Towards the Syntheses of Biologically Relevant Secondary Metabolites.

A thesis submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

By Eric Benjamin Jacques Harris

Research School of Chemistry

College of Physical & Mathematical Sciences

The Australian National University

July 2016

Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for award of any other degree or diploma at the Australian National University or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked with at the Australian National University, is explicitly acknowledged in the thesis.

Acknowledgements

I would like to acknowledge Professor Martin Banwell as my academic supervisor for chapters 2, 3 and 4. I owe a huge debt of gratitude to the Banwell group, with honorary mentions for Dr. Brett Schwartz and Mr Joshua Buckler whose advice and academic support were invaluable.

I would also like to acknowledge and sincerely thank Associate Professor Malcolm McLeod for his unerring patience as a most gracious supervisor and the McLeod group more generally for their open, welcoming and friendly attitude.

It is worthwhile giving additional thanks to the Australian National University, Research School of Chemistry as a whole. They have done their best to foster a strong sense of community and a fantastic culture whilst maintaining a professional environment. Specific thanks go to the Bramley's team, particularly Adam and Prue.

This thesis is dedicated to my parents, John and Yvonne, to whom I am eternally grateful.

Glossary of terms

°C	degrees Celsius
µg	microgram
µM	micromolar
µwave	microwave
Å	angstroms
Ac	acetyl
AIBN	azobisisobutyronitrile
AR	analytic reagent
AV	arteriovenous
b.p.	boiling point
BBEDA	bisbenzylideneethylenediamine
Bn	benzyl
Boc	tert-butyloxycarbonyl
br	broad
BTAC	benzyltriethylammonium chloride
Bu	butyl
Bz	benzoyl
calc.	calculated
cat	catalytic
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
Cy	cyclohexyl
d	doublet
D_2O	deuterium oxide
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets

ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQD	dihydroquinidine
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMM	dimethoxymethane
DMSO	dimethylsulfoxide
DNP	2,4-dinitrophenyl
dt	doublet of triplets
e.e.	enantiomeric excess
E_1cB	elimination unimolecular conjugate base
EDTA	ethylenediaminetetraacetic acid
EI	electron impact
ESI	electrospray ionisation
Et	ethyl
eV	electron Volts
FG	functional group
FGI	functional group interconversion
FTIR	Fourier transform infra red
g	grams
GABA	gamma aminobutyric acid
Glc	glycoside
h	hours
Hex	hexanes
HMDS	bis(trimethylsilyl)amide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half maximal inhibitory concentration

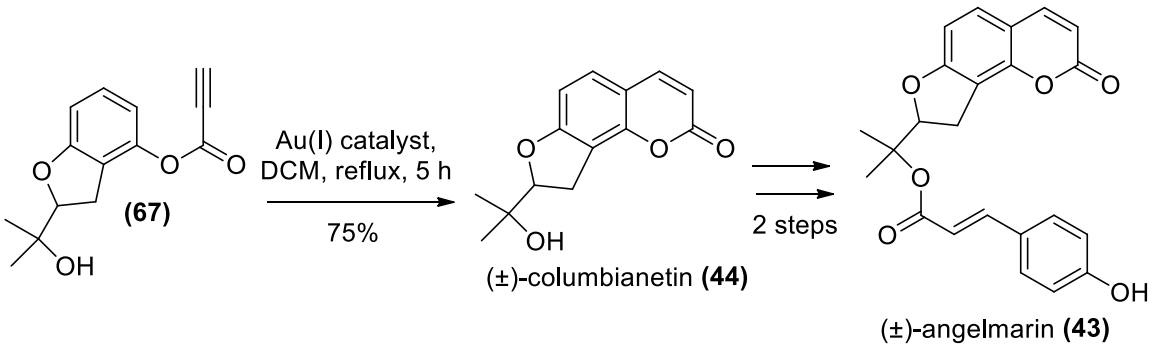
Im	imidazole
IMAE	intramolecular Alder-ene
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand/litre
LC	liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
m	multiplet
m.p.	melting point
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MHz	megaHertz
MIDA	methyliminodiacetyl
mL	millilitre
mmHg	millimeters of mercury
MOM	methoxymethyl
Ms	methanesulfonyl
nAChRs	nicotinic acetylcholine receptors
NADP	nicotinamide adenine dinucleotide phosphate
nm	nanometers
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nitrobenzenesulfonyl
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p	pentet
PCC	pyridinium chlorochromate
Ph	phenyl
PHAL	phthalazine

PhMe	toluene
Phth	phthalyl
pKa	negative log of acid ionisation constant
PMB	para-methoxybenzene
ppm	parts per million
pyr	pyridine
q	quartet
rt	room temperature
s	singlet
S_NAr	nucleophilic aromatic substitution
Sphos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAOH	tetrabutylammonium hydroxide
TBAS	tetrabutylammonium sulfate
TBS	tertbutyldimethylsilyl
t-Bu	tert-butyl
td	triplet of doublets
tdd	triplet of doublets of doublets
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate / trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMOF	trimethylorthoformate
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
Ts	toluenesulfonyl
ZMD	Zspray Mass Detector
δ	chemical shift

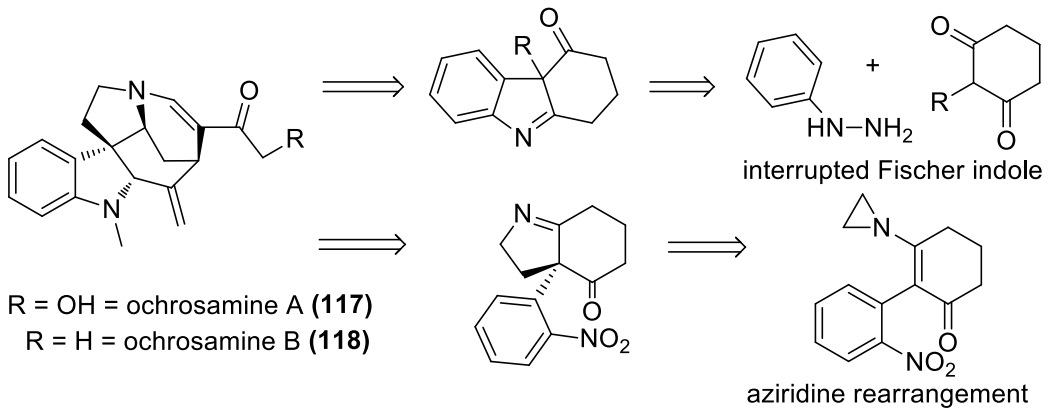
Abstract

The realm of natural product synthesis constitutes a major part of the interactions between chemistry and the living world. By designing and developing new synthetic routes to natural products, a better insight is gained in terms of new methodology, biological activity and structural novelty. As the field of natural products chemistry advances, ideal syntheses must be strived towards with the investigation of new methodology with high efficiency. Outlined herein are efforts towards the synthesis of four natural products of varying synthetic interests. Although many factors drive interest in their synthesis, they are united by a common goal of pursuing good synthesis.

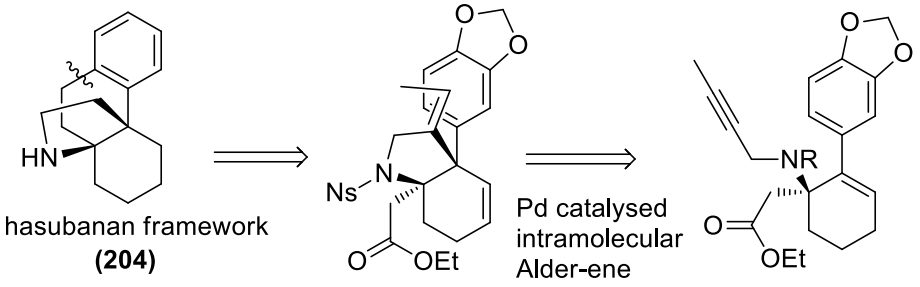
(±)-Angelmarin **(43)** has potential a therapeutic agent in the treatment of pancreatic cancer and was synthesised in only 7 linear steps without the use of protecting groups. This was enabled by the recently developed gold(I) catalysed intramolecular hydroarylation chemistry which allowed synthesis of the key coumarin heterocycle in (±)-columbianetin **(44)** under mild conditions from the propiolate ester.



Investigations were made into the synthesis of the ochrosamines A **(117)** and B **(118)**, isolated from the endangered rainforest tree *Ochrosia moorei*, exploring the scope and limitations of novel chemistry such as the vinyl aziridine rearrangement and interrupted Fischer indole synthesis. A number of interesting results were obtained from which much was learnt about the polycyclic system.



The hasubanan framework **(204)** was of synthetic interest as the unnatural enantiomer has potential as a new opiate analogue. The research hoped to expand on recently developed methodology for an intramolecular Alder-ene reaction and its application in a high value context.



Lastly, significant progress was made towards the synthesis of bicuculline **(228)** with the successful synthesis of the advanced intermediate **(326)** utilising an innovative osmium catalysed intramolecular amidohydroxylation reaction. This carries the possibility of developing an enantioselective synthesis. It is hoped that the natural product can ultimately be synthesised from this late stage material.

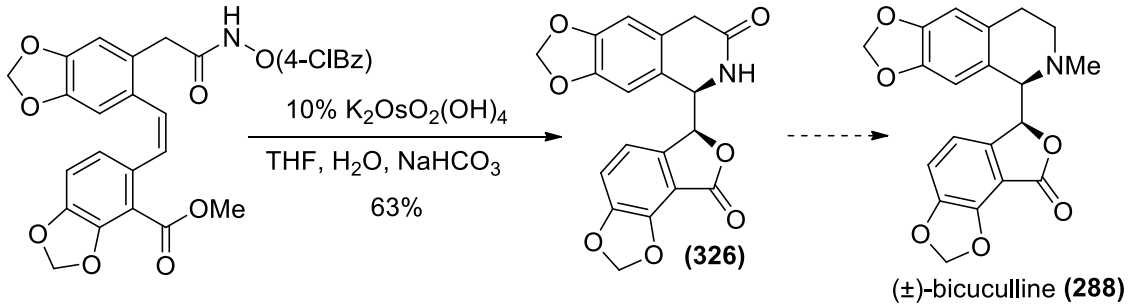


Table of Contents

Chapter 1 - Introduction

1.1 Towards the syntheses of biologically relevant secondary metabolites.

To its broadest extent natural products encompass all of the molecules of life; featuring extremely diverse classes of chemical compounds, from large scale polymers and organometallic complexes to steroid hormones and complex alkaloids[1] (Figure 1.1). As such natural products are inexorably intertwined with the field of organic chemistry. Friederich Wöhler's 1828 synthesis of the natural product, urea, fundamentally changed how the world was seen from a chemical perspective.[2] The molecules of life were no longer seen as the exclusive domain of living organisms. In essence this momentous discovery opened the door to the development of organic chemistry as a discipline in its own right.[3] Sitting at the interface of chemistry and the natural world, total synthesis pushes the boundaries of what is achievable whilst furthering our understanding of inherent chemical reactivity.[4]

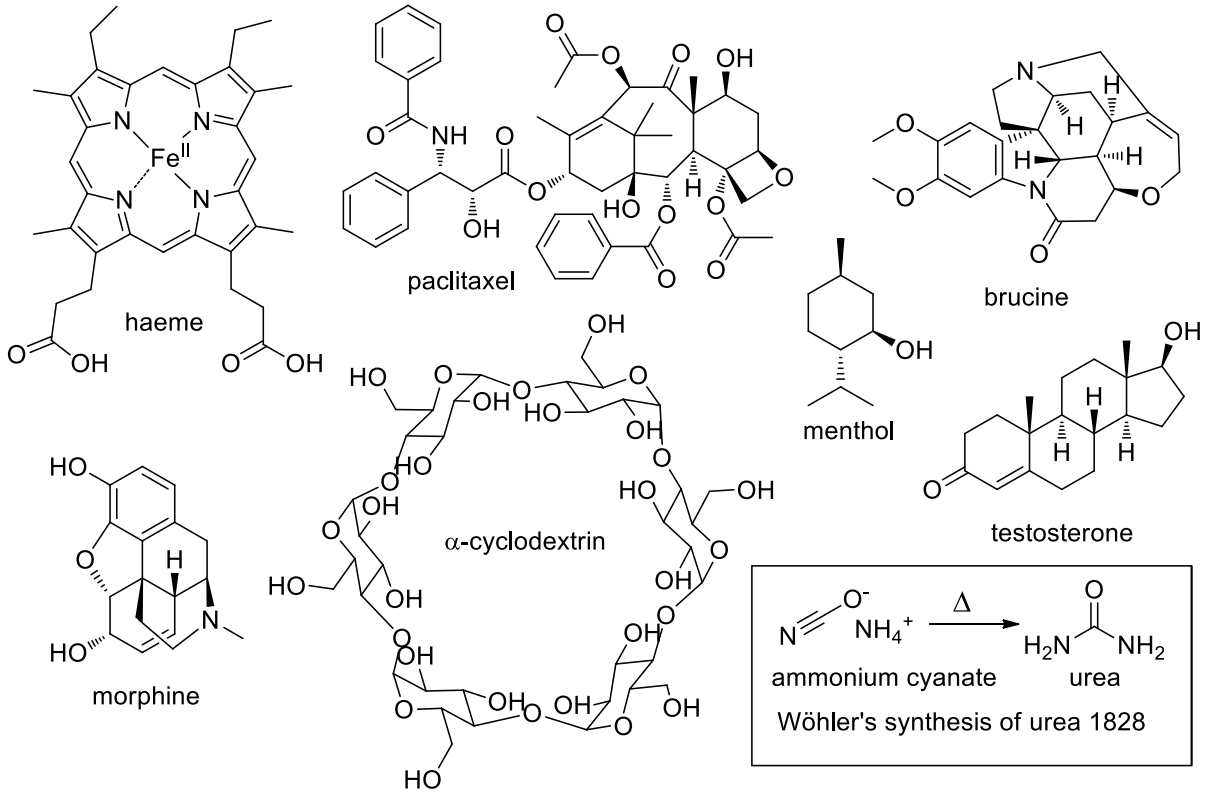


Figure 1.1 : Assorted Natural Products

One of the more fascinating aspects of natural products are the secondary metabolites. They are as their name suggests, molecules produced by an organism

that are not essential to its structure or metabolism.[5] Within various species these secondary metabolites have been shown to possess diverse roles from insecticides and pheremones, to antibiotics and venomous toxins.[6] This broad range of activities allows further understanding and manipulation of the biological systems in which they are found.[7]

One of the keenest examples of this is in drug design and development.[8] In the twenty-five years spanning 1981-2006, over 60% of new chemical entities registered for use as drugs have been either natural products or of naturally inspired origin.[9] Upon isolation, secondary metabolites are commonly assayed for potential bioactivity, thereby identifying possible lead compounds for drug development. It has been proposed that one of the key reasons for the relatively high success rate of naturally inspired drugs is that their biosynthesis has evolved alongside key biological targets.[10] If a secondary metabolite interacts with a biological target to benefit the producing organism, the genes controlling the synthesis and expression of that metabolite are more likely to be passed on. This constitutes a significant evolutionary selection pressure at the molecular level for the production of structures that interact strongly with biological systems.[11] In this fashion the field of natural products aids in the provision of relevant structural novelty in drug design and the discovery of potential biological targets for the treatment of disease.

1.2 Why do we synthesise Natural Products?

Given the inherent natural availability of these compounds, a salient question is raised; why make them? Indeed many such natural products are used or produced commercially in their natural form.[9] However a broad range of reasons from the practical to the intellectual, sit as the driving forces of synthesis. Isolation of material is often laborious, requiring multiple procedures at high expense with poor reproducibility.[1b] From an economic perspective, synthesis may be the only choice. When the yield from natural sources is a mere fraction of a percent it becomes commercially untenable to isolate compounds on any reasonable scale. At the moment of discovery, world supplies of such isolated products are often in the range of only a few milligrams of material.

Natural sources may also be ecologically sensitive, where obtaining large quantities of the source organism may significantly endanger the species population.[12] In order to commence further research as a potential drug target, synthetic methods are commonly required in order to provide the required quantities. A recent and notable example of this has been in the development of an anticancer compound taxol **(1)**, derived from the bark of the pacific yew tree.[13] Having demonstrated significant pharmaceutical potential, the demand for material became a threat to the relatively uncommon species. One of the early solutions to this problem was establishing a semi-synthetic procedure[14] as part of an effort towards a total synthesis, from 10-deacetylbaccatin III **(2)** which could be obtained in larger quantities from the european yew,[15] which can be sustainably forested (Figure 1.2).

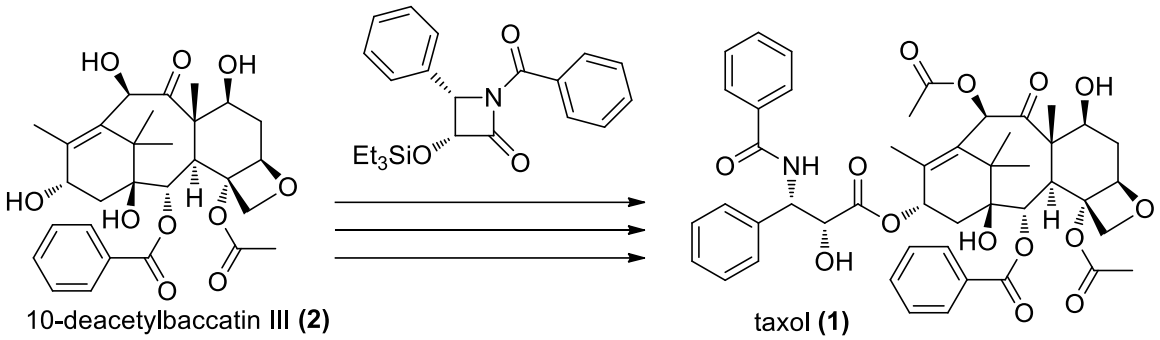


Figure 1.2 Semisynthesis of taxol

As a secondary consideration, the synthesis of natural products can also be seen as a worthwhile intellectual pursuit; often there is a race to be the first to achieve a synthesis of a novel structure.[4] This competitive element provides a strong impetus for the discovery of new processes and further development of the field. Due to the often complex and multifunctional nature of the intermediates, total synthesis also acts as a robust proving ground for the demonstration and validation of new methodology.[16]

The realm of natural product synthesis thereby serves as a theatre for the exposition of skill in the field of organic chemistry. Some of the greatest organic chemists have showcased their mastery in meeting the challenge provided by a complex natural product.[17] Some of these syntheses represent a marathon of time and effort to achieve a total synthesis of monumental status such as the selective total synthesis of palytoxin **(3)** by Kishi *et al.*[18] Palytoxin itself is one of the largest molecules of its kind ever synthesised; It possesses a molar mass of over 2600, with 64 stereogenic

centres. It was accomplished over several years in a longest linear sequence of 39 steps from 7 different building blocks with as many as 140 steps overall.[16, 19] (Figure 1.3).

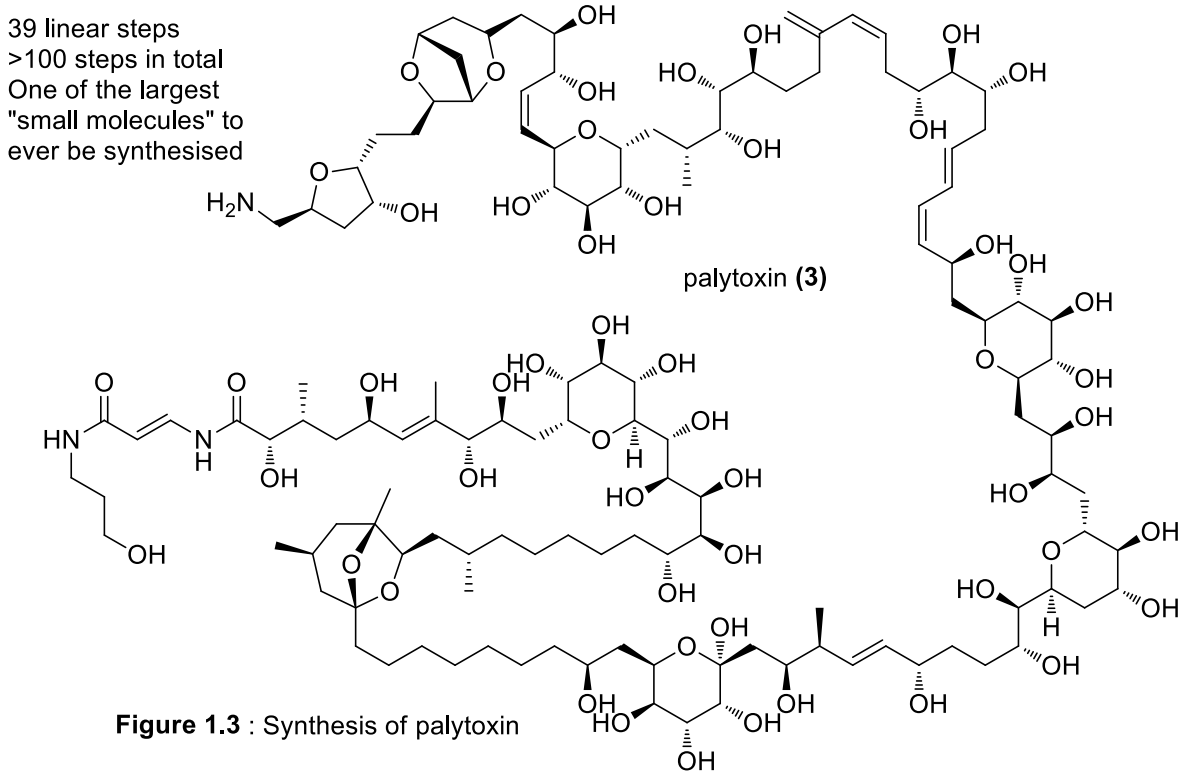


Figure 1.3 : Synthesis of palytoxin

In contrast to this other syntheses are a sophisticated work of art and strategy. R.B. Woodward's landmark synthesis of strychnine **(4)** in 1954 remains a testament to his genius, achieved before the invention of many reactions and techniques that would now be seen as essential.[20] However with the advancement of the field there has been a distillation of simplicity with Vanderwal's total synthesis of strychnine in 2011 requiring one fifth the number of steps.[21] (Figure 1.4).

