}$H$_2$), 26.6 (CH=CH$\underline{C}$H$_2$), 27.0 (NCH$_2\underline{C}$H$_2$CH), 27.9 (CH=CHCH$_2\underline{C}$H$_2$), 33.4 (CH$_2$=CH$\underline{C}$H$_2$), 35.1 (NCH$\underline{C}$H$_2$), 40.6 (N$\underline{C}$H$_2$CH$_2$CH), 45.6 ($C_{quat}\underline{C}$H), 45.7 (CHN$\underline{C}$H$_2$), 47.7 (CH$_2$=CH(CH$_2$)$_3\underline{C}$H$_2$), 52.1 (COO$\underline{C}$H$_3$), 53.1 (N$\underline{C}$H), 56.0 ($\underline{C}_{quat}$CH), 60.5 ($\underline{C}$H$_2$OSi), 114.6 ($\underline{C}$H$_2$=CH), 128.8 (Ar$\underline{C}$), 128.9 (Ar$\underline{C}$), 129.1 (Ar$\underline{C}_{quat}$), 129.5 (NCH$\underline{C}$H=CH), 130.3 (C_{quat}=$\underline{C}$HCH$_2$), 133.8 (Ar$\underline{C}_{quat}$), 135.1 (NCHCH=$\underline{C}$H), 138.5 (CH$_2$=$\underline{C}$H), 140.8 (Ar$\underline{C}_{quat}$), 144.0 (CH$_2$=$\underline{C}_{quat}$CH), 169.9 ($\underline{C}$=O), 171.8 ($\underline{C}$=O), 200.0 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 635 (40%, [M+H]$^+$), 657 (100, [M+Na]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{37}H_{54}N_2O_5Si$) requires *m/z* 635.3875, found *m/z* 635.3868.

454b: **$[\alpha]_D^{24}$** = −36.5 (c = 0.1, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2929(C-H), 2856 (C-H), 1699 (C=O), 1631 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H -0.9 (s, 6 H, Si(C$\underline{H}_3$)$_2$), 0.85 (s, 9 H, Si(C$\underline{H}_3$)$_3$), 1.22 - 1.53 (m, 7 H, CHNCH$_2$C$\underline{H}_A$H$_B$, CH$_2$=CHCH$_2$C$\underline{H}_2$, CHNCH$_2$CH$_2$C$\underline{H}_2$, CH$_2$=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.68 - 1.92 (m, 2 H, CHNCH$_2$CH$_A\underline{H}_B$, CCHC$\underline{H}_A$H$_B$), 2.03 - 2.13 (m, 3 H, CH$_2$=CHC$\underline{H}_2$, NCHCH=CHC$\underline{H}_A$H$_B$), 2.15 - 2.30 (m, 2 H, CCHCH$_A\underline{H}_B$, NCHC$\underline{H}_A$H$_B$), 2.49 - 2.54 (m, 2 H, NCHCH$_A\underline{H}_B$, NCHCH=CHCH$_A\underline{H}_B$), 2.70 - 2.86 (m, 2 H, CHNC$\underline{H}_2$), 3.26 - 3.45 (m, 3 H, NC$\underline{H}_A$H$_B$CH$_2$CHC, NC$\underline{H}_2$), 3.47 - 3.58 (m, 2 H, NCH$_A\underline{H}_B$CH$_2$CHC, N(CH$_2$)$_2$C$\underline{H}$), 3.92 (s, 3 H, COOC$\underline{H}_3$), 3.95 - 4.07 (m, 2 H, NC$\underline{H}$, C=CHC$\underline{H}_A$H$_B$), 4.12 (dd, *J* = 13.0, 6.5 Hz, 1 H, C=CHCH$_A\underline{H}_B$), 4.91 - 5.04 (m, 2 H, C$\underline{H}_2$=CH), 5.50 - 5.57 (m, 1 H, NCHC$\underline{H}$=CH), 5.67 (t, *J* = 6.5 Hz, 1 H, CHC=C$\underline{H}$), 5.73 - 5.87 (m, 2 H, NCHCH=C$\underline{H}$, CH$_2$=C$\underline{H}$),

7.22 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.99 (d, *J* = 8.0 Hz, 2 H, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C -5.3 (Si*C*H_3), -5.1 (Si*C*H_3), 18.2 (*C*$(CH_3)_3$), 25.1 (C_{quat}CH*C*H_2), 25.5 (CH=CH*C*H_2), 25.8 (C(*C*$H_3)_3$), 25.9 (CHNCH$_2$*C*H_2), 26.1 (CH_2=CHCH$_2$*C*H_2), 26.3 (CH_2=CH(CH$_2)_2$*C*H_2), 27.3 (CH=CHCH$_2$*C*H_2), 33.4 (CH_2=CH*C*H_2), 34.3 (NCH*C*H_2), 41.9 (CHN*C*H_2), 44.5 (C_{quat}*C*HCH$_2$), 46.2 (N*C*H$_2$CH$_2$CH), 47.8 (N*C*H$_2$(CH$_2)_3$CH=CH$_2$), 52.1 (COO*C*H_3), 54.9 (N*C*H), 57.1 (C(O)*C*C(O)), 60.5 (*C*H_2OSi), 114.6 (*C*H_2=CH), 128.5 (Ar*C*), 129.1 (Ar*C*), 129.4 (ArC_{quat}), 129.8 (NCH*C*H=CH), 130.6 (CHC=*C*H), 133.1 (CH_2=*C*H), 138.6 (NCHCH=*C*H), 140.8 (ArC_{quat}), 143.0 (CH*C*=CH), 166.7 (*C*=O), 170.6 (*C*=O), 172.2 (*C*=O); ***m/z*** (ESI$^+$) 635 (40%, $[M+H]^+$), 657 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{37}H_{54}N_2NaO_5Si$) requires *m/z* 635.3875, found *m/z* 635.3884.

(9'*Z*,10a'*S*)-4-[(1*E*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}prop-1-en-1-yl]-1-(hex-5-en-1-yl)-1',5',6',7',8',10a'-hexahydro-2*H*-spiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocine]-2,3'-dione (455)

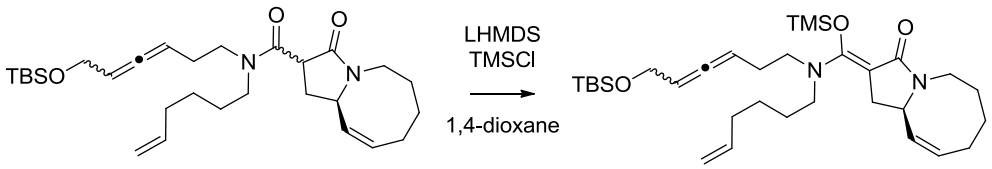


450 **260** **455a/a':455b/b'**

To amide **450** (1.5 eq, 0.060 mmol, 30 mg) was added KHMDS (1.7 eq, 0.068 mmol, 1.0 M soln. in hexanes, 68 µL) dropwise and the resulting mixture was stirred for 20 min. To the solution was added a suspension of $Pd(dppf)Cl_2$ (10 mol%, 0.004 mmol, 3 mg) and aryl iodide **260** (1.0 eq, 0.040 mmol, 11 mg) in 1,4-dioxane (10 mL/mmol **450**, 0.60 mL) and the resulting mixture was stirred at 95 °C. After 16 h, the reaction mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (1:1 EtOAc:PE → EtOAc) to yield the title compound **455** (15 mg, 78%, dr 2:1 **455a/a'**:**455b/b'**) as a yellow oil. **$[\alpha]_D^{24}$** = −22.2 (c = 0.04, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2927 (C-H), 1645 (C=O), 1626 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.03 (s, 6 H, Si(C*H*$_3)_2$ of 2 diastereomers), 0.04 (s, 6 H, Si(C*H*$_3)_2$ of

2 diastereomers), 0.86 (s, 9 H, SiC(C$\underline{H}_3$)$_3$ of 2 diastereomers), 0.90 (s, 9 H, SiC(C$\underline{H}_3$)$_3$ of 2 diastereomers), 1.12 - 1.74 (m, 8 H, CHNCH$_2$C$\underline{H}_2$, CH$_2$=CHCH$_2$C$\underline{H}_2$, CH=CHCH$_2$C$\underline{H}_A$H$_B$, CCHC$\underline{H}_A$H$_B$, CH$_2$=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.78 - 2.56 (m, 8 H, CCHCH$_A$$\underline{H}_B$, CH=CHCH$_2CH_A$$\underline{H}_B$, NCHC$\underline{H}_2$, CH$_2$=CHC$\underline{H}_2$, CH=CHC$\underline{H}_2$), 3.02 - 3.79 (m, 7 H, CHNC$\underline{H}_2$, NC$\underline{H}_2$CH$_2$CHC, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_2$, C$_{quat}$C$\underline{H}$), 3.81 - 3.93 (m, 2 H, C$\underline{H}_2$OTBS), 4.25 - 4.35 (m, 1 H, NC$\underline{H}$ of 2 diastereomers), 4.42 - 4.58 (m, 1 H, NC$\underline{H}$ of 2 diastereomers), 4.88 - 5.06 (m, 2 H, C$\underline{H}_2$=CHCH$_2$), 5.31 - 5.60 (m, 2 H, NCHC$\underline{H}$=CH, TBSOCH$_2$C$\underline{H}$), 5.69 - 6.00 (m, 3 H, NCHCH=C$\underline{H}$, CH$_2$=C$\underline{H}$, TBSOCH$_2$CH=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C [-5.4, -5.3, -5.3, -5.1] (Si($\underline{C}$H$_3$)$_2$), [18.0, 18.2, 18.2, 18.3] ($\underline{C}$(CH$_3$)$_3$), 23.1 (CHNCH$_2$$\underline{C}H_2$), [25.4, 25.5, 25.6, 25.9] (C($\underline{C}$H$_3$)$_3$), 26.1 (CH$_2$=CH(CH$_2$)$_2$$\underline{C}H_2$), 26.2 (CH$_2$=CHCH$_2$$\underline{C}H_2$), 26.4 (CH=CH$\underline{C}H_2$), [26.9, 27.0, 27.0] (NCH$_2$$\underline{C}H_2$CH), [27.3, 27.4, 27.6] (CH=CHCH$_2$$\underline{C}H_2$), [29.9, 30.8, 31.0, 31.9] (CH$_2$=CH$\underline{C}$H$_2$), [33.2, 33.3, 33.4, 33.4] (NCH$\underline{C}$H$_2$), 40.9 (N$\underline{C}$H$_2$CH$_2$CH), [41.4, 41.4] (CH$_2$=CH(CH$_2$)$_3$$\underline{C}H_2$), [45.2, 45.2, 45.5, 45.7] (C$_{quat}$$\underline{C}$H), [46.3, 46.4, 46.5, 46.6] (CHN$\underline{C}$H$_2$), [47.6, 48.1, 48.3] (TBSO$\underline{C}$H$_2$), 53.8 (N$\underline{C}$H of 2 diastereomers), [55.3, 55.5] (N$\underline{C}$H of 2 diastereomers), 62.0 ($\underline{C}_{quat}$CH) [114.5, 114.5, 114.6, 114.9] ($\underline{C}$H$_2$=CH), [117.0, 117.4] (TBSOCH$_2$CH=$\underline{C}$H), [128.5, 128.8] (NCH$\underline{C}$H=CH), 130.3 (TBSOCH$_2$$\underline{C}$H), 132.6 (CH$_2$=$\underline{C}$H), [138.1, 138.6, 138.7] (NCHCH=$\underline{C}$H), [166.8, 167.0, 168.5, 169.0, 170.0, 170.1, 170.4] ($\underline{C}$=O); ***m/z*** (ESI$^+$) 501 (35%, [M+H]$^+$), 523 (100, [M+Na]$^+$); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{29}H_{48}N_2NaO_3Si$) requires *m/z* 523.3326, found *m/z* 523.3321.

(2*Z*,9*Z*,10a*R*)-2-[5-(Hex-5-en-1-yl)-2,2,12,12,13,13-hexamethyl-3,11-dioxa-5-aza-2,12-disilatetradeca-8,9-dien-4-ylidene]-1,5,6,7,8,10a-hexahydropyrrolo[1,2-*a*]azocin-3(2H)-one (456)



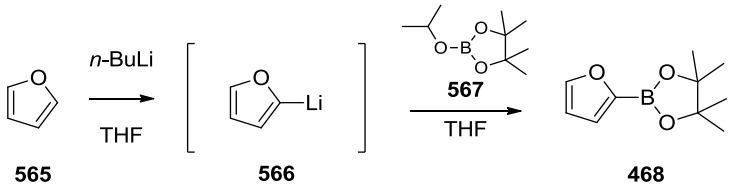
450 **456a/a'**

To bis-amide **450** (1.0 eq., 0.040 mmol, 20 mg) was added LHMDS (1.2 eq., 0.05 mmol, 1.0 M soln. in hexanes, 50 µL) dropwise at RT. After 30 min, TMSCl (3.0 eq., 0.12 mmol, 15 µL) was added. After 1 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (9:1 PE: EtOAc → 4:1 PE:EtOAc → 1:1 PE:EtOAc) to yield the title compound **456** (6 mg, 26%, dr 1:1[xxv]) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 2929 (C-H), 2856 (C-H), 1964 (C=C=C), 1701 (C=O), 1636 (C=O); **$[\alpha]_D^{24}$ =** −20.4 (c = 0.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.08 (s, 6 H, O(*t*BuSi(C$\underline{H}_3$)$_2$), 0.18 (s, 9 H, C=COSi(C$\underline{H}_3$)$_3$ DS1), 0.90 (s, 9 H, OSiC(C$\underline{H}_3$)$_3$), 1.49 - 1.69 (m, 6 H, CHNCH$_2$CH$_2$C$\underline{H}_2$, CH$_2$=CHCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 2.02 - 2.40 (m, 9 H, CHNCH$_2$C$\underline{H}_2$, NCHC$\underline{H}_A$H$_B$, CH=C=CHC$\underline{H}_2$, CH$_2$=CHC$\underline{H}_2$, NCHCH=CHC$\underline{H}_2$), 2.47 - 2.58 (m, 1 H, NCHCH$_A$$\underline{H}_B$), 2.98 - 3.09 (m, 1 H, CHNC$\underline{H}_A$H$_B$), 3.19 - 3.65 (m, 5 H, NC$\underline{H}_2$CH$_2$C=C$_{quat}$, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_2$, CHNCH$_A$$\underline{H}_B$), 4.11 - 4.22 (m, 2 H, TBSOC$\underline{H}_2$), 4.31 - 4.35 (m, 1 H, NC$\underline{H}$CH=CH), 4.93 - 5.04 (m, 2 H, C$\underline{H}_2$=CHCH$_2$), 5.12 - 5.34 (m, 2 H, $\underline{H}$C=C=C$\underline{H}$), 5.39 - 5.54 (m, 1 H, NCHC$\underline{H}$=CH), 5.75 - 5.88 (m, 2 H, NCHCH=C$\underline{H}$, CH$_2$=C$\underline{H}$CH$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C -5.3 (Si(*t*Bu)($\underline{C}$H$_3$)$_2$), [1.5, 1.8] (C=COSiC($\underline{C}$H$_3$)$_3$), 18.3 ($\underline{C}$(CH$_3$)$_3$), [25.1, 25.5, 25.9, 26.2, 26.2, 26.4, 26.6, 27.5, 27.6, 27.8, 27.9, 28.3, 29.2, 29.7] (SiC($\underline{C}$H$_3$)$_3$, $\underline{C}$H$_2$$\underline{C}H_2$CH=CHCH, $\underline{C}$H$_2$$\underline{C}H_2CH_2$CH=CH$_2$, NCH$_2$$\underline{C}H_2$CH=C$_{quat}$, CHNCH$_2$$\underline{C}H_2$), [33.5, 33.6] (CH$_2$=CH$\underline{C}H_2$), [40.8, 40.9] (CHN$\underline{C}H_2$), 41.0 (NCH$\underline{C}H_2$), 41.9 (CH$_2$=CH(CH$_2$)$_3$$\underline{C}H_2$), [46.8, 47.0] (N$\underline{C}H_2CH_2$C=C$_{quat}$), 52.7 (N$\underline{C}HCH_2$), [61.7, 61.8] (TBSO$\underline{C}H_2$), [82.8, 82.9] (NC(O)$\underline{C}$=COTMS), [83.4, 83.5] (NC(O)C=$\underline{C}$OTMS), [89.1, 92.2, 92.4] (H$\underline{C}$=C=$\underline{C}$H), [114.5, 114.8] ($\underline{C}$H$_2$=CH), [129.2,

[xxv] By ^{13}C NMR spectroscopy

129.3] (NCH<u>C</u>H=CH), [132.7, 132.7] (NCHCH=<u>C</u>H), [138.3, 138.4] (CH_2=<u>C</u>H), [170.2, 170.4] (C=O), 203.7 (HC=<u>C</u>=CH); ***m/z*** (ESI^+) 611 (100%, $[M+K]^+$); **HRMS** (TOF MS EI+) exact mass calculated for $[M+H]^+$ ($C_{32}H_{57}N_2O_3Si_2$) requires *m/z* 573.3902 found $[M+H]^+$ *m/z* 573.4779.

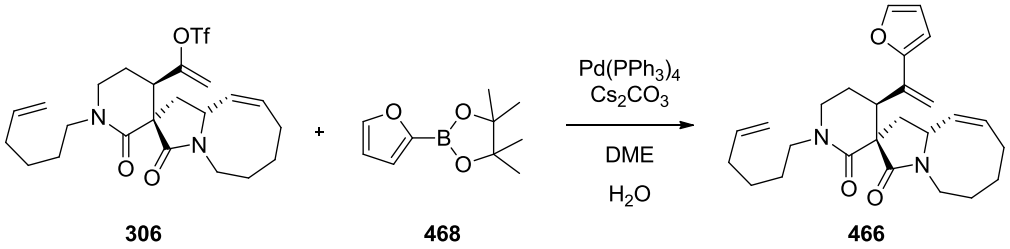
2-(2-Furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (468)



565 **566** **468**

According to literature procedure,[177] to furan **565** (1.2 eq, 14.0 mol, 1.06 mL) in tetrahydrofuran (5 mL/mmol **565**, 70 mL) was added *n*-BuLi (1.0 eq, 12.4 mmol, 2.5 M in cyclohexanes, 4.9 mL) at 0 ˚C. After 30 min, the reaction was warmed to RT and was stirred for a further 30 min before being cooled to −78 ˚C. Neat 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **567** (1.3 eq, 16.0 mmol, 3.28 mL) was added dropwise and the reaction mixture was warmed to RT. Ammonium chloride (saturated aqueous, 30 mL) and Et_2O (40 mL) were added and the aqueous and organic layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed (water, 40 mL then brine, 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (PE → 9:1 PE:EtOAc) to yield the title compound **468** (1.79 g, 66%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.32 (s, 12 H, 4 × C<u>*H*</u>$_3$), 6.41 (dd, *J* = 3.5, 1.5 Hz, 1 H, Ar<u>*H*</u>), 7.04 (d, *J* = 3.5 Hz, 1 H, Ar<u>*H*</u>), 7.62 (d, *J* = 1.5 Hz, 1 H, Ar<u>*H*</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.7 (<u>*C*</u>H$_3$), 67.2 (<u>*C*</u>$_{quat}$(CH$_3$)$_2$), 84.1 (Ar<u>*C*</u>$_{quat}$), 110.3 (Ar<u>*C*</u>), 123.2 (Ar<u>*C*</u>), 147.3 (Ar<u>*C*</u>). Data in accordance with literature.[177]

(3*R*,4*S*,9'*Z*,10a'*R*)-4-[1-(2-Furyl)vinyl]-1-(hex-5-en-1-yl)-1',5',6',7',8',10a'-hexahydro-2 H-spiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocine]-2,3'-dione (466)

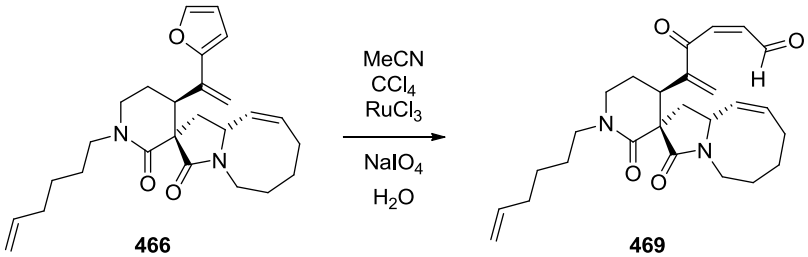


306 **468** **466**

Triflate **306** (1.0 eq, 0.022 mmol, 11 mg), boronate ester **468** (3.0 eq, 0.065 mmol, 13 mg), $Pd(PPh_3)_4$ (0.1 eq, 0.0022 mmol, 2 mg) and Cs_2CO_3 (2.0 eq, 0.044 mmol, 14 mg) in dimethoxyethane (6.7 mL/mmol **306**, 0.15 mL) and water (1.3 mL/mmol **306**, 0.029 mL) was stirred at 75 ˚C for 4 h. Dichloromethane (1 mL) and water (1 mL) were added and the organic layer was separated. The aqueous layer was extracted (CH_2Cl_2, 3 × 1 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the title compound **466** (7 mg, 75%) as a yellow oil. $\mathbf{[\alpha]_D^{24}}$ = +61.4 (c = 0.35, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2931 (C-H), 2860 (C-H), 1758 (C=O), 1674 (C=O), 1636 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.26 - 1.48 (m, 4 H, $CHNCH_2C\underline{H}_AH_B$, $CHNCH_2CH_2C\underline{H}_AH_B$, $CH_2{=}CHCH_2C\underline{H}_2$), 1.60 - 1.69 (m, 3 H, $CHNCH_2CH_2CH_A\underline{H}_B$, $CH_2{=}CH(CH_2)_2C\underline{H}_2$), 1.69 - 1.76 (m, 1 H, $CCHC\underline{H}_AH_B$), 1.93 - 2.03 (m, 2 H, $CHNCH_2CH_A\underline{H}_B$, $CH{=}CHC\underline{H}_AH_B$), 2.04 - 2.14 (m, 3 H, $CH_2{=}CHC\underline{H}_2$, $NCHC\underline{H}_AH_B$), 2.21 - 2.31 (m, 1 H, $CH{=}CHCH_A\underline{H}_B$), 2.88 - 2.99 (m, 2 H, $NCHCH_A\underline{H}_B$, $CHNC\underline{H}_AH_B$), 2.99 - 3.04 (m, 1 H, $CC\underline{H}C$), 3.04 - 3.15 (m, 1 H, $CCHCH_A\underline{H}_B$), 3.40 - 3.48 (m, 4 H, $CH_2{=}CH(CH_2)_3C\underline{H}_2$, $NC\underline{H}_2CH_2CH$), 3.67 - 3.77 (m, 1 H, $CHNCH_A\underline{H}_B$), 3.85 (q, *J* = 8.0 Hz, 1 H, $NC\underline{H}$), 4.92 - 5.05 (m, 2 H, $C\underline{H}_2{=}CH$), 5.24 (br. s, 1 H, $C{=}C\underline{H}_AH_B$), 5.31 (dd, *J* = 10.0, 8.0 Hz, 1 H, $NCHC\underline{H}{=}CH$), 5.70 (br. s, 1 H, $C{=}CH_A\underline{H}_B$), 5.76 - 5.90 (m, 2 H, $CH_2{=}C\underline{H}$, $CHCH{=}C\underline{H}$), 6.42 (dd, *J* = 2.0 Hz, 1 H, $Ar\underline{H}$), 6.43 - 6.45 (m, 1 H, $Ar\underline{H}$), 7.40 (d, *J* = 1.5 Hz, 1 H, $Ar\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.8 ($NCH_2\underline{C}H_2CH$), 26.4 ($CH{=}CH\underline{C}H_2$), 27.8 ($CH_2{=}CH\underline{C}H_2$), 33.5 ($NCH\underline{C}H_2$), 36.7 ($CHN\underline{C}H_2$), 40.6 ($C\underline{C}HC$), 43.9 ($N\underline{C}H_2$), 47.7 ($N\underline{C}H_2$), 48.4 ($N\underline{C}H$), 57.3 ($C(O)\underline{C}C(O)$), 75.0 $CH\underline{C}{=}CH_2$), 106.1 ($Ar\underline{C}$), 111.4 ($Ar\underline{C}$), 112.6 ($C{=}\underline{C}H_2$), 114.6 ($\underline{C}H_2{=}CH$), 129.3 ($CH\underline{C}H{=}CH$), 134.9 ($CHCH{=}\underline{C}H$), 137.3 ($Ar\underline{C}_{quat}$), 138.7

(CH_2=<u>C</u>H), 142.4 (Ar<u>C</u>), 154.8 (Ar$\underline{C}_{quat}$), 169.4 (<u>C</u>=O), 171.6 (<u>C</u>=O); ***m/z*** (ESI^+) 423 (50%, $[M+H]^+$), 445 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{34}N_2O_3Na$) requires *m/z* 445.2462, found *m/z* 445.2448.