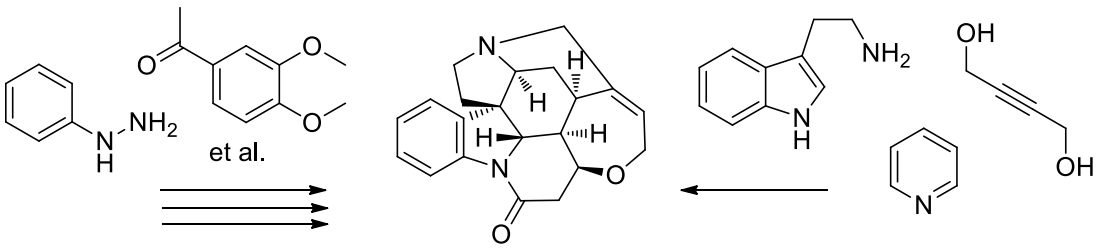


Figure 1.4 : Strychnine syntheses

1.3 What constitutes a good synthesis?

As the field of organic chemistry has progressed and matured, it has been established that given enough time and effort almost any natural product can be synthesised. It is no longer enough to merely synthesise a target molecule, instead the ideal synthesis must be strived toward.[16] One of the most obvious measures of an ideal synthesis is the overall yield of a synthetic sequence. Even with quite high individual yields, the overall yield decreases exponentially with the number of linear steps (Figure 1.5). At later stages setbacks becomes extremely costly in terms of resources as large quantities must be advanced through the synthesis to provide enough material for experimentation.[17] It therefore becomes imperative to strategically minimise the number of steps in the sequence. One of the simpler ways of achieving this is to develop a convergent synthesis, where two or more separate fragments are synthesised and then combined at a later stage to give a substantially more complicated product. By telescoping the synthetic scheme in this fashion, the number of linear steps can be dramatically reduced.[4]

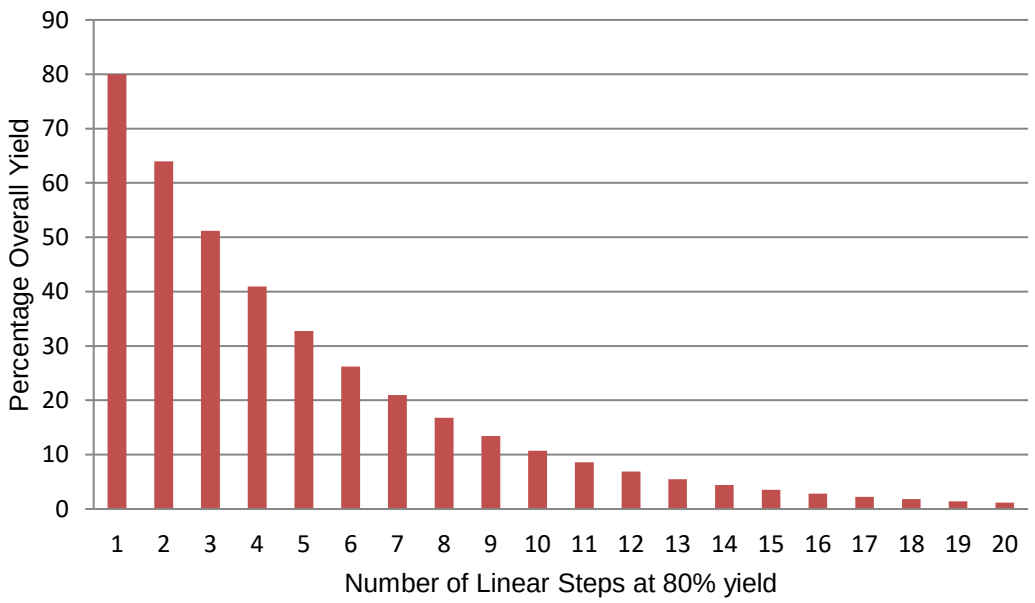


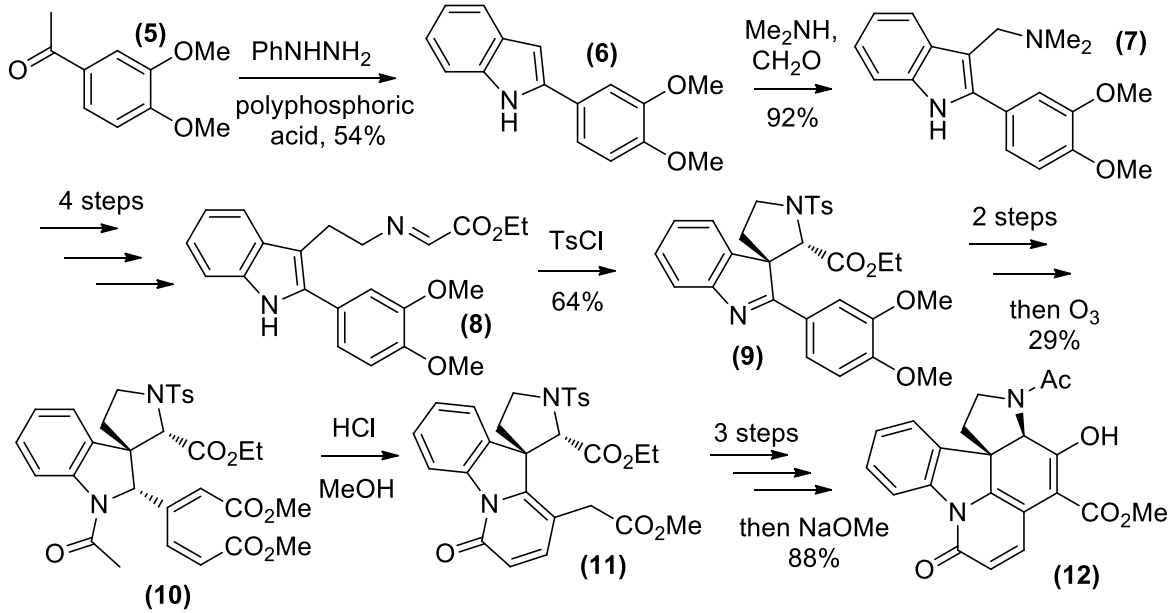
Figure 1.5: Linear inefficiency

In a more nuanced fashion one can also consider the efficiency of a synthesis in terms of its atom economy. Originally coined by Trost,[22] atom economy is a measure of what proportion of the mass used in reagents becomes incorporated into the

desired product. Atom economic syntheses generate minimal additional waste and are a hallmark of a well-designed synthesis. As such they tend to feature catalytic reactions with high levels of selectivity, exploiting the natural reactivity of the system.[23] Typically poor atom economy reactions feature stoichiometric reagents of high molecular weight that effect minimal change, such as the use of protecting groups or extensive changes in oxidation states.[22]

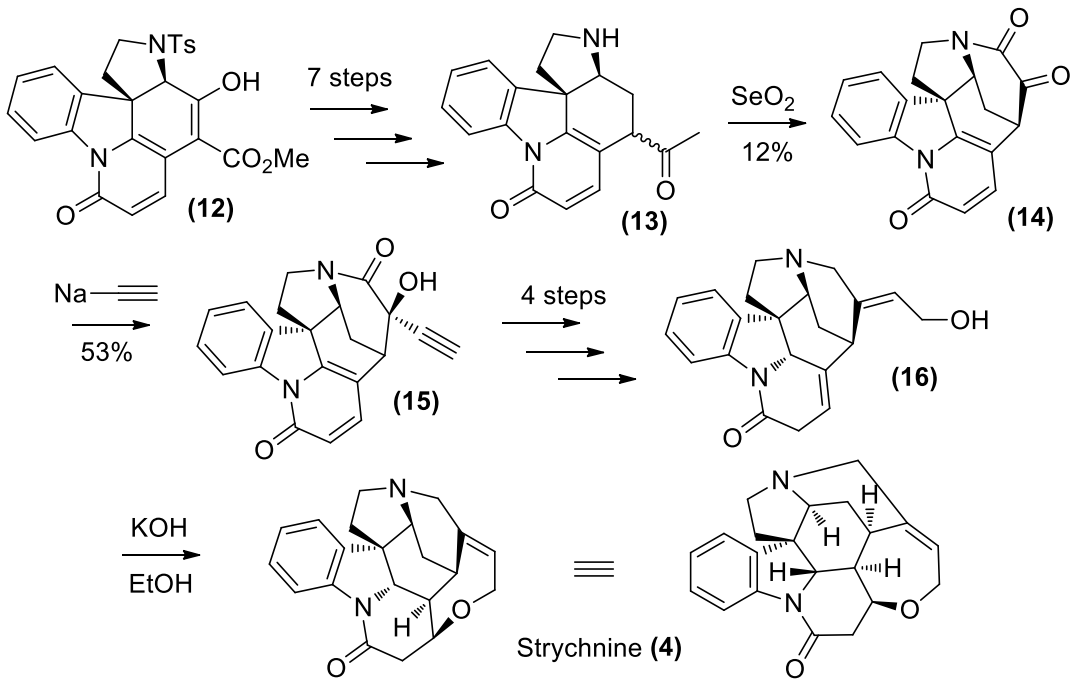
1.4 Exemplary syntheses

To demonstrate the importance of strategy, one can compare the aforementioned syntheses of strychnine by Woodward[24] and Vanderwal[21]. As an overview of the key steps, Woodward initially utilised a Fischer indole synthesis on a readily available ketone **(5)** to build a core framework **(6)** around which, the rest of the molecule was artfully constructed. The inherent reactivity of the indole towards electrophilic substitution was exploited *via* initial formation of the gramine **(7)** which was further elaborated to an imine **(8)** which underwent a second electrophilic substitution to generate a key spirocycle **(9)**. After some functional group manipulation, an inspired ozonolytic opening of the aromatic ring reveals a diester **(10)** one of which then cyclises form a pyridone **(11)** under acidic conditions. After an exchange of protecting groups an intramolecular Dieckmann condensation establishes the central six-membered ring (**12**).[25] (Scheme 1.1).



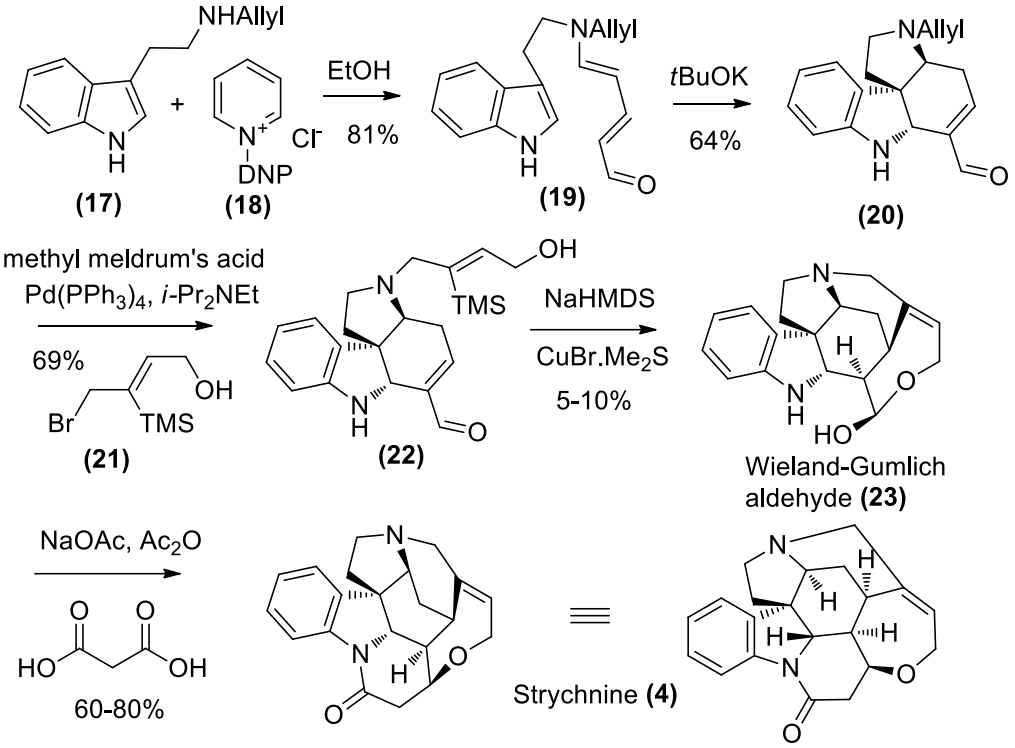
Scheme 1.1

After a lengthy reductive procedure the methyl ester is converted into an acyl group and the amine deprotected to give intermediate **(13)**. Oxidative cyclisation with selenium dioxide then effects an additional ring closure to give the alpha ketoamide **(14)**. Nucleophilic addition of sodium acetylide introduces the remaining two carbon fragment to give compound **(15)** which, after some manipulation generates the allylic alcohol **(16)** that subsequently undergoes cyclisation under basic conditions to give strychnine **(4)**.[25] (Scheme 1.2).



Scheme 1.2

Comparatively the synthesis by Vanderwal starts with a readily obtained allyl tryptamine **(17)** which is condensed with an *N*-aryl pyridinium salt **(18)** to give the Zincke aldehyde **(19)**. Under basic conditions this then undergoes a formal Diels-Alder reaction to rapidly assemble an advanced tetracyclic system **(20)**. This was then deprotected and alkylated with a silyl substituted allylic bromide **(21)** to give a tethered allylic alcohol **(22)**. A copper mediated Brook rearrangement then generates an organocopper species *in situ* that undergoes Michael addition to the conjugated aldehyde to give the known Wieland-Gumlich aldehyde **(23)**, albeit in 5-10% yield. This was then converted under literature conditions to give strychnine **(4)** in just 6 linear steps.[21] (Scheme 1.3).



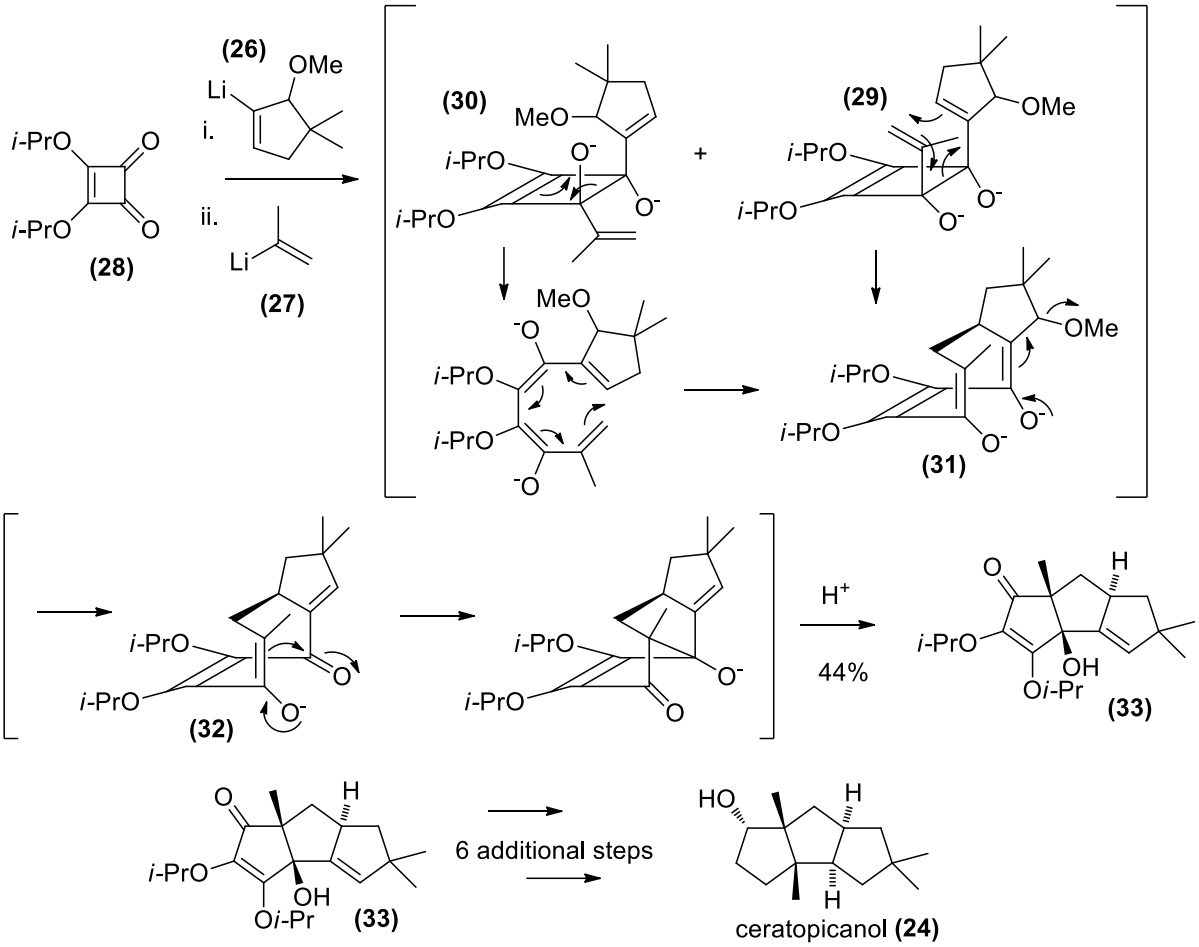
Scheme 1.3

Woodward's synthesis is a thoughtful and robust implementation of the limited chemistry known at that time; building upon the inherent reactivity of the system to generate complex motifs. However it is limited by its lengthy manipulations in protecting groups and oxidations states. When we compare this to the more recent synthesis by Vanderwal, the steps therein are highly productive, resulting in complex transformations with minimal accessory manipulation.

Two further examples of brilliant and concise synthesis can be found in the Paquette[26] synthesis of ceratopicanol **(24)**, and the Wender[27] synthesis of α-cedrene **(25)**. These approaches are characterised by the employment of powerful methodology to generate high levels of chemical complexity from relatively simple starting materials.

Demonstrating robust methodology developed around squarate esters, Paquette undertook a one pot nucleophilic addition of two vinyl nucleophiles **(26)** and **(27)** to isopropyl squarate **(28)**. After initial addition, the two resulting diastereomers **(29)** and **(30)** converge respectively *via* a dianionic oxy-Cope rearrangement, or by strain assisted 4π electrocyclic ring opening and 8π electrocyclic ring closing; to give an 8-membered dienolate **(31)**. The presence of an ether in the beta position of one the

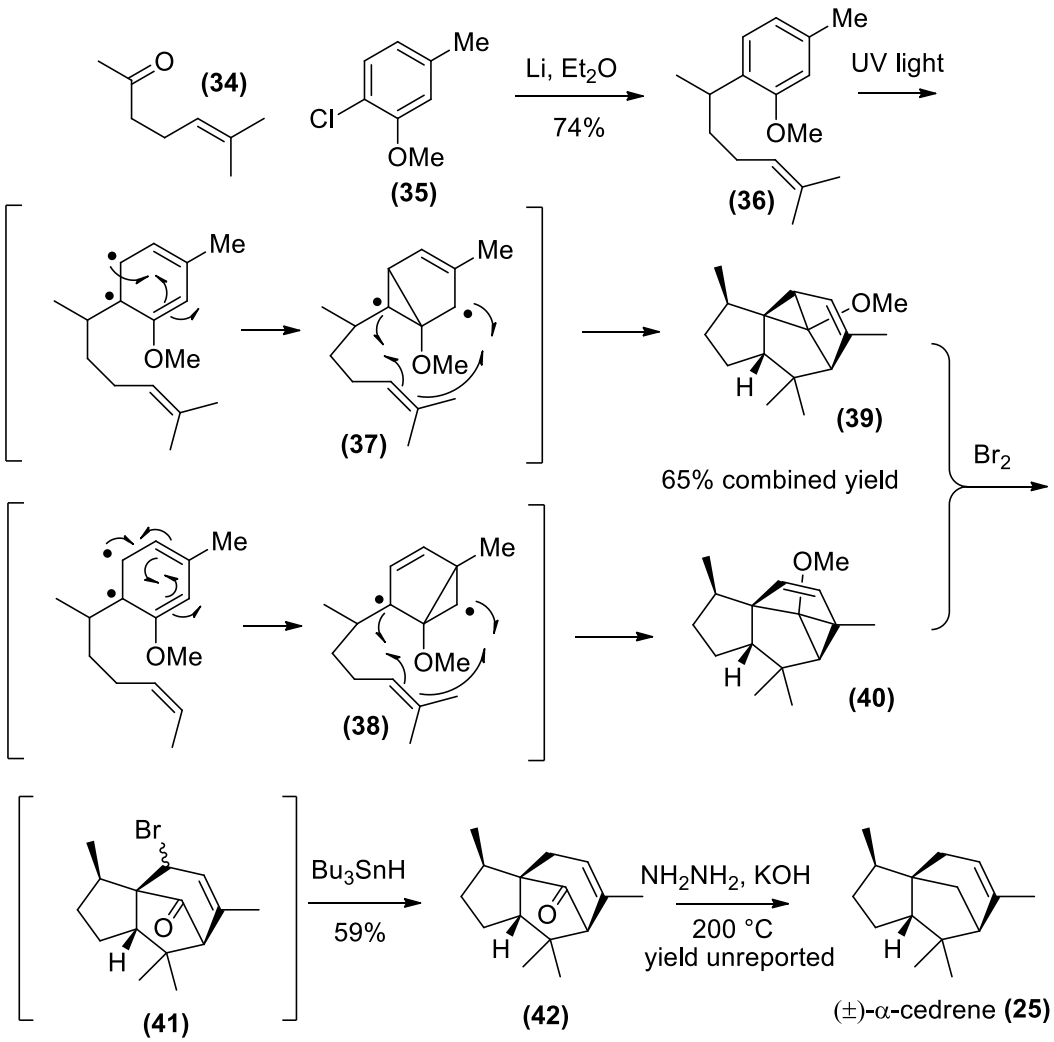
nascent enolates results in elimination to give a ketone enolate **(32)** that allows for a regioselective transannular aldol reaction to yield the product **(33)**. In practice this occurs in a single reaction, resulting in the isolation of the triquinane core of the natural product after a single step in 44% yield. The trade-off of the methodology is that an additional 6 steps were required to introduce the remaining methyl group and reduce the system to the desired oxidation state in ceratopicanol **(24)**.[26] (Scheme 1.4).