(2*Z*)-5-[(3*R*,4*S*,9'*Z*,10a'*R*)-1-(Hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]-4-oxohexa-2,5-dienal (469)

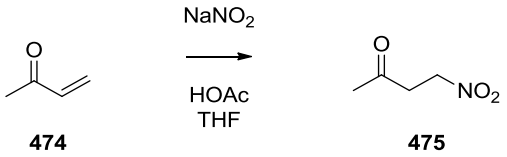


466 **469**

To furan **466** (1.0 eq, 0.024 mmol, 10 mg) and $RuCl_3$ (10% wt/wt, 1 mg) in acetonitrile (2.4 mL/mmol **466**, 0.057 mL) and tetrachloromethane (2.4 mL/mmol **466**, 0.057 mL) was added a solution of $NaIO_4$ (4.5 eq, 0.11 mmol, 23 mg) in water (3.6 mL/mmol **466**, 0.085 mL) and the reaction miuxture was stirred at RT. After 12 h, the reaction mixture was filtered through Celite®, the filter cake was washed with ethyl acetate (5 × 2 mL) and the eluent was concentrated *in vacuo*. The crude residue was partitioned between ethyl acetate (10 mL) and HCl (1 M, 10 mL) and the organic phase was washed (water, 2 mL then brine, 2 mL) dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:10 EtOAc:PE → MeOH) to yield the title compound **469** (4 mg, 39%) as a yellow oil. $\mathbf{[\alpha]_D^{24}}$ = +73.5 (c = 0.20, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2928 (C-H), 2858 (C-H), 1759 (C=O), 1671 (NC=O), 1634 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.18 - 1.70 (m, 8 H, CHNCH$_2$C<u>*H*</u>$_A$H$_B$, CH$_2$=CHCH$_2$C<u>*H*</u>$_2$, NCH$_2$C<u>*H*</u>$_A$H$_B$CH CH=CHCH$_2$C<u>*H*</u>$_A$H$_B$, CH=CHCH$_2$CH$_A$<u>*H*</u>$_B$, CH$_2$=CH(CH$_2$)$_2$C<u>*H*</u>$_2$), 1.94 - 2.18 (m, 5 H, CHNCH$_2$CH$_A$<u>*H*</u>$_B$, NCHC<u>*H*</u>$_A$H$_B$, CH$_2$=CHC<u>*H*</u>$_2$, CH=CHC<u>*H*</u>$_A$H$_B$), 2.29 - 2.39 (m, 1 H, CH=CHCH$_A$<u>*H*</u>$_B$), 2.81 (dd, *J* = 13.5, 8.5 Hz, 1 H, NCHCH$_A$<u>*H*</u>$_B$), 2.89 - 3.09 (m, 2 H, NCH$_2$CH$_A$<u>*H*</u>$_B$CH, CHNC<u>*H*</u>$_A$H$_B$), 3.31 - 3.57 (m, 5 H, CC<u>*H*</u>C, 2 × NC<u>*H*</u>$_2$), 3.59 - 3.68 (m, 1 H, CHNCH$_A$<u>*H*</u>$_B$), 3.75 (q, *J* = 8.0 Hz, 1 H, NC<u>*H*</u>), 4.91 - 5.07 (m, 2 H, C<u>*H*</u>$_2$=CH), 5.40

(dd, *J* = 11.0, 7.0 Hz, 1 H, NCHC*H*=CH), 5.73 - 5.97 (m, 2 H, CH_2=C*H*CH_2, NCHCH=C*H*), 6.34 (br. s, 1 H, CHC=CH_AH_B), 6.35 (br. s, 1 H, CHC=CH_AH_B), 6.92 (dd, *J* = 15.5, 7.0 Hz, 1 H, C(O)CH=C*H*C(O)H), 7.54 (d, *J* = 15.5 Hz, 1 H, C(O)C*H*=CHC(O)H), 9.84 (d, *J* = 7.0 Hz, 1 H, C(O)*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.5 (NCH_2CH_2CH), 26.1 (CH_2=$CHCH_2CH_2$), 26.4 (CH_2=$CH(CH_2)_2CH_2$), 26.4 (CHCH=$CHCH_2$), 27.5 ($HCNCH_2CH_2CH_2$), 27.6 ($HCNCH_2CH_2$), 33.4 (CH_2=$CHCH_2$), 36.6 ($NCHCH_2$), 39.0 ($C_{quat}CH$), 40.8 ($HCNCH_2$), 47.4 (CH_2=$CH(CH_2)_3CH_2$), 48.5 (NCH_2CH_2CH), 53.5 (NCH), 57.1 ($C_{quat}CH$), 114.7 (CH_2=CH), 129.0 ($NCHCH$=CH), 131.0 (C=CH_2), 134.7 (NCHCH=CH), 138.6 (CH_2=CH), 139.2 (CH=CHCHO), 140.4 (CH=CHCHO), 148.6 (C_{quat}=CH_2), 169.0 (NC=O), 171.6 (NC=O), 190.3 (C=O), 192.1 (C=O); ***m/z*** (ESI^+) 437 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{34}N_2O_4Na$) requires *m/z* 461.2411, found *m/z* 461.2410.

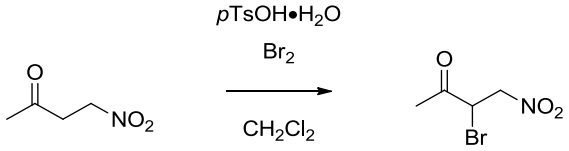
4-Nitrobutan-2-one (475)



474 **475**

To methyl vinyl ketone **474** (1.0 eq, 0.071 mol, 5.8 mL) and sodium nitrite (2.0 eq, 0.14 mol, 9.7 g) in tetrahydrofuran (0.41 mL/mmol **474**, 29 mL) was added glacial acetic acid (2.0 eq, 0.14 mol, 8.0 mL) at RT. After 24 h, water (30 mL) and ethyl acetate (30 mL) were added. The organic and aqueous layers were separated and the aqueous layer was extracted (EtOAc, 3 × 30 mL). The combined organics were washed (water, 40 mL then brine, 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (toluene → 20:1 toluene:Et_2O) to yield the title compound **475** (4.79 g, 58%) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 1718 (C=O), 1553 (NO_2), 1374 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.27 (s, 3 H, C$\underline{H}_3$), 3.10 (t, *J* = 6.0 Hz, 2 H, C(O)C$\underline{H}_2$), 4.64 (t, *J* = 6.0 Hz, 2 H, C$\underline{H}_2NO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 29.8 ($\underline{C}H_3$), 39.0 ($\underline{C}H_2CH_2NO_2$), 68.9 ($\underline{C}H_2NO_2$), 203.8 ($\underline{C}$=O). Data are in agreement with literature.[184]

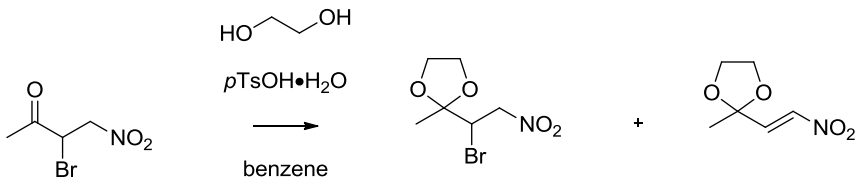
3-Bromo-4-nitrobutan-2-one (476)



475 **476**

To 4-nitrobutan-2-one **475** (1.0 eq, 88 mmol, 10.3 g) and *p*-toluenesulfonic acid monohydrate (0.1 eq, 8.80 mmol, 1.23 g) in dichloromethane (1.17 mL/mmol **475**, 96.8 mL) was added bromine (1.0 eq, 88.0 mmol, 4.52 mL) dropwise at RT. After 20 min, the reaction mixture was poured on to ice water (60 mL) and extracted (CH_2Cl_2, 3 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude title compound **476** (15.8 g, 91%) which was used without further purification. **IR** ν_{max}(film)/cm^{-1} 1722 (C=O), 1558 (NO_2), 1377 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.49 (s, 3 H, C$\underline{H}_3$), 4.68 (dd, *J* = 15.0, 5.0 Hz, 1 H, C$\underline{H}_A$H$_B$NO$_2$), 4.88 (dd, *J* = 9.0, 5.0 Hz, 1 H, C$\underline{H}$Br), 5.09 (dd, *J* = 15.0, 9.0 Hz, 1 H, CH$_A$$\underline{H}_BNO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 27.1 ($\underline{C}H_3$), 41.3 ($\underline{C}$HBr), 74.2 ($\underline{C}H_2NO_2$), 198.4 ($\underline{C}$=O). Data are in agreement with literature.[184]

2-(1-Bromo-2-nitroethyl)-2-methyl-1,3-dioxolane (477)

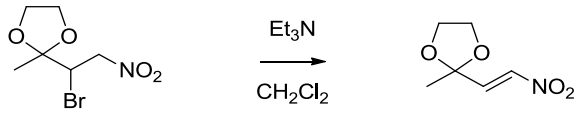


476 **477** **473**

To 3-bromo-4-nitrobutan-2-one **476** (1.0 eq, 93.3 mmol, 15.8 g) in benzene (1.51 mL/mmol **476**, 140.8 mL) was added ethylene glycol (2.36 mL/mmol **476**, 37.2 mL) and *p*-toluenesulfonic acid monohydrate (0.1 eq, 9.33 mmol, 1.31 g) at RT and the reaction mixture was stirred at reflux for 16 h with azeotropic removal of water. After cooling to RT, $NaHCO_3$ (saturated aqeous, 120 mL) was added and the organic and aqueous layers were separated. The aqueous layer was extracted (EtOAc, 3 × 100 mL), and the combined organics were washed (water, 200 mL then brine, 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude residue as a 3:1 mixture **477**:**473** which was passed through a plug of silica (1:10 EtOAc:PE) to yield a mixture of **477** and **473** (3:1 **477**:**473,** 11 g). **IR** ν_{max}(film)/cm^{-1} 1722 (C=O), 1558 (NO_2), 1377 (NO_2); **^{1}H NMR**[xxvi] (400 MHz, $CDCl_3$) δ_H 1.55 (s, 3H, C$\underline{H}_3$), 4.05 - 4.21 (m, 4H, OC$\underline{H}_2$C$\underline{H}_2$O), 4.60 - 4.64 (m, 1 H, C$\underline{H}$Br), 4.94 (dd, *J* = 12.0, 3.0 Hz, 2 H, C$\underline{H}_2NO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.6 ($\underline{C}H_3$), 49.4 ($\underline{C}H_2$Br), 65.6, 65.7 (O$\underline{C}H_2\underline{C}H_2$O), 77.8 ($\underline{C}H_2NO_2$), 108.4 ($\underline{C}_{quat}$). Data are in agreement with literature.[184]

[xxvi] Only peaks of bromide **477** are quoted. See the next page for elimination product **473**.

2-Methyl-2-[(*E*)-2-nitrovinyl]-1,3-dioxolane (473)

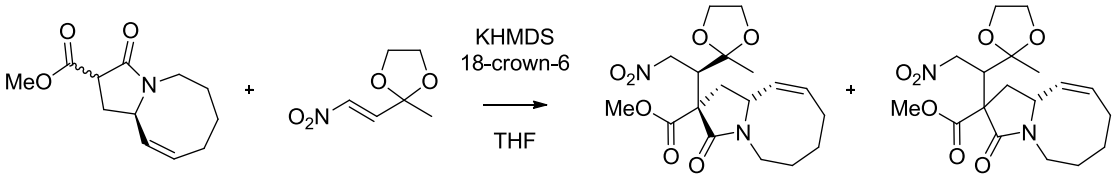


477 **473**

To a 3:1 mixture of **477**:**473** (1.0 eq, 45.8 mmol, 11.0 g) in dichloromethane (3.4 mL/mmol **477**, 116 mL) was added triethylamine (0.8 eq, 36.6 mmol, 4.9 mL) at RT. When the reaction was complete by TLC (typically 30 min) the reaction mixture was diluted with water. The organic layer was separated and the aqueous layer was extracted (CH_2Cl_2, 3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the crude residue which was purified by flash column chromatography (1:10 EtOAc:PE) to yield the title compound **473** (6.58 g, 90%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.56 (s, 3 H, C$\underline{H}_3$), 3.89 - 3.95 (m, 2 H, OC$\underline{H}_2$), 4.01 - 4.07 (m, 2 H, OC$\underline{H}_2$), 7.02 - 7.08 (m, 1 H, CC$\underline{H}$=CH), 7.10 - 7.19 (m, 1 H, CCH=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.8 ($\underline{C}H_3$), 60.4 (O$\underline{C}H_2$), 65.2 (O$\underline{C}H_2$), 105.3 ($\underline{C}_{quat}$), 140.1 (HC=$\underline{C}$H), 140.3 (HC=$\underline{C}$H). Data are in agreement with literature.[12]

Methyl (2*S*,9*Z*,10a*R*)-2-[(1*S*)-1-(2-methyl-1,3-dioxolan-2-yl)-2-nitroethyl]-3-oxo-1,2,3,5,6,7,8, 10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylate (472a)

Methyl (2*S*,9*Z*,10a*R*)-2-[(1*R*)-1-(2-methyl-1,3-dioxolan-2-yl)-2-nitroethyl]-3-oxo-1,2,3,5,6,7,8, 10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylate (472b)



146 **473** **472a** **472b**

A solution of ester **146** (1.0 eq, 0.450 mmol, 101 mg) in tetrahydrofuran (6.3 mL/mmol **146**, 2.8 mL) was cooled to −78 ˚C. KHMDS (1.05 eq, 0.47 mmol, 0.5 M in toluene, 0.94 mL) was added dropwise and the reaction mixture was stirred for 15 min. The reaction mixture was cooled to −94 ˚C and the nitroalkene **473** (2.0 eq, 0.910 mmol, 145 mg) and 18-crown-6 (1.05 eq, 0.470 mmol, 124 mg) in tetrahydrofuran (2.4 mL/mmol **146**, 2.2 mL) were added to the reaction mixture over 1 h.[xxvii] After 1 h, acetic acid was added (glacial, 3.0 eq, 1.35 mmol, 76 µL) and and reaction mixture was warmed to RT before being concentrated *in vacuo* to furnish the crude residue (dr 5:1) which was purified by flash column chromatography (2:1 Et_2O:PE → 4:1 Et_2O:PE → Et_2O) to yield **472a** (139 mg, 81%) and **472b** (22 mg, 13%) as a colourless solid and an orange oil respectively.

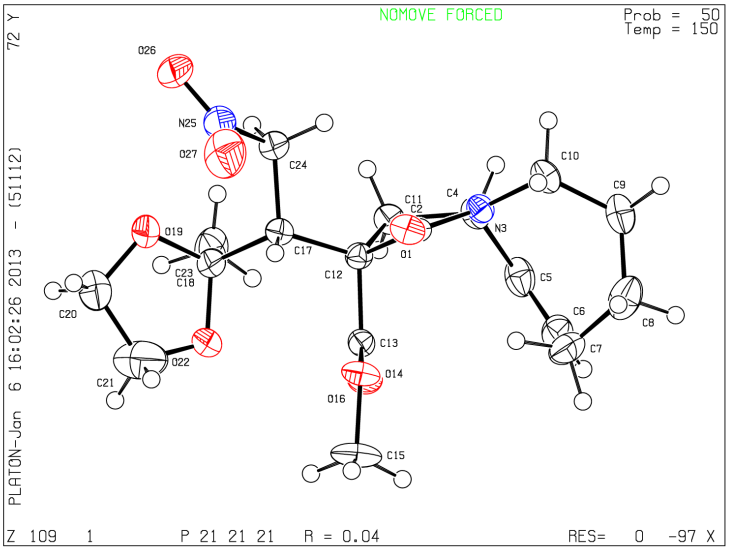
472a (desired): **m.p.** 148 – 150 ˚C (MeOH:Et_2O 1:1); **$[\alpha]_D^{24}$** = −23.1 (c = 1.09, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2935 (C-H), 1733 (C=O), 1686 (C=O), 1556 (NO_2), 1379 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.31 (s, 3 H, $C_{quat}C\underline{H}_3$), 1.53 (td, *J* = 9.0, 5.0 Hz, 1 H, $NCH_2CH_2C\underline{H}_AH_B$), 1.60 - 1.73 (m, 2 H, $NCH_2C\underline{H}_AH_B$, $NCH_2CH_2CH_A\underline{H}_B$), 1.74 - 1.87 (m, 1 H, $NCH_2CH_A\underline{H}_B$), 2.08 - 2.28 (m, 2 H, $CH{=}CHC\underline{H}_2$), 2.40 - 2.50 (m, 1 H, $NCHC\underline{H}_AH_B$), 2.53 - 2.61 (m, 1 H, $NCHCH_A\underline{H}_B$), 3.32 - 3.41 (m, 1 H, $NC\underline{H}_AH_B$), 3.47 - 3.57 (m, 1 H, $NCH_A\underline{H}_B$), 3.73 (s, 3 H, $OC\underline{H}_3$), 3.82 - 3.96 (m, 5 H,

[xxvii] When nitroalkene **473** and 18-crown-6 was added at −78 ˚C, crude dr = 3:1.

$O_2NCH_2C\underline{H}$, $OC\underline{H}_2C\underline{H}_2O$), 4.20 - 4.31 (m, 2 H, $NC\underline{H}$, $O_2NC\underline{H}_AH_B$), 4.64 (dd, *J* = 14.5, 7.5 Hz, 1 H, $O_2NCH_A\underline{H}_B$), 5.57 (dd, *J* = 11.0, 6.0 Hz, 1 H, $CHC\underline{H}$=CH), 5.69 - 5.83 (m, 1 H, CHCH=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 22.9 ($HCC_{quat}\underline{C}H_3$), 24.6 (CH=CH$\underline{C}H_2$), 24.8 ($NCH_2\underline{C}H_2$), 27.3 ($NCH_2CH_2\underline{C}H_2$), 31.4 ($NCH\underline{C}H_2$), 42.5 ($N\underline{C}H_2$), 47.4 ($O_2NCH_2\underline{C}H$), 52.9 ($O\underline{C}H_3$), 54.2 ($N\underline{C}HCH_2$), 57.3 (C(O)$\underline{C}_{quat}$C(O)), 64.1, 64.7 ($O\underline{C}H_2\underline{C}H_2O$), 74.2 ($O_2N\underline{C}H_2$), 109.8 ($HC\underline{C}_{quat}CH_3$), 130.1 (CHCH=$\underline{C}$H), 131.4 (CH$\underline{C}$H=CH), 169.3 ($\underline{C}$=O), 170.8 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 383 (40%, $[M+H]^+$), 405 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2O_7Na$) requires *m/z* 405.1632, found *m/z* 405.1621.

472b: **$[\alpha]_D^{24}$** = +97.6 (c = 0.25, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2936 (C-H), 2898 (C-H), 1736 (MeOC=O), 1681 (NC=O), 1556 (NO_2), 1380 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.30 (s, 3 H, $C_{quat}C\underline{H}_3$), 1.40 - 1.77 (m, 3 H, $CHCH=CHCH_2C\underline{H}_2$, $CHNCH_2C\underline{H}_AH_B$), 1.87 - 2.00 (m, 1 H, $CHNCH_2CH_A\underline{H}_B$), 2.19 - 2.35 (m, 2 H, $CHCH=CHC\underline{H}_2$), 2.58 (dd, *J* = 13.5, 7.0 Hz, 1 H, $NCHC\underline{H}_AH_B$), 2.87 (dd, *J* = 13.5, 7.0 Hz, 1 H, $NCHCH_A\underline{H}_B$), 3.21 - 3.33 (m, 2 H, $CHNC\underline{H}_AH_B$, $C_{quat}C\underline{H}$), 3.56 - 3.61 (m, 1 H, $CHNCH_A\underline{H}_B$), 3.73 (s, 3 H, $COOC\underline{H}_3$), 3.75 - 4.01 (4 H, $OC\underline{H}_2C\underline{H}_2O$), 4.33 (d, *J* = 7.0 Hz, 1 H, $NC\underline{H}$), 4.81 (dd, *J* = 15.0, 8.0 Hz, 1 H, $NO_2C\underline{H}_AH_B$), 5.24 - 5.33 (m, 1 H, $NO_2CH_A\underline{H}_B$), 5.48 (dd, *J* = 11.0, 7.0 Hz, 1 H, $NCHC\underline{H}$=CH), 5.88 - 5.97 (m, 1 H, NCHCH=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 23.5 ($C_{quat}\underline{C}H_3$), 26.3 ($CH=CHC\underline{H}_2$), 26.9 ($CHNCH_2\underline{C}H_2$), 27.7 ($CH=CHCH_2\underline{C}H_2$), 34.8 ($NCH\underline{C}H_2$), 42.2 ($CHN\underline{C}H_2$), 48.0 ($C_{quat}\underline{C}H$), 53.3 ($H_3\underline{C}OOC$), 53.4 ($N\underline{C}H$), 57.0 ($\underline{C}_{quat}CO$), 65.0 ($O\underline{C}H_2CH_2O$), 65.1 ($OCH_2\underline{C}H_2O$), 74.6 ($\underline{C}H_2NO_2$), 110.6 ($\underline{C}_{quat}(O)_2$), 129.1 ($NCH\underline{C}H$=CH), 134.6 (NCHCH=$\underline{C}$H), 170.5 ($\underline{C}$=O), 171.1 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 383 (60%, $[M+H]^+$), 405 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2O_7Na$) requires *m/z* 405.1632, found *m/z* 405.1630.

Single crystal X-ray diffraction data for 472a



Crystal data ***472a***

$C_{18}H_{26}N_2O_7$	D_x = 1.350 Mg m^{-3}
M_r = 382.41	Mo $K\alpha$ radiation, λ = 0.71073 Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 2483 reflections
a = 6.2343 (1) Å	θ = 5–27°
b = 13.9146 (2) Å	μ = 0.10 mm^{-1}
c = 21.6936 (3) Å	T = 150 K
V = 1881.87 (5) Å^3	Block, Colourless
Z = 4	0.48 × 0.36 × 0.20 mm
F(000) = 816	

Data collection

Nonius KappaCCD diffractometer	2024 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	R_{int} = 0.023
ω scans	θ_{max} = 27.5°, θ_{min} = 5.2°
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	h = −8→8

T_{min} = 0.96, T_{max} = 0.98	k = −17→18
4280 measured reflections	l = −27→28
2464 independent reflections	

Refinement

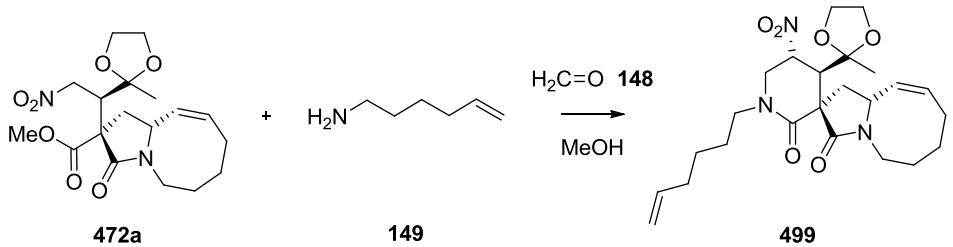
Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.041	H-atom parameters constrained
	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)]
$wR(F^2)$ = 0.103	where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 17.9 28.5 15.9 5.80 1.01
S = 0.91	$(\Delta/\sigma)_{max}$ = 0.0003268
2464 reflections	$\Delta\rho_{max}$ = 0.25 e Å^{-3}
244 parameters	$\Delta\rho_{min}$ = −0.27 e Å^{-3}
0 restraints	

Special details

Experimental. The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1K.