Scheme 1.4

In comparison, the Wender synthesis of α-cedrene **(25)** is extremely concise. A reductive coupling of keto alkene **(34)** with chloroarene **(35)** generates a simple aromatic system with a tethered alkene **(36)**. This system was then irradiated under UV light to generate excited state *meta*-diradical intermediates **(37)** and **(38)** in the aromatic system that undergo cycloaddition to the tethered alkene. The system was designed so that between the steric limitations of the tether and the electronics of the aromatic ring, out of the 36 possible products only two were observed **(39)** and **(40)**

in a combined yield of 65%. These were converted by treatment with bromine to a pair of epimeric bromides **(41)** which were reduced directly with tributyltin hydride to the ketone **(42)** in a single reaction. Wolff-Kishner reduction thus afforded α-cedrene **(25)** in only 4 steps.[27] (Scheme 1.5).



Scheme 1.5

An overarching theme of these works is that they employ sophisticated chemistry to achieve highly specific results generating a high degree of complexity. The products of these powerful reactions are then tailored towards the final target. It is this pursuit of novelty and the use of such sophisticated chemistry that is a hallmark of great synthesis, these classic works of total synthesis stand out primarily for the chemistry upon which they are based.

1.5 Foreword

This body of work shall elaborate on efforts made to produce a range of quite different natural products each of which has its own motivations for synthesis. However, within this body of work are a number of overarching themes with respect to pursuing good synthesis, investigating chemical novelty, and demonstrating robust methodology in a high value context.

Chapter 2 - Angelmarin and Columbianetin

2.1 Introduction

Over the last twenty years the pharmaceutical sector has seen a proliferation in new treatments for cancer. Much of this has been driven at an academic level by the isolation of novel cytotoxic natural products such as taxol.[13] In the treatment of cancer one of the most difficult problems to address is in establishing selective toxicity for tumour cells over otherwise healthy cells.[7] One of the distinct physiological properties of solid cancerous tumours is that, as a result of rampant cellular growth, the associated vasculature is often deficient.[28] (Figure 2.1). The expanding cellular masses often occlude any existing blood vessels and result in areas that are starved of oxygen and nutrients. Cancer cells respond to this in developing a considerable tolerance to these conditions by reversible modulation of their metabolism.[29] Furthermore, such tolerance has been shown to be a key factor in resistance to standard chemotherapy, general malignancy and poor clinical prognosis.[30]

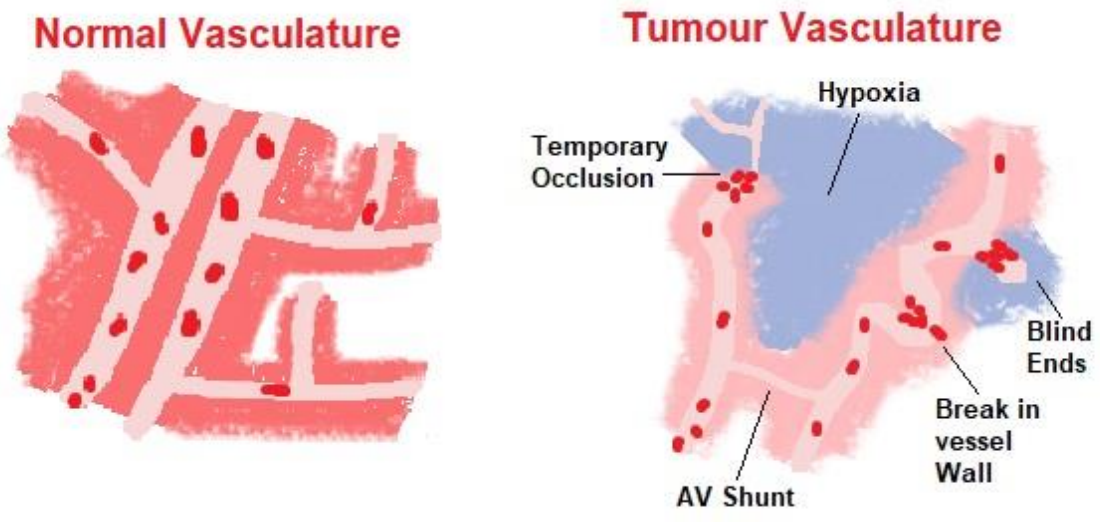
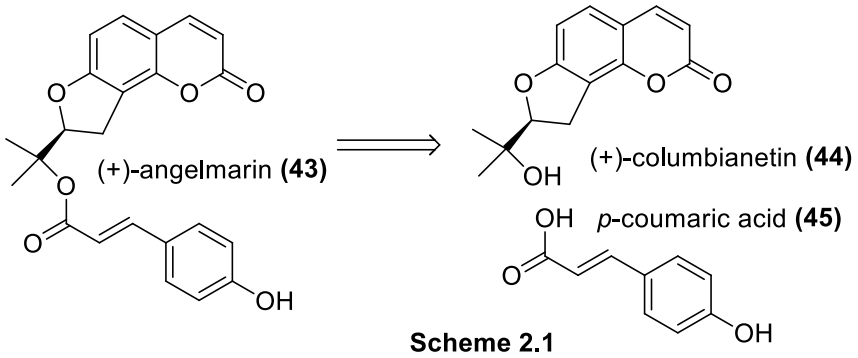


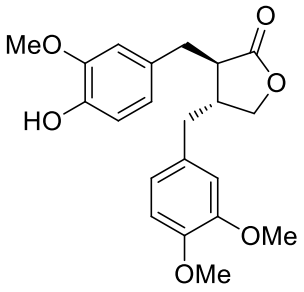
Figure 2.1: Comparative vasculature of normal and tumour tissues; adapted from Brown and Giaccia.[31]

In order to address this notable deficiency in medical treatment Kadota *et al.* sought compounds that could counter this metabolic tolerance as a potential new method in the treatment of cancer.[32] In this regard they developed a new screening methodology whereby a variety of resistant cancer cell lines were screened for selective cytotoxicity under nutrient deprived conditions compared to a control of non-cancerous cells with adequate nutrition. Based on this "anti-austerity" strategy over 500 plant extracts were screened from a library of those used in traditional Japanese Kampo medicine. In doing so they discovered that extracts of one of these plants; *Angelica pubescens*, was particularly active in eliminating resistance of cancer cells to nutrient starved conditions;[32] exhibiting preferential cytotoxicity at concentrations of 50 µg/mL. Following further bio-assay guided fractionation and purification, they isolated a new compound named (+)-angelmarin **(43)**, whose structure was determined to be that shown below in Scheme 2.1; an ester derived from the known natural products (+)-columbianetin **(44)** and *p*-coumaric acid **(45)**.[33]

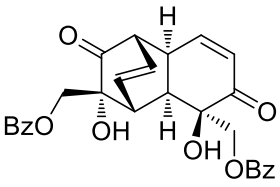


Scheme 2.1

Angelmarin **(43)** was then further tested against the pancreatic cancer cell line PANC-1 to determine the extent of its cytotoxicity. It was found to dose dependently inhibit tolerance to nutrient starved conditions, displaying 100% cell death at concentrations as little as 0.01µg/ml within 24 hours. The effect was more pronounced at a concentration of 10 µg/ml, at which 100% cell death was effected in only 6 hours.[32] Intriguingly neither p-coumaric acid **(45)** nor (+)-columbianetin **(44)** showed any activity in the essay, implying that the bioactivity of angelmarin **(43)** relies on the complete structure. Although exact information regarding the mode of action of angelmarin **(43)** has not yet been established; a number of other potential drug candidates have been found through the same anti-austerity methodology.[34] Two notable examples are (-)-arctigenin[35] **(46)** and (+)-grandifloracin[36] **(47)** (Figure 2.2).



(-)-arctigenin **(46)**



(+)-grandifloracin **(47)**

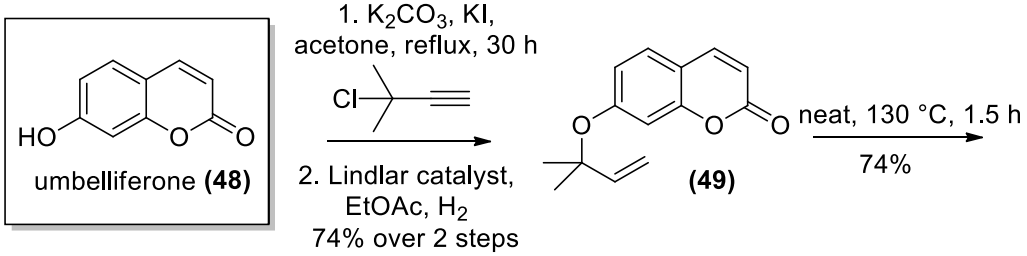
Figure 2.2 : antiausterity compounds

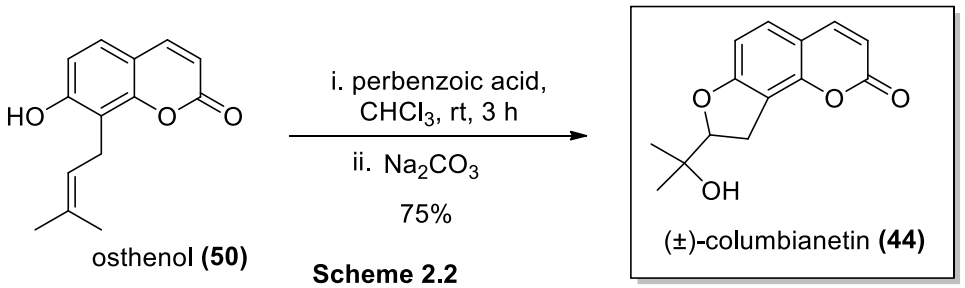
Although distinct molecular targets have not been identified, it has been demonstrated that both grandifloracin **(47)** and arctigenin **(46)** both inhibit the activity of Akt, a cytosolic protein kinase that is upregulated under nutrient deprived conditions.[37] Grandifloracin **(47)** has also been shown to additionally suppress the phosphorylation state of mTOR, another protein kinase in the same signalling pathway. It has been suggested that grandifloracin **(47)** mediates cell death by activating autophagy,[36] a process that recycles cellular proteins and redundant organelles[38]. Arctigenin **(46)** has also shown potent *in vivo* activity using mouse xenografts and has since progressed into clinical trials for the treatment of pancreatic cancer.[39] Pancreatic cancer remains one of the most severe forms of cancer with the lowest known five year survival rate. It is resistant to most forms of modern chemotherapy with surgery representing the only major treatment option.[28] As a potential lead candidate in drug development, (+)-angelmarin **(43)** was seen as an excellent target for total synthesis.

2.2 Previous syntheses

The related natural product (+)-columbianetin **(44)** has been known for some forty years,[33] and multiple syntheses have been carried out.[40] However, the somewhat recently isolated (+)-angelmarin **(43)** has only been synthesised twice, the first time by Coster[41] and the second by Hamada.[42] These syntheses are both somewhat semisynthetic, starting from the commercially available coumarin natural product, umbelliferone **(48)** and can be viewed as modifications of the 1971 synthesis of racemic columbianetin **(44)** by Bohlmann and Franke.[40b] In the synthesis of columbianetin **(44)** by Franke, umbelliferone **(48)** was *O*-alkylated under Finkelstein

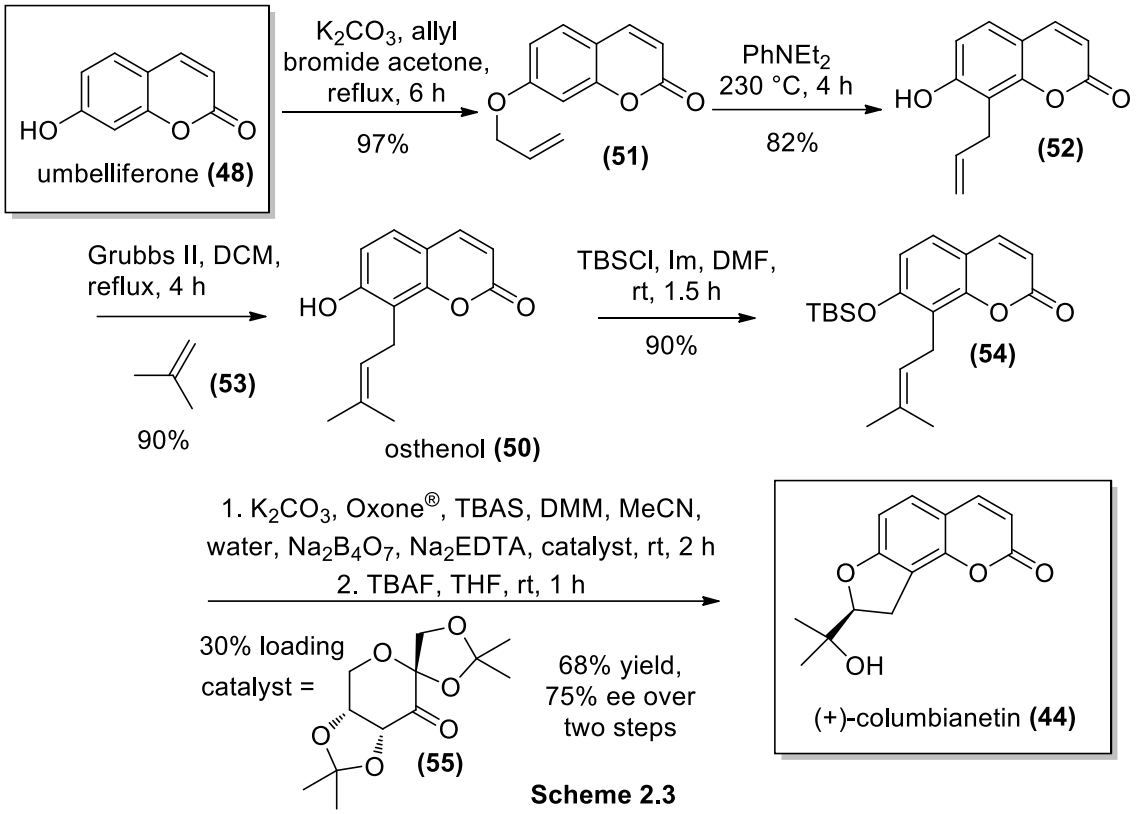
conditions using 2-chloro-2-methyl-3-butyne then subjected to a Lindlar reduction to form the required *O*-isoprenyl umbelliferone **(49)**. This alkene was then heated to effect a surprisingly regioselective Claisen rearrangement, generating the natural product osthenol **(50)**, as an intermediate. The common osthenol intermediate was converted by Franke to racemic columbianetin **(44)** *via* peracid epoxidation and 5-exo-tet cyclisation under basic conditions.[40b] (Scheme 2.2).





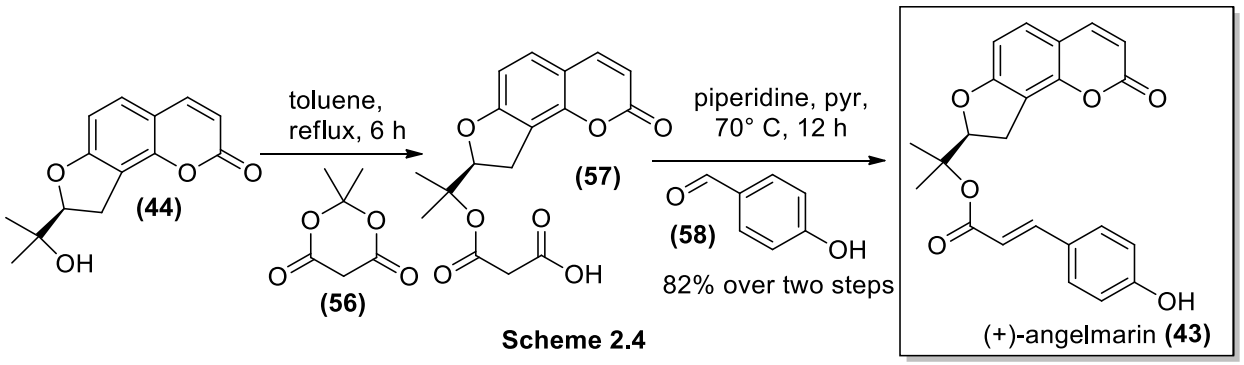
Scheme 2.2

Similarly, in the synthesis by Coster, umbelliferone **(48)** is alkylated with the considerably cheaper allyl bromide to form compound **(51)**. Following regioselective claisen rearrangement under thermal conditions, allyl derivative **(52)** is then converted into osthenol **(50)** by olefin metathesis with isobutene **(53)** using Grubb's second generation catalyst. Coster then protected the free phenol of osthenol **(50)** with a TBS group to form silyl ether **(54)** prior to subjection to Shi epoxidation conditions with the classic fructose derived organocatalyst **(55)**.[43] The crude epoxide product was then deprotected using tetrabutylammonium fluoride which was accompanied by a 5 exo-tet cyclisation to yield (+)-columbianetin **(44)**.[41] (Scheme 2.3).



Scheme 2.3

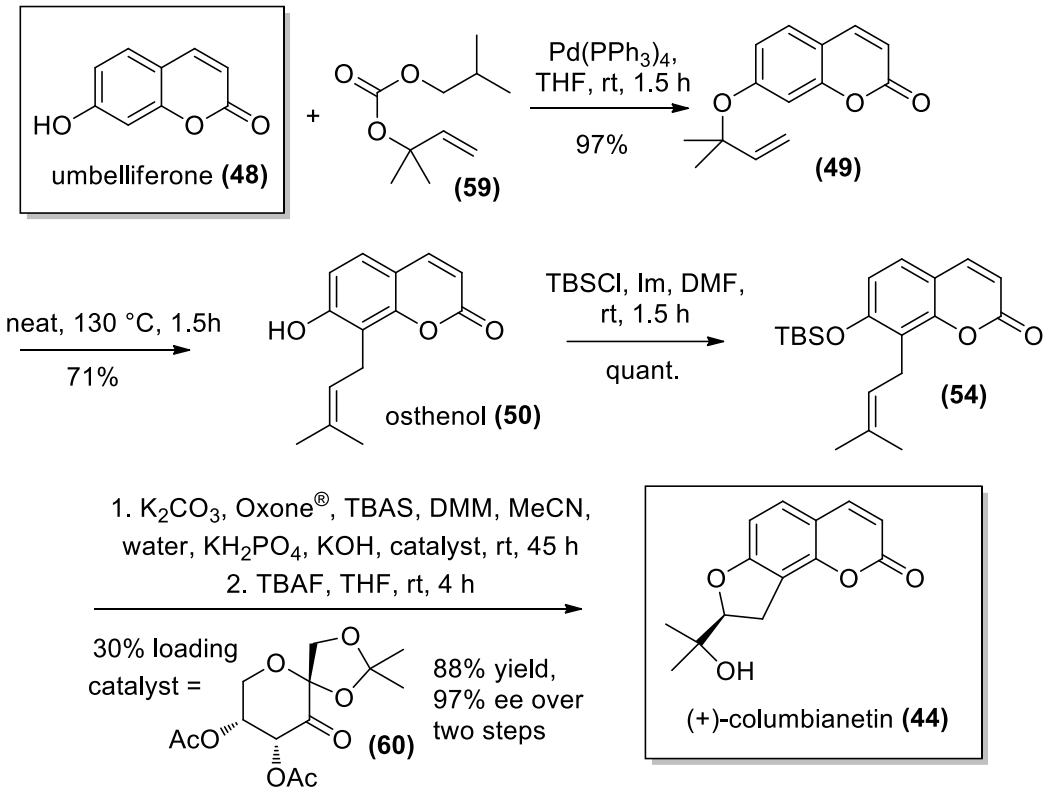
Coster's approach was to functionalise the hindered tertiary alcohol with Meldrum's acid **(56)**, which undergoes cycloreversion to generate an active ketene intermediate, forming a malonate ester **(57)** under neutral conditions. The crude malonate ester **(57)** was then directly subjected to a Doebner Knoevenagel condensation with *p*-hydroxybenzaldehyde **(58)** generating (+)-angelmarin **(43)** in good yield over two steps.[41] (Scheme 2.4).