Cosier, J. & Glazer, A.M., 1986. J. Appl. Cryst. 105-107.

(3*R*,4*S*,5*R*,9'*Z*,10a'*R*)-1-(Hex-5-en-1-yl)-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitro-1',5',6',7',8', 10a'-hexahydro-2 H-spiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocine]-2,3'-dione (499)

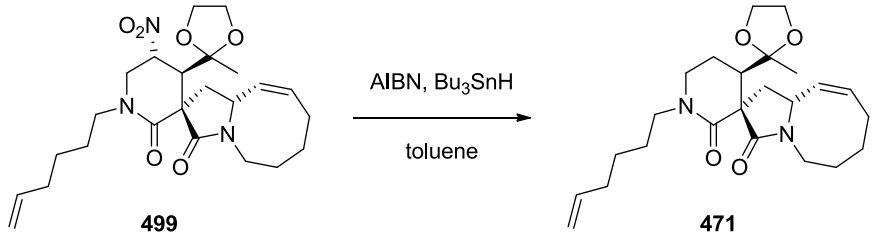


472a **149** **499**

A solution of ester **472a** (1.0 eq, 7.6 mmol, 2.9 g), amine **149** (3.0 eq, 23 mmol, 2.3 g) and formaldehyde **148** (3.0 eq, 23 mmol, 37% soln in water, 1.7 mL) in methanol (1 mL) was heated to 70 ˚C. After 2 h, the reaction mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (2:1 PE:Et_2O → 3:1 PE:Et_2O → 5:1 PE:Et_2O) to yield the title compound **499** (3.2 g, 91%) as a yellow oil. **$[\alpha]_D^{24}$** = +70.3 (c = 1.6, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2931 (C-H), 2859 (C-H), 1669 (2 × NC=O), 1555 (NO_2), 1372 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.29 - 1.37 (m, 2 H, CH_2=CHCH$_2$C$\underline{H}_2$), 1.39 - 1.50 (m, 3 H, CH=CHCH$_2$C$\underline{H}_A$H$_B$, CH_2=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.51 - 1.60 (m, 1 H, CHNCH$_2$C$\underline{H}_A$H$_B$), 1.65 - 1.74 (m, 1 H, CH=CHCH$_2$CH$_A\underline{H}_B$), 1.82 - 1.94 (m, 1 H, CHNCH$_2$CH$_A\underline{H}_B$), 2.00 - 2.09 (m, 2 H, CH_2=CHC$\underline{H}_2$), 2.17 (s, 3 H, C$\underline{H}_3$), 2.19 - 2.31 (m, 2 H, CH=CHC$\underline{H}_2$), 2.65 (dd, *J* = 13.0, 9.0 Hz, 1 H, NCHC$\underline{H}_A$H$_B$), 2.97 (dd, *J* = 13.0, 5.0 Hz, 1 H, NCHCH$_A\underline{H}_B$), 3.15 - 3.22 (m, 2 H, CC$\underline{H}$, CHNC$\underline{H}_A$H$_B$), 3.26 - 3.33 (m, 1 H, CH_2=CH(CH$_2$)$_3$C$\underline{H}_A$H$_B$), 3.34 - 3.42 (m, 1 H, CH_2=CH(CH$_2$)$_3$CH$_A\underline{H}_B$), 3.47 (dd, *J* = 14.0, 3.5 Hz, 1 H, NC$\underline{H}_A$H$_B$CHNO$_2$CH), 3.52 (dd, *J* = 14.0, 9.0 Hz, 1 H, CHNCH$_A\underline{H}_B$), 3.68 - 3.75 (m, 1 H, OCH$_2$C$\underline{H}_A$H$_B$O), 3.79 - 3.85 (m, 1 H, OCH$_2$CH$_A\underline{H}_B$O), 3.89 - 4.00 (m, 2 H, OC$\underline{H}_2$CH$_A$H$_B$O), 4.37 - 4.45 (m, 1 H, NC$\underline{H}$), 4.87 (dd, *J* = 14.0, 6.5 Hz, 1 H, NCH$_A\underline{H}_B$C(H)NO$_2$CH), 4.91 - 5.03 (m, 2 H, C$\underline{H}_2$=CH), 5.43 (ddd, *J* = 8.0, 6.5, 3.0 Hz, 1 H, C($\underline{H}$)NO$_2$), 5.66 - 5.83 (m, 1 H, CHC$\underline{H}$=CH, CH_2=C$\underline{H}$), 5.84 - 5.92 (m, 2 H, CH_2=C$\underline{H}$, CHCH=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.7 (CH=CH$\underline{C}$H$_2$), 25.8 (CH_2=CHCH$_2\underline{C}$H$_2$), 25.9 (CHNCH$_2\underline{C}$H$_2$), 26.5 (CH_2=CH(CH$_2$)$_2\underline{C}$H$_2$), 27.8 (CH=CHCH$_2\underline{C}$H$_2$), 30.9 ($\underline{C}$H$_3$), 33.0 (NCH$\underline{C}$H$_2$), 33.3 (CH_2=CH$\underline{C}$H$_2$), 41.8 (CHN$\underline{C}$H$_2$), 47.2 (CH_2=CH(CH$_2$)$_3\underline{C}$H$_2$), 48.9 (N$\underline{C}$H$_2$C(H)NO$_2$), 49.5 (C$_{quat}\underline{C}$H), 52.2 (N$\underline{C}$H), 54.3 (C(O)$\underline{C}_{quat}$C(O)),

64.6, 65.1 (O<u>C</u>H$_2$<u>C</u>H$_2$O), 82.7 (<u>C</u>(H)NO$_2$), 109.8 (<u>C</u>(OCH$_2$CH$_2$O)), 113.8 (<u>C</u>H$_2$=CH), 130.3 (CH<u>C</u>H=CH), 132.6 (CHCH=<u>C</u>H), 138.4 (CH$_2$=<u>C</u>H), 168.4 (<u>C</u>=O), 170.9 (<u>C</u>=O); ***m/z*** (ESI$^+$) 462 (40%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{24}H_{35}N_3O_6Na$) requires *m/z* 484.2418, found *m/z* 484.2405.

(3*R*,4*R*,9'*Z*,10a'*R*)-1-(Hex-5-en-1-yl)-4-(2-methyl-1,3-dioxolan-2-yl)-1',5',6',7',8',10a'-hexa hydro-2H-spiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocine]-2,3'-dione (471)

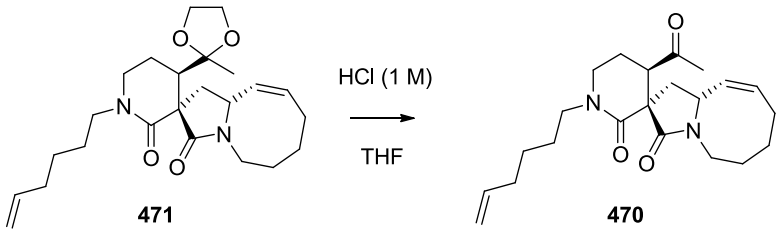


499 **471**

A solution of nitro acetal **499** (1.0 eq, 1.73 mmol, 0.798 g) in toluene (25 mL/mmol **499**, 43.2 mL) was degassed and purged (five cycles) with nitrogen. Bu_3SnH (5.0 eq, 8.65 mmol, 2.32 mL) and AIBN (0.2 eq, 0.34 mmol, 0.056 g) were added and the reaction mixture was further degassed and purged (five cycles). The reaction mixture was heated at reflux for 3 h before being cooled to RT and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Et_2O) to yield title compound **471** (0.51 g, 71%) as a yellow oil. $\mathbf{[\alpha]_D^{24}}$ = +97.6 (c = 0.25, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 3078 (C-H), 2930 (C-H), 1671 (C=C), 1632 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.25 (s, 3 H, C<u>H$_3$</u>), 1.34 - 1.72 (m, 7 H, CH$_2$=CHCH$_2$C<u>H$_2$</u>, CH=CHCH$_2$C<u>H$_2$</u>, CH$_2$=CH(CH$_2$)$_2$C<u>H$_2$</u>, CHNCH$_2$C<u>H$_A$</u>H$_B$), 1.86 - 1.92 (m, 1 H, CCHC<u>H$_A$</u>H$_B$) 1.94 - 2.10 (m, 4 H, CHNCH$_2$CH$_A$<u>H$_B$</u>, CC<u>H</u>C, CH$_2$=CHC<u>H$_2$</u>), 2.18 - 2.28 (m, 1 H, CH=CHC<u>H$_A$</u>H$_B$), 2.39 - 2.49 (m, 2 H, CH=CHCH$_A$<u>H$_B$</u>, NCHC<u>H$_A$</u>H$_B$), 2.72 - 2.82 (m, 2 H, CCHCH$_A$<u>H$_B$</u>, NCHCH$_A$<u>H$_B$</u>), 3.06 - 3.16 (m, 1 H, CHNC<u>H$_A$</u>H$_B$), 3.25 - 3.33 (m, 1 H, NC<u>H$_A$</u>H$_B$CH$_2$CH), 3.34 - 3.40 (m, 2 H, CH$_2$=CH(CH$_2$)$_3$C<u>H$_2$</u>), 3.47 (ddd, *J* = 13.0, 9.5, 6.0 Hz, 1 H, NCH$_A$<u>H$_B$</u>CH$_2$CH), 3.62 - 3.73 (m, 1 H, CHNCH$_A$<u>H$_B$</u>), 3.87 - 3.98 (m, 3 H, OC<u>H$_2$</u>, C<u>H$_A$</u>H$_B$O), 3.99 - 4.04 (m, 1 H, CH$_A$<u>H$_B$</u>O), 4.53 (q, *J* = 7.5 Hz, 1 H, NC<u>H</u>), 4.91 - 5.03 (m, 2 H, C<u>H$_2$</u>=CH), 5.55 (dd, *J* = 11.0, 7.5 Hz, 1 H,

NCHC*H*=CH), 5.79 (ddt, *J* = 17.0, 10.0, 6.5, 6.5 Hz, 1 H, CH_2=C*H*CH_2), 5.87 - 5.96 (m, 1 H, CHCH=C*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.3 (*C*H_3), 22.1 (NCH_2*C*H_2CH), 26.1 (CH_2=$CHCH_2$*C*H_2), 26.4 (CH_2=$CH(CH_2)_2$*C*H_2), 26.4 (CH=CH*C*H_2), 26.6 ($CHNCH_2$*C*H_2), 27.8 ($CHNCH_2CH_2$*C*H_2), 33.5 (CH_2=CH*C*H_2), 37.9 (NCH*C*H_2), 41.2 (CHN*C*H_2), 47.5 (N*C*H_2CH_2CH), 48.5 (N*C*$H_2(CH_2)_3CH$=CH_2), 50.5 (C_{quat}*C*HC), 53.4 (N*C*H), 55.7 (C(O)*C*$_{quat}$C(O)), 63.8 (O*C*H_2), 65.0 (O*C*H_2), 111.1 (*C*(OCH_2CH_2O)), 114.5 (*C*H_2=CH), 130.4 (NCH*C*H=CH), 133.8 (NCHCH=*C*H), 138.7 (CH_2=*C*H), 170.6 (*C*=O), 172.0 (*C*=O); ***m/z*** (ESI^+) 417 (100%, $[M+H]^+$), 439 (60, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{36}N_2O_4Na$) requires *m/z* 439.2567, found *m/z* 439.2555.

(3*R*,4*R*,9'*Z*,10a'*R*)-4-Acetyl-1-(hex-5-en-1-yl)-1',5',6',7',8',10a'-hexahydro-2H-spiro [piperidine-3,2'-pyrrolo[1,2-*α*]azocine]-2,3'-dione (470)

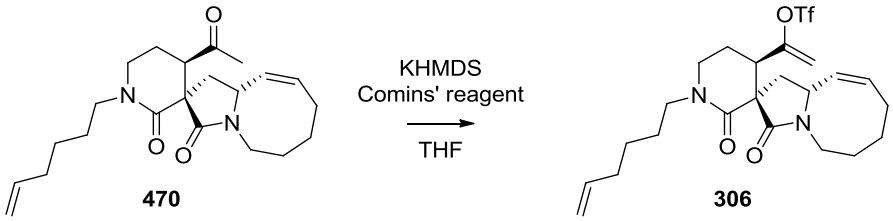


471 **470**

A solution of acetal **471** (1.0 eq, 5.11 mmol, 2.13 g) in tetrahydrofuran (50 mL/mmol **471**, 255 mL) and HCl (1 M, 149 mL/mmol **471,** 760 mL) was stirred at RT. After 16 h, diethyl ether (100 mL) was added. The organic layer was separated and the aqueous layer was extracted (diethyl ether, 2 × 100 mL). The combined organic layers were washed (brine, 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield title compound **470** (1.70 g, 89%) as a pale yellow oil. **$[\alpha]_D^{24}$** = +48.2 (c = 0.6, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 3078 (C-H), 2930 (C-H), 1671 (NC=O), 1632 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.34 - 1.43 (m, 2 H, CH_2=$CHCH_2C$*H*$_2$), 1.43 - 1.50 (m, 1 H, CH=$CHCH_2C$*H*$_A$H$_B$), 1.52 - 1.63 (m, 3 H, CH_2=$CH(CH_2)_2C$*H*$_2$, $CHNCH_2C$*H*$_A$H$_B$), 1.67 - 1.72 (m, 1 H, CH=$CHCH_2CH_A$*H*$_B$), 1.89 - 1.97 (m, 1 H, $CHNCH_2CH_A$*H*$_B$), 1.98 - 2.04 (m, 1 H, $CCHC$*H*$_A$H$_B$), 2.04 - 2.11 (m, 3 H, CH_2=CHC*H*$_2$, $NCHC$*H*$_A$H$_B$), 2.17 - 2.26 (m, 4 H, C(O)C*H*$_3$,

CH=CHC$\underline{H}_A$H$_B$), 2.35 - 2.45 (m, 1 H, CH=CHCH$_A\underline{H}_B$), 2.73 (dd, *J* = 13.0, 6.5 Hz, 1 H, NCHCH$_A\underline{H}_B$), 2.85 (dd, *J* = 13.0, 3.0 Hz, 1 H, CC$\underline{H}$C(O)), 3.02 - 3.11 (m, 1 H, CCHCH$_A\underline{H}_B$), 3.16 (dd, *J* = 14.0, 9.0 Hz, 1 H, CHNC$\underline{H}_A$H$_B$), 3.33 (ddd, *J* = 13.0, 9.0, 6.0 Hz, 1 H, CH$_2$=CH(CH$_2$)$_3$C$\underline{H}_A$H$_B$), 3.40 - 3.50 (m, 3 H, CH$_2$=CH(CH$_2$)$_3$CH$_A\underline{H}_B$, NC$\underline{H}_2$CH$_2$CH), 3.67 (dd, *J* = 14.0, 9.0 Hz, 1 H, CHNCH$_A\underline{H}_B$), 4.28 (q, *J* = 7.5 Hz, 1 H, NC$\underline{H}$), 4.92 - 5.03 (m, 2 H, C$\underline{H}_2$=CH), 5.56 (dd, *J* = 11.0, 7.5 Hz, 1 H, CHC$\underline{H}$=CH), 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1 H, CH$_2$=C$\underline{H}$CH$_2$), 5.85 - 5.94 (m, 1 H, CHCH=C$\underline{H}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 22.5 (CCH$\underline{C}$H$_2$), 26.0 (CH=CH$\underline{C}$H$_2$), 26.1 (CH$_2$=CHCH$_2\underline{C}$H$_2$), 26.2 (CHNCH$_2\underline{C}$H$_2$), 26.3 (CH$_2$=CH(CH$_2$)$_2\underline{C}$H$_2$), 27.9 (CH=CHCH$_2\underline{C}$H$_2$), 28.6 (C(O)$\underline{C}$H$_3$), 33.4 (CH$_2$=CH$\underline{C}$H$_2$), 37.0 (NCH$\underline{C}$H$_2$), 41.6 (CHN$\underline{C}$H$_2$), 47.1 (N$\underline{C}$H$_2$CH$_2$CH), 48.4 (CH$_2$=CH(CH$_2$)$_3\underline{C}$H$_2$), 53.5 (N$\underline{C}$H), 53.7 (C(O)$\underline{C}$C(O)), 56.2 (C$\underline{C}$HC(O)), 114.6 ($\underline{C}$H$_2$=CH), 130.1 (CH$\underline{C}$H=CH), 133.4 (CHCH=$\underline{C}$H), 138.6 (CH$_2$=$\underline{C}$H), 169.0 (N$\underline{C}$(O)), 171.6 (N$\underline{C}$(O)), 207.8 (CH$_3\underline{C}$=O); ***m/z*** (ESI$^+$) 417 (100%, [M+H]$^+$), 439 (65, [M+Na]$^+$); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{22}H_{32}N_2O_3Na$) requires *m/z* 395.2305, found *m/z* 395.2292.

1-[(3*R*,4*R*,9'*Z*,10a'*R*)-1-(Hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine 3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]vinyl trifluoromethanesulfonate (306)

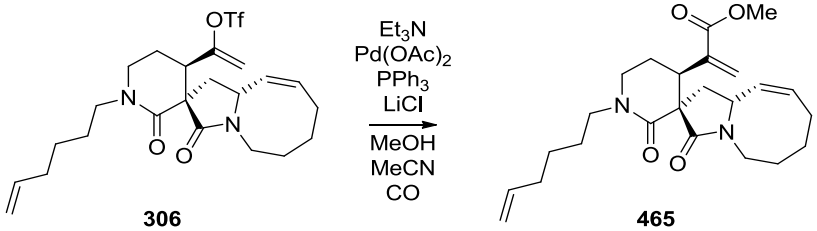


470 **306**

To ketone **470** (1.0 eq, 0.285 mmol, 107 mg) and Comins' reagent (2.4 eq, 0.684 mmol, 225 mg) in tetrahydrofuran (100 mL/g **470**, 10.7 mL) was added KHMDS (3.4 eq, 0.968 mmol, 0.5 M in toluene, 1.93 mL) dropwise at −78 °C. After 30 min, the reaction mixture was concentrated *in vacuo* to approximately half the volume. The crude residue was purified by flash column chromatography (1:1 Et$_2$O:PE → Et$_2$O → 9:1 Et$_2$O:MeOH) to yield the title compound **306** (84 mg, 58%) as a pale yellow oil. **$[\alpha]_D^{24}$** = +65.0 (c = 0.1, CHCl$_3$); **IR** ν_{max}(film)/cm^{-1} 2988 (C-H), 2895 (C-H), 1630 (NC=O), 1559 (C=C), 1034 (S=O); **^{1}H**

NMR (400 MHz, $CDCl_3$) δ_H 1.31 - 1.51 (m, 4 H, $CHNCH_2CH_2C\underline{H}_AH_B$, $CHNCH_2C\underline{H}_AH_B$, $CH_2{=}CHCH_2C\underline{H}_2$), 1.51 - 1.73 (m, 4 H, $CHNCH_2CH_2CH_A\underline{H}_B$, $CH_2{=}CH(CH_2)_2C\underline{H}_2$, $CHNCH_2C\underline{H}_AH_B$), 1.84 - 1.92 (m, 1 H, $CCHC\underline{H}_AH_B$), 1.93 - 2.02 (m, 1 H, $CHNCH_2CH_A\underline{H}_B$), 2.08 (q, *J* = 7.0 Hz, 2 H, $CH_2{=}CHC\underline{H}_2$), 2.13 - 2.28 (m, 2 H, $CH{=}CHC\underline{H}_AH_B$, $NCHC\underline{H}_AH_B$), 2.31 - 2.42 (m, 1 H, $CH{=}CHCH_A\underline{H}_B$), 2.72 (dd, *J* = 13.0, 2.5 Hz, 1 H, $CC\underline{H}$), 2.91 - 3.09 (m, 3 H, $CCHCH_A\underline{H}_B$, $CHNC\underline{H}_AH_B$, $NCHCH_A\underline{H}_B$), 3.35 - 3.46 (m, 4 H, 2 × $NC\underline{H}_2$), 3.60 - 3.72 (m, 1 H, $CHNCH_A\underline{H}_B$), 4.29 (q, *J* = 7.5 Hz, 1 H, $NC\underline{H}$), 4.91 - 5.04 (m, 2 H, $C\underline{H}_2{=}CH$), 5.18 (d, *J* = 4.0 Hz, 1 H, $C{=}C\underline{H}_AH_B$), 5.29 (d, *J* = 4.0 Hz, 1 H, $C{=}CH_A\underline{H}_B$), 5.50 (dd, *J* = 10.5, 8.0 Hz, 1 H, $CHC\underline{H}{=}CH$), 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1 H, $CH_2{=}C\underline{H}$), 5.90 - 6.01 (m, 1 H, $CHCH{=}C\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.1 ($\underline{C}H_2CHC_{quat}$), 26.1 ($CH_2{=}CHCH_2\underline{C}H_2$), 26.3 ($CH_2{=}CH(CH_2)_2\underline{C}H_2$), 26.3 ($CH{=}CH\underline{C}H_2$), 27.0 ($CHNCH_2\underline{C}H_2$), 27.7 ($CHNCH_2CH_2\underline{C}H_2$), 33.4 ($CH_2{=}CH\underline{C}H_2$), 36.6 ($NCH\underline{C}H_2$), 41.1 ($CHN\underline{C}H_2$), 46.8 ($N\underline{C}H_2CH_2CH$), 47.9 ($C_{quat}\underline{C}H$), 48.5 ($CH_2{=}CH(CH_2)_3\underline{C}H_2$), 53.0 ($N\underline{C}H$), 56.0 ($\underline{C}_{quat}(CO)_2$), 106.8 ($C_{quat}{=}\underline{C}H_2$), 114.7 ($\underline{C}H_2{=}CH$), 118.3 (d, *J* = 311 Hz, $\underline{C}F_3$) 129.2 ($NCH\underline{C}H{=}CH$), 134.8 ($NCHCH{=}\underline{C}H$), 138.5 ($CH_2{=}\underline{C}H$), 155.8 ($\underline{C}_{quat}{=}CH_2$), 168.1 ($\underline{C}{=}O$), 170.3 ($\underline{C}{=}O$); **^{19}F NMR** (470 MHz, $CDCl_3$) δ_F -73.62 ($C\underline{F}_3$); ***m/z*** (ESI^+) 505 (80%, $[M+H]^+$), 527 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{31}F_3N_2O_5SNa$) requires *m/z* 527.1798, found *m/z* 527.1783.