Scheme 2.4

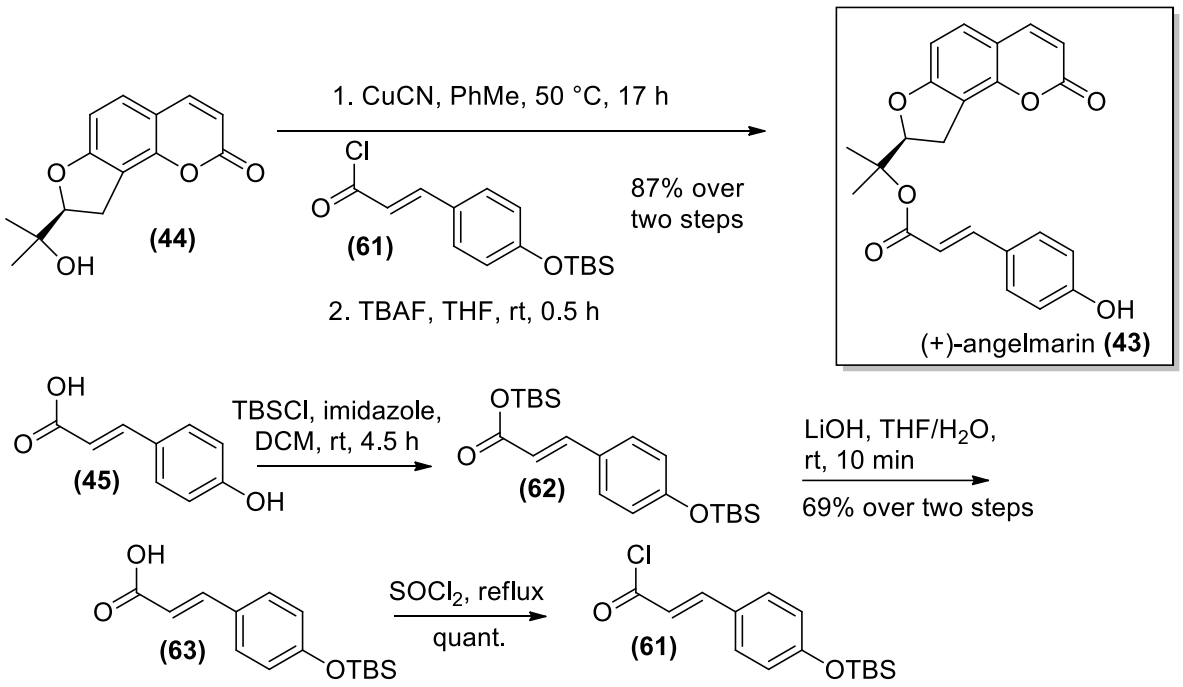
In the synthesis by Hamada, the isoprenylated derivative **(49)** was accessed directly *via* a Tsuji-Trost allylation of umbelliferone **(48)** with the carbonate derivative **(59)** followed by regioselective Claisen rearrangement under conditions identical to those described by Franke. Like Coster, Hamada protected the free phenol of osthenole **(50)** with a TBS group prior to subjection to Shi epoxidation conditions, however

Hamada was able to obtain substantially better enantiomeric excesses and yields by utilising the diacetate catalyst **(60)**. The crude epoxide product was then deprotected using tetrabutylammonium fluoride which was accompanied by a 5 exo-tet cyclisation to yield (+)-columbianetin **(44)**.[42] (Scheme 2.5).



Scheme 2.5

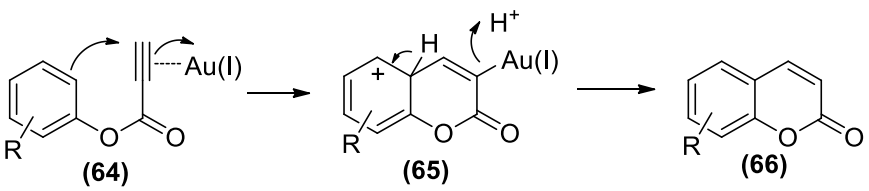
In contrast to the approach by Coster, Hamada subjected columbianetin **(44)** directly to a copper cyanide mediated esterification with the TBS protected acid chloride **(61)** derived from p-coumaric acid **(45)**, followed by deprotection with TBAF to form the natural product (+)-angelmarin **(43)**. The acid chloride derivative was prepared somewhat inefficiently in three steps, involving bis TBS protection to form compound **(62)**, selective cleavage to regenerate the carboxylic acid functionality in compound **(63)** followed by conversion to the acid chloride **(61)** using thionyl chloride.[42] (Scheme 2.6).



Scheme 2.6

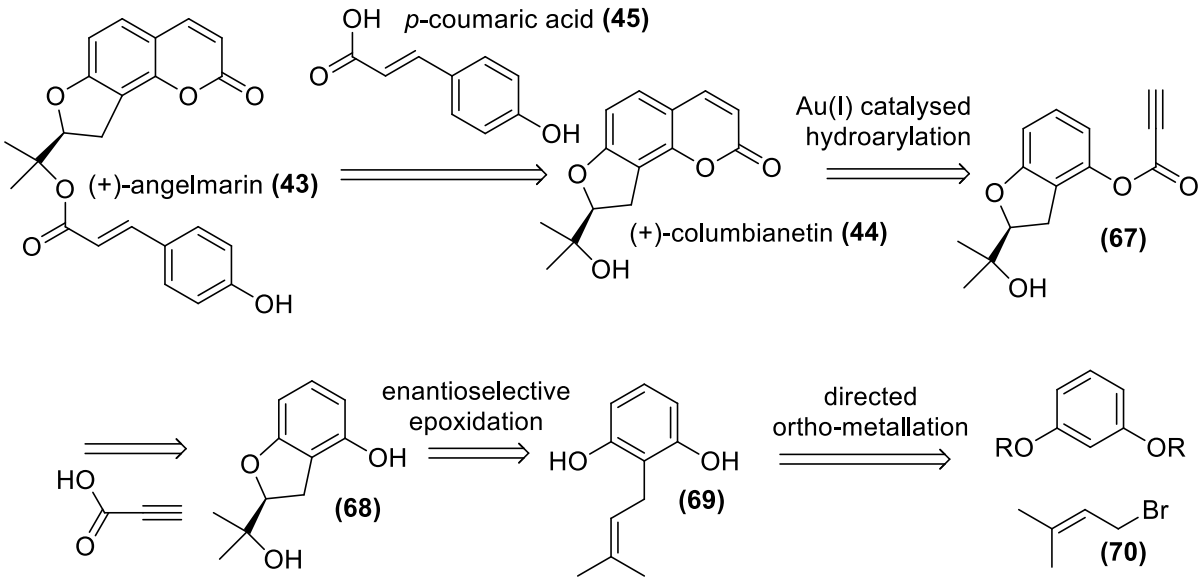
2.3 Initial strategy and retrosynthetic analysis

In order to set ourselves aside from the two known synthetic approaches it was decided that we would undertake a *de novo* synthesis of angelmarin **(43)** and form the often difficult to synthesise coumarin functionality by a gold(I) catalysed intramolecular hydroarylation reaction, which had been previously developed in the group.[44] Although originally considered to be an inert metal, gold has since encountered a renewed level of interest in its catalytic activity.[45] The high relativistic effects at the gold(I) centre enable it to act as a highly efficient pi acid.[46] In this system the gold(I) centre activates the tethered alkyne **(64)** to act as an electrophile for the nucleophilic aromatic ring resulting in an alkenyl gold species **(65)**. Protodeauration then regenerates the Au(I) catalyst (Scheme 2.7) and furnishes the coumarin **(66)**. Gold catalysis is capable of activating alkenes, allenes and alkynes to a wide variety of nucleophilic species and has seen diverse use in synthesis.[45]



Scheme 2.7

Key disconnections similar to the syntheses reported by Coster[41] and Hamada[42] were employed, including the formation of the ester linkage from p-coumaric acid **(45)** and columbianetin **(44)**. Disconnection of the coumarin ring *via* the propiolate **(67)**, required a synthesis of the dihydrobenzofuran derivative **(68)**. In a similar fashion to the known literature,[40b, 41-42] this was disconnected to the epoxide which could be available from prenyl resorcinol **(69)** which we envisioned could be available *via* a directed *ortho*-metalation[47] of appropriately protected resorcinol and alkylation with prenyl bromide **(70)**. Use of an appropriate enantioselective epoxidation method would allow access to either enantiomer of the natural product (Scheme 2.8).

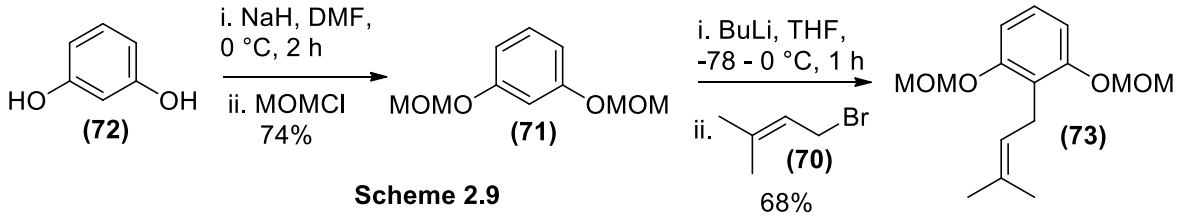


Scheme 2.8

This approach offers a number of key advantages over the ones that were reported by Coster and Hamada; most notably is that there is no requirement to start from umbelliferone **(48)** in an arguably semi-synthetic fashion. By use of appropriate methodology one could envision modification of the structural framework of angelmarin **(43)** at almost every position by variation of the resorcinol structure used in the *ortho* directed metalation, or by variation of the prenyl bromide electrophile. Additionally it has been demonstrated that through use of the intramolecular hydroarylation methodology that substitution is possible at both the 3 and 4 positions of the coumarin ring system by addition of an electrophilic source of iodine and varying the alkyne terminal functionality respectively.[48]

2.4 Results and Discussion

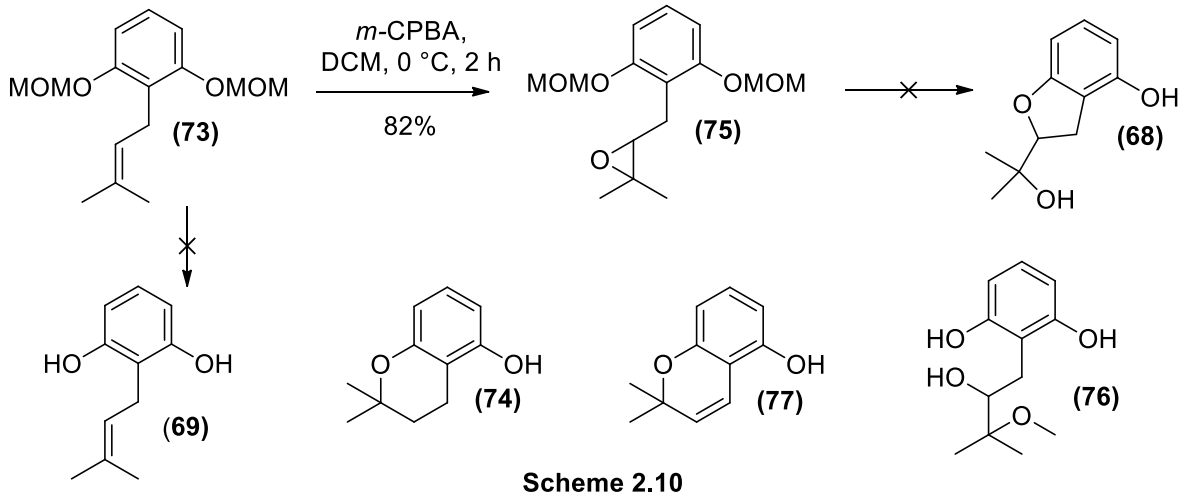
In the initial strategy to form the key aryl-prenyl bond, it was envisioned that this could be achieved *via* the directed *ortho*-metallation of bis MOM-protected resorcinol **(71)**. As such, resorcinol **(72)** was subjected to MOM protection with sodium hydride and MOMCl in DMF, this proceeded smoothly to afford the bis MOM protected resorcinol **(71)** in good yield.[49] In order to deprotonate at the desired position, protected resorcinol **(71)** was dissolved in anhydrous, degassed THF and cooled to -78 °C, BuLi was then added dropwise and the solution heated 0 °C and stirred for 1 hour in order to accelerate the rate of deprotonation. This was then cooled to -78 °C and the electrophile, prenyl bromide **(70)** added, which was allowed to return to room temperature overnight, furnishing the desired prenylated resorcinol derivative[50] **(73)** in 68% yield (Scheme 2.9).



Scheme 2.9

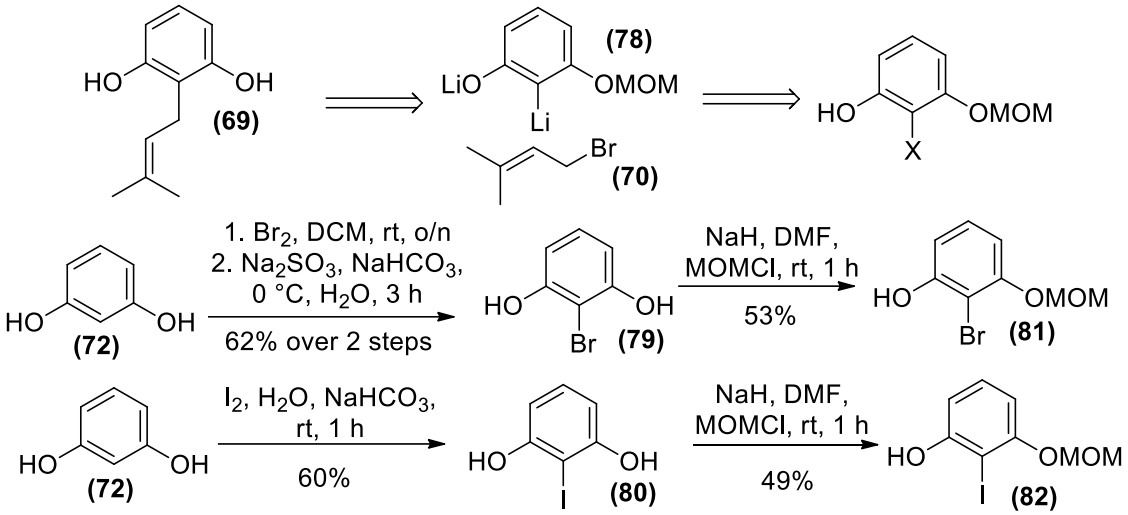
However when attention was turned to the deprotection of the MOM groups under acid catalysed conditions[51] (dilute aqueous acid in tetrahydrofuran) this primarily resulted in decomposition, presumably due to the formation of stabilised tertiary carbocation intermediates. This was supported by the isolation of the known[52] dihydrochromene **(74)** which featured a desymmetrisation of the aromatic ring protons in the ^{1}H NMR spectrum and two characteristic triplet signals at 2.68 and 1.83 ppm; indicating an intramolecular cyclisation and loss of the alkene functionality. Attempts to use milder conditions such as pyridinium *p*-toluenesulfonate in methanol resulted in incomplete deprotection and no isolation of the desired product.[53] In an attempt to avoid this problem, the prenyl group was epoxidised with *m*-CPBA to yield the protected epoxide derivative **(75)**, in the hope that cyclisation may occur *in situ* to afford the desired dihydrobenzofuran derivative **(68)**. However when the epoxidised derivative was subjected to similar and even quite mild conditions such as $NaHSO_4$ on silica in methanol,[51] only solvent attack at the more hindered site was observed **(76)** with some isolation of chromene **(77)**.[54] The isolated material **(77)** possessed a pair of signals at 5.58 and 6.61 ppm with a

coupling constant of 10 Hz, indicative of the cyclised system. This occurred presumably by a 6-endo-tet cyclisation and elimination (Scheme 2.10).



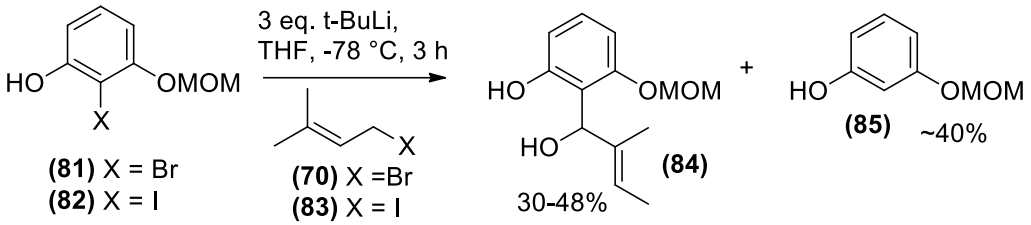
Scheme 2.10

Continuing on from this, it was decided that an alternative approach featuring a phenolic dianion **(78)** derived from deprotonation and lithium halogen exchange of a monoprotected, halogenated resorcinol derivative could furnish the desired product **(69)** by selective C alkylation with prenyl bromide **(70)**.[53] As such the halogenated, monoprotected resorcinol derivatives were synthesized by sequential regioselective halogenation and mono protection. In the case of the bromide derivative **(79)**, regioselectivity was accomplished by perbromination of resorcinol **(72)** followed by selective reduction of the more sterically available 4 and 6 ring positions.[55] The iodinated derivative **(80)** was more readily available, by a direct base catalysed process which increases the electron density at the 2 position of resorcinol **(72)**.[56] Mono protection was then achieved using MOMCl as a limiting reagent in the presence of an excess of base[57] to give modest yields of the requisite ethers **(81)** and **(82)** in spite of the inherent statistical effects, presumably due to the enhanced nucleophilicity of the resorcinol dianion (Scheme 2.11).



Scheme 2.11

Treatment of the halogenated, monoprotected resorcinol derivatives (**81)** and **(82)**, with 3 equivalents of *t*-BuLi followed by addition of either prenyl bromide **(70)** or prenyl iodide **(83)** did not furnish the desired product, giving only the rearranged and formally oxidised product as a single stereoisomer **(84)** in moderate yield along with dehalogenated starting material **(85)** (Scheme 2.12).



Scheme 2.12

This result was fairly consistent with both halogenated resorcinol derivatives **(81)** and **(82)** and with either prenyl bromide **(70)** or prenyl iodide **(83)** as the electrophile. It seemed that dianion formation was more efficient with the aryl iodide **(82)**, as the reactions involving aryl bromide **(81)** resulted in the recovery of minor quantities of starting material **(81)**. Attempts to use a mixed anion approach with NaH or KH followed by *t*-BuLi yielded only a small quantity of dehalogenated material with most of the starting material unchanged. The structure of the product **(84)** was unequivocally confirmed by X-ray crystallography as the *E*-stereoisomer, consistent with the NMR of the bulk material, and a positive NOE effect between the adjacent methyl groups on the alkene (Figure 2.3).

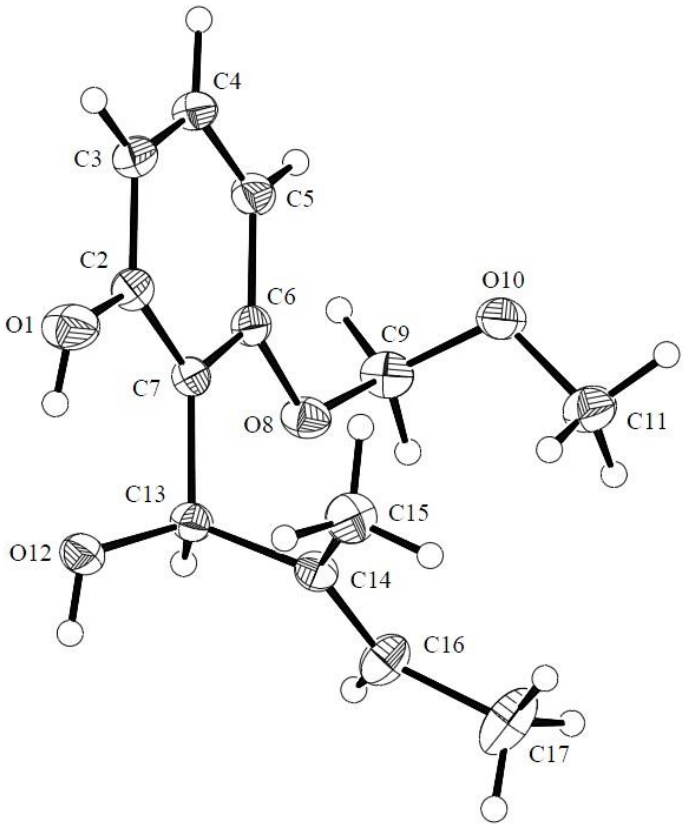
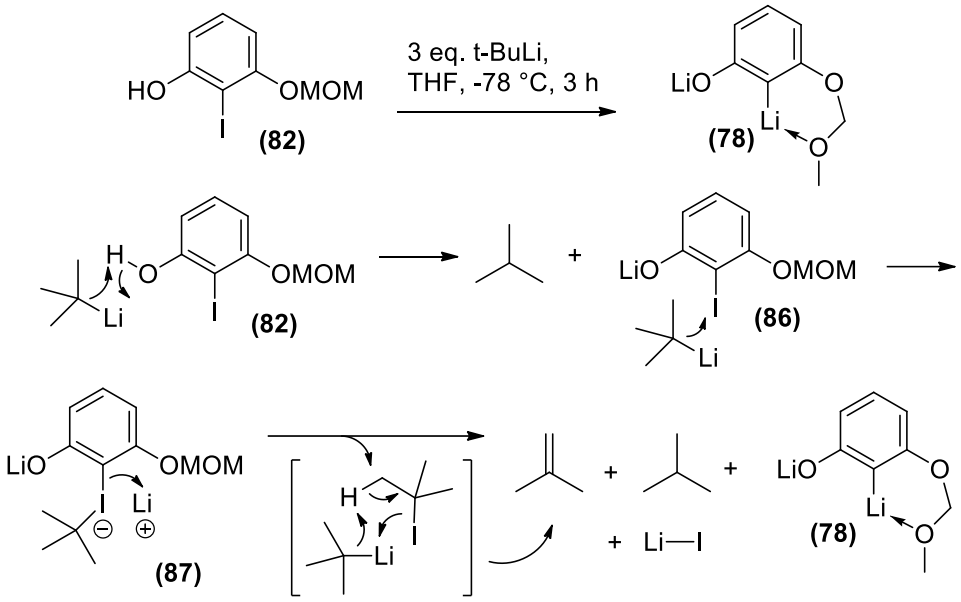


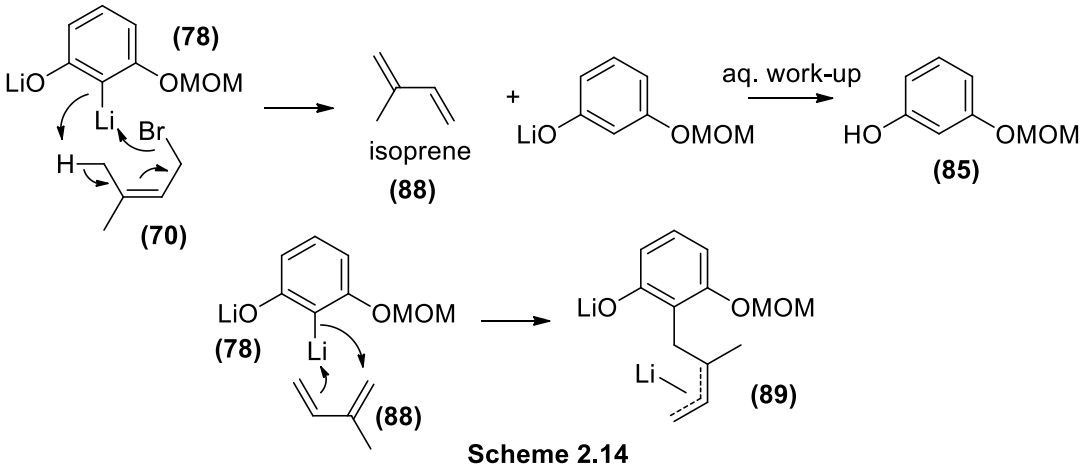
Figure 2.3: ORTEP derived from the single-crystal X-ray analysis of compound **(84)** with labelling of non-hydrogen atoms. Anisotropic ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

The absence of halide from any of the major products and the similarities between the aryl halides is consistent with the notion that initial formation of the MOM-stabilised dianion **(78)** does successfully occur. Illustrated for the iodide **(82)** in scheme 2.13, three full equivalents of t-butyl lithium are required, the first deprotonates the acidic phenol functionality generating the lithium oxide salt **(86)** and isobutane. The second equivalent is involved in lithium halogen exchange which occurs *via* the hypervalent ate complex **(87)**, generating t-butyl iodide and the dianion **(78)**. The third equivalent is required to effect E_2 elimination of the t-butyl iodide which drives the lithium halogen exchange to completion, liberating lithium iodide, isobutane and isobutene as unreactive side products.[58]



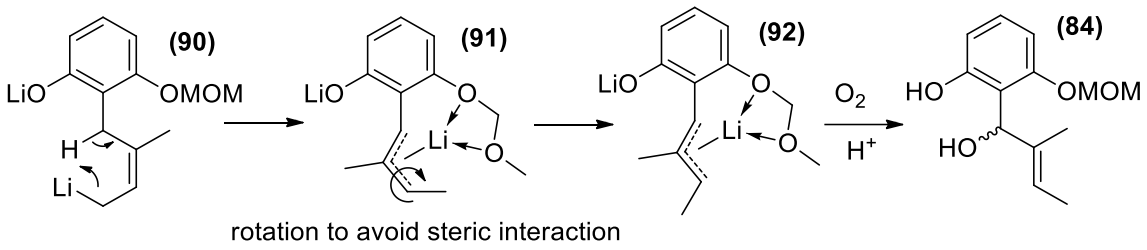
Scheme 2.13

From the dianion **(78)**, formation of the observed product is non-trivial. Low temperature conditions significantly limit the relative energy of most intermediates required for rearrangement. The following explanation is somewhat speculative but fits the available information (Scheme 2.14). The high energy dianion would be expected to be extremely basic in character, thus upon addition of prenyl bromide **(70)** it is assumed that rapid vinylogous E2 elimination occurs to generate isoprene **(88)** and the observed dehalogenated starting material **(85)** after quenching. Isoprene **(88)** itself is extremely reactive and is known to polymerise *via* carbolithiation in the presence of catalytic quantities of highly anionic organometallic species such as butyl lithium.[59] Using this as precedence it is assumed that any formed isoprene **(88)** is immediately consumed in carbolithiation by a second equivalent of dianion **(78)**. Addition to the 4 position of isoprene **(88)** explains the observed skeletal rearrangement of the electrophile resulting in a transient allyl lithium species **(89)**.



Scheme 2.14

Thus far the mechanism is yet to explain the stereoselectivity of the olefin or the observed oxidation. Speculatively, the allyl anion system could then undergo an intramolecular proton transfer[60] *via* a localised anion **(90)** to give the conjugated anion **(91)**. Theoretically this could be driven by the higher acidity of the benzylic position and the resulting delocalisation with the aromatic ring.[61] As allyl lithiums are configurationally unstable[62] a rotation of the terminal methyl group may occur due to an unfavourable interaction with the chelating MOM group. This would establish the observed alkene regioselectivity and functionalise the benzylic position as the anion **(92)** for oxidation (Scheme 2.15).

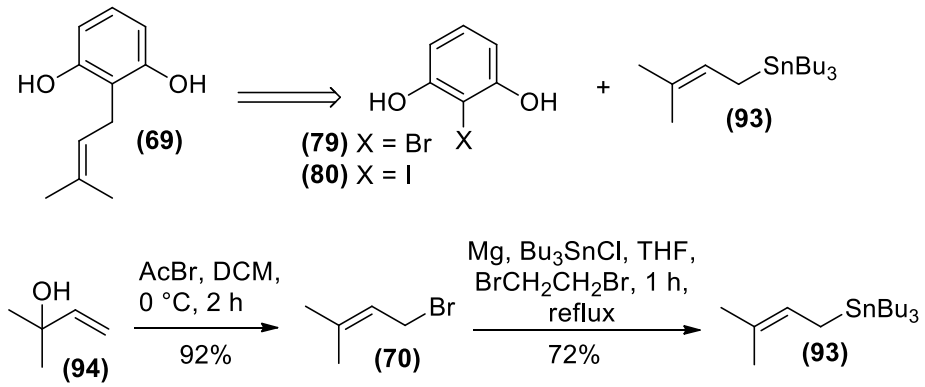


Scheme 2.15

Introduction of the oxygen atom to this anionic system was not established, and could be from oxygen or from the aqueous quench. The simplest explanation is the reaction with adventitious oxygen at the least hindered benzylic site of the allylic anion to give the observed product **(84)** upon quenching. Alternatively subsequent lithium halogen exchange would yield and intermediary bromide that could hydrolyse in the aqueous conditions used in isolation. Any true explanation in the mechanism of the observed product would warrant significant further research, ideally backed by

calculations; as such that was determined to be beyond the scope of this body of work.

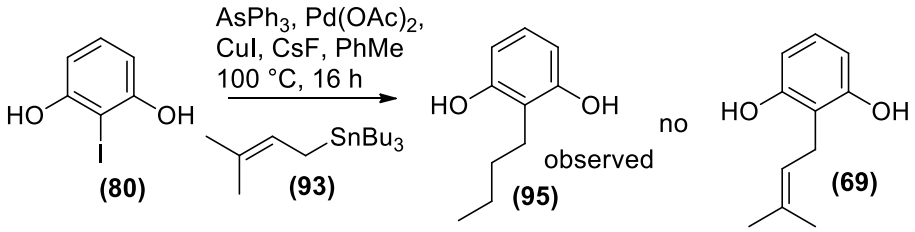
Although fascinating in its own right, the observed product was not a productive intermediate in the potential synthesis of (+)-angelmarin **(43)**. Consequently, in order to avoid the problem of using cumbersome protecting groups in the presence of demonstrably acid sensitive functionalities[41] it was decided that that the desired alkene **(69)** could instead be formed by a Stille cross coupling[63] of a halogenated resorcinol derivative **(79)** or **(80),** and the corresponding organotin species **(93)**. As such the prenyl stannane derivative **(93)** was synthesised by a Barbier reaction of prenyl bromide **(70)** with tributyltin chloride using magnesium metal; the magnesium required activation with 1,2-dibromoethane to initiate the reaction.[64] Owing to its relative cost, prenyl bromide **(70)** was synthesised on a larger scale using the method reported by Kara *et al.*, from the isoprenyl alcohol **(94)** and acetyl bromide *via* an S_N' reaction.[65] (Scheme 2.16).



Scheme 2.16

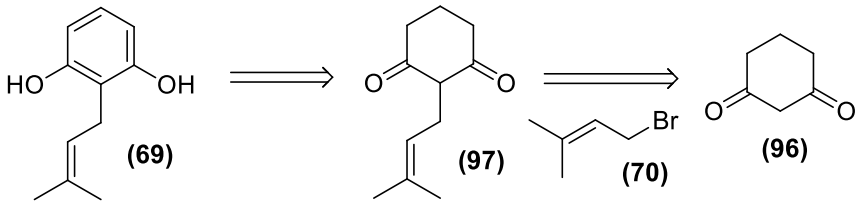
A large range of conditions common to the Stille cross coupling were screened in an attempt to effect the desired transformation. This included variations in the source of palladium, different ligands, the use of LiCl to stabilise the transmetallation transition state,[66] use of catalytic copper(I) salts to decrease the energy requirement for transmetallation,[67] and addition of caesium fluoride to encourage elimination of tributyltin species.[68] However in spite of these efforts, this approach was abandoned without any of the prenyl resorcinol **(69)** being isolated. The major product of these reactions was the formation or resorcinol **(72)**, presumably due to the acidity of the phenolic groups. Under more forcing conditions using triphenylarsine as a ligand the butyl resorcinol derivative **(95)** was observed by ^{1}H NMR (not further characterised)

indicating a potential steric limitation of the prenyl group. In addition to the resorcinol peaks the compound bore the characteristic shifts of the butyl group with a triplet at 2.63 ppm corresponding to the two benzylic hydrogens, two multiplets at 1.53 and 1.40 ppm, corresponding to the aliphatic methylene protons and a triplet at 0.94 ppm integrating to three protons (Scheme 2.17).



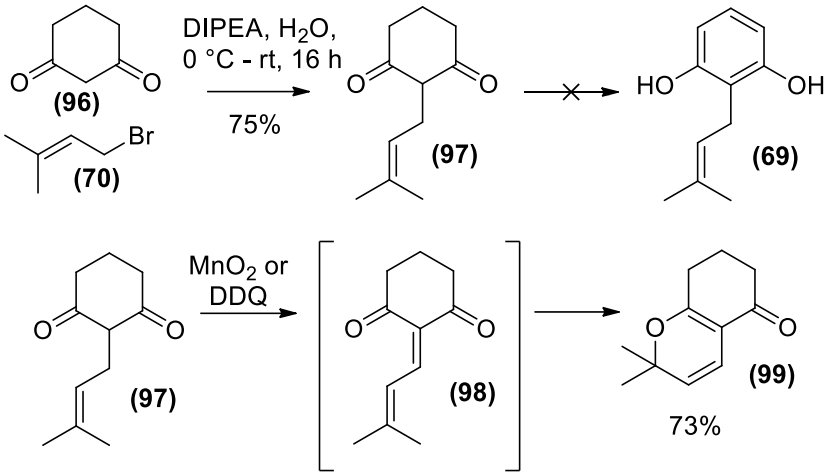
Scheme 2.17

In order to get around this problem, it was decided that this key bond could be selectively formed by starting with 1,3-cyclohexanedione **(96)**, utilizing the specific activity of the doubly activated methylene position to introduce the prenyl substituent with complete regioselectivity. The known prenylated cyclohexanedione **(97)**[69] could then be oxidatively aromatized to give 2-prenyl resorcinol **(69)** (Scheme 2.18).



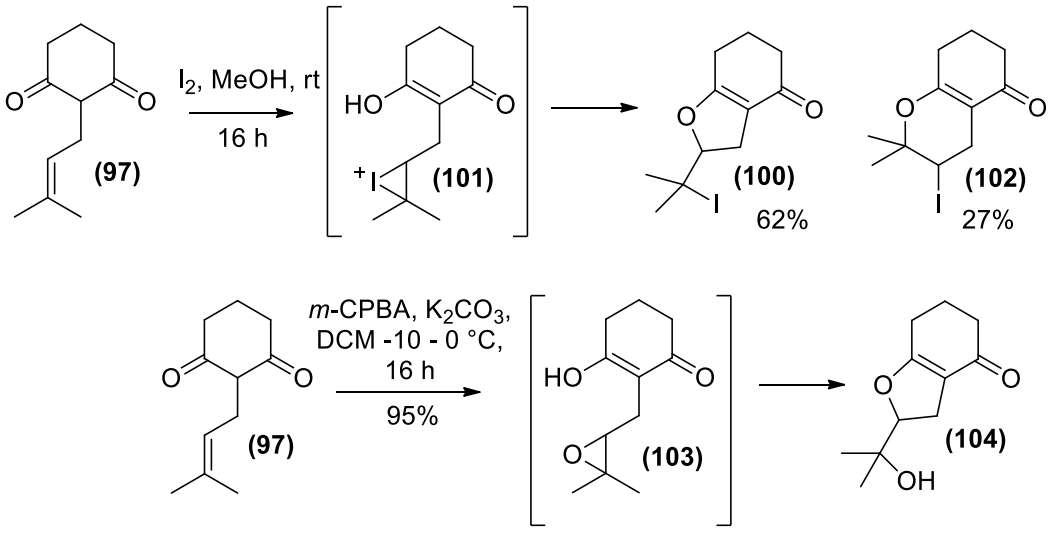
Scheme 2.18

The prenylated cyclohexanedione **(97)** was therefore synthesised according to the procedure described by Marazano *et al.,*[69] proceeding in good yield. Disappointingly, subjection of prenylated cyclohexanedione **(97)** to common oxidative aromatisation and dehydrogenation protocols[70] such as manganese dioxide or DDQ did not result in formation of the desired prenyl resorcinol derivative **(69)**, it seemed that dehydrogenation was occurring across the activated methine and allylic sites to form compound **(98)** which then undergoes electrocyclic ring closure to form the known[54] pyran **(99)** which was isolated in modest yield and confirmed by comparison to the literature data (Scheme 2.19).



Scheme 2.19

Interestingly when the aromatisation was attempted utilising molecular iodine in methanol, as described by Mphalele,[71] the iodinated dihydrofuran **(100)** was formed *via* a 5-exo-tet cyclisation of the iodonium intermediate **(101)** as the major product along with the dihydropyran **(102)**. Hoping to capitalise on this, the prenyl cyclohexane derivative **(97)** was subjected to epoxidation with m-chloroperbenzoic acid in the presence of potassium carbonate which was gratifyingly accompanied by ring opening of the epoxide **(103)** *in situ* exclusively *via* the analogous 5-exo-tet cyclisation to give the desired tetrahydrobenzofuran derivative **(104)** which was confirmed by X-ray crystallography (Scheme 2.20, Figure 2.4).



Scheme 2.20

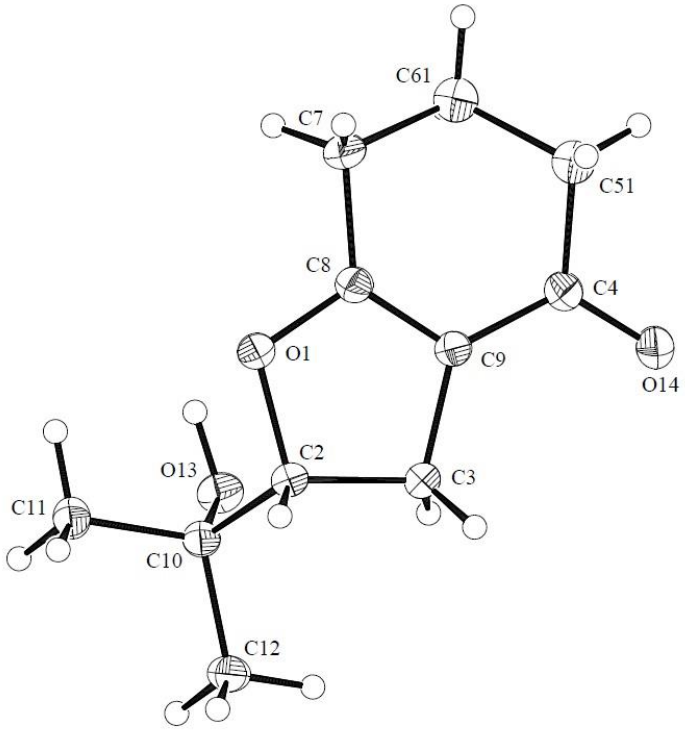
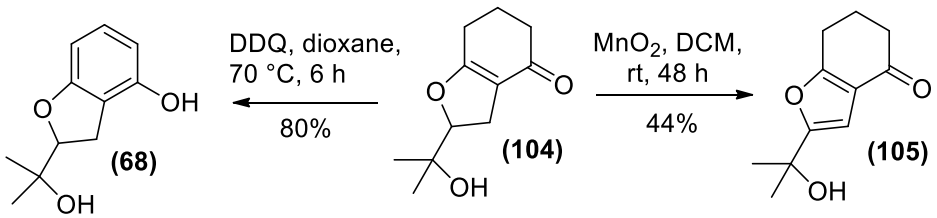


Figure 2.4: ORTEP derived from the single-crystal X-ray analysis of compound **(104)** with labelling of non-hydrogen atoms. Anisotropic ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Intriguingly treatment of the dihydrofuran **(104)** with manganese dioxide gave the furan derivative **(105)** in 44% yield, however when DDQ was used as an oxidizing agent the selectivity of the aromatization was reversed, forming the desired benzannulated compound **(68)** in good yield.[72] This can be rationalised by the fact that manganese dioxide is known to act *via* sequential single electron transfer which would be selective for the allylic position,[73] DDQ however is known to react *via* sequential deprotonation and hydride abstraction which would be selective for the acidic protons alpha to the ketone.[74] (Scheme 2.21).



Scheme 2.21

The free phenol **(68)** was then regioselectively functionalized with propiolic acid under neutral conditions using DCC, affording the corresponding phenylpropiolate

(67) in moderate to good yields.[44] It is important to note that it must be done in the absence of a nucleophilic catalyst to prevent base promoted Michael type addition to the propiolate ester. Exposure to Echavarren's Au(I) catalyst **(106)**[75] resulted in smooth conversion of to form (±)-columbianetin **(44)** *via* an intramolecular hydroarylation, the result of which was confirmed by X-ray crystallography (Figure 2.5, Scheme 2.22).

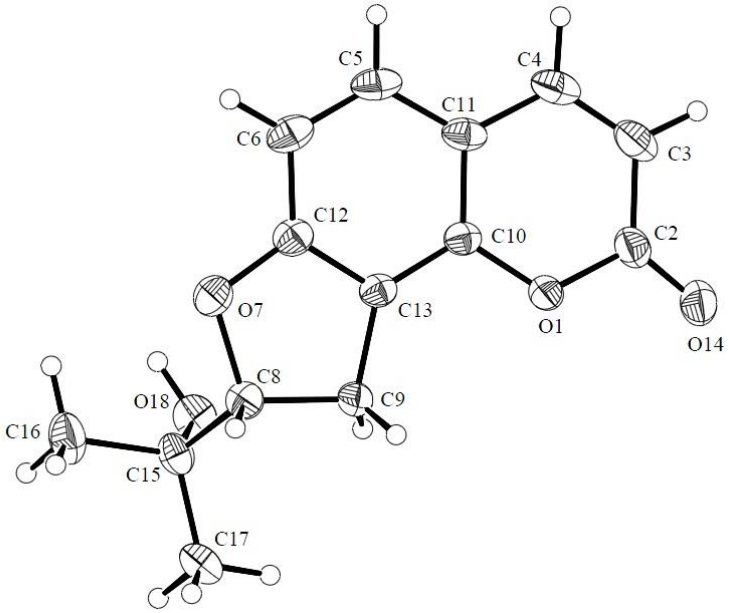
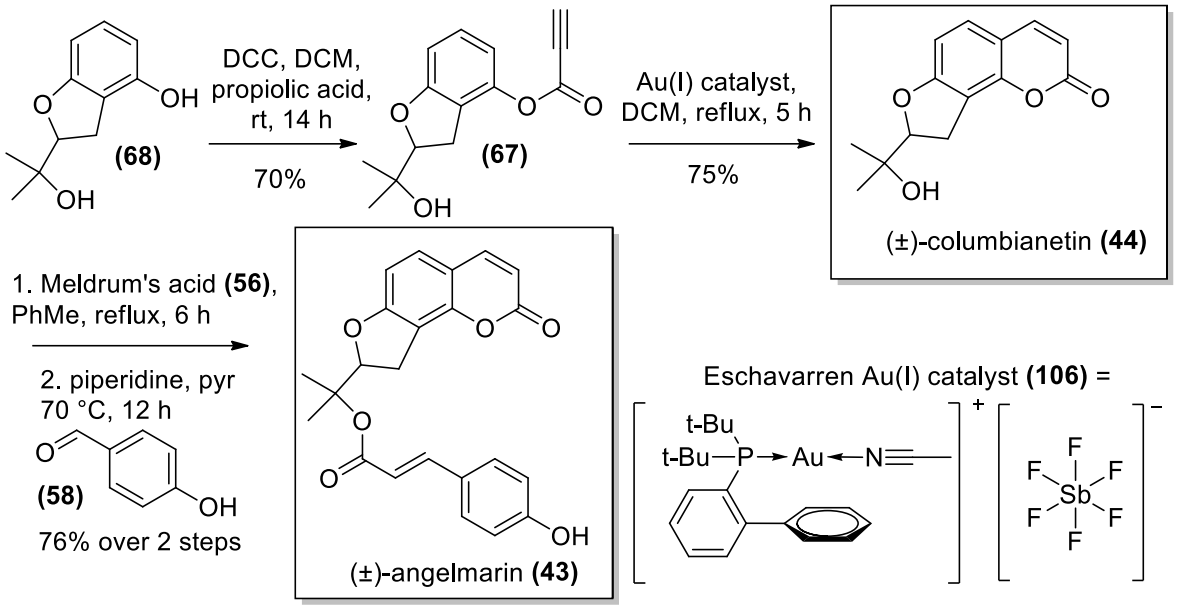


Figure 2.5: ORTEP derived from the single-crystal X-ray analysis of (±)-columbianetin **(44)** with labelling of non-hydrogen atoms. Anisotropic ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Attachment of the remaining p-coumaric acid residue was then accomplished according to the method reported by Coster.[41] As such columbianetin **(44)** was heated under reflux in toluene in the presence of Meldrum's acid **(56)** to form the crude malonate ester, which was in turn subjected to Doebner Knoevenagel condensation with p-hydroxybenzaldehyde **(58)** to form the racemic natural product (±)-angelmarin **(43)** in 76% yield over two steps (Scheme 2.22).