Methyl 2-[(3*R*,4*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]acrylate (306)

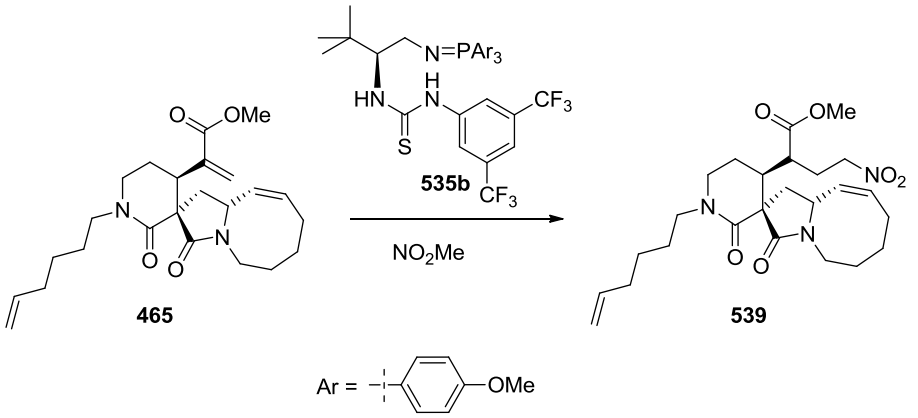


306 **465**

A solution of triflate **306** (1.0 eq, 0.067 mmol, 34 mg) and PPh_3 (0.4 eq, 0.026 mmol, 7 mg) in methanol (4 mL/mmol **306**, 0.27 mL) and MeCN (9 mL/mmol **306**, 0.6 mL) was degassed

and purged with nitrogen and then CO was bubbled through the reaction mixture for 10 min. Et_3N (2.0 eq, 0.13 mmol, 18 µL) was then added followed by $Pd(OAc)_2$ (0.2 eq, 0.013 mmol, 3 mg). The reaction mixture was degassed and purged with CO five times and stirred at RT. After 16 h, diethyl ether (5 mL) was added and the reaction mixture was filtered through Celite® which in turn was eluted with diethyl ether (10 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (1:1 PE:Et_2O) to yield the title compound **465** (24 mg, 86%) as a pale yellow oil. $\mathbf{[\alpha]_D^{24}}$ = +55.2 (c = 0.55, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2930 (C-H), 2860 (C-H), 1714 (MeOC=O), 1673 (NC=O), 1634 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.16 - 1.31 (m, 1 H, $CHNCH_2C\underline{H}_AH_B$), 1.34 - 1.47 (m, 3 H, $CHNCH_2CH_2C\underline{H}_AH_B$, CH_2=$CHCH_2C\underline{H}_2$), 1.52 - 1.71 (m, 4 H, $NCH_2C\underline{H}_AH_BCH$, $CHNCH_2CH_2CH_A\underline{H}_B$, CH_2=$CH(CH_2)_2C\underline{H}_2$), 1.92 - 1.99 (m, 1 H, $CHNCH_2CH_A\underline{H}_B$), 2.04 - 2.13 (m, 3 H, CH_2=$CHC\underline{H}_2$, CH=$CHC\underline{H}_AH_B$), 2.16 - 2.25 (m, 1 H, $NCHC\underline{H}_AH_B$), 2.27 - 2.40 (m, 1 H, CH=$CHCH_A\underline{H}_B$), 2.80 - 3.04 (m, 3 H, $CHNC\underline{H}_AH_B$, $NCH_2CH_A\underline{H}_BCH$, $NCHCH_A\underline{H}_B$), 3.30 - 3.41 (m, 3 H, $NCH_2CH_2C\underline{H}$, CH_2=$CH(CH_2)_3C\underline{H}_AH_B$, $NC\underline{H}_AH_BCH_2CH$), 3.42 - 3.54 (m, 2 H, CH_2=$CH(CH_2)_3CH_A\underline{H}_B$, $NCH_A\underline{H}_BCH_2CH$), 3.64 - 3.79 (m, 1 H, $CHNCH_A\underline{H}_B$), 3.82 (s, 3 H, $COOC\underline{H}_3$), 3.90 (q, *J* = 8.0 Hz, 1 H, $NC\underline{H}$), 4.91 - 5.06 (m, 2 H, $C\underline{H}_2$=CH), 5.39 (dd, *J* = 10.5, 8.0 Hz, 1 H, $CHC\underline{H}$=CH), 5.72 - 5.87 (m, 2 H, CH_2=$C\underline{H}$, C=$C\underline{H}_AH_B$), 5.88 - 5.97 (m, 1 H, $CHCH$=$C\underline{H}$), 6.40 (br. s, 1 H, C=$CH_A\underline{H}_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.5 ($NCH_2\underline{C}H_2CH$), 26.1 (CH_2=$CHCH_2\underline{C}H_2$), 26.3 (CH_2=$CH(CH_2)_2\underline{C}H_2$), 26.6 ($CHCH$=$CH\underline{C}H_2$), 27.6 ($CHNCH_2\underline{C}H_2$), 27.8 ($CHNCH_2CH_2\underline{C}H_2$), 33.4 ($CH_2$=$CH\underline{C}H_2$), 36.4 ($NCH\underline{C}H_2$), 40.6 ($CHN\underline{C}H_2$), 41.0 ($C_{quat}\underline{C}H$), 47.5 ($CH_2$=$CH(CH_2)_3\underline{C}H_2$), 48.4 ($N\underline{C}H_2CH_2CH$), 52.4 ($COO\underline{C}H_3$), 52.8 ($N\underline{C}H$), 57.4 ($\underline{C}_{quat}CH$), 114.6 ($\underline{C}H_2$=$CH$), 128.4 ($C$=$\underline{C}H_2$), 129.3 ($NCH\underline{C}H$=$CH$), 134.9 ($NCHCH$=$\underline{C}H$), 138.6 ($CH_2$=$\underline{C}H$), 139.9 ($\underline{C}$=$CH_2$), 168.0 ($\underline{C}$=O), 169.1 ($\underline{C}$=O), 171.4 ($\underline{C}$=O); ***m/z*** ($ESI^+$) 415 (85%, $[M+H]^+$), 437 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{34}N_2O_4Na$) requires *m/z* 437.2411, found *m/z* 437.2397.

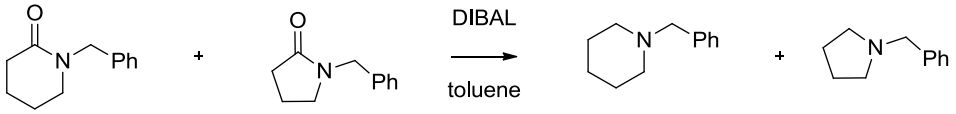
Methyl (2*S*)-2-[(3*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-2,3'-dioxo-1',5',6',7',8',10a'-hexahydro spiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]-4-nitrobutanoate (539)



To α,β-unsaturated ester **465** (1.0 eq, 0.084 mmol, 35 mg) in nitromethane (4.76 mL/mmol **465**, 0.4 mL) was added organocatalyst **535b** (0.2 eq, 0.017 mmol, 12 mg) at RT. After 24 h, the reaction mixture was loaded on to silica gel and was purified by flash column chromatography (Et_2O) to yield the title compound **539** (24 mg, 62%) as a yellow oil. $\mathbf{[\alpha]_D^{24}}$ = −34.1 (c = 0.4, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2926 (C-H), 1734 (MeOC=O), 1673 (NC=O), 1554 (NO_2), 1433 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.34 - 1.42 (m, 2 H, CH_2=CHCH$_2$C$\underline{H}_2$), 1.45 - 1.64 (m, 4 H, CH=CHCH$_2$C$\underline{H}_A$H$_B$, CH_2=CH(CH$_2$)$_2$C$\underline{H}_2$, CHNCH$_2$C$\underline{H}_A$H$_B$), 1.65 - 1.74 (m, 1 H, CH=CHCH$_2$CH$_A\underline{H}_B$), 1.80 - 1.88 (m, 1 H, CCHC$\underline{H}_A$H$_B$), 1.90 - 2.00 (m, 2 H, CHNCH$_2$CH$_A\underline{H}_B$, CC$\underline{H}$), 2.03 - 2.13 (m, 3 H, CH_2=CHC$\underline{H}_2$, NCHC$\underline{H}_A$H$_B$), 2.14 - 2.30 (m, 2 H, CH=CHC$\underline{H}_A$H$_B$, $NO_2CH_2C\underline{H}_A$H$_B$), 2.37 - 2.49 (m, 2 H, CH=CHCH$_A\underline{H}_B$, $NO_2CH_2CH_A\underline{H}_B$), 2.65 - 2.76 (m, 2 H, CCHCH$_A\underline{H}_B$, C$\underline{H}$COOMe), 2.82 (dd, *J* = 13.5, 6.5 Hz, 1 H, NCHCH$_A\underline{H}_B$), 3.08 - 3.18 (m, 1 H, CHNC$\underline{H}_A$H$_B$), 3.27 - 3.44 (m, 4 H, 2 × NC$\underline{H}_2$), 3.55 - 3.64 (m, 1 H, CHNCH$_A\underline{H}_B$), 3.67 (s, 3 H, COOC$\underline{H}_3$), 4.28 - 4.47 (m, 3 H, C$\underline{H}_2NO_2$, NC$\underline{H}$), 4.91 - 5.03 (m, 2 H, C$\underline{H}_2$=CH), 5.61 (dd, *J* = 10.5, 7.5 Hz, 1 H, CHC$\underline{H}$=CH), 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1 H, CH_2=C$\underline{H}$), 5.88 - 5.97 (m, 1 H, CHCH=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 21.7 (CCH$\underline{C}$H$_2$), 26.0 (CH_2=CHCH$_2\underline{C}$H$_2$), 26.1 (CH=CH$\underline{C}$H$_2$), 26.1 (CHNCH$_2\underline{C}$H$_2$), 26.3 (CH_2=CH(CH$_2$)$_2\underline{C}$H$_2$), 27.9 (CH=CHCH$_2\underline{C}$H$_2$), 30.2 ($NO_2CH_2\underline{C}H_2$), 33.4 (CH_2=CH$\underline{C}$H$_2$), 36.8 (NCH$\underline{C}$H$_2$), 41.4 (CHN$\underline{C}$H$_2$), 42.8 ($\underline{C}$HCOOMe), 46.3 ($C_{quat}C\underline{H}$), 47.1 (N$\underline{C}$H$_2$CH$_2$CH), 48.2 (CH_2=CH(CH$_2$)$_3\underline{C}$H$_2$), 52.0 (COO$\underline{C}$H$_3$), 53.6 (N$\underline{C}$H), 56.2

(C(O)$\underline{C}_{quat}$C(O)), 73.2 ($NO_2\underline{C}H_2$), 114.6 ($\underline{C}H_2$=CH), 129.9 (CH$\underline{C}$H=CH), 133.8 (CHCH=$\underline{C}$H), 138.6 (CH_2=$\underline{C}$H), 169.5 ($\underline{C}$=O), 170.7 ($\underline{C}$=O), 172.5 ($\underline{C}$=O); ***m/z*** (ESI^+) 476 (80%, $[M+H]^+$), 498 (100, $[M+Na]^+$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{25}H_{37}N_3O_6Na$) requires *m/z* 498.2575, found *m/z* 498.2563.

***N*-Benzyl piperidine (550)** and ***N*-benzyl pyrrolidinone (546)**



545 **546** **550** **546**

A solution of lactam **545** (1 eq, 0.396 mmol, 75 mg) and lactam **546** (1 eq, 0.396 mmol, 69 mg) in toluene (30 mL/mmol **545**, 11.8 mL) was made (solution 1). 1 mL aliqots (0.066 mmol, 0.033 mmol **545** and **546**) were used for each reaction and six reactions were set up.

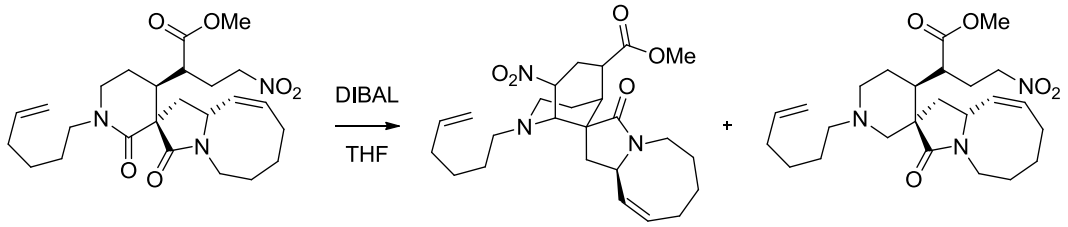
A solution of mesitylene (0.33 mmol, 46 μL) in $CDCl_3$ (6 mL) was made (solution 2).

To solution 1 (1 mL, 0.066 mmol in total, 0.033 mmol of **545** and **546**) was added DIBAL (6 eq, 0.198 mmol, 0.198 mL) at −78 ˚C. After 1 min, MeOH (0.5 mL) was added and the reaction was warmed to RT. $Na_2SO_4 \bullet 10H_2O$ (500 mg) and Et_2O (2.5 mL) were added and the reaction mixture was stirred at RT for 2 h. The colourless solids were filtered and the filtrate was concentrated *in vacuo*. The crude residue was left under vacuum for 1 h. To the crude residue was added solution 2 (0.6 mL) and the ^1H NMR spectrum was measured. The benzylic protons of **545** and **546** were integrated against the internal standard (mesitylene).

The same procedure was repeated with 2, 3, 4, 5 and 10 minute reaction times and the collected data were normalised.

Methyl (6*S*,9*R*,9'*Z*,10a'*R*)-2-(hex-5-en-1-yl)-8-nitro-3'-oxo-1',5',6',7',8',10a'-hexahydro spiro[2-azabicyclo[3.3.1]nonane-9,2'-pyrrolo[1,2-*a*]azocine]-6-carboxylate (551)

Methyl (2*S*)-2-[(3*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-3'-oxo-1',5',6',7',8',10a'-hexahydro spiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]-4-nitrobutanoate (464)



539 **551** **464**

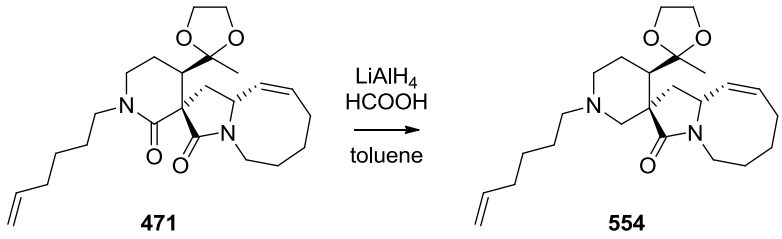
To bis-amide **539** (1.0 eq, 0.023 mmol, 11 mg) in toluene (0.3 mL) was added DIBAL (3.0 eq, 0.069 mmol, 1.0 M in cyclohexanes, 0.069 mL) at −78 °C. After 1 h, MeOH (0.36 mL) was added at −78 °C and the reaction mixture was warmed to RT. $Na_2SO_4 \bullet 10H_2O$ (0.36 g) and Et_2O (5 mL) were added and the reaction mixture was stirred at RT. After 16 h, the colourless solids were removed *via* filtration, eluted with Et_2O (2 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Et_2O → 9:1 Et_2O:MeOH) to yield tetracycle **551** (3 mg, 28%) and piperidine **464** (4 mg, 40%) as yellow oils.

551: $\mathbf{[\alpha]_D^{24}}$ = −21.8 (c = 0.6, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2930 (C-H), 2858 (C-H), 1731 (MeOC=O), 1669 (NC=O), 1540 (NO_2), 1379 (NO_2); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 1.09 (dd, 1 H, *J* = 14.0, 6.0 Hz, $NCH_2CH_AH_BCHCHCOOMe$), 1.18 - 1.58 (m, 7 H, CH_2=$CHCH_2CH_2$, $CON(CH_2)_2CH_2$, $CONCH_2CH_AH_B$), 1.62 - 1.71 (m, 1 H, $CONCH_2CH_AH_B$), 1.80 - 1.93 (m, 2 H, $NCH_2CH_AH_BCHCHCOOMe$, $NCHCH_AH_BC_{quat}$), 1.95 - 2.10 (m, 4 H, CH_2=$CHCH_2$, $NCHCH_AH_BC_{quat}$, CH=$CHCH_AH_B$), 2.13 - 2.24 (m, 1 H, CH=$CHCH_AH_B$), 2.44 (d, 1 H, *J* = 9.0 Hz, $CHCOOMe$), 2.50 (dd, 1 H, *J* = 12.0, 8.0 Hz, $NCH_AH_BCH_2CH$), 2.63 - 2.77 (m, 3 H, CH_2=$CH(CH_2)_3CH_2$, $CCHCHCOOMe$), 2.90 (ddd, 1 H, *J* = 14.5, 12.5, 9.0 Hz, $NO_2CHCH_AH_B$), 3.02 - 3.10 (m, 1 H, $NCH_AH_BCH_2CH$), 3.24 - 3.33 (m, 2 H, $NO_2CHCH_AH_B$, $CONCH_AH_B$), 3.40 - 3.46 (m, 1 H, $CONCH_AH_B$), 3.69 (s, 3 H, $COOCH_3$), 3.77 (d, 1 H, *J* = 3.5 Hz, $NCHCHNO_2$), 3.80 - 3.86 (m, 1 H,

NC*H*CH=CH), 5.05 - 5.17 (m, 2 H, C*H*$_2$=CH), 5.22 (dd, 1 H, *J* = 11.0, 6.0 Hz, CHC*H*=CH), 5.61 - 5.71 (m, 1 H, CHCH=C*H*), 5.80 - 5.91 (m, 1 H, CH$_2$=C*H*), 6.22 - 6.29 (m, 1 H, CH$_2$C*H*NO$_2$); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 24.8 (CH*C*H$_2$CHNO$_2$), 25.8 (CH=CH*C*H$_2$), 26.2 (CONCH$_2$*C*H$_2$, CH$_2$=CH(CH$_2$)$_2$*C*H$_2$), 27.3 (CH=CHCH$_2$*C*H$_2$), 28.0 (NCH$_2$*C*H$_2$CH), 28.2 (CH$_2$=CHCH$_2$*C*H$_2$), 31.7 (C$_{quat}$*C*HCHCOOMe), 33.8 (CH$_2$=CH*C*H$_2$), 39.0 (C$_{quat}$*C*H$_2$), 41.2 (CON*C*H$_2$), 43.6 (*C*HCOOMe), 43.9 (N*C*H$_2$CH$_2$CH), 49.8 (*C*$_{quat}$CO), 51.7 (COO*C*H$_3$), 52.4 (CON*C*H), 54.6 (CH$_2$=CH(CH$_2$)$_3$*C*H$_2$), 61.7 (NO$_2$CH*C*HN), 82.4 (*C*HNO$_2$), 114.5 (*C*H$_2$=CH), 130.7 (CH*C*H=CH), 132.4 (CHCH=*C*H), 139.1 (CH$_2$=*C*H), 172.2 (*C*OOMe), 174.4 (N*C*O); ***m/z*** (ESI$^+$) 460 (100%, [M+H]$^+$), 482 (80, [M+Na]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{25}H_{38}N_3O_5$) requires *m/z* 460.2806, found *m/z* 460.2793.

464: $[\alpha]_D^{24}$ = −34.1 (c = 0.15, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2930 (C-H), 1674 (NC=O), 1660 (MeOC=O), 1553 (NO_2), 1434 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.18 - 1.76 (m, 10 H, CH$_2$=CHCH$_2$C*H*$_2$C*H*$_2$, CH=CHCH$_2$C*H*$_2$, NCH$_2$C*H*$_A$H$_B$CH, NCHC*H*$_A$H$_B$, CHNCH$_2$C*H*$_A$H$_B$, C$_{quat}$C*H*), 1.77 - 2.09 (m, 5 H, C$_{quat}$C*H*$_A$H$_B$N, CHNCH$_2$CH$_A$*H*$_B$, NO$_2$CH$_2$C*H*$_A$H$_B$, CH$_2$=CHC*H*$_2$), 2.12 - 2.51 (m, 9 H, CH=CHC*H*$_2$, NC*H*$_2$CH$_A$*H*$_B$CH, CH$_2$=CH(CH$_2$)$_3$C*H*$_2$, NCHCH$_A$*H*$_B$, NO$_2$CH$_2$CH$_A$*H*$_B$), 2.75 - 2.86 (m, 1 H, C$_{quat}$CH$_A$*H*$_B$N), 2.91 - 2.97 (m, 1 H, C$_{quat}$CHC*H*COOMe), 3.12 - 3.25 (m, 1 H, CHNC*H*$_A$H$_B$), 3.57 - 3.63 (m, 1 H, CHNCH$_A$*H*$_B$), 3.68 (s, 3 H, COOC*H*$_3$), 4.23 - 4.44 (m, 3 H, C*H*$_2$NO$_2$, NC*H*), 4.91 - 5.04 (m, 2 H, C*H*$_2$=CH), 5.37 (dd, *J* = 11.0, 6.5 Hz, 1 H, NCHC*H*=CH), 5.72 - 5.84 (m, 1 H, CH$_2$=C*H*), 5.87 - 5.97 (m, 1 H, NCHCH=C*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.5 (NCH$_2$*C*H$_2$CH), 26.0 (CH=CH*C*H$_2$), 26.2 (CHNCH$_2$*C*H$_2$), 26.4 (CH$_2$=CHCH$_2$*C*H$_2$), 27.0 (CH$_2$=CH(CH$_2$)$_2$*C*H$_2$, CH=CHCH$_2$*C*H$_2$), 30.4 (NO$_2$CH$_2$*C*H$_2$), 30.7 (C$_{quat}$*C*H), 33.5 (CH$_2$=CH*C*H$_2$), 39.7 (NCH*C*H$_2$), 40.7 (CHN*C*H$_2$), 41.9 (NO$_2$CH$_2$CH$_2$*C*H), 46.6 (*C*$_{quat}$CH$_2$N), 51.8 (COO*C*H$_3$), 52.7 (N*C*H), 58.4 (CH$_2$=CH(CH$_2$)$_3$*C*H$_2$, N*C*H$_2$CH$_2$CH), 60.2 (C$_{quat}$*C*H$_2$N), 73.3 (NO$_2$*C*H$_2$), 114.6 (*C*H$_2$=CH), 127.0 (NCH*C*H=CH), 135.7 (NCHCH=*C*H), 137.6 (CH$_2$=*C*H), 174.5 (*C*=O), 175.3 (*C*=O); ***m/z*** (ESI$^+$) 462 (100%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{25}H_{40}N_3O_5$) requires *m/z* 462.2962, found *m/z* 462.2959.