Scheme 2.22

With a workable synthesis of the racemic natural product in hand, attention was then turned towards an asymmetric modification. In order to determine the success of any enantioselective steps, conditions were sought for separation of the enantiomeric tetrahydrobenzofurans **(104)** by chiral HPLC. This was achieved by the use of a DAICEL chiralcel OJ-H column which features a tris p-toluate cellulose stationary phase; with a flow rate of 0.5 mL/min using a 5% solution of isopropanol and hexane.

Following on from the success encountered by Coster[41] and Hamada,[42] initial attempts at introducing chirality were focused around the use of a Shi epoxidation. The Shi epoxidation utilises a ketone organo catalyst which is readily derived from fructose **(107)**. The fructose catalyst **(55)** reacts with OXONE® to generate a dioxirane intermediate *in situ*. The dioxirane is the active species that carries out the epoxidation; it is thought to proceed *via* a spiro transition state with the two three membered rings being at right angles to one another.[76] (Figure 2.6).

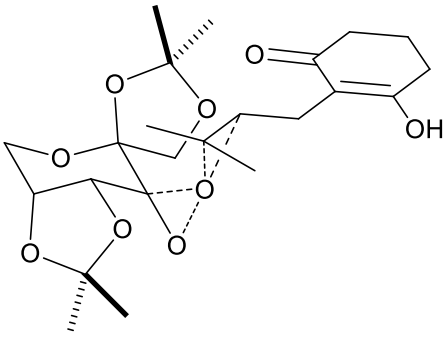
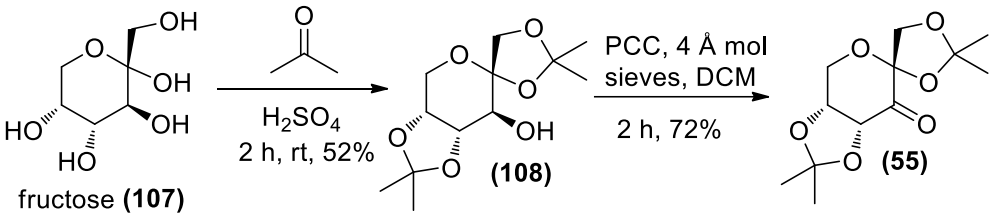


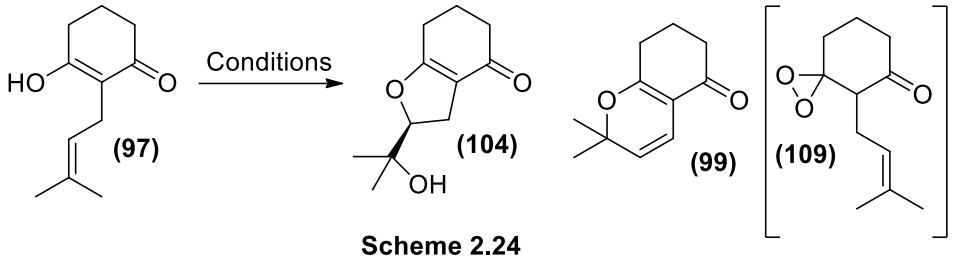
Figure 2.6: Proposed transition state for *in situ* epoxidation

Accordingly, the Shi catalyst **(55)** was synthesised following literature precedent by kinetic protection of fructose **(107)** in sulfuric acid and acetone to form the bis acetonide **(108)**; followed by oxidation to the ketone **(55)** using pyridinium chlorochromate.[77] (Scheme 2.23).



Scheme 2.23

The prenylated cyclohexanedione derivative **(97)** was then subjected to a range of known Shi epoxidation conditions[78] featuring different oxidants,[79] solvent combinations[41] and addition rates. Attempts were even made at generating the TBS enol ether *in situ*. However, ultimately this was not particularly successful in forming the desired tetrahydrobenzofuran adduct **(104)**, with a best yield of 18% and a negligible 15% enantiomeric excess by chiral HPLC analysis. This is thought to be due to competing formation of a dioxirane intermediate **(109)** which would result in racemic epoxidation, additionally it would seem that the dioxirane forming conditions also effected formation of the previously observed pyran **(99)**, detectable by proton NMR; most likely by oxidation of the enolate. A representative selection of the conditions used is presented below (Scheme 2.24, Table 2.1).



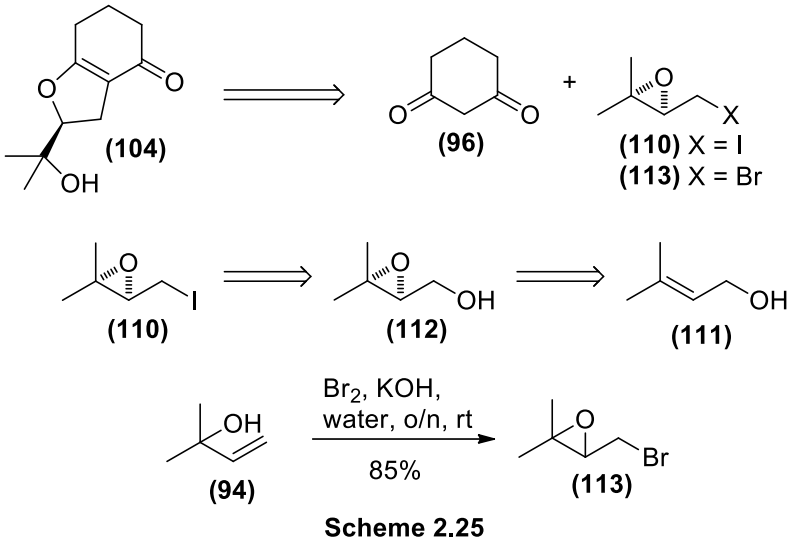
Scheme 2.24

Table 2.1: Conditions representative of those used in the attempted Shi epoxidation

Conditions	**R S M**	**yield**	**e.e.**
30% loading, Na_2EDTA, buffer, BTAC, K_2CO_3, Oxone, MeCN:DMM (1:1)	30%	5%	0%
30% loading, buffer, BTAC, K_2CO_3, Oxone, MeCN:DMM (1:1)	30%	trace	-
30% loading, Na_2EDTA, buffer, BTAC, K_2CO_3, Oxone, MeCN,	10%	trace	-
100% loading, Na_2EDTA, buffer, BTAC, K_2CO_3, Oxone, MeCN:DMM (1:1)	0%	trace	-
30% loading, H_2O_2, MeCN	80%	trace	-
100% loading, H_2O_2, MeCN	100%	0	-
30% loading, sodium percarbonate, MeCN, H_2O	80%	0	-
TBSCl, K_2CO_3, MeCN, then 30% loading, Oxone, buffer, then TBAF	80%	15%	8%
30% loading, KOH, H_2O, MeCN, Oxone	0	18%	15%

buffer = 0.05 M $Na_2B_4O_7.10H_2O$, 1.5 eq. oxidant, 2.5 eq. K_2CO_3

It was then considered that chirality could perhaps be established prior to the alkylation step by using the known chiral epoxide species[80] **(110)** which could then annulate onto the doubly activated methylene compound by sequential alkylation and epoxide ring opening. This epoxide could be accessed according to literature precedent *via* a Katsuki-Sharpless asymmetric epoxidation of prenyl alcohol **(111)** and subsequent transformation of the epoxy alcohol **(112)** into the primary halide.[81] As this was a change over the existing procedure it was decided to optimize the annulation step with the racemic material **(113)**, which was readily available from alcohol **(94)** on a large scale by the procedure described by Shimizu *et al.*[82] (Scheme 2.25).



Scheme 2.25

Initial attempts to obtain the tetrahydrobenzofuran **(104)** in a similar fashion to the formation of prenylated cyclohexanedione **(97)** were unsuccessful, featuring decomposition of the starting material, presumably through an aldol like mechanism, in addition to some *O*-alkylated product **(114)** which was confirmed by X-ray crystallography (Figure 2.7).

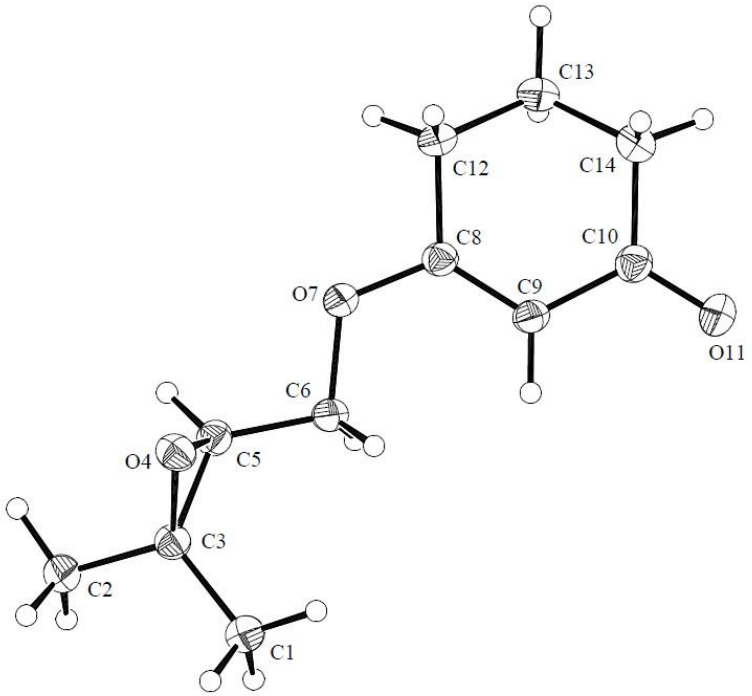
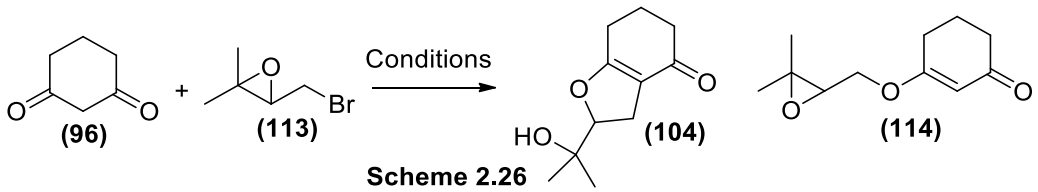


Figure 2.7 : ORTEP derived from the single-crystal X-ray analysis of **(114)** with labelling of non-hydrogen atoms. Anisotropic ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

As the hypothesised annulation chemistry lacked literature precedent, a systematic approach was taken to establish favourable conditions. Quenching of the reaction with saturated aqueous sodium carbonate and subsequent extraction and evaporation of the extracts under reduced pressure removes any starting materials or acidic side products, allowing the crude residues to be rapidly analysed directly by ^{1}H NMR *via* integration of the key oxymethine proton of the desired product **(104)** and the enol proton of the *O*-alkylated side product **(114)**. As such, some fifty reaction conditions were rapidly screened, including standard variations in reaction time and temperature, solvent, and base. The major observation was that the product distribution varied between *O*-alkylation **(114)** and the desired tetrahydrobenzofuran **(104)**. A collection of the more salient results is presented in Table 2.2, (Scheme 2.26).



Scheme 2.26

Table 2.2 : Conditions representative of those used in the attempted annulation

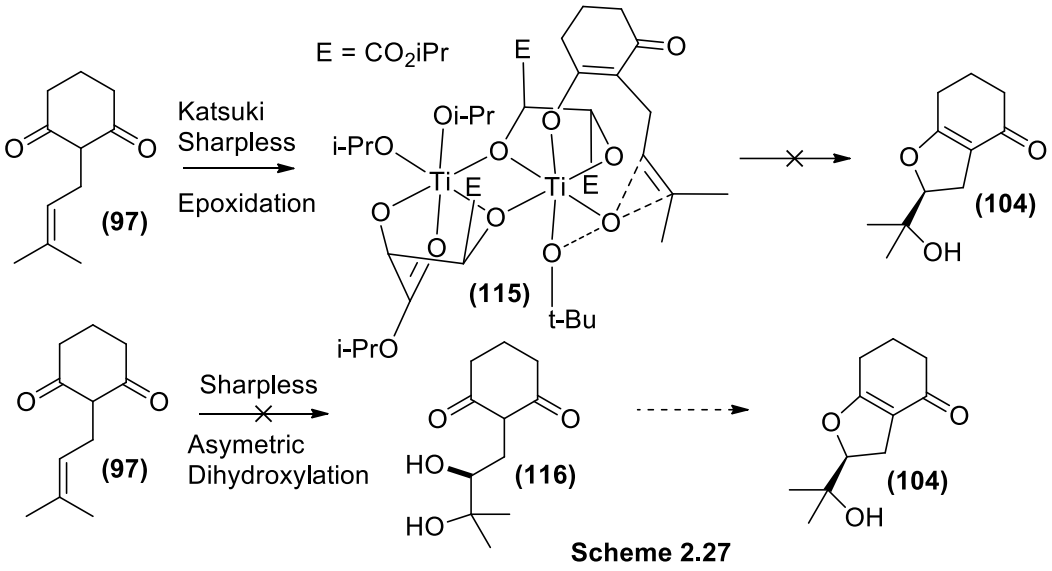
Base	Solvent	Comment	Yield	Ratio (114:104)
DIPEA	DIPEA/H_2O	Decomposition	8	1:0
K_2CO_3	DMF	Trace **104** detected	81	80:1
Ag_2O	DCM	Electrophile hydrolysis		-
Pyridine	neat	Minimal reactivity	10	1:0
NEt_3	neat	No reaction observed		-
TBAOH	$CHCl_3$ H_2O	Slow	22	1:0
LiOH	DMSO, 50 °C	Isolated yields	81	8:1
i-PrMgBr	Dioxane	Decomposition	34	9:1
NaH	DMF	Trace **104** detected	83	80:1
i-PrMgBr	THF	No recovery		-
Neat	µwave, 100 °C	~15% pyran **74**		-
Al(O*i*-Pr)$_3$	i-PrOH	Complex mixture	38	0:1
NaOEt	EtOH	Poor conversion	49	9:1

Na_2CO_3	MeCN	NaI catalyst	96	7:1
Na_2CO_3	Acetone	NaI catalyst	95	9:2
K_2CO_3	Acetone	KI catalyst	92	8:1
Li_2CO_3	Acetone	LiI catalyst	86	5:2
Li_2CO_3	**MeCN**	**LiI catalyst, isolated**	**93**	**2:1**

In order to fully assess the chemistry at hand a broad range of potential bases were explored; a variation of reversible, irreversible, organic and inorganic. In addition to this, these bases were employed across a broad range of various solvents capable of dissolving the starting material, including phase transfer conditions, microwave irradiation and sonication. Invariably the major product was *O*-alkylation **(114)** accompanied at times by small to trace quantities of the desired product **(104)**. Attempts to activate the halide leaving group with a silver oxide presumably resulted in hydrolysis of the electrophile, a characteristic cream white precipitate of AgBr formed but no alkylation products were isolated. The use of organic bases was generally unsuccessful. Fascinatingly, when using *i*-PrMgBr, it was decided to exploit the Schlenk equilibrium[83] by the use of dioxane as a solvent, this results in precipitation of $MgBr_2$ and the formation of Mg(*i*-Pr)$_2$ which had a dramatic effect on the observed results, either by enhancing the activity of the base or by altering the local structure of the formed enolate. Some success was encountered late in the project by employing *in situ* Finkelstein alkylation conditions;[84] by varying the group 1 counterion and solvent, the maximum isolated yield of the desired product **(104)** was 31%. Minimal attempts were made to utilise the corresponding iodo epoxide,[80] isolated crudely from Finkelstein halogen exchange however it proved to be modestly unstable. Given the relative success of the *in situ* Finkelstein conditions, it may warrant further investigation, along with other potential leaving groups.

In addition to this approach it was envisioned that it may be possible to effect chiral epoxidation using a Katsuki-Sharpless asymmetric epoxidation.[85] Although in the literature this is usually carried out on allylic alcohols, the limited number of degrees of freedom inherent to the prenylated cyclohexanedione **(97)** could potentially allow for a stable 7 membered transition state **(115)**. Unfortunately preliminary work into this approach was negative and it was not further pursued. Similarly attempts in

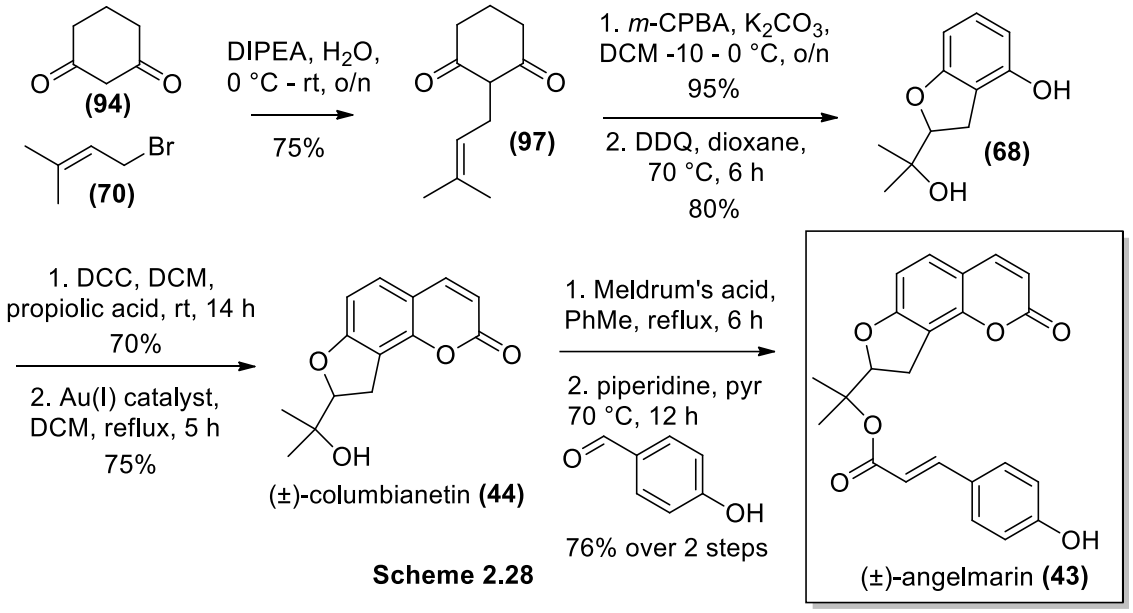
carrying out a Sharpless asymmetric dihydroxylation[86] and forming the desired structure **(104)** by acetalisation and elimination of the diol **(116)** resulted only in decomposition upon dihydroxylation, presumably due to an incompatibility of the electron rich enol to the osmium reagent (Scheme 2.27).



Scheme 2.27

2.5 Summary

The work described above represents a novel synthetic approach to angelmarin **(43)** and columbianetin **(44)**, utilising the highly versatile intramolecular hydroarylation[44] reaction under mild conditions and in the presence of a notably fragile tertiary alcohol.[41] The synthesis is only 7 linear steps, a number of which can be carried out without chromatographic separation, and in the complete absence of any protecting groups. In addition to this, some progress has been made in the annulation of a potentially chiral electrophile[80] which could be used in the synthesis of many dihydrofuran derivatives and to develop a synthesis of either enantiomer of the natural products, angelmarin **(43)** and columbianetin **(44)** (Scheme 2.28).