(3*R*,4*R*,9'*Z*,10a'*R*)-1-(Hex-5-en-1-yl)-4-(2-methyl-1,3-dioxolan-2-yl)-1',5',6',7',8',10a'-hexahydrospiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-3'-one (554)

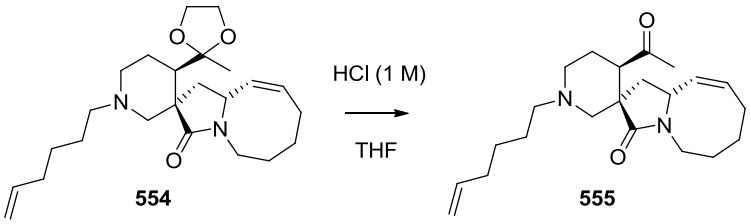


471 **554**

To a solution of amide **471** (1.0 eq, 2.90 mmol, 1.21 g) in toluene (20 mL/mmol **471**, 58 mL) was added $LiAlH_4$ (3.0 eq, 8.73 mmol, 1.0 M in Et_2O, 8.73 mL) dropwise at −78 °C. The reaction mixture was warmed to −20 °C and stirred for 1 h before being cooled to −78 °C. Formic acid (71 eq, 205 mmol, 7.76 mL) was added carefully and the reaction mixture was warmed to RT. After 16 h, Rochelle salt (20 wt% in water, 58 mL) was added before the careful addition of solid K_2CO_3 until pH > 10 was reached and two clear phases appeared. The layers were separated and the aqueous layer was extracted (EtOAc, 3 × 30 mL then CH_2Cl_2, 2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Et_2O → 9:1 Et_2O:MeOH) to yield the title compound **554** (0.987 g, 85%) as a yellow oil. $\mathbf{[\alpha]_D^{24}}$ = −11.4 (c = 1.35, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2930 (C-H), 2863 (C-H), 1681 (C=O), 1679 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.25 - 1.40 (m, 6 H, C$\underline{H}_3$, NCHC$\underline{H}_A$H$_B$, CH_2=CHCH$_2$C$\underline{H}_2$), 1.40 - 1.57 (m, 4 H, CH=CHCH$_2$C$\underline{H}_A$H$_B$, CH_2=CH(CH$_2$)$_2$C$\underline{H}_2$, CHNCH$_2$C$\underline{H}_A$H$_B$), 1.59 - 1.69 (m, 2 H, C$_{quat}$C$\underline{H}$, CH=CHCH$_2$CH$_A$$\underline{H}_B$), 1.70 - 1.81 (m, 1 H, NCH$_2$C$\underline{H}_A$H$_B$CH), 1.84 - 2.44 (m, 10 H, CHNCH$_2$CH$_A$$\underline{H}_B$, C$_{quat}C\underline{H}_AH_B$, CH_2=CHC$\underline{H}_2$, NC$\underline{H}_AH_BCH_2$CH, CH=CHC$\underline{H}_2$, CH_2=CH(CH$_2$)$_3C\underline{H}_2$, NCH$_2CH_A$$\underline{H}_B$CH), 2.69 (dd, *J* = 13.0, 7.5 Hz, 1 H, NCHCH$_A$$\underline{H}_B$), 2.75 - 2.83 (m, 1 H, NCH$_A$$\underline{H}_BCH_2$CH), 2.90 (d, *J* = 11.0 Hz, 1 H, C$_{quat}$CH$_A$$\underline{H}_B$), 3.15 - 3.26 (m, 1 H, CHNC$\underline{H}_A$H$_B$), 3.54 - 3.65 (m, 1 H, CHNCH$_A$$\underline{H}_B$), 3.81 - 3.99 (m, 4 H, OC$\underline{H}_2$C$\underline{H}_2$O), 4.30 (q, *J* = 7.0 Hz, 1 H, NC$\underline{H}$), 4.86 - 5.02 (m, 2 H, C$\underline{H}_2$=CH), 5.35 (dd, *J* = 11.0, 6.5 Hz, 1 H, NCHC$\underline{H}$=CH), 5.70 - 5.86 (m, 2 H, NCHCH=C$\underline{H}$, CH_2=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 22.7 (C$\underline{H}_3$), 24.3 (NCH$_2$C$\underline{H}_2$CH), 26.2

(CH=CH<u>*C*</u>H_2), 26.2 (CHNCH_2<u>*C*</u>H_2), 26.3 (CH_2=CH(CH_2)$_2$<u>*C*</u>H_2), 26.9 (CH_2=CHCH_2<u>*C*</u>H_2), 27.5 (CH=CHCH_2<u>*C*</u>H_2), 33.7 (CH_2=CH<u>*C*</u>H_2), 40.7 (NCH<u>*C*</u>H_2), 40.9 (CHN<u>*C*</u>H_2), 45.7 (<u>*C*</u>$_{quat}$CO), 49.5 (C_{quat}<u>*C*</u>H), 52.8 (N<u>*C*</u>H), 53.5 (N<u>*C*</u>H_2CH_2CH), 58.7 (CH_2=CH(CH_2)$_3$<u>*C*</u>H_2), 63.0 (C_{quat}<u>*C*</u>H_2), 63.5, 64.8 (O<u>*C*</u>H_2<u>*C*</u>H_2O), 111.8 (<u>*C*</u>$_{quat}$(O)$_2$), 114.3 (<u>*C*</u>H_2=CH), 131.1 (NCH<u>*C*</u>H=CH), 132.3 (NCHCH=<u>*C*</u>H), 138.9 (CH_2=<u>*C*</u>H), 175.3 (<u>*C*</u>=O); ***m/z*** (ESI$^+$) 403 (100%, [M+H]$^+$); **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_{24}H_{39}N_2O_3$) requires *m/z* 403.2955, found *m/z* 403.2950.

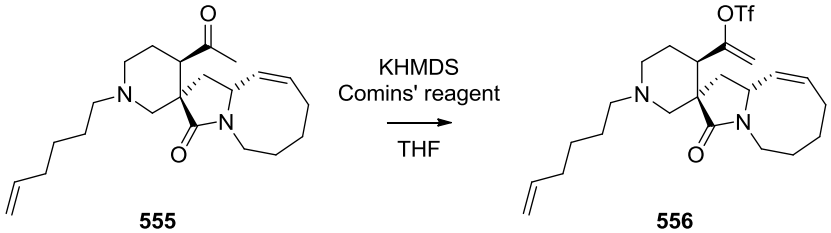
(3*R*,4*R*,9'*Z*,10a'*R*)-4-Acetyl-1-(hex-5-en-1-yl)-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-3'-one (555)



554 **555**

To acetal **554** (1.0 eq, 2.41 mmol, 0.97 g) was added HCl (1 M, 40.7 mL/mmol **554**, 98 mL) and the reaction mixture was stirred at RT. After 16 h, solid K_2CO_3 was added until pH > 10 was reached. The reaction mixture was extracted (EtOAc, 3 × 20 mL then CH_2Cl_2, 3 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Et_2O → 9:1 Et_2O:MeOH) to yield title compound **555** (0.82 g, 95%) as an orange oil. $\mathbf{[\alpha]_D^{24}}$ = −36.8 (c = 0.2, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2930 (C-H), 2856 (C-H), 1709 (C=O), 1676 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.28 - 1.38 (m, 2 H, CH_2=CHCH$_2$C$\underline{H}_2$), 1.39 - 1.48 (m, 2 H, CH_2=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.49 - 1.63 (m, 3 H, CH=CHCH$_2$$\underline{C}H_2$, NCHC$\underline{H}_AH_B$), 1.64 - 1.96 (m, 4 H, CHNCH$_2$$\underline{C}H_2$, C_{quat}C$\underline{H}_AH_B$, NCH$_2C\underline{H}_AH_B$CH), 1.97 - 2.23 (m, 8 H, CH_2=CHC$\underline{H}_2$, C$\underline{H}_3$, CH=CHC$\underline{H}_A$H$_B$, CH_2=CH(CH$_2$)$_3$C$\underline{H}_A$H$_B$, NC$\underline{H}_A$H$_B$CH$_2$CH), 2.24 - 2.31 (m, 1 H, NCHCH$_A$$\underline{H}_B$), 2.33 - 2.56 (m, 4 H, C_{quat}C$\underline{H}$, CH=CHCH$_A$$\underline{H}_B$, CH_2=CH(CH$_2$)$_3CH_A$$\underline{H}_B$, NCH$_2CH_A$$\underline{H}_B$CH), 2.97 - 3.12 (m, 2 H, NCH$_A$$\underline{H}_BCH_2$CH, C_{quat}CH$_A$$\underline{H}_B$), 3.34 (dd, *J* = 13.0, 5.5 Hz, 1 H, CHNC$\underline{H}_A$H$_B$), 3.56 - 3.60 (m, 1 H, CHNCH$_A$$\underline{H}_B$), 4.13 - 4.22 (m, 1 H, NC$\underline{H}$), 4.87 - 5.01 (m, 2 H, C$\underline{H}_2$=CH), 5.44 (dd, *J* = 11.0, 5.0 Hz, 1 H, NCHC$\underline{H}$=CH), 5.62 - 5.84 (m, 2 H, NCHCH=C$\underline{H}$, CH_2=C$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.6 (CHNCH$_2$$\underline{C}H_2$), 25.0 (CH=CH$\underline{C}H_2$), 25.3 (NCH$_2$$\underline{C}H_2$CH), 26.2 ($CH_2$=CH(CH$_2$)$_2$$\underline{C}H_2$), 26.8 ($CH_2$=CHCH$_2$$\underline{C}H_2$), 27.1 (CHNCH$_2CH_2$$\underline{C}H_2$), 29.6 ($\underline{C}H_3$), 33.7 ($CH_2$=CH$\underline{C}H_2$), 38.7 (NCH$\underline{C}H_2$), 41.9 (CHN$\underline{C}H_2$), 45.6 ($\underline{C}_{quat}CH_2$), 53.1 (N$\underline{C}H_2CH_2$CH), 54.4 (N$\underline{C}$H), 54.8 ($C_{quat}$$\underline{C}$H), 58.5 ($CH_2$=CH(CH$_2$)$_3$$\underline{C}H_2$), 60.3 ($C_{quat}$$\underline{C}H_2$N), 114.4 ($\underline{C}H_2$=CH), 129.4 (NCHCH=$\underline{C}$H), 132.5 (NCH$\underline{C}$H=CH), 138.8 ($CH_2$=$\underline{C}$H), 175.1 (N$\underline{C}$=O), 209.5 ($\underline{C}$=O); ***m/z*** (ESI$^+$) 359 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{35}N_2O_2$) requires *m/z* 359.2693, found *m/z* 359.2684.

1-[(3*R*,4*R*,9'*Z*,10a'*R*)-1-(Hex-5-en-1-yl)-3'-oxo-1',5',6',7',8',10a'-hexahydrospiro[piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]vinyl trifluoromethanesulfonate (556)

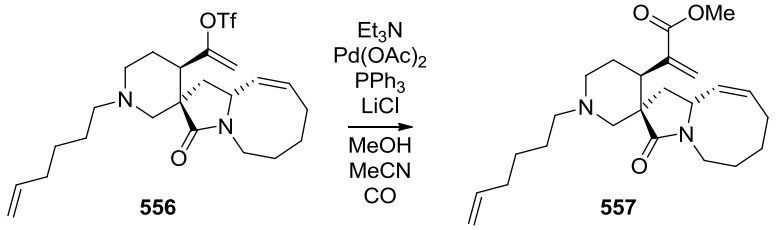


555 **556**

To amine **555** (1.0 eq, 0.200 mmol, 72 mg) in tetrahydrofuran (100 mL/g **555**, 7.20 mL) was added Comins' reagent (2.4 eq, 0.418 mmol, 158 mg) at RT. The reaction mixture was cooled to −78 °C. KHMDS (3.4 eq, 0.680 mmol, 0.5 M in toluene, 1.36 mL) was added dropwise. After 10 min, NH_4Cl (saturated aqueous, 7.20 mL) was added and the reaction mixture was warmed to RT. The organic and aqueous layers were separated and the aqueous layer was extracted (Et_2O, 1 × 15 mL). The aqueous layer was washed with HCl (1 M, 2 × 10 mL) before the combined acidic aqueous layer was extracted (Et_2O, 1 × 10 mL). The pH of the acidic aqueous layer was adjusted to pH > 10 *via* the addition of solid NaOH. The basified aqueous layer was extracted (CH_2Cl_2, 4 × 10 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (Et_2O → 9:1 Et_2O:MeOH) to yield the title compound **556** (41 mg, 42%) as a yellow oil. **$[\alpha]_D^{24}$** = −26.0 (c = 0.45, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2931 (C-H), 2857 (C-H), 1680 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.33 - 1.41 (m, 2 H, CH_2=CHCH$_2$C$\underline{H}_2$), 1.43 - 1.50 (m, 2 H, CH_2=CH(CH$_2$)$_2$C$\underline{H}_2$), 1.51 - 1.67 (m, 4 H, CHN(CH$_2$)$_2$C$\underline{H}_2$, CHNCH$_2$C$\underline{H}_A$H$_B$, NCHC$\underline{H}_A$H$_B$), 1.68 - 1.86 (m, 3 H, NCH$_2$C$\underline{H}_A$H$_B$CH, CHNCH$_2$CH$_A\underline{H}_B$, C_{quat}C$\underline{H}_A$H$_B$N), 2.01 - 2.13 (m, 4 H, CH_2=CHC$\underline{H}_2$, NC$\underline{H}_A$H$_B$CH$_2$CH, CHCH=CHC$\underline{H}_A$H$_B$), 2.16 - 2.29 (m, 2 H, C_{quat}C$\underline{H}$C, CH_2=CH(CH$_2$)$_3$C$\underline{H}_A$H$_B$), 2.30 - 2.47 (m, 3 H, CHCH=CHCH$_A\underline{H}_B$, NCHCH$_A\underline{H}_B$, CH_2=CH(CH$_2$)$_3$CH$_A\underline{H}_B$), 2.61 - 2.66 (m, 1 H, NCH$_2$CH$_A\underline{H}_B$CH), 2.95 - 2.99 (m, 1 H, NCH$_A\underline{H}_B$CH$_2$CH), 3.16 (d, *J* = 12.0 Hz, 1 H, C_{quat}CH$_A\underline{H}_B$N), 3.34 - 3.43 (m, 1 H, CHNC$\underline{H}_A$H$_B$), 3.43 - 3.53 (m, 1 H, CHNCH$_A\underline{H}_B$), 4.13 - 4.23 (m, 1 H, NC$\underline{H}$), 4.91 - 5.03 (m, 2 H, C$\underline{H}_2$=CH), 5.24 (br. s, 2 H, C_{quat}=C$\underline{H}_2$), 5.42 (dd, *J* =

11.0, 5.5 Hz, 1 H, CHC*H*=CH), 5.72 - 5.85 (m, 2 H, CHCH=C*H*, CH_2=C*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.1 ($CHNCH_2CH_2\underline{C}H_2$), 25.3 ($CHCH=CH\underline{C}H_2$), 26.1 ($CH_2=CH(CH_2)_2\underline{C}H_2$), 26.7 ($CH_2=CHCH_2\underline{C}H_2$), 27.1 ($CHNCH_2\underline{C}H_2$), 27.2 ($NCH_2\underline{C}H_2CH$), 33.6 ($CH_2=CH\underline{C}H_2$), 38.2 ($NCH\underline{C}H_2$), 41.5 ($CHN\underline{C}H_2$), 47.1 ($NC(O)\underline{C}_{quat}CH$), 48.2 ($C_{quat}\underline{C}H$), 53.6 ($N\underline{C}H_2CH_2CH$), 53.7 ($N\underline{C}HCH=CH$), 58.5 ($CH_2=CH(CH_2)_3\underline{C}H_2$), 61.4 ($C_{quat}\underline{C}H_2N$), 107.1 ($C_{quat}=\underline{C}H_2$), 114.5 ($\underline{C}H_2=CH$), 118.4 (q, *J* = 120.9 Hz, $\underline{C}F_3$), 130.8 ($CHCH=\underline{C}H$), 131.5 ($CH\underline{C}H=CH$), 138.8 ($CH_2=\underline{C}H$), 157.3 ($\underline{C}_{quat}=CH_2$), 173.3 ($\underline{C}$=O); ***m/z*** ($ESI^+$) 491 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{34}N_2O_4F_3S$) requires *m/z* 491.2186, found *m/z* 491.2180.

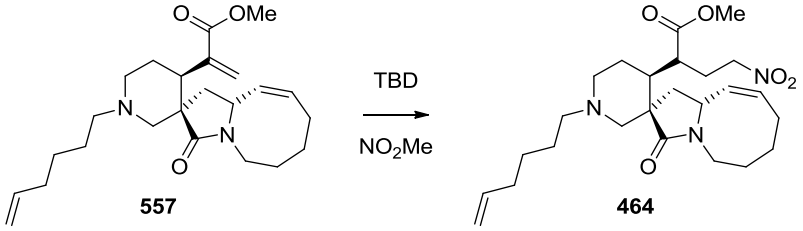
Methyl 2-[(3*R*,4*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-3'-oxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]acrylate (557)



To triflate **556** (1.0 eq, 0.059 mmol, 29 mg) in MeCN (27 mL/mmol **556**, 1.6 mL) and MeOH (4 mL/mmol **556**, 0.23 mL that had had CO bubbled through for 15 min, was added PPh_3 (0.4 eq, 0.024 mmol, 6 mg) and LiCl (1.0 eq, 0.059 mmol, 3 mg) at RT. The reaction mixture was purged with CO which was bubbled through the reaction mixture for 3 min. Triethylamine (2.0 eq, 0.12 mmol, 16 µL) and $Pd(OAc)_2$ (0.2 eq, 0.012 mmol, 3 mg) were sequentionally added and CO was bubbled through the reaction mixture for a further minute. The reaction mixture was stirred at RT for 48 h before being filtered through a plug of celite which was eluted with Et_2O (5 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (Et_2O → 9:1 Et_2O:MeOH) to yield the title compound **557** (20 mg, 85%) as a yellow oil. $\mathbf{[\alpha]_D^{24}}$ = −54.3 (c = 0.03, $CHCl_3$); **IR** ν_{max}(film)/cm^{-1} 2931 (C-H), 2861 (C-H), 1677 (C=O), 1637 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.20 - 1.74 (m, 19 H, CH_2=CHCH$_2$C$\underline{H}_2$C$\underline{H}_2$, CHNCH$_2$C$\underline{H}_2$, NCHC$\underline{H}_A$H$_B$, CHNCH$_2$CH$_2$C$\underline{H}_2$, C_{quat}CHC$\underline{H}_A$H$_B$), 1.76 - 2.61 (m, 15 H, C_{quat}C$\underline{H}_A$H$_B$N, CH_2=CHC$\underline{H}_2$, CH_2=CH(CH$_2$)$_3$C$\underline{H}_2$, NC$\underline{H}_2$CH$_2$CH, NCHCH$_A$$\underline{H}_B$, CH=CHC$\underline{H}_2$, C_{quat}C$\underline{H}$,), 2.78 - 2.88 (m, 1 H, C_{quat}CHCH$_A$$\underline{H}_B$), 2.98 - 3.07 (m, 1 H, C_{quat}CH$_A$$\underline{H}_B$N), 3.12 - 3.26 (m, 1 H, CHNC$\underline{H}_A$H$_B$), 3.48 - 3.60 (m, 1 H, CHNCH$_A$$\underline{H}_B$), 3.77 (s, 3 H, COOC$\underline{H}_3$), 3.95 - 4.04 (m, 1 H, NC$\underline{H}$), 4.90 - 5.04 (m, 2 H, C$\underline{H}_2$=CH), 5.32 (dd, *J* = 11.0, 6.5 Hz, 1 H, NCHC$\underline{H}$=CH), 5.80 (m, 2 H, NCHCH=C$\underline{H}$, CH_2=C$\underline{H}$), 5.92 (br. s, 1 H, C_{quat}=C$\underline{H}_A$H$_B$), 6.35 (br. s, 1 H, C_{quat}=CH$_A$$\underline{H}_B$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 25.2 (CHNCH$_2$CH$_2$$\underline{C}H_2$), 25.4 (CHCH=CH$\underline{C}H_2$), 26.1 (CH$_2$=CH(CH$_2$)$_2$$\underline{C}H_2$), 26.6 (CH$_2$=CHCH$_2$$\underline{C}H_2$), 27.3 (NCH$_2$$\underline{C}H_2$CH), 27.5 (CHNCH$_2$$\underline{C}H_2$), 33.5 (CH$_2$=CH$\underline{C}H_2$), 38.6 (NCH$\underline{C}H_2$), 40.0 ($C_{quat}$$\underline{C}$H), 40.8 (CHN$\underline{C}H_2$), 54.3 (COO$\underline{C}H_3$), 55.7 (N$\underline{C}H_2CH_2$CH), 56.5 (CH$_2$=CH(CH$_2$)$_3$$\underline{C}H_2$), 52.5 (N$\underline{C}$H), 48.2 ($\underline{C}_{quat}$CH), 63.5

($C_{quat}\underline{C}H_2N$), 114.4 ($\underline{C}H_2$=CH), 128.7 (C=$\underline{C}H_2$), 130.6 (NCH$\underline{C}$H=CH), 131.7 (NCHCH=$\underline{C}$H), 138.6 ($CH_2$=$\underline{C}$H), 141.2 ($\underline{C}$=$CH_2$), 168.3 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 174.5 ($\underline{C}$=O); ***m/z*** ($ESI^+$) 401 (100%, $[M+H]^+$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{37}N_2O_3$) requires *m/z* 401.2799 , found *m/z* 401.2796.

Methyl (2*S*)-2-[(3*R*,9'*Z*,10a'*R*)-1-(hex-5-en-1-yl)-3'-oxo-1',5',6',7',8',10a'-hexahydrospiro [piperidine-3,2'-pyrrolo[1,2-*a*]azocin]-4-yl]-4-nitrobutanoate (464)



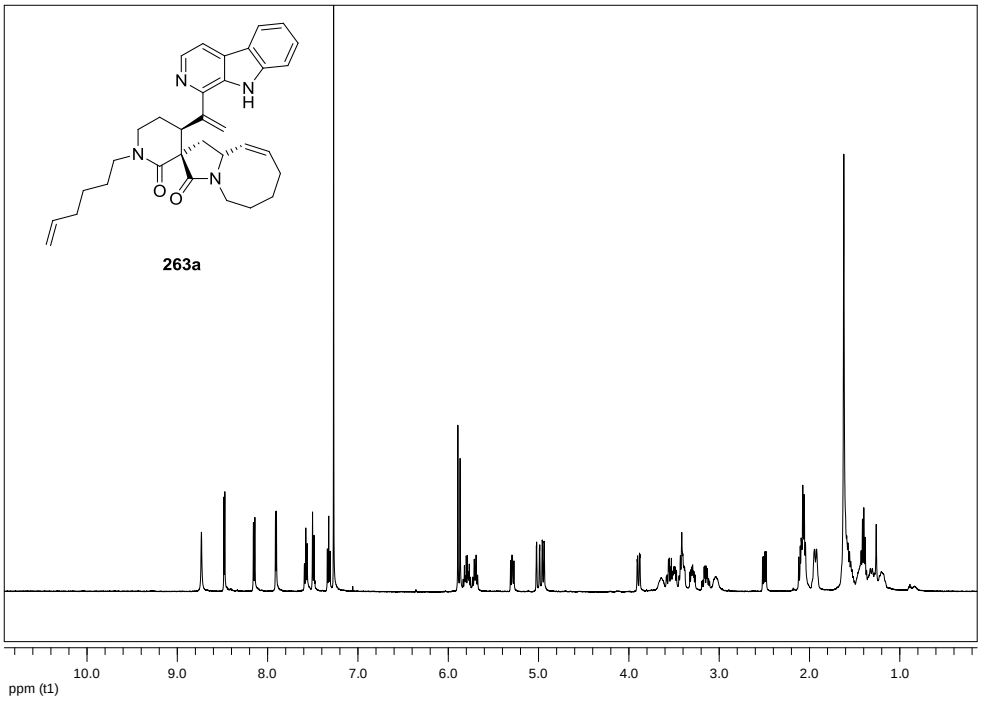
557 464

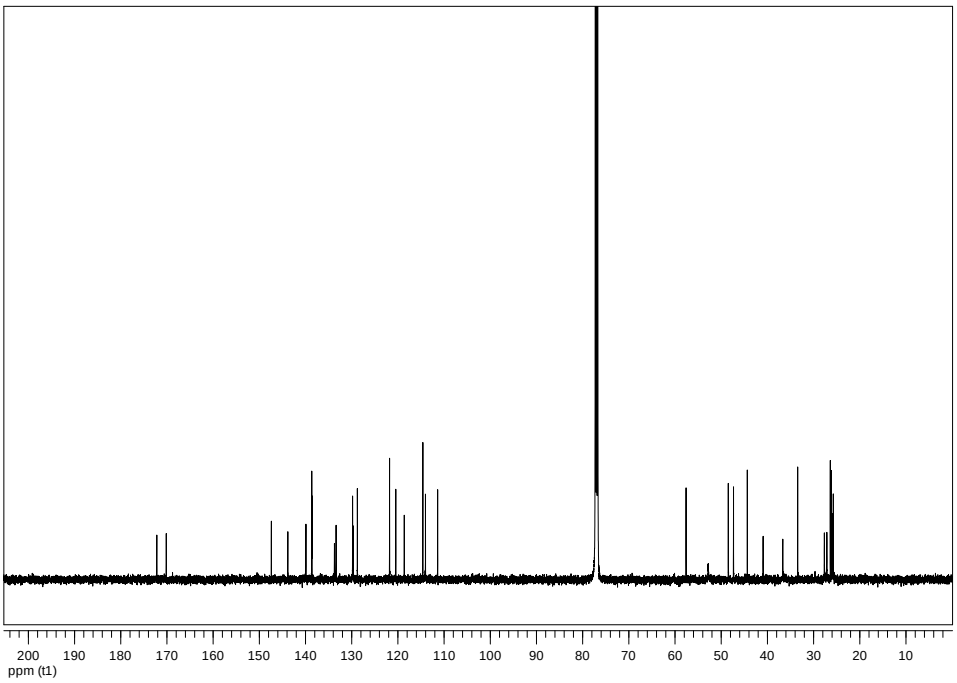
To α,β-unsaturated ester **557** (1.0 eq, 0.02 mmol, 8 mg) in nitromethane (5 mL/mmol **557**, 0.1 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (0.3 eq, 0.006 mmol, 1 mg) at RT. After 48 h, the reaction mixture was loaded on to a silica gel column and purified by flash column chromatography (Et_2O → 9:1 Et_2O:MeOH) to yield the title compound **464** (5 mg, 54%) as a pale yellow oil. See above for characterisation.