(94)
Br
(70)
DIPEA, H2O,
0 °C - rt, o/n
75%
(97)
1. m-CPBA, K2CO3,
DCM -10 - 0 °C, o/n
95%
2. DDQ, dioxane,
70 °C, 6 h
80%
OH
OH
(68)
1. DCC, DCM,
propiolic acid, rt, 14 h
70%
2. Au(I) catalyst,
DCM, reflux, 5 h
75%
OH
(±)-columbianetin (44)
1. Meldrum's acid,
PhMe, reflux, 6 h
2. piperidine, pyr
70 °C, 12 h
OH
76% over 2 steps
OH
(±)-angelmarin (43)

Scheme 2.28

Chapter 3 - Ochrosamines

3.1. Introduction

In a search for potential new anti-inflammatory drug therapies, Quinn *et al*. embarked on a high throughput library screen of locally obtained plant and marine invertebrate extracts. Over the course of this study they identified a stem and leaf extract of the endangered Australian rainforest tree, *Ochrosia moorei*, as being bioactive in the down regulation of pro-inflammatory gene expression. An assay guided isolation protocol resulted in the discovery of two novel natural products, the ochrosamines A **(117)** and B **(118)**.[87] (Figure 3.1)

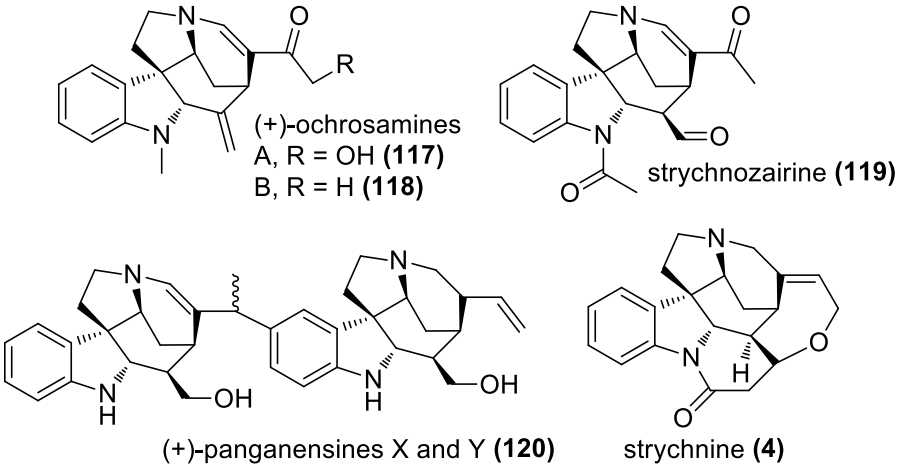


Figure 3.1 : The ochrosamines and related natural products

Although they were determined to be inactive components in the assay, the ochrosamines **(117,118)**, are part of the large strychnos family of alkaloids, the most iconic of which, strychnine **(4)** shares a similar scaffold.[88] The ochrosamines themselves are structurally quite intriguing; in particular the endocyclic enamine functionality present in the D ring is quite rare, with only a few examples occurring in the literature such as strychnozairine **(119)**[89] and the dimeric (+)-panganensine epimers X and Y **(120)**.[90] All of which have been of interest as potential lead compounds for the development of novel antimalarials.[91] (Figure 3.1). This suggests that the enamine functionality may play a role in bioactivity; however similar to the ochrosamines, the limited natural availability has limited further studies. As the *Ochrosia* rainforest tree is endangered,[87] this makes the ochrosamines prime

synthetic targets, allowing for the investigation of any bioactivity specific to the novel structural functionality whilst safeguarding environmental biodiversity.

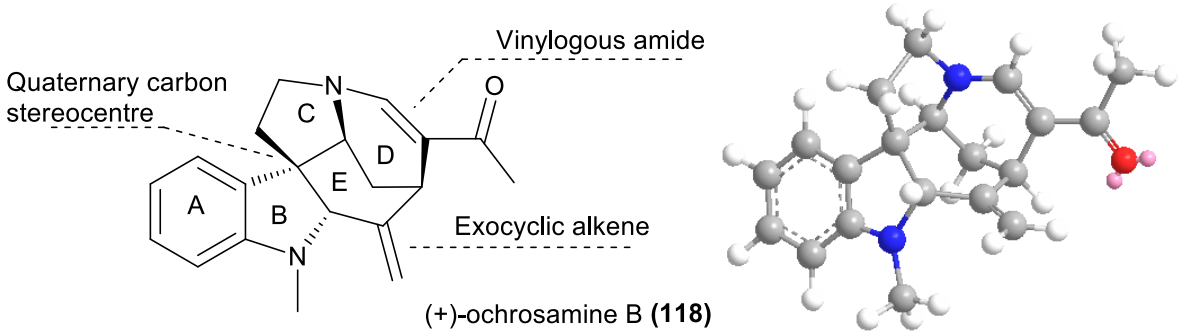
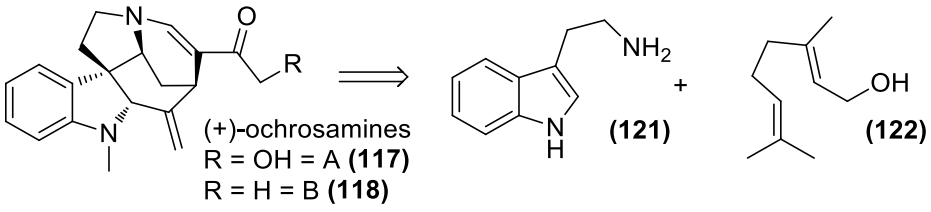


Figure 3.2: structural features of (+)-ochrosamine B together with a ball-and-stick model generated in Chem3D

The structural elements of the ochrosamines are quite complex (Figure 3.2), possessing a cage like ABCDE pentacyclic framework with three contiguous stereocentres including a quaternary carbon stereocentre. Coupled with the interesting vinylogous amide functionality and the isolated exocyclic alkene, these factors make the ochrosamines an excellent synthetic challenge, further driven by a lack of any existing total syntheses.

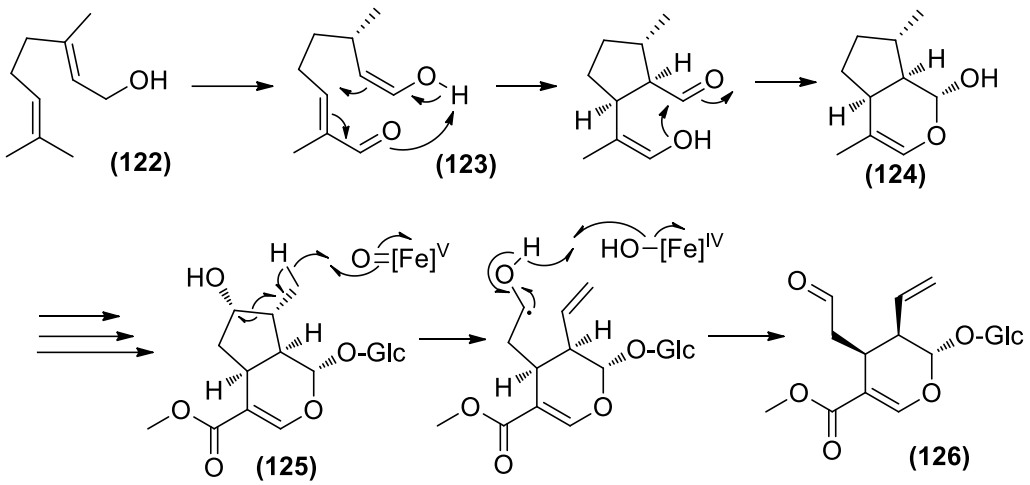
3.2. Biosynthetic origins



Scheme 3.1

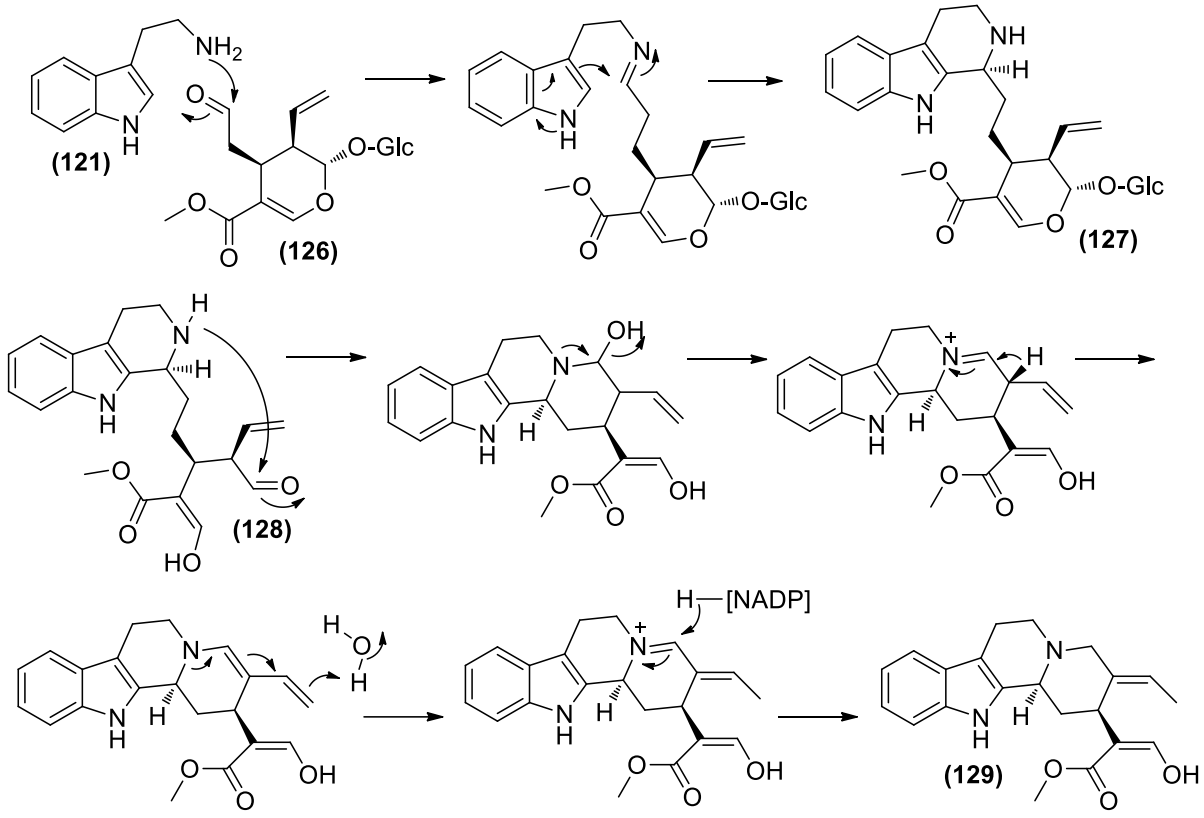
Biosynthetically it is presumed that the ochrosamines are ultimately derived from the amino acid tryptamine **(121)** and the simple monoterpenoid geraniol **(122)**, in a fashion common to the strychnos class (Scheme 3.1). The following brief description highlights the key bond forming events, for further information see O'Connor and Maresh.[92] Initially geraniol **(122)** is enzymatically oxidised to the dialdehyde followed by an enantioselective 1,4-hydride reduction. This yields an intermediate **(123)**, depicted as the enol, which is believed to undergo an intramolecular Michael addition

and acetalisation to form nepetalactol **(124)**.[93] This system is further oxidised, glycosylated, and esterified over numerous steps resulting in loganin **(125)**.[92] The glycosylation of the hemiacetal is quite interesting and consitutes a biosynthetic example of the use of a protecting group for a highly reactive functional group.[94] Loganin **(125)** then undergoes an oxidative cleavage to generate secologanin **(126)** which is a common intermediate in the formation of many natural products (Scheme 3.2).



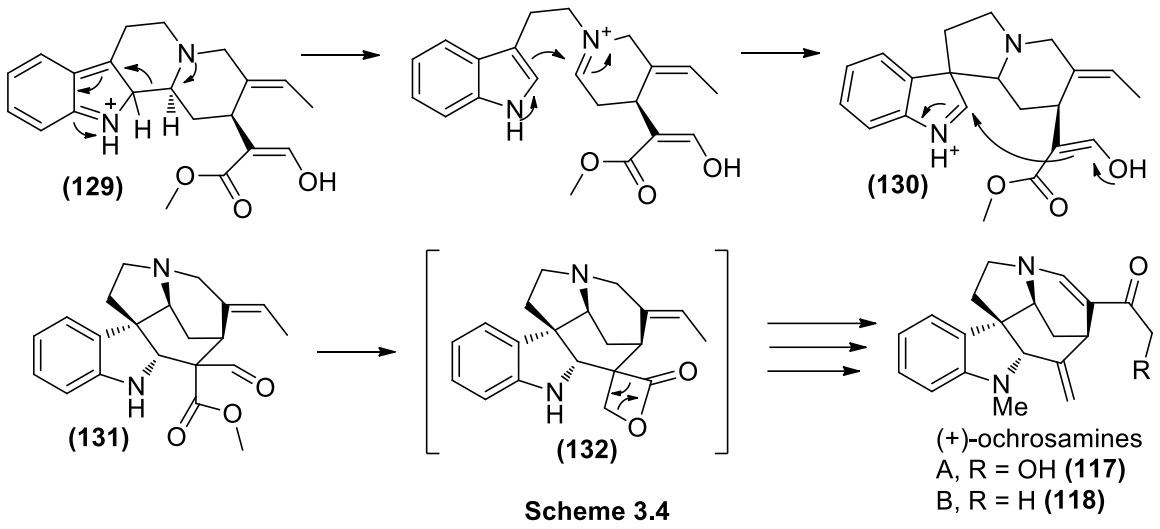
Scheme 3.2

An enzymatically controlled Pictet-Spengler reaction between tryptamine **(121)** and secologanin **(126)** generates strictosidine **(127)** as an intermediate. This occurs *via* initial Schiff base condensation followed by an electrophilic aromatic substitution of the indole. Glycoside hydrolysis then reveals a dialdehyde **(128)** which undergoes reductive amination with the secondary amine, accompanied by a tautomeric alkene shift to yield geissoschizine **(129)**.[92] (Scheme 3.3).



Scheme 3.3

The exact mechanism of the rearrangement of geissoschizine **(129)** to form the strychnos alkaloid carboskeleton has not been conclusively established; however Scott *et al*.[95] have proposed an acid catalysed retro Pictet-Spengler, which reoccurs at the 3 position of the indole. The spirocyclic iminium intermediate **(130)** then undergoes nucleophilic attack from the pendent enol thus generating the strychnos scaffold **(131)**.[95]. Any particular order of events from the generalised strychnos intermediate to the ochrosamines has yet to be established. Based on speculative analogy with similar natural products,[92] reductive decarboxylation *via* a beta lactone **(132)** reasonably establishes the isolated exocyclic alkene; which, accompanied by methylation and oxidation events, would yield the ochrosamines **(117,118)** (Scheme 3.4).



Scheme 3.4

3.3. Relevant previous work

Synthesising such a complex framework presents a significant synthetic challenge. Prior work within the research group resulted in the successful synthesis of the structurally and biosynthetically related alkaloid, aspidospermidine **(132)**.[96] The similarities between the two molecules are quite striking, both bearing a pentacyclic ABCDE ring system and a characteristic quaternary carbon at the three position of the indoline with aspidospermidine bearing an additional quaternary carbon. The ochrosamines possess a greater degree of functionalisation and differ in the connectivity of the D ring (Figure 3.3).

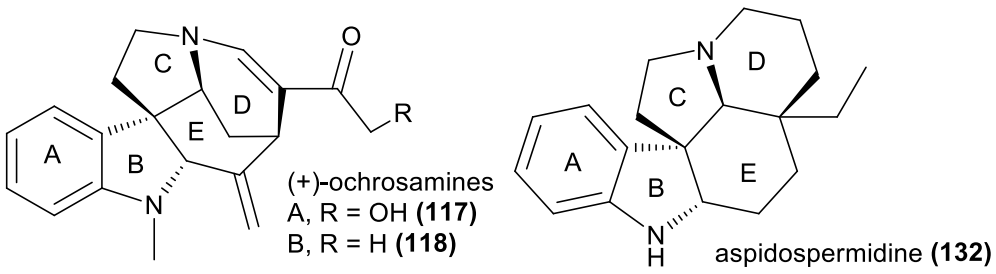
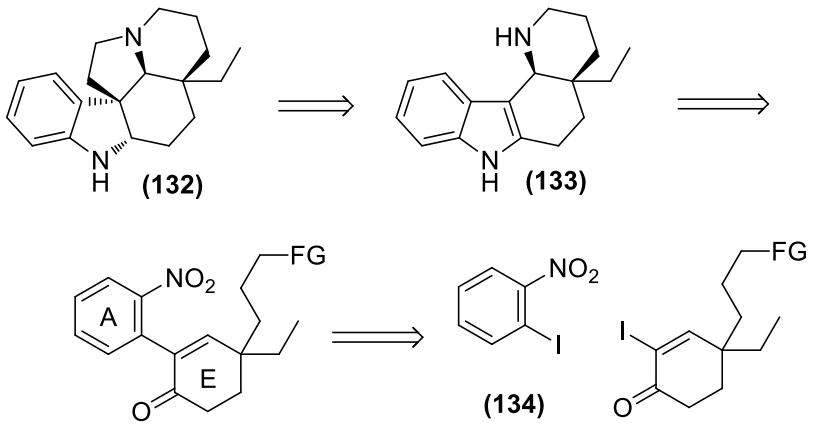


Figure 3.3 : Similarities between ochrosamine and aspidospermidine

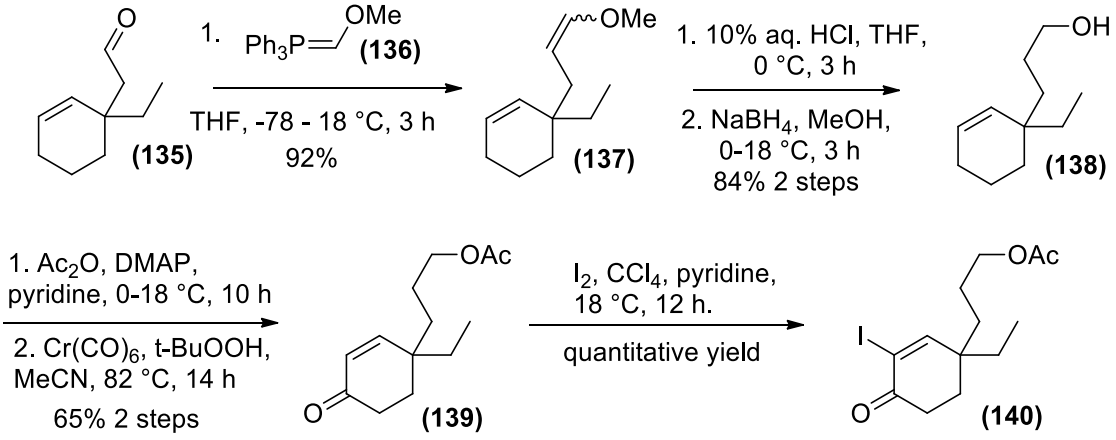
Retrosynthetically aspidospermidine **(132)** was disconnected to the known[97] intermediate **(133)**; aiming to exploit in house chemistry for the synthesis of indoles based on an Ullman coupling and reductive cyclisation.[98] Disconnection of the D and B rings reveals a complex A-E scaffold onto which the remaining rings are annulated. This system in turn would be synthesised *via* an Ullman type coupling

between the commercially available *o*-iodonitrobenzene **(134)** and an appropriately functionalised enone (Scheme 3.5.).



Scheme 3.5

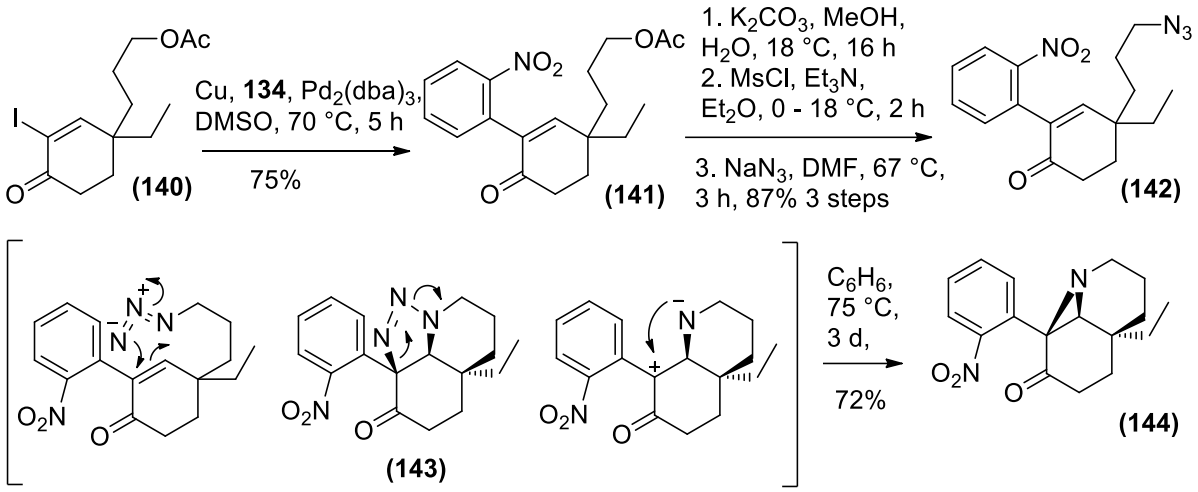
Synthesis of the key iodoenone building block was achieved by Wittig homologation the known aldehyde[99] **(135)** with the methoxy substituted phosphorous ylid **(136)**, producing the corresponding enol ether as a mixture of diastereomers **(137)**. Acid mediated hydrolysis revealed the homologated aldehyde which was immediately reduced with sodium borohydride to give the corresponding alcohol **(138)**. The free alcohol was protected as the acetate and subjected to a chromium mediated allylic oxidation developed by Pearson *et al.*[100] resulting in the enone **(139)**. The enone underwent facile alpha iodination under the Johnson conditions[101] to give desired coupling partner **(140)** in essentially quantitative yield (Scheme 3.6).