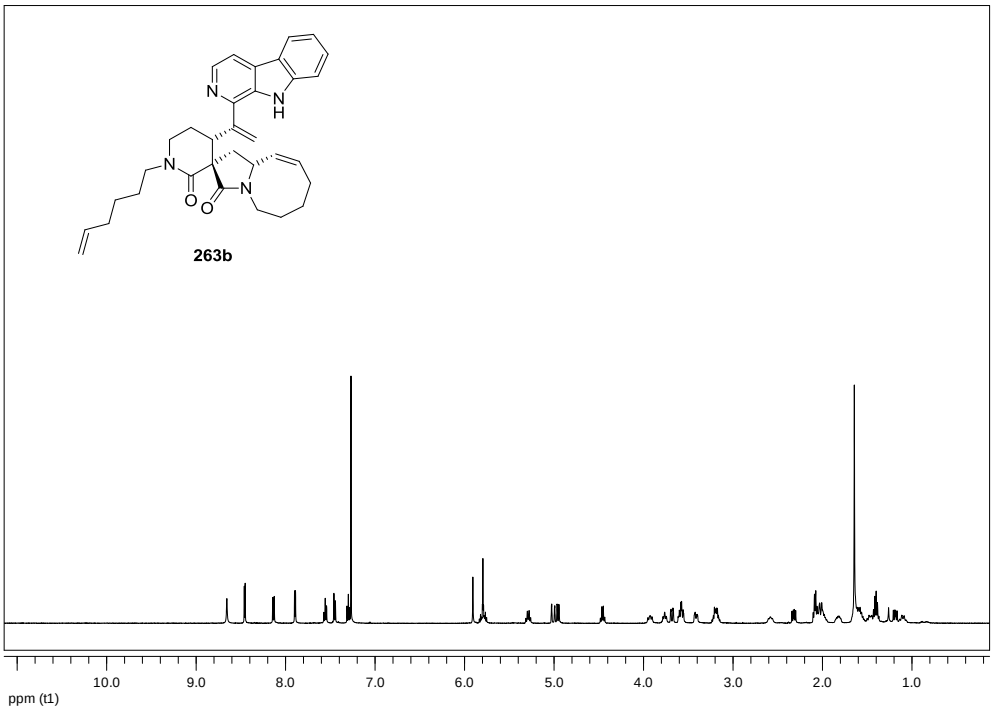
Chapter 6
Appendices

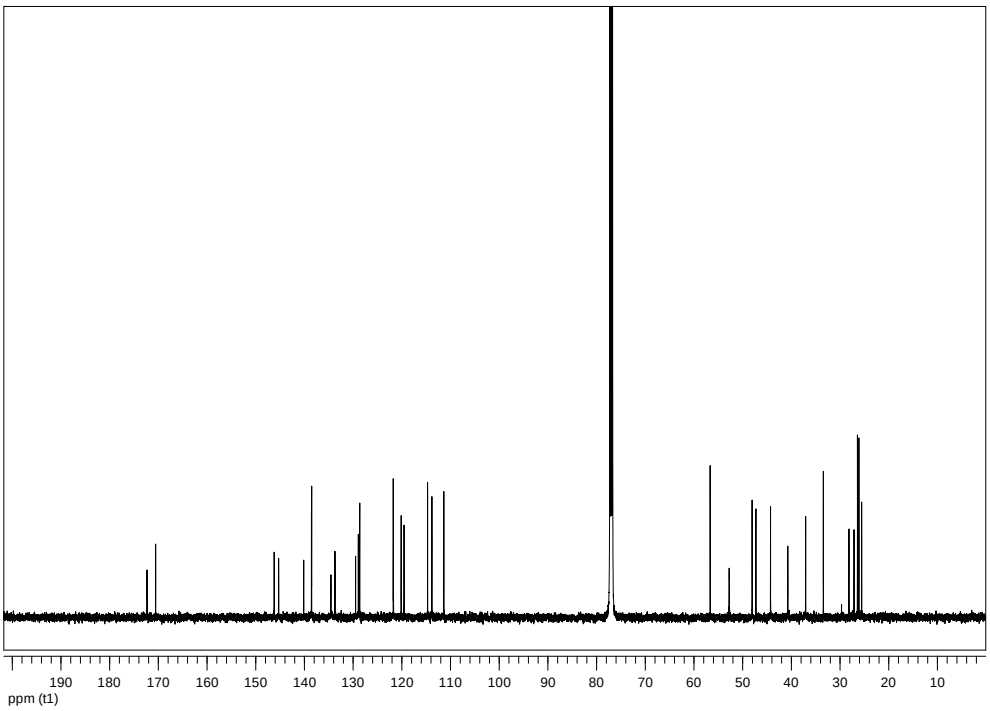
6.1 Appendix 1: Data for 263a and 263b

*6.1.1 ^{1}H and ^{13}C NMR data of **263a** and **263b***

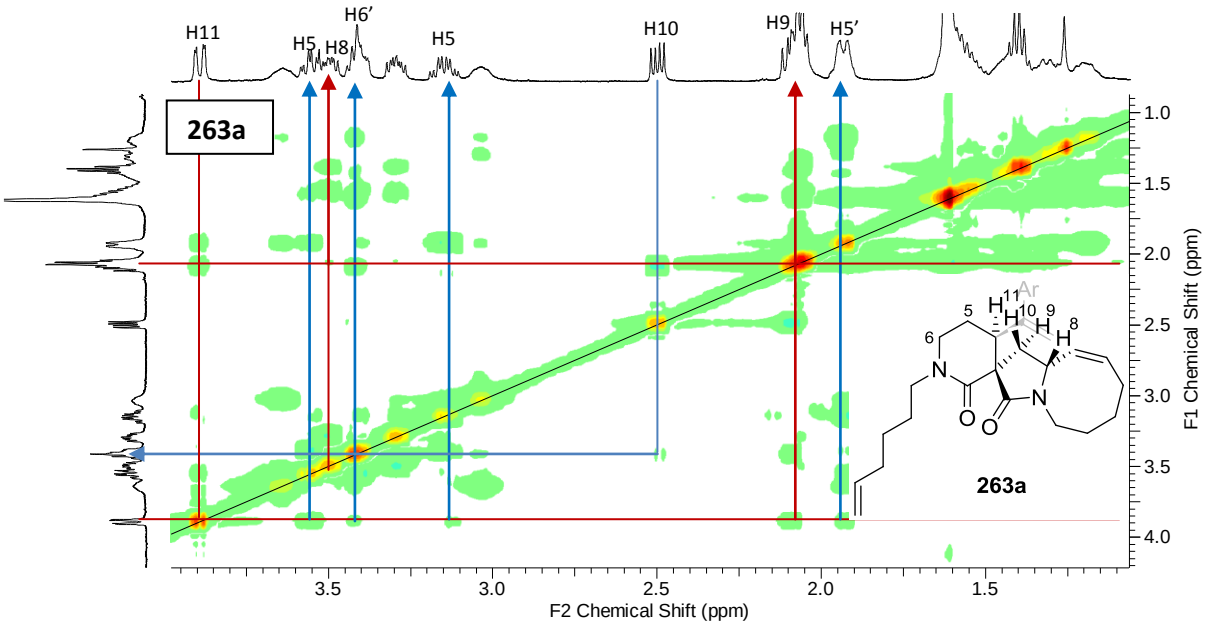


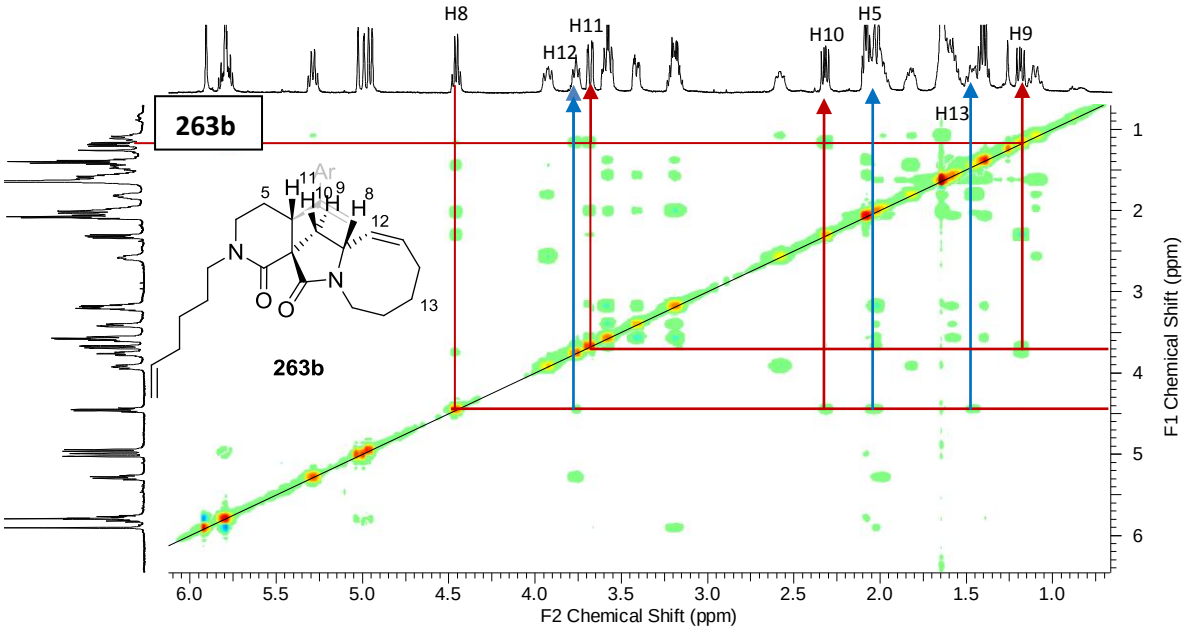



N
N
H
N
O
O
N
263b
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm (t1)

6.1.2 NOESY experimental data for **263a** and **263b**





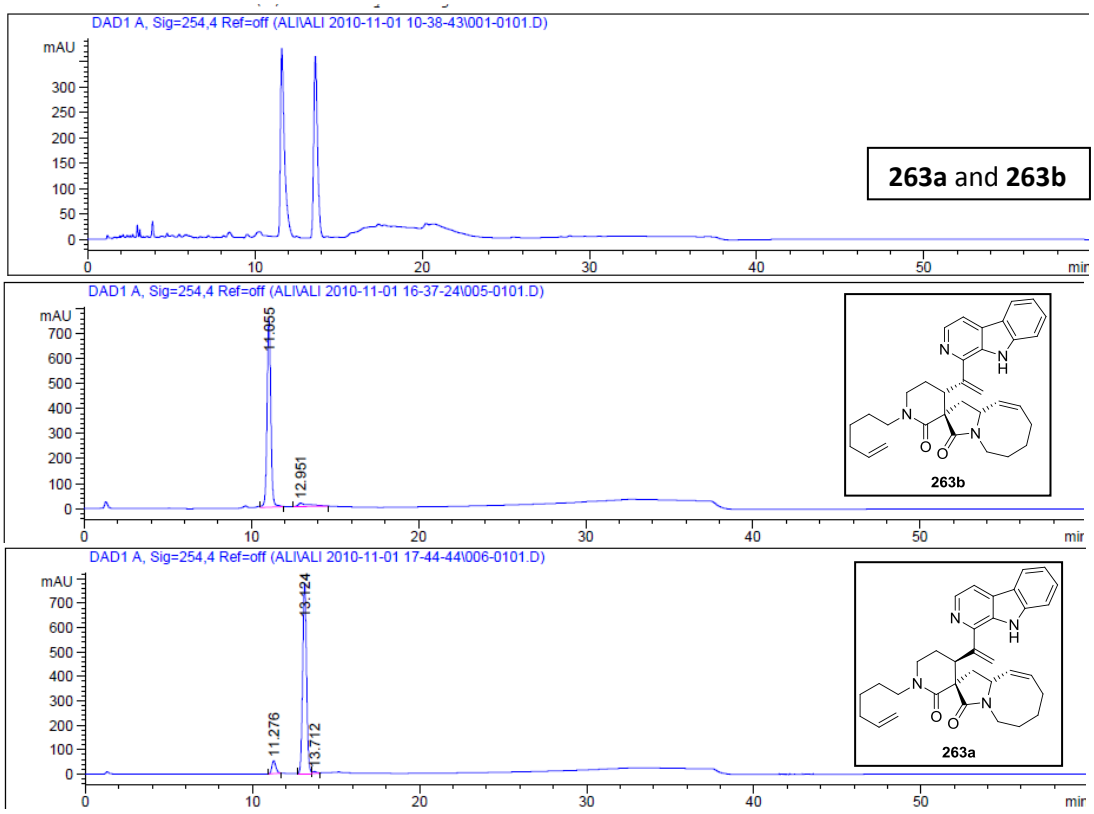
For **263a**, important interactions are shown in red:

- H9 – H11 strong
- H8 – H9 weak

For **263b**, important interactions are shown in red:

- H8 – H10 strong
- H11 – H9 strong

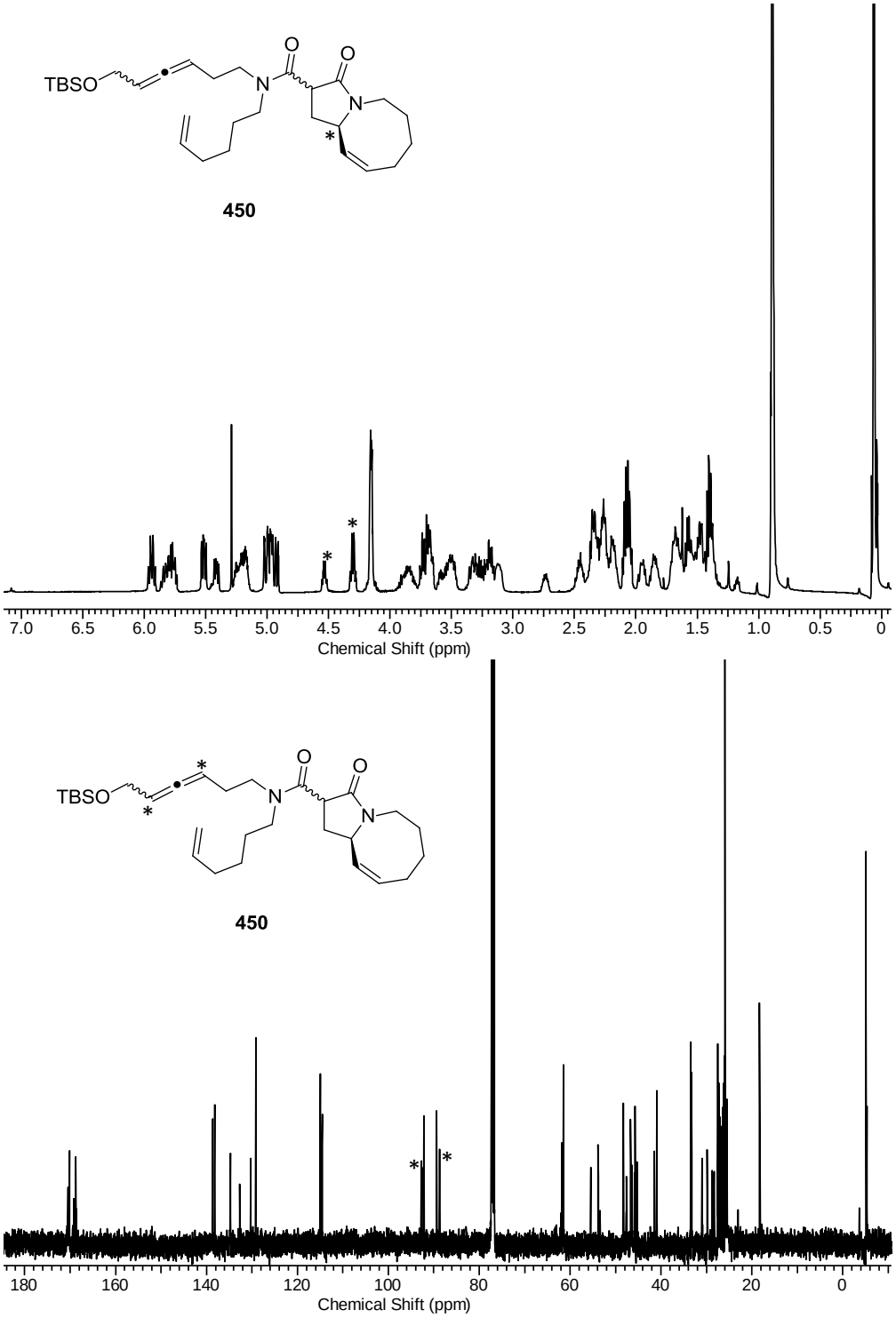
6.1.3 HPLC data for **263a** and **263b**



Reverse phase column Kromasil 100-3.5C18 15; 0 times 4.6 mm. Eluent A: MeCN:MeOH:H_2O 38:38:22, eluent B: MeCN:MeOH 50:50, RAMP; 19 mg dissolved in 1.0 mL of MeOH, analytical run, injection 10 micro-litres

6.2 Appendix 2

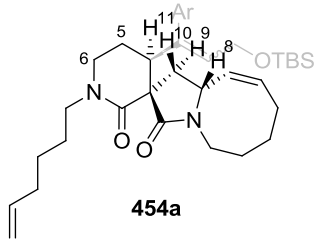
*6.2.1 ^{1}H and ^{13}C NMR data for **450***



Two diastereomers by ^{1}H NMR (H*), but four diastereomers by ^{13}C (C*).

6.3 Appendix 3

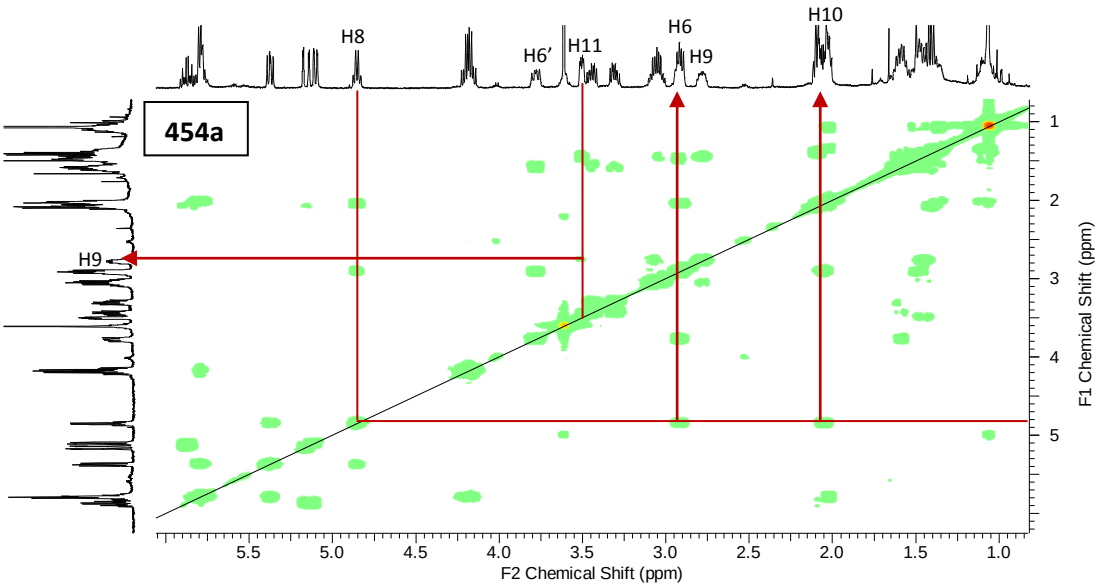
*6.3.1 NOESY experimental data for **454a** and **454b***

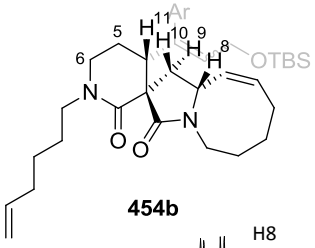


454a

Key interactions for **454a**:

- H9 – H11
- H8 – H10

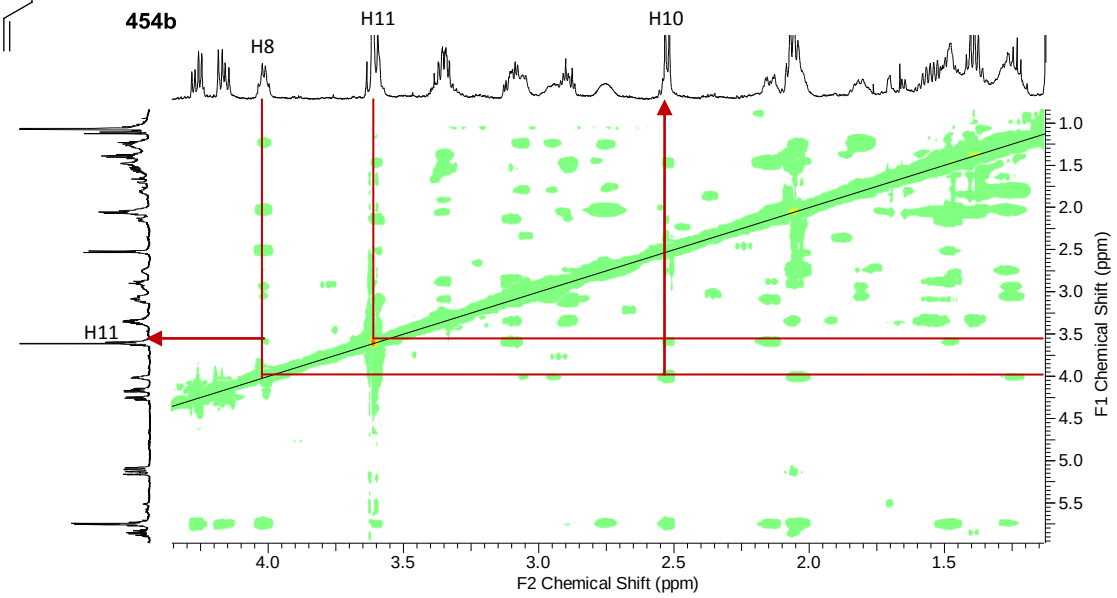




454b

Key interactions for **454b**:

- H11 – H8
- H8/H11 – H10



Chapter 7
References

1. Haefner, B. Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today* **8**, 536–544 (2003).
2. Rinehart, K. L. Antitumor compounds from tunicates. *Med. Res. Rev.* **20**, 1–27 (2000).
3. Corey, E. J., Gin, D. Y. & Kania, R. S. Enantioselective Total Synthesis of Ecteinascidin 743. *J. Am. Chem. Soc.* **118,** 9202–9203 (1996).
4. Moore, K. S., Wehrli, S., Roder, H., Rogers, M., Forrest, J. N., McCrimmon, D. & Zasloff, M. Squalamine: an aminosterol antibiotic from the shark. *PNAS* **90**, 1354–1358 (1993).
5. Moriarty, R. M., Tuladhar, S. M., Guo, L. & Wehrli, S. Synthesis of squalamine. A steroidal antibiotic from the shark. *Tet. Lett.* **35**, 8103–8106 (1994).
6. Nishida, A., Nagata, T. & Nakagawa, M. *Marine Natural Products* 255–280 (Springer Berlin Heidelberg, 2006).
7. Magnier, E. & Langlois, Y. Manzamine alkaloids, syntheses and synthetic approaches. *Tetrahedron* **54,** 6201–IN2 (1998).
8. Winkler, J. D. & Axten, J. M. The First Total Syntheses of Ircinol A, Ircinal A, and Manzamines A and D. *J. Am. Chem. Soc.* **120,** 6425–6426 (1998).
9. Martin, S. F., Humphrey, J. M., Ali, A. & Hillier, M. C. Enantioselective Total Syntheses of Ircinal A and Related Manzamine Alkaloids. *J. Am. Chem. Soc.* **121,** 866–867 (1999).
10. Humphrey, J. M., Liao, Y., Ali, A., Rein, T., Wong, Y.-L., Chen, H.-J., Courtney, A. K., Martin, S. F. Enantioselective Total Syntheses of Manzamine A and Related Alkaloids. *J. Am. Chem. Soc.* **124**, 8584–8592 (2002).
11. Toma, T., Kita, Y. & Fukuyama, T. Total Synthesis of (+)-Manzamine A. *J. Am. Chem. Soc.* **132,** 10233–10235 (2010).
12. Jakubec, P., Hawkins, A., Felzmann, W. & Dixon, D. J. Total Synthesis of Manzamine A and Related Alkaloids. *J. Am. Chem. Soc.* **134,** 17482–17485 (2012).
13. Barrett, A. G. M., Boys, M. L. & Boehm, T. L. Total Synthesis of (+)-Papuamine: An Antifungal Pentacyclic Alkaloid from a Marine Sponge, Haliclona sp. *J. Org. Chem.* **61,** 685–699 (1996).
14. McDermott, T. S., Mortlock, A. A. & Heathcock, C. H. Total Syntheses of (−)-Papuamine and (−)-Haliclonadiamine. *J. Org. Chem.* **61,** 700–709 (1996).
15. Nagata, T., Nakagawa, M. & Nishida, A. The First Total Synthesis of Nakadomarin A. *J. Am. Chem. Soc.* **125,** 7484–7485 (2003).
16. Ono, K., Nakagawa, M. & Nishida, A. Asymmetric Total Synthesis of (−)-Nakadomarin A. *Angew. Chem. Int. Ed.* **43**, 2020–2023 (2004).
17. Jakubec, P., Cockfield, D. M. & Dixon, D. J. Total Synthesis of (−)-Nakadomarin A. *J. Am. Chem. Soc.* **131,** 16632–16633 (2009).
18. Torisawa, Y., Hashimoto, A., Nakagawa, M. & Hino, T. A total synthesis of manzamine c. *Tet. Lett.* **30**, 6549–6550 (1989).
19. Torisawa, Y., Hashimoto, A., Nakagawa, M., Seki, H., Hara, R. & Hino, T. A total synthesis of manzamine C and its geometrical isomer. *Tetrahedron* **47**, 8067–8078 (1991).
20. Nowak, W. & Gerlach, H. Synthese von Manzamin C, Infractin und 6-Hydroxyinfractin. *Liebig. Ann. Chem.* **1993**, 153–159 (1993).

21. Torisawa, Y., Hashimoto, A., Okouchi, M., Iimori, T., Nagasawa, M., Hino, T. & Nakagawa, M. Manzamine C congeners with modified azacyclic rings: Synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* **6**, 2565–2570 (1996).
22. MaGee, D. I. & Beck, E. J. The use of the Ramberg– Bäcklund rearrangement for the formation of aza-macrocycles: a total synthesis of manzamine C. *Can. J. Chem.* **78**, 1060–1066 (2000).
23. Morimoto, Y. & Yokoe, C. Total synthesis of haliclamine A, a macrocyclic marine alkaloid related to the key biogenetic intermediate of manzamines. *Tet. Lett.* **38**, 8981–8984 (1997).
24. Morimoto, Y., Yokoe, C., Kurihara, H. & Kinoshita, T. Total syntheses of macrocyclic marine alkaloids, haliclamines A and B: A convenient and expeditious assembly of 3-substituted pyridine derivatives with different alkyl chains to the bispyridinium macrocycle. *Tetrahedron* **54,** 12197–12214 (1998).
25. Michelliza, S., Al-Mourabit, A., Gateau-Olesker, A. & Marazano, C. Synthesis of the Cytotoxic Sponge Metabolite Haliclamine A. *J. Org. Chem.* **67,** 6474–6478 (2002).
26. Sakai, R., Higa, T., Jefford, C. W. & Bernardinelli, G. Manzamine A, a novel antitumor alkaloid from a sponge. *J. Am. Chem. Soc.* **108,** 6404–6405 (1986).
27. Ang, K. K. H., Holmes, M. J., Higa, T., Hamann, M. T. & Kara, U. A. K. In Vivo Antimalarial Activity of the Beta-Carboline Alkaloid Manzamine A. *Antimicrob. Agents Chemother.* **44,** 1645–1649 (2000).
28. Peng, J., Kudrimoti, S., Prasanna, S., Odde, S., Doesrksen, R. J., Pennaka, H. K., Choo, Y.-M., Rao, K. V., Tekwani, B. L., Madgula, V., Khan, S. I., Wang, B., Mayer, A. M. S., Jacob, M. R., Tu, L. C., Gertsch, J. & Hamann, M. T. Structure−Activity Relationship and Mechanism of Action Studies of Manzamine Analogues for the Control of Neuroinflammation and Cerebral Infections. *J. Med. Chem.* **53**, 61–76 (2010).
29. Winkler, J. D., Londregan, A. T., Ragains, J. R. & Hamann, M. T. Synthesis and Biological Evaluation of Manzamine Analogues. *Org. Lett.* **8,** 3407–3409 (2006).
30. Yin, W., Sarma, P. V. V. S., Ma, J., Han, D., Chen, J. L. & Cook, J. M. Synthesis of bivalent ligands of β-carboline-3-carboxylates via a palladium-catalyzed homocoupling process. *Tet. Lett.* **46**, 6363–6368 (2005).
31. Hamann, M., Alonso, D., Martin-Aparicio, E., Fuertes, A., Perez-Puerto, M. J., Castro, A., Morales, S., Navarro, M. L., del Monte-Millan, M., Medina, M., Pennaka, H., Balaiah, A., Peng, J., Cook, J., Wahyuono, S. & artinez, A. Glycogen Synthase Kinase-3 (GSK-3) Inhibitory Activity and Structure–Activity Relationship (SAR) Studies of the Manzamine Alkaloids. Potential for Alzheimer's Disease. *J. Nat. Prod.* **70**, 1397–1405 (2007).
32. Baldwin, J. E. & Whitehead, R. C. On the Biosynthesis of Manzamines. *Tet. Lett.* **33**, 2059–2062 (1992).
33. Kobayashi, J., Tsuda, M., Kawasaki, N., Matsumoto, K. & Adachi, T. Keramaphidin B, a novel pentacyclic alkaloid from a marine sponge Amphimedon sp.□: A plausible biogenetic precursor of manzamine alkaloids. *Tet. Lett.* **35**, 4383–4386 (1994).
34. Kondo, K., Shigemori, H., Kikuchi, Y., Ishibashi, M., Sasaki, T. & Kobayashi, J. Ircinals A and B from the Okinawan marine sponge Ircinia sp.: plausible biogenetic precursors of manzamine alkaloids. *J. Org. Chem.* **57**, 2480–2483 (1992).
35. Torisawa, Y., Nakagawa, M., Hosaka, T., Tanabe, K., Lai, Z., Ogata, K., Nakata, T., Oishi, T. & Hino, T. Diels-Alder reactions of dihydropyridinones: synthetic entry to the manzamine A tricyclic core. *J. Org. Chem.* **57**, 5741–5747 (1992).
36. Jakubowicz, K., Abdeljelil, K. B., Herdemann, M., Martin, M.-T., Gateau-Olesker, A., Mouabit, A. A., Marazano, C. & Das, B. C. Reactions of Aminopentadienal Derivatives with 5,6-Dihydropyridinium Salts as an Approach to Manzamine

Alkaloids Based upon Biogenetic Considerations. *J. Org. Chem.* **64**, 7381–7387 (1999).
37. Herdemann, M., Al-Mourabit, A., Martin, M.-T. & Marazano, C. From a Biogenetic Scenario to a Synthesis of the ABC Ring of Manzamine A. *J. Org. Chem.* **67,** 1890–1897 (2002).
38. Nakagawa, M., Torisawa, Y., Hosaka, T., Tanabe, K., Da-te, T., Okamura, K. & Hino, T. Dihydropyridinone approach to manzamines: An expedient construction of the tetracyclic core of manzamine A. *Tet. Lett.* **34**, 4543–4546 (1993).
39. Torisawa, Y., Hosaka, T., Tanabe, K., Suzuki, N., Motohashi, Y., Hino, T. & Nakagawa, M. Synthesis of a tetracyclic substructure of manzamine A via the Diels-Alder reaction of dihydropyridinones. *Tetrahedron* **52**, 10597–10608 (1996).
40. Nakagawa, M., Torisawa, Y., Uchida, H. & Nishida, A. New Approaches to Total Synthesis of Manzamine A, Ircinal A and Related Compounds. *J. Syn. Org. Chem. Jpn.* **57**, 1004–1015 (1999).
41. Uchida, H., Nishida, A. & Nakagawa, M. An efficient access to the optically active manzamine tetracyclic ring system. *Tet. Lett.* **40**, 113–116 (1999).
42. Imbroisi, D. de O. & Simpkins, N. S. A Diels–Alder approach to functionalized cis-hydroisoquinolines. Attempts to prepare a tricyclic core unit of manzamine A. *J. Chem. Soc., Perkin Trans. 1* 1815–1823 (1991).
43. Magnier, E. & Langlois, Y. Zincke-bradsher convergent strategy for the synthesis of the ABE tricyclic core of Manzamine A. *Tet. Lett.* **39**, 837–840 (1998).
44. Urban, D., Duval, E. & Langlois, Y. New developments in asymmetric Bradsher cycloadditions: use of chiral dienes. *Tet. Lett.* **41**, 9251–9256 (2000).
45. Crabtree, S. R., Chu, W. L. A. & Mander, L. N. C-Acylation of Enolates by Methyl Cyanoformate: An Examination of Site- and Stereoselectivity. *Synlett* **1990,** 169–170 (1990).
46. Zincke, T., Heuser, G. & Möller, W. I. Ueber Dinitrophenylpyridiniumchlorid und dessen Umwandlungsproducte. *J. Liebig. Ann. Chem.* **333**, 296–345 (1904).
47. Chen, T.-K. & Bradsher, C. K. Stereoselectivity in the cycloaddition reactions of 2-ethoxy-3-methylisoquinolinium salts. *J. Org. Chem.* **44,** 4680–4683 (1979).
48. Markó, I. E., Southern, J. M. & Adams, H. Towards the total synthesis of manzamines. Rapid and efficient assembly of a middle core model. *Tet. Lett.* **33**, 4657–4660 (1992).
49. Turet, L., Markó, I. E., Tinant, B., Declercq, J.-P. & Touillaux, R. Novel anionic polycyclisation cascade. Highly stereocontrolled assembly of functionalised tetracycles akin to the middle core of the manzamines. *Tet. Lett.* **43**, 6591–6595 (2002).
50. Leonard, J., Fearnley, S. P., Finlay, M. R., Knight, J. A. & Wong, G. A sulfolene-based intramolecular Diels–Alder approach to the synthesis of manzamine A. *J. Chem. Soc., Perkin Trans. 1* 2359–2361 (1994).
51. Brands, K. M. J., Meekel, A. A. P. & Pandit, U. K. Synthesis of the homochiral 'tricyclic heart' of manzamine A. *Tetrahedron* **47,** 2005–2026 (1991).
52. Borer, B. C., Deerenberg, S., Bieräugel, H. & Pandit, U. K. The first synthesis of the ABCD ring system of manzamine A. Construction of the macrocyclic ring D. *Tet. Lett.* **35**, 3191–3194 (1994).
53. Pandit, U. K., Borer, B. C., Bieraugel, H. & Deerenberg, S. Studies on the total synthesis of manzamine A. *Pure Appl. Chem.* **66**, 2131–2134 (1994).
54. Pandit, U. K., Borer, B. C. & Bieräugel, H. Synthetic studies on manzamine A. *Pure Appl. Chem.* **68**, 659–662 (1996).

55. Pandit, U. K., Overkleeft, H. S., Borer, B. C. & Bieräugel, H. Synthesis Mediated by Ring-Closing Metathesis – Applications in the Synthesis of Azasugars and Alkaloids. *Eur. J. Org. Chem.* **1999**, 959–968 (1999).
56. Kamenecka, T. M. & Overman, L. E. An enantioselective approach to the synthesis of manzamine A. *Tet. Lett.* **35**, 4279–4282 (1994).
57. Tokumaru, K., Arai, S. & Nishida, A. Stereoselective Furan-Iminium Cation Cyclization in the Construction of the Core Structure of Manzamine A. *Org. Lett.* **8,** 27–30 (2006).
58. Brands, K. M. J. & DiMichele, L. M. An efficient and stereoselective construction of the core structure of the manzamines via an intramolecular Michael reaction. *Tet. Lett.* **39**, 1677–1680 (1998).
59. Fürstner, A., Guth, Oliver, Düffels, A., Seidel, G., Liebl, M., Gabor, B., Mynott, R. Indenylidene Complexes of Ruthenium: Optimized Synthesis, Structure Elucidation, and Performance as Catalysts for Olefin Metathesis—Application to the Synthesis of the ADE-Ring System of Nakadomarin A. *Chem. Eur. J.* **7**, 4811–4820 (2001).
60. Li, S. & Yamamura, S. Synthesis of the tetracyclic ABCE ring subunit I, bearing the 13-membered azacycle, of manzamine A. *Tetrahedron* **54,** 8691–8710 (1998).
61. Magnus, P., Fielding, M. R., Wells, C. & Lynch, V. Stereoselective synthesis of the tricyclic core ABC-rings of nakadomarin and manzamine from a common intermediate. *Tet. Lett.* **43**, 947–950 (2002).
62. Sugihara, T., Yamada, M., Yamaguchi, M. & Nishizawa, M. The Intra- and Intermolecular Pauson-Khand Reaction Promoted by Alkyl Methyl Sulfides. *Synlett* **1999,** 771–773 (1999).
63. Coldham, I., Crapnell, K. M., Fernàndez, J.-C., Moseley, J. D. & Rabot, R. Synthesis of the ABC Ring System of Manzamine A. *J. Org. Chem.* **67,** 6181–6187 (2002).
64. Coldham, I., Crapnell, K. M., Fernandez, J.-C., Haxell, T. F. N., Treacy, A. B., Coles, S. J., Hursthouse M. B. & Moseley, J. D. A new stereoselective approach to the manzamine alkaloids. *Chem. Commun.* 1757–1758 (1999).
65. Coldham, I., Pih, S. M. & Rabot, R. Dipolar Cycloaddition and Ring-Closing Metathesis in the Synthesis of the Tetracyclic ABCE Ring System of Manzamine A. *Synlett* 1743–1745 (2005).
66. Ahrendt, K. A. & Williams, R. M. A Concise Asymmetric Synthesis of the ADE Fragment of Nakadomarin A. *Org. Lett.* **6,** 4539–4541 (2004).
67. Winkler, J. D., Muller, C. L. & Scott, R. D. A new method for the formation of nitrogen-containing ring systems via the intramolecular photocycloaddition of vinylogous amides. A synthesis of mesembrine. *J. Am. Chem. Soc.* **110,** 4831–4832 (1988).
68. Winkler, J. D., Siegel, M. G. & Stelmach, J. E. A highly stereoselective approach to the synthesis of the manzamine alkaloids via the intramolecular vinylogous amide photocycloaddition. *Tet. Lett.* **34**, 6509–6512 (1993).
69. Winkler, J. D., Axten, J., Hammach, A. H., Kwak, Y.-S., Lengweiler, U., Lucero, M. J. & Houk, K. N. Stereoselective synthesis of the tetracyclic core of manzamine via the vinylogous amide photocycloaddition cascade. *Tetrahedron* **54**, 7045–7056 (1998).
70. Hawkins, A., Jakubec, P., Ironmonger, A. & Dixon, D. J. An expedient stereoselective route to the ACE tricyclic core of manzamine A via a palladium-catalysed arylative allene spirocyclisation cascade. *Tet. Lett.* **54**, 365–369 (2013).
71. Martin, S. F., Liao, Y., Wong, Y. & Rein, T. A novel approach to the asymmetric synthesis of manzamine A. Construction of the tetracyclic ABCE ring system. *Tet. Lett.* **35**, 691–694 (1994).

72. Salmond, W. G., Barta, M. A. & Havens, J. L. Allylic oxidation with 3,5-dimethylpyrazole. Chromium trioxide complex steroidal .DELTA.5-7-ketones. *J. Org. Chem.* **43,** 2057–2059 (1978).
73. Mander, L. N. & Sethi, S. P. Regioselective synthesis of β-ketoesters from lithium enolates and methyl cyanoformate. *Tet. Lett.* **24**, 5425–5428 (1983).
74. Bower, S., Kreutzer, K. A. & Buchwald, S. L. A Mild General Procedure for the One-Pot Conversion of Amides to Aldehydes. *Angew. Chem. Int. Ed. Eng.* **35**, 1515–1516 (1996).
75. McMurry, J. E. & Melton, J. New method for the conversion of nitro groups into carbonyls. *J. Org. Chem.* **38,** 4367–4373 (1973).
76. Comins, D. L. & Dehghani, A. Pyridine-derived triflating reagents: An improved preparation of vinyl triflates from metallo enolates. *Tet. Lett.* **33**, 6299–6302 (1992).
77. Clayden, J., Greeves, N., Warren, S. & Wothers, P. *Organic Chemistry* (Oxford University Press, 2005).
78. Burton, B. S. & Von Pechmann, H. Ueber die Einwirkung von Chlorphosphor auf Acetondicarbonsäureäther. *Ber. Deutsch. Chem. Gesellschaft* **20**, 145–149 (1887).
79. Jones, E. R. H., Mansfield, G. H. & Whiting, M. C. Researches on acetylenic compounds. Part XLVII. The prototropic rearrangements of some acetylenic dicarboxylic acids. *J. Chem. Soc.* 3208–3212 (1954).
80. van't Hoff, J. H. *La Chimie dans l'Espace* (Bazendijk: Rotterdam, 1875).
81. Staudinger, H. & Ruzicka, L. Insektentötende Stoffe I. Über Isolierung und Konstitution des wirksamen Teiles des dalmatinischen Insektenpulvers. *Helv. Chim. Acta* **7**, 177–201 (1924).
82. Searles, S., Li, Y., Nassim, B., Lopes, M.-T. R., Tran, P. T. Crabbé, P. Observation on the synthesis of allenes by homologation of alk-1-ynes. *J. Chem. Soc., Perkin Trans. 1* 747–751 (1984).
83. Fillion, H., André, D. & Luche, J.-L. Mecanisme de l'homologation directe d'acetyleniques en allenes. *Tet. Lett.* **21**, 929–930 (1980).
84. González, M., Rodríguez, R. Á., Cid, M. M. & López, C. S. A stepwise retro-imino-ene as a key step in the mechanism of allene formation via the Crabbé acetylene homologation. *J. Comp. Chem.* **33**, 1236–1239 (2012).
85. Bestmann, H.-J. & Hartung, H. Reaktionen mit Phosphinalkylenen, XII. Eine neue Synthese von Allen-carbonsäureestern. *Chem. Ber.* **99**, 1198–1207 (1966).
86. Taylor, D. R. The Chemistry of Allenes. *Chem. Rev.* **67,** 317–359 (1967).
87. Zimmer, R., Dinesh, C. U., Nandanan, E. & Khan, F. A. Palladium-Catalyzed Reactions of Allenes. *Chem. Rev.* **100**, 3067–3126 (2000).
88. Schultz, R. G. π-Allylic complexes from allene. *Tetrahedron* **20,** 2809–2813 (1964).
89. Lupin, M. S., Powell, J. & Shaw, B. L. Transition metal–carbon bonds. Part VII. The formation of π-allylic–palladium complexes from allenes and palladium halides and the reversed reactions. *J. Chem. Soc. A* 1687–1691 (1966).
90. Coulson, D. R. Transition metal catalyzed reactions of allene. *J. Org. Chem.* **38,** 1483–1490 (1973).
91. Gamez, P., Ariente, C., Goré, J. & Cazes, B. Stereoselectivity of the carbopalladation-functionalization of allenic compounds: A mechanistic study. *Tetrahedron* **54,** 14835–14844 (1998).
92. Bates, R. W. & Satcharoen, V. Nucleophilic transition metal based cyclization of allenes. *Chem. Soc. Rev.* **31,** 12–21 (2002).
93. Besson, L., Goré, J. & Cazes, B. Synthesis of allylic amines through the palladium-catalyzed hydroamination of allenes. *Tet. Lett.* **36**, 3857–3860 (1995).

94. Al-Masum, M., Meguro, M. & Yamamoto, Y. The two component palladium catalyst system for intermolecular hydroamination of allenes. *Tet. Lett.* **38**, 6071–6074 (1997).
95. Grigg, R., Sridharan, V. & Terrier, C. Palladium catalysed cyclisation-allene insertion-anion capture cascades. *Tet. Lett.* **37**, 4221–4224 (1996).
96. Grigg, R. & Savic, V. Palladium catalysed termolecular queuing cascades. Facile cyclisation-anion capture routes to heterocyclic dienes via allene insertion processes. *Tet. Lett.* **37**, 6565–6568 (1996).
97. Gardiner, M., Grigg, R., Sridharan, V. & Vicker, N. Cascade and sequential palladium catalysed cyclisation-azide capture-1,3-dipolar cycloaddition route to complex triazoles. *Tet. Lett.* **39**, 435–438 (1998).
98. Grigg, R., Sridharan, V. & Xu, L.-H. Palladium-catalysed cyclisation–amination of allenes-effect of base on regioselectivity of formation of allylic amines. *J. Chem. Soc., Chem. Commun.* 1903–1904 (1995).
99. Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **105,** 2829–2872 (2005).
100. Yamamoto, Y. & Al-Masum, M. Palladium Catalyzed α-Addition of Certain Pronucleophiles to Alkoxyallenes. *Synlett* **1995,** 969–970 (1995).
101. Yamamoto, Y., Al-Masum, M., Fujiwara, N. & Asao, N. Remarkable reversal of the regioselectivity in the palladium catalyzed hydrocarbonation reaction of allenes with methylmalononitrile. *Tet. Lett.* **36**, 2811–2814 (1995).
102. Yamamoto, Y., Al-Masum, M. & Asao, N. Palladium-Catalyzed Addition of Activated Methylene and Methyne Compounds to Allenes. *J. Am. Chem. Soc.* **116,** 6019–6020 (1994).
103. Ahmar, M., Cazes, B. & Gore, J. Synthese de dienes-1,3 et de styrenes fonctionnalises par carbopalladation catalytique d'allenes. *Tet. Lett.* **25**, 4505–4508 (1984).
104. Ahmar, M., Cazes, B. & Gore, J. Carbopalladation of β-allenylmalonates□: a way to cyclopentenyl or vinylcyclopropyl derivatives. *Tet. Lett.* **26**, 3795–3798 (1985).
105. Ahmar, M., Cazes, B. & Gore, J. Formation de derives cyclopenteniques et vinylcyclopropaniques lors de la carbopalladation de diesters et d' α-sulfonylesters alleniques. *Tetrahedron* **43,** 3453–3463 (1987).
106. Cazes, B. Synthetic methodology involving the carbopalladation of allenes. *Pure Appl. Chem.* **62**, 1867–1878 (1990).
107. Besson, L., Goré, J. & Cazes, B. Palladium-catalyzed addition of malonate type compounds to allenes via a hydropalladation process. *Tet. Lett.* **36**, 3853–3856 (1995).
108. Trost, B. M. & Gerusz, V. J. Palladium-Catalyzed Addition of Pronucleophiles to Allenes. *J. Am. Chem. Soc.* **117,** 5156–5157 (1995).
109. Meguro, M., Kamijo, S. & Yamamoto, Y. Palladium catalyzed intramolecular hydrocarbonation of allenes leading to carbocycles. *Tet. Lett.* **37**, 7453–7456 (1996).
110. Trost, B. M., Jäkel, C. & Plietker, B. Palladium-Catalyzed Asymmetric Addition of Pronucleophiles to Allenes. *J. Am. Chem. Soc.* **125,** 4438–4439 (2003).
111. Trost, B. M., Simas, A. B. C., Plietker, B., Jäkel, C. & Xie, J. Enantioselective Palladium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to an Allene Derivative. *Chem. Eur. J.* **11**, 7075–7082 (2005).
112. Hiroi, K., Kato, F. & Yamagata, A. Asymmetric Direct α,β-Functionalization of Allenes via Asymmetric Carbopalladation. *Chem. Lett.* **27**, 397–398 (1998).
113. Kato, F. & Hiroi, K. Stereochemistry of the Asymmetric Carbopalladation of Allenes Followed by Nucleophilic Substitution Reactions with Carbo- and Aminonucleophiles. *Chem. Pharm. Bull.* **52**, 95–103 (2004).

114. Jiang, X., Yang, Q., Yu, Y., Fu, C. & Ma, S. Highly Regio- and Stereoselective Synthesis of Nine- to Twelve-Membered Cyclic Compounds by a Pd0-Catalyzed Cyclization Reaction between Allenes with a Nucleophilic Functionality and Organic Halides. *Chem. Eur. J.* **15**, 7283–7286 (2009).
115. Li, M. & Dixon, D. J. Stereoselective Spirolactam Synthesis via Palladium Catalyzed Arylative Allene Carbocyclization Cascades. *Org. Lett.* **12,** 3784–3787 (2010).
116. Baker, J. K. & Little, T. L. Metabolism of phencyclidine. The role of the carbinolamine intermediate in the formation of lactam and amino acid metabolites of nitrogen heterocycles. *J. Med. Chem.* **28**, 46–50 (1985).
117. Philip J. Kocienski, Alan Bell & Paul R. Blakemore. 1-tert-Butyl-1H-tetrazol-5-yl Sulfones in the Modified Julia Olefination. *Synlett* **3,** 365 – 366 (2000).
118. Trost, B. M., Pinkerton, A. B. & Seidel, M. Ruthenium-Catalyzed Two-Component Addition To Form 1,3-Dienes: Optimization, Scope, Applications, and Mechanism. *J. Am. Chem. Soc.* **123,** 12466–12476 (2001).
119. Gabriel, S. Synthesis of primary amines from the corrosponding alkyl halides. *Ber.* **20**, 2224–2236 (1887).
120. Bracher, F. & Hildebrand, D. β-Carbolin-Alkaloide, I. Synthese von 1-Aryl- und 1-Alkenyl-β-carbolinen durch Palladium-katalysierte Kupplungsreaktionen. *Liebig. Ann. Chem.* **1992**, 1315–1319 (1992).
121. Bracher, F. & Hildebrand, D. 1,9-Dimetalated ß-carbolines. Versatile building blocks for the total synthesis of Alkaloids. *Tetrahedron* **50,** 12329–12336 (1994).
122. Bordwell, F. G. & Fried, H. E. Heterocyclic aromatic anions with 4n + 2 .pi.-electrons. *J. Org. Chem.* **56,** 4218–4223 (1991).
123. Hess, W. & Burton, J. W. Palladium-Catalysed Cyclisation of N-Alkynyl Aminomalonates. *Chem. Eur. J.* **16**, 12303–12306 (2010).
124. Rathke, M. W. Preparation of lithio ethyl acetate. Procedure for the conversion of aldehydes and ketones to .beta.-hydroxy esters. *J. Am. Chem. Soc.* **92,** 3222–3223 (1970).
125. Zook, H. & Miller, J. Chemistry of Enolates .7. Kinetics and Orientation in Dimethyl Sulfoxide - Relative Nucleophilicities of Enolates. *J. Org. Chem.* **36,** 1112–1116 (1971).
126. Pohmakotr, M., Numechai, P., Prateeptongkum, S., Tuchinda, P. & Reutrakul, V. A general synthetic route to 1-azabicyclo[m.n.0]alkenes via cyclisation based on α-sulfinyl carbanions. *Org. Biomol. Chem.* **1,** 3495–3497 (2003).
128. Xiao, K.-J., Luo, J.-M., Ye, K.-Y., Wang, Y. & Huang, P.-Q. Direct, One-pot Sequential Reductive Alkylation of Lactams/Amides with Grignard and Organolithium Reagents through Lactam/Amide Activation. *Angew. Chem. Int. Ed.* **49**, 3037–3040 (2010).
129. Seebach, D. & Lehr, F. α,α-Doubly Deprotonated Nitroalkanes. Enhancement of the C-Nucleophilicity of Nitronates. *Angew. Chem. Int. Ed. Eng.* **15**, 505–506 (1976).
130. Chambers, A. Part II thesis "Novel Stereoselective Nitro-Mannich Reaction Cascades" (2012).
131. Motoyama, Y., Aoki, M., Takaoka, N., Aoto, R. & Nagashima, H. Highly efficient synthesis of aldenamines from carboxamides by iridium-catalyzed silane-reduction/dehydration under mild conditions. *Chem. Commun.* 1574–1576 (2009).
132. Bracher, F., Hildebrand, D. & Ernst, L. Total Synthesis of the Antimicrobial Marine Alkaloid Eudistomin T. *Arch. Pharm.* **327**, 121–122 (1994).
132. Moran, W. J. & Morken, J. P. Rh-Catalyzed Enantioselective Hydrogenation of Vinyl Boronates for the Construction of Secondary Boronic Esters. *Org. Lett.* **8,** 2413–2415 (2006).

134. Miyaura, N. & Suzuki, A. Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst. *J. Chem. Soc., Chem. Commun.* 866–867 (1979).
134. Barder, T. E., Walker, S. D., Martinelli, J. R. & Buchwald, S. L. Catalysts for Suzuki−Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **127,** 4685–4696 (2005).
136. Proutiere, F. & Schoenebeck, F. Solvent Effect on Palladium-Catalyzed Cross-Coupling Reactions and Implications on the Active Catalytic Species. *Angew. Chem. Int. Ed.* **50**, 8192–8195 (2011).
136. Knudsen, K. R. & Jørgensen, K. A. A chiral molecular recognition approach to the formation of optically active quaternary centres in aza-Henry reactions. *Org. Biomol. Chem.* **3,** 1362–1364 (2005).
137. Anderson, J. C., Howell, G. P., Lawrence, R. M. & Wilson, C. S. An Asymmetric Nitro-Mannich Reaction Applicable to Alkyl, Aryl, and Heterocyclic Imines. *J. Org. Chem.* **70,** 5665–5670 (2005).
139. Powell, L. H., Docherty, P. H., Hulcoop, D. G., Kemmitt, P. D. & Burton, J. W. Oxidative radical cyclisations for the synthesis of γ-lactones. *Chem. Commun.* 2559–2561 (2008).
140. Jasperse, C. P., Curran, D. P. & Fevig, T. L. Radical reactions in natural product synthesis. *Chem. Rev.* **91**, 1237–1286 (1991).
141. Davies, H. M. L., DuBois, J. & Yu, J.-Q. C–H Functionalization in organic synthesis. *Chem. Soc. Rev.* **40,** 1855–1856 (2011).
141. Collet, F., Lescot, C. & Dauban, P. Catalytic C–H amination: the stereoselectivity issue. *Chem. Soc. Rev.* **40,** 1926–1936 (2011).
143. Ishiyama, T., Takagi, J., Ishida, K., Miyaura, N., Anastasi, N. R., Hartwig, J. F. Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **124**, 390–391 (2002).
144. Takagi, J., Sato, K., Hartwig, J. F., Ishiyama, T. & Miyaura, N. Iridium-catalyzed C–H coupling reaction of heteroaromatic compounds with bis(pinacolato)diboron: regioselective synthesis of heteroarylboronates. *Tet. Lett.* **43**, 5649–5651 (2002).
144. Díaz-Requejo, M. M. & Pérez, P. J. Coinage Metal Catalyzed C−H Bond Functionalization of Hydrocarbons. *Chem. Rev.* **108,** 3379–3394 (2008).
145. Simmons, E. M. & Hartwig, J. F. Catalytic functionalization of unactivated primary C-H bonds directed by an alcohol. *Nature* **483,** 70–73 (2012).
146. Desai, L. V., Hull, K. L. & Sanford, M. S. Palladium-Catalyzed Oxygenation of Unactivated sp3 C−H Bonds. *J. Am. Chem. Soc.* **126,** 9542–9543 (2004).
147. Boorman, T. C. & Larrosa, I. Gold-mediated C–H bond functionalisation. *Chem. Soc. Rev.* **40,** 1910–1925 (2011).
149. Collet, F., Dodd, R. H. & Dauban, P. Catalytic C–H amination: recent progress and future directions. *Chem. Commun.* 5061–5074 (2009).
150. Chen, X., Hao, X.-S., Goodhue, C. E. & Yu, J.-Q. Cu(II)-Catalyzed Functionalizations of Aryl C−H Bonds Using Oxygen as an Oxidant. *J. Am. Chem. Soc.* **128,** 6790–6791 (2006).
150. Peng, X., Zhu, Y., Ramirez, T. A., Zhao, B. & Shi, Y. New Reactivity of Oxaziridine: Pd(II)-Catalyzed Aromatic C–H Ethoxycarbonylation via C–C Bond Cleavage. *Org. Lett.* **13,** 5244–5247 (2011).
152. Guan, Z.-H., Ren, Z.-H., Spinella, S. M., Yu, S., Liang, Y.-M. & Zhang, X. Rhodium-Catalyzed Direct Oxidative Carbonylation of Aromatic C−H Bond with CO and Alcohols. *J. Am. Chem. Soc.* **131**, 729–733 (2009).

152. Ritleng, V., Sirlin, C. & Pfeffer, M. Ru-, Rh-, and Pd-Catalyzed C−C Bond Formation Involving C−H Activation and Addition on Unsaturated Substrates: Reactions and Mechanistic Aspects. *Chem. Rev.* **102,** 1731–1770 (2002).
153. Shilov, A. E. & Shul'pin, G. B. Activation of C−H Bonds by Metal Complexes. *Chem. Rev.* **97,** 2879–2932 (1997).
154. Wiedemann, S. H., Lewis, J. C., Ellman, J. A. & Bergman, R. G. Experimental and Computational Studies on the Mechanism of N-Heterocycle C−H Activation by Rh(I). *J. Am. Chem. Soc.* **128,** 2452–2462 (2006).
156. Ma, S. & Zhang, J. Pd0-catalyzed cyclization reaction of aryl or alk-1-enyl halides with 1,2-dienyl ketones: a general and efficient synthesis of polysubstituted furans. *Chem. Commun.* 117–118 (2000).
157. Ma, S., Zhang, J. & Lu, L. Pd0-Catalyzed Coupling Cyclization Reaction of Aryl or 1Alkenyl Halides with 1,2-Allenyl Ketones: Scope and Mechanism. An Efficient Assembly of 2,3,4-, 2,3,5-Tri- and 2,3,4,5-Tetrasubstituted Furans. *Chem. Eur. J.* **9**, 2447–2456 (2003).
157. Weibel, J.-M., Blanc, A. & Pale, P. Ag-Mediated Reactions: Coupling and Heterocyclization Reactions. *Chem. Rev.* **108,** 3149–3173 (2008).
158. Zhu, G. & Zhang, Z. Palladium-Catalyzed Tandem Cyclization/Suzuki Coupling Reaction of 1,2,7-Trienes. *Org. Lett.* **6,** 4041–4044 (2004).
160. Kammerer, C., Prestat, G., Madec, D. & Poli, G. Phosphine-Free Palladium-Catalyzed Allene Carbopalladation/Allylic Alkylation Domino Sequence: A New Route to 4-(α-Styryl) γ-Lactams. *Chem. Eur. J.* **15**, 4224–4227 (2009).
160. Ma, S. & Zhao, S. Reverse of Regioselectivity in Intramolecular Nucleophilic Substitution of π-Allyl Palladium Species. Highly Selective Formation of Vinylic Cyclopropanes via the Pd(0)-Catalyzed Coupling−Cyclization Reaction of Organic Iodides with 2-(2',3'-Dienyl)malonates. *Org. Lett.* **2,** 2495–2497 (2000).
162. Bayón, J. C., Claver, C. & Masdeu-Bultó, A. M. Homogeneous catalysis with transition metal complexes containing sulfur ligands. *Coord. Chem. Rev.* **193–195**, 73–145 (1999).
163. Negishi, E., Takahashi, T. & Akiyoshi, K. 'Bis(triphenylphosphine)palladium:' its generation, characterization, and reactions. *J. Chem. Soc., Chem. Commun.* 1338–1339 (1986).
163. Bottex, M., Cavicchioli, M., Hartmann, B., Monteiro, N. & Balme, G. A Versatile Palladium-Mediated Three-Component Reaction for the One-Pot Synthesis of Stereodefined 3-Arylidene-(or 3-Alkenylidene-)tetrahydrofurans. *J. Org. Chem.* **66,** 175–179 (2001).
164. Siqueira, J. B. G., Zoghbi, M. das G. B., Cabral, J. A. & Filho, W. W. Lignans from Protium tenuifolium. *J. Nat. Prod.* **58,** 730–732 (1995).
166. Fu, C. & Ma, S. Efficient Preparation of 4-Iodofuran-2(5H)-ones by Iodolactonisation of 2,3-Allenoates with Iodine. *Eur. J. Org. Chem.* **2005**, 3942–3945 (2005).
166. Trost, B. M., Fandrick, D. R. & Dinh, D. C. Dynamic Kinetic Asymmetric Allylic Alkylations of Allenes. *J. Am. Chem. Soc.* **127,** 14186–14187 (2005).
167. Ma, S., Jiao, N., Zhao, S. & Hou, H. Control of Regioselectivity in Pd(0)-Catalyzed Coupling−Cyclization Reaction of 2-(2',3'-Allenyl)malonates with Organic Halides. *J. Org. Chem.* **67,** 2837–2847 (2002).
169. Oh, C. H., Gupta, A. K., Park, D. I. & Kim, N. Highly efficient [2 + 2] intramolecular cyclizations of allenynes under microwave irradiation: construction of fused bicyclic compounds. *Chem. Commun.* 5670–5672 (2005).
169. Taylor, E. C., Macor, J. E. & Pont, J. L. Intramolecular diels-alder reactions of 1,2,4-triazines.□: A general synthesis of furo[2,3-b]pyridines, 2,3-dihydropyrano[2,3-b]pyridines, and pyrrolo[2,3-b]pyridines. *Tetrahedron* **43,** 5145–5158 (1987).

171. Holschbach, M. H., Bier, D., Wutz, W., Sihver, W., Schüller, M. & Olsson, R. A. Derivatives of 4,6-diamino-1,2-dihydro-2-phenyl-1,2,4-triazolo[4,3-a]quinoxalin-2H-1-one: potential antagonist ligands for imaging the A2A adenosine receptor by positron emission tomography (PET). *Eur. J. Med. Chem.* **40**, 421–437 (2005).
171. Li, Z., Brouwer, C. & He, C. Gold-Catalyzed Organic Transformations. *Chem. Rev.* **108,** 3239–3265 (2008).
172. Kato, Y., Conn, M. M. & Rebek, J. J. Water-Soluble Receptors for Cyclic-AMP and Their Use for Evaluating Phosphate-Guanidinium Interactions. *J. Am. Chem. Soc.* **116,** 3279–3284 (1994).
173. Kourra, C., Klotter, F., Sladojevich, F. & Dixon, D. J. Alkali Base-Initiated Michael Addition/Alkyne Carbocyclization Cascades. *Org. Lett.* **14,** 1016–1019 (2012).
175. Mukaiyama, T., Narasaka, K. & Banno, K. New Aldol Type Reaction. *Chem. Lett.* **2**, 1011–1014 (1973).
176. Herrero-Gómez, E., Nieto-Oberhuber, C., López, S., Benet-Buchholz, J. & Echavarren, A. M. Cationic η1/η2-Gold(I) Complexes of Simple Arenes. *Angew. Chem. Int. Ed.* **45**, 5455–5459 (2006).
177. Allan, M., Manku, S., Therrien, E., Nguyen, N., Styhler, S., Robert, M.-F., Goulet, A.-C., Petschner, A. J., Rahil, G., Robert MacLeod, A., Déziel, R., Besterman, J. M., Nguyen, H. & Wahhab, A. N-Benzyl-1-heteroaryl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamides as inhibitors of co-activator associated arginine methyltransferase 1 (CARM1). *Bioorg. Med. Chem. Lett.* **19**, 1218–1223 (2009).
178. Ebner, D. C., Bagdanoff, J. T., Ferreira, E. M., McFadden, R. M. Caspi, D. D., Trend, R. M., Stoltz, B. M. The Palladium-Catalyzed Aerobic Kinetic Resolution of Secondary Alcohols: Reaction Development, Scope, and Applications. *Chem. Eur. J.* **15**, 12978–12992 (2009).
178. Jakubec, P., Helliwell, M. & Dixon, D. J. Cyclic Imine Nitro-Mannich/Lactamization Cascades: A Direct Stereoselective Synthesis of Multicyclic Piperidinone Derivatives. *Org. Lett.* **10,** 4267–4270 (2008).
180. Jakubec, P., Cockfield, D. M., Helliwell, M., Raftery, J. & Dixon, D. Stereoselective, nitro-Mannich/lactamisation cascades for the direct synthesis of heavily decorated 5-nitropiperidin-2-ones and related heterocycles. *Beilstein J. Org. Chem.* **8**, 567–578 (2012).
180. Pelletier, S. M.-C., Ray, P. C. & Dixon, D. J. Nitro-Mannich/Lactamization Cascades for the Direct Stereoselective Synthesis of Pyrrolidin-2-ones. *Org. Lett.* **11,** 4512–4515 (2009).
181. Pelletier, S. M.-C., Ray, P. C. & Dixon, D. J. Diastereoselective Synthesis of 1,3,5-Trisubstituted 4-Nitropyrrolidin-2-ones via a Nitro-Mannich/Lactamization Cascade. *Org. Lett.* **13,** 6406–6409 (2011).
182. Barber, D. M., Sanganee, H. & Dixon, D. J. One-pot nitro-Mannich/hydroamination cascades for the direct synthesis of 2,5-disubstituted pyrroles using base and gold catalysis. *Chem. Commun.* **47,** 4379–4381 (2011).
183. Barber, D. M., Sanganee, H. J. & Dixon, D. J. One-Pot Catalytic Enantioselective Synthesis of Tetrahydropyridines via a Nitro-Mannich/Hydroamination Cascade. *Org. Lett.* **14,** 5290–5293 (2012).
184. Boëlle, J., Schneider, R., Gérardin, P. & Loubinoux, B. A New Preparation of Functionalized 3-Alkanoylpyrroles and 7-Oxoisoindoles. *Synthesis* **1997,** 1451–1456 (1997).
186. Mühlstädt, M. & Schulze, B. Nitrovinylverbindungen. III. Nitrovinylcarbonsäureester durch Kondensation von ω-Nitrocarbonsäureestern mit aromatischen Aldehyden. *J. Prakt. Chem.* **317**, 919–925 (1975).

186. Bhagwatheeswaran, H., Gaur, S. P. & Jain, P. C. A Novel Synthesis of Substituted 2-Oxopiperidines. *Synthesis* **1976,** 615–616 (1976).
188. Jakubec, P., Kyle, A. F., Calleja, J. & Dixon, D. J. Total synthesis of (−)-nakadomarin A: alkyne ring-closing metathesis. *Tet. Lett.* **52**, 6094–6097 (2011).
189. Kyle, A. F., Jakubec, P., Cockfield, D. M., Cleator, E., Skidmore, J., Dixon, D. J. Total synthesis of (−)-nakadomarin A. *Chem. Commun.* **47**, 10037–10039 (2011).
190. Ono, N., Miyake, H., Kamimura, A., Hamamoto, I., Tamura, R. & Kaji, A. Denitrohydrogenation of aliphatic nitro compounds and a new use of aliphatic nitro compounds as radical precursors. *Tetrahedron* **41**, 4013–4023 (1985).
190. Stang, P. J. & Summerville, R. Preparation and solvolysis of vinyl trifluoromethanesulfonates. I. Evidence for simple alkylvinyl cation intermediates. *J. Am. Chem. Soc.* **91,** 4600–4601 (1969).
191. Jones, W. M. & Maness, D. D. Solvolysis of sulfonic acid esters of triphenylvinyl alcohol by a heterolytic mechanism. *J. Am. Chem. Soc.* **91,** 4314–4315 (1969).
193. Dueber, T. E., Stang, P. J., Pfeifer, W. D., Summerville, R. H., Imhoff, M. A. Schleyer, P. v. R., Hummel, K., Bocher, S., Harding, C. E. & Hanack, M. Preparation of Cyclic and Acyclic Vinyl Trifluoromethanesulfonates. *Angew. Chem. Int. Ed. Eng.* **9**, 521–522 (1970).
194. Cacchi, S., Morera, E. & Ortar, G. Palladium-catalysed vinylation of enol triflates. *Tet. Lett.* **25**, 2271–2274 (1984).
195. Cacchi, S., Morera, E. & Ortar, G. Palladium-catalyzed carbonylation of enol triflates. A novel method for one-carbon homologation of ketones to α,β-unsaturated carboxylic acid derivatives. *Tet. Lett.* **26**, 1109–1112 (1985).
195. Baillargeon, V. P. & Stille, J. K. Palladium-catalyzed formylation of organic halides with carbon monoxide and tin hydride. *J. Am. Chem. Soc.* **108,** 452–461 (1986).
197. McBriar, M. D., Clader, J. W., Chu, I., Del Vecchio, R. A., Favreau, L., Greenlee, W. J., Hyde, L. A., Nomeir, A. A., Parker, E. M., Pissarnitski, D. A., Song, L. Zhang, L. & Zhao, Z. Discovery of amide and heteroaryl isosteres as carbamate replacements in a series of orally active γ-secretase inhibitors. *Bioorg. Med. Chem. Lett.* **18**, 215–219 (2008).
198. Johnson, K. M., Rattley, M. S., Sladojevich, F., Barber, D. M., Nuñez, M. G., Goldys, A. M., Dixon, D. J. A New Family of Cinchona-Derived Bifunctional Asymmetric Phase-Transfer Catalysts: Application to the Enantio- and Diastereoselective Nitro-Mannich Reaction of Amidosulfones. *Org. Lett.* **14**, 2492–2495 (2012).
199. Patent Application 1219300.9, Bifunctional Organic Catalysts. (2012).
199. Leonard, N. J. & Shoemaker, G. L. The Synthesis of Pyrrolizidines. IV. Condensation of Nitroparaffins with Methyl Methacrylate and Subsequent Formation of 2-, 6- and 8-Alkyl-Substituted Pyrrolizidines. *J. Am. Chem. Soc.* **71,** 1760–1762 (1949).
200. Escalante, J. & Díaz-Coutiño, F. D. Synthesis of g-Nitro Aliphatic Methyl Esters Via Michael Additions Promoted by Microwave Irradiation. *Molecules* **14,** 1595–1604 (2009).
202. Rõõm, E.-I., Kütt, A., Kaljurand, I., Koppel, I., Leito, I., Koppel, I. A., Mishima, M., Goto, K. & Miyahara, Y. Brønsted Basicities of Diamines in the Gas Phase, Acetonitrile, and Tetrahydrofuran. *Chem. Eur. J.* **13**, 7631–7643 (2007).
203. Yu, M., Wang, C., Kyle, A. F., Jakubec, P. J., Dixon, D. J., Schrock, R. R., Hoveyda, A. H. Synthesis of macrocyclic natural products by catalyst-controlled stereoselective ring-closing metathesis. *Nature* **479**, 88–93 (2011).
204. Li, D., Zhou, H.-Q., Dakoji, S., Shin, I., Oh, E. & Liu, H.-W. Spiropentylacetyl-CoA, A Mechanism-Based Inactivator of Acyl-CoA Dehydrogenases. *J. Am. Chem. Soc.* **120**, 2008–2017 (1998).

205. Tidwell, T. T. & Fenwick, M. H. Heptafulvenone, Vinylketene, Butadienylketene, and Allenylketene − Facile Generation, Observation, and Radical Reaction with TEMPO. *Eur. J. Org. Chem.* **2001**, 3415–3419 (2001).
206. Goumri-Magnet, S., Guerret, O., Gornitzka, H., Cazaux, J. B., Bigg, D., Palacious, F. & Bertrand, G. Free and Supported Phosphorus Ylides as Strong Neutral Brønsted Bases. *J. Org. Chem.* **64**, 3741–3744 (1999).
207. Yamamoto, Y., Fujikawa, R., Yamada, A. & Miyaura, N. A Regio- and Stereoselective Platinum(0)-Catalyzed Hydroboration of Allenes Controlled by Phosphine Ligands. *Chem. Lett.* **28**, 1069–1070 (1999).