Scheme 3.6.

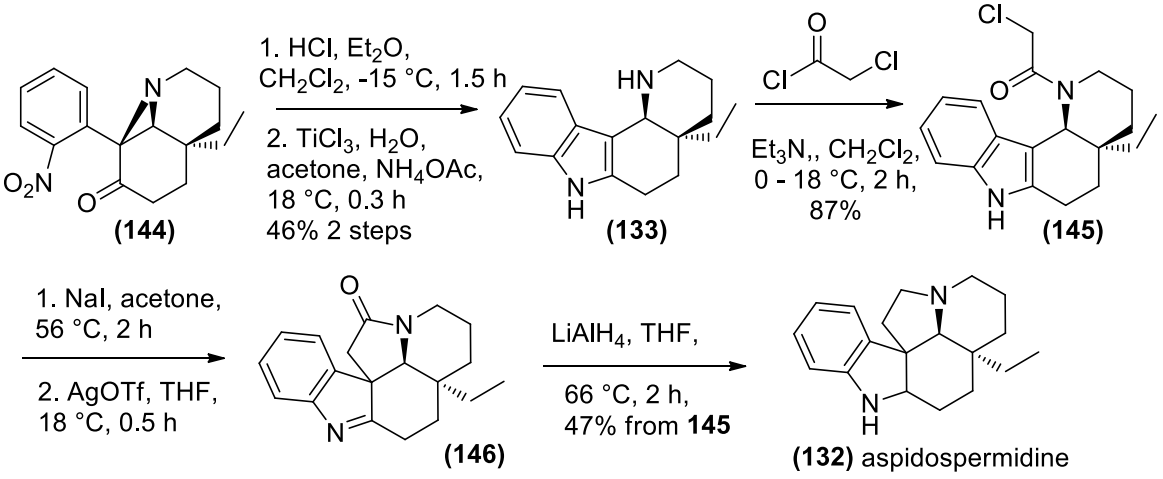
The pivotal Pd catalysed Ullman coupling with *o*-iodonitrobenzene **(134)** proceeded smoothly, affording the required A-E ring scaffold **(141)** in good yield. The protected

alcohol was converted *via* its mesylate to the corresponding azide **(142)**. Upon heating, the azide underwent an intramolecular Huisgen 1,3-dipolar cycloaddition, interestingly this was accompanied by the immediate expulsion of dinitrogen from the triazole intermediate **(143)**, giving aziridine **(144)** as the only isolated product.[96] (Scheme 3.7).



Scheme 3.7

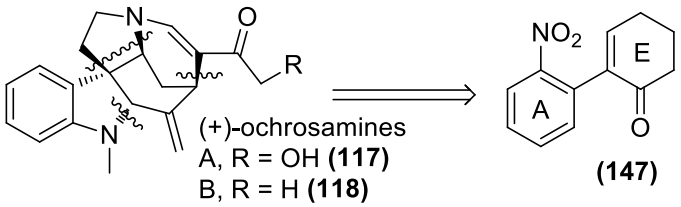
Sequential acid mediated opening of the aziridine ring and titanium (III) mediated reductive cyclisation of the nitro group resulted in isolation of indole **(133)**; a known precursor to aspidospermidine. This was then elaborated according to the method published by Toczko and Heathcock,[102] featuring amidation with chloroacetyl chloride to give the amide **(145)**. Finkelstein iodination and a silver promoted intramolecular alkylation of the indole gave the lactam **(146)** which was then reduced to give the natural product aspidospermidine **(132)** (Scheme 3.8).



Scheme 3.8.

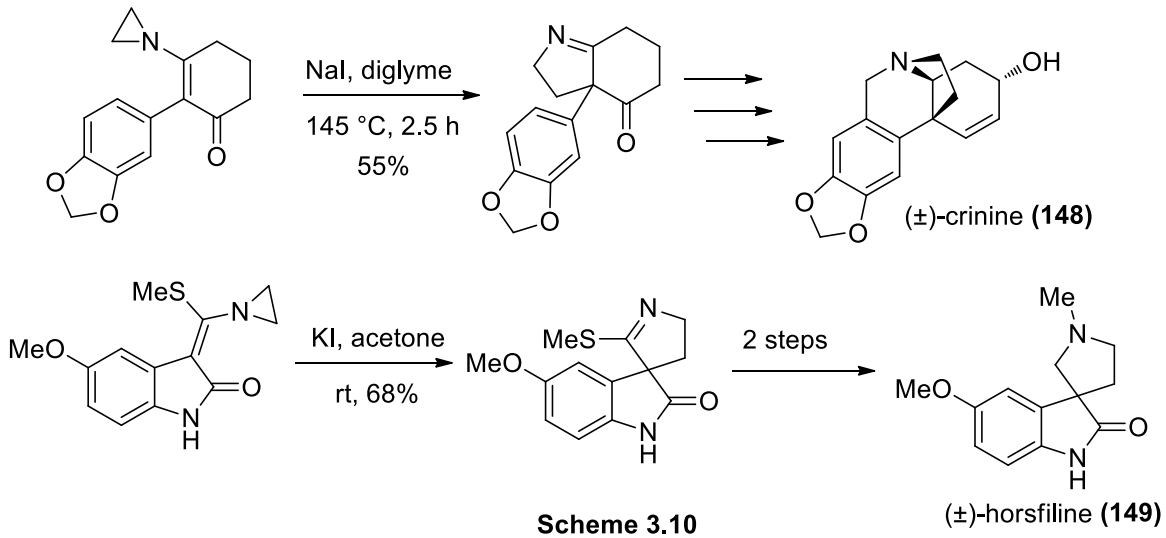
3.4. Retrosynthetic analysis

Seeking to replicate the success of the aspidospermidine work, it was again decided to generate a key A-E ring system onto which the remainder of rings could be annulated. Early introduction of the alpha aryl quaternary centre would allow it to be used as a cornerstone upon which synthesis could be constructed. Owing to the structural similarities it was again sought to exploit the powerful Ullman cross coupling/reductive strategy[98] to introduce the B ring. As such the simple nitro aryl enone **(147)** was chosen as an ideal starting material, which could be accessed through the known Ullman cross coupling.[98]



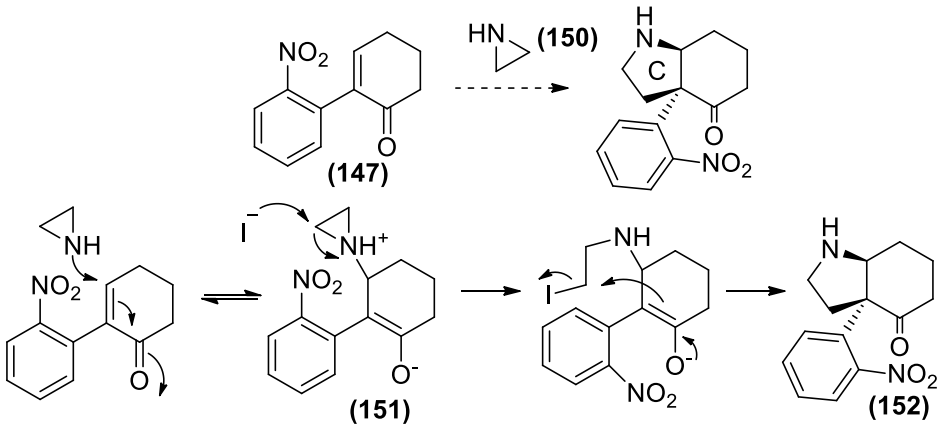
Scheme 3.9

Synthetically, two novel annulation strategies were envisioned to annulate the desired C and D rings. Following some modest precedence, an iodide catalysed aziridine annulation strategy was proposed to introduce the C ring and the quaternary carbon centre. Th rearrangement of aziridines has been previously employed in a successful synthesis of the natural products crinine[103] **(148)** and horsfiline[104] **(149)** (Scheme 3.10).



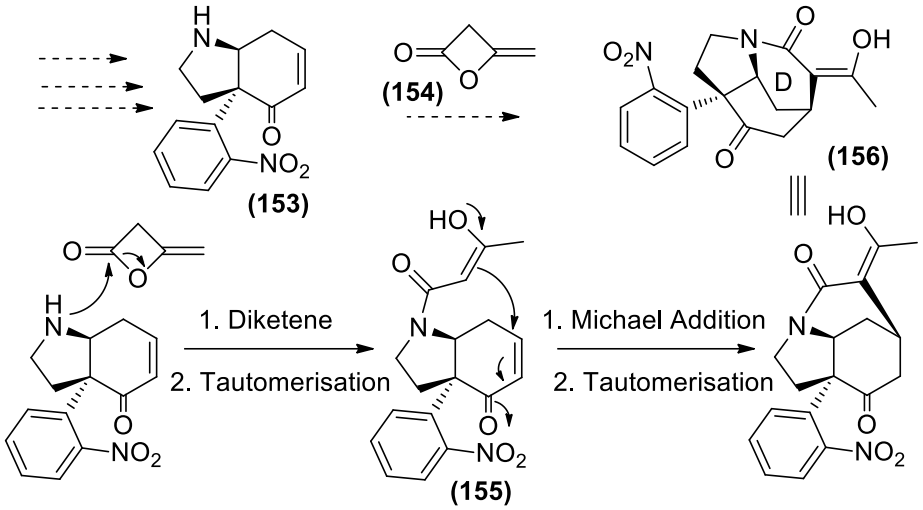
Scheme 3.10

As an intermolecular variant, conjugate addition of the free aziridine **(150)** would result in an activated zwitterionic intermediate **(151)** that can undergo ring opening in the presence of iodide which would act as a nucleophilic catalyst. The thus generated primary iodide could then act as a tethered alkylating agent allowing nucleophilic annulation onto the nascent enolate functionality. This would allow relatively rapid assembly of a complex intermediate **(152)** from relatively simple starting materials, leveraging the thermodynamic driving force of the aziridine ring strain. The lower oxidation state of this variant would also prevent the need for subsequent imine reduction (Scheme 3.11).



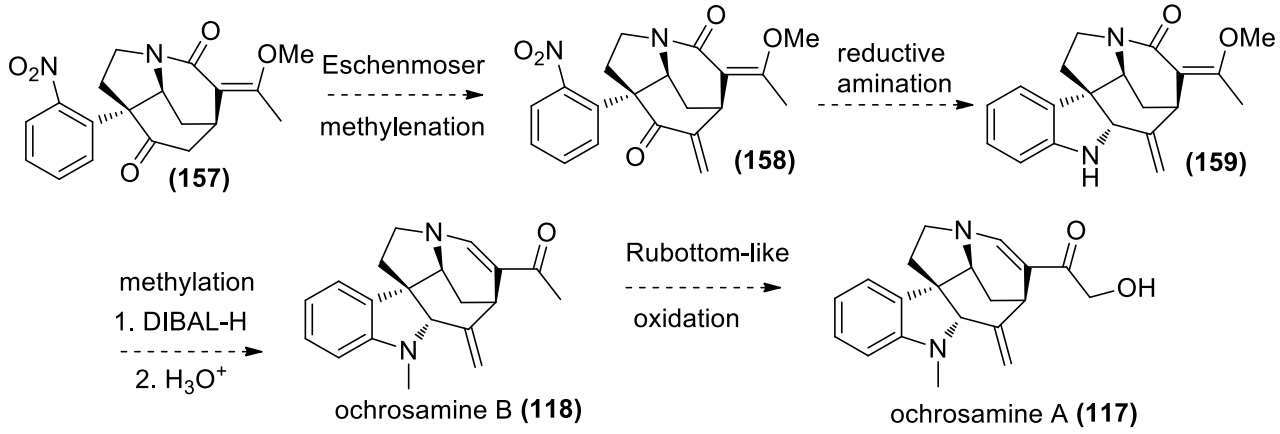
Scheme 3.11

Once the quaternary centre and C ring are established, an appropriate dehydrogenation protocol would then reveal a second Michael acceptor system **(153)** that would allow for an annulation of the D ring system using diketene **(154)**. Under relatively neutral conditions the nitrogen centre could undergo nucleophilic ring opening of the highly electrophilic diketene, once again driven by ring strain. Tautomerisation of the ring opened product creates a beta-keto amide **(155)** which is a strong Michael donor. It was envisioned that this would then be able to undergo an intramolecular conjugate addition potentially as a one pot reaction that would then establish the D ring and give rise to the advanced tricyclic intermediate **(156)** (Scheme 3.12).



Scheme 3.12

Protection of the more enolisable ketone as the enol ether **(157)** would allow an exo methylenation using the conditions established by Eschenmoser[105] to establish the last of the carbon-carbon bonds. A late stage reduction of the aromatic nitro group in compound **(158)**, in a fashion similar to the aspidospermidine work, followed by reductive amination would thus afford the desired pentacyclic framework **(159)**. *N*-Methylation and semireduction of the amide followed by an acidic workup would thus furnish the natural product ochrosamine B **(118)** which may be able to be converted *via* a Rubottom like oxidation[106] to give ochrosamine A **(117)** (Scheme 3.13).

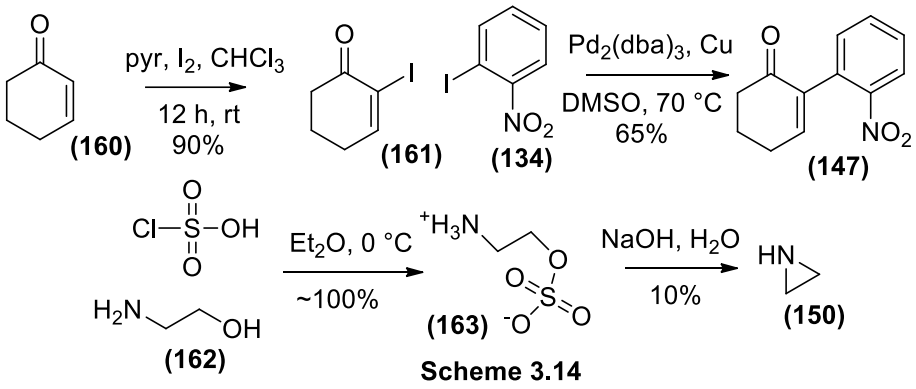


Scheme 3.13

The proposed synthetic scheme would allow for extremely rapid assembly of ochrosamine skeleton with the development of some novel and powerful annulation chemistry. This would be built around a solid foundation of the established Ullman chemistry for generating substituted indolines.[98]

3.5 Results and Discussion

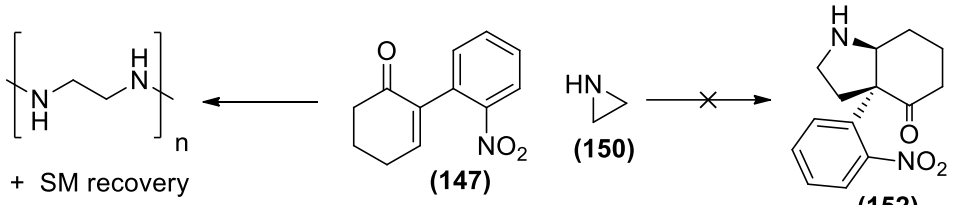
In order to investigate the proposed aziridine chemistry, the known AE ring system **(147)** was synthesised. Following the in house protocol cyclohexenone **(160)** was first converted to the alpha iodoenone **(161)** *via* a Johnson iodination.[101] The iodoenone was then subjected to an Ullman coupling with *o*-iodonitrobenzene **(134)** to generate significant quantities of the initial AE ring scaffold[98] **(147)**. Commercially available ethanolamine **(162)** was treated with chlorosulfonic acid in ether to quantitatively yield the sulfonate zwitterion **(163)** which rapidly precipitates.[107] Treatment of the zwitterion with concentrated sodium hydroxide allows for the distillation of free aziridine **(150)** albeit in poor yield.[108] In its isolated form, the aziridine proved to be quite unstable with a relatively short half-life that necessitated fresh preparation from the zwitterion (Scheme 3.14).



Scheme 3.14

With the required materials in hand, the aziridine annulation chemistry was investigated. Given the proposed mechanism and precedence for the aziridine annulation,[103-104, 109] initial conditions focused on the use of tetrabutylammonium iodide (TBAI) as an organosoluble source of iodide under the assumption that the best conditions would be relatively anhydrous and require a strong, “naked”, nucleophile. Initial results were not encouraging and the major observations were the return of starting material and polymerisation of the relatively unstable aziridine, **(150)** this was consistent across a range of different solvents ($CHCl_3$, DMSO, THF, Toluene) and temperatures. Use of TBAI was abandoned as its removal additionally complicated both extraction and analysis of the reaction mixture. Capitalising on the high solubility of potassium iodide,[110] the solvent was changed to acetone however this proved to be too reactive, showing some crude spectroscopic evidence of solvent condensation with the aziridine without isolation of any distinct products.

Given that the proposed annulation requires a relatively long lived zwitterion, the solvent was changed to acetonitrile to take advantage of the relatively high dielectric constant.[111] This had the added advantage of maintaining a relatively high solubility of potassium iodide,[112] with a lower inherent solvent reactivity as the nitrile functionality is substantially less electrophilic than the ketone of acetone. Disappointingly this failed to result in the isolation of any of the desired product **(152)**. Attempts at further promoting the reaction by addition of an oxophilic Lewis acid ($SnCl_4$, TMSCl) to promote Michael addition hastened aziridine decomposition. Varying the rate of addition and dilution of aziridine did not affect results in any noticeable fashion (Scheme 3.15).

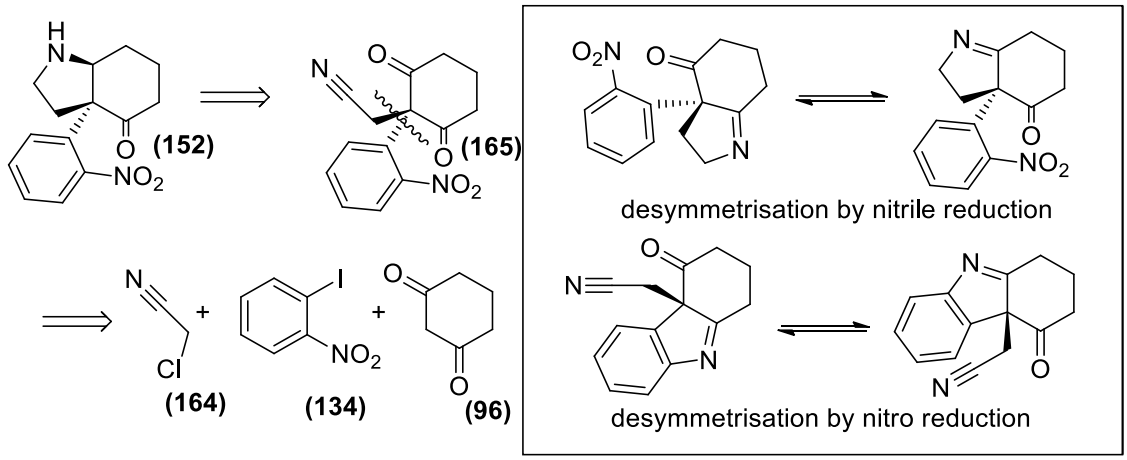


Scheme 3.15

In addition to difficulties arising from the polymerisation of aziridine, it was presumed that the enone system being worked upon was not sufficiently electrophilic to result in significant generation of the required zwitterionic intermediate **(151)**. A potential reason for this is the relatively high steric strain of the resulting aryl substituted *Z*-enolate which would promote retro Michael addition. Faced with a lack of results and the inherent difficulties of working with aziridine, which is toxic, volatile, and prone to polymerisation; it was ultimately decided to revise the synthetic strategy.

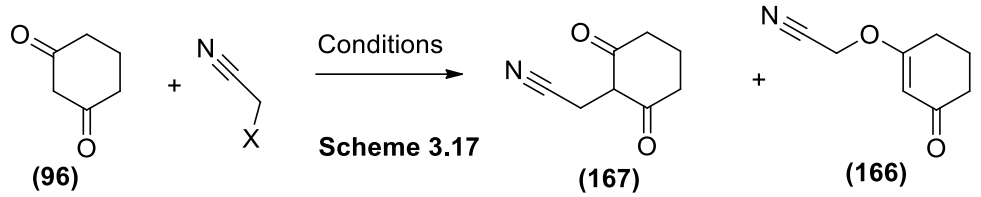
Given the previous experience in the use of activated methylene systems (see chapter 2), the earlier proposed A, C, E ring system intermediate **(152)** was instead disconnected to 1,3-cyclohexanedione **(96)**. Following previously established results within the group regarding chemoselective reductive cyclisations of nitriles with Raney cobalt,[113] it was decided that the nitrogen atom of the C ring would be introduced as a nitrile functional group. The activated methylene could be arylated *via* nucleophilic aromatic substitution[114] and further alkylated with chloroacetonitrile **(164)** to yield an appropriately functionalised symmetric intermediate **(165)**. Chemoselective reduction of the nitrile or nitro functionality, followed by imine condensation with one of the ketones would desymmetrise the system and would

then direct regioselectivity in constructing the rest of the molecule. Further elaboration of A, C, E ring system **(152)** would be achieved *via* the earlier proposed ketene methodology, to access the natural product. Condensation of remaining ketone with a chiral amine could potentially be used to allow resolution of a single enantiomer.



Scheme 3.16

Utilising the experiences developed in the previous chapter, commercially available 1,3-cyclohexanedione **(96)** was subjected to the previously more successful conditions to establish the best method of alkylation. A familiar pattern thus emerged in that the major observed product was typically *O*-alkylation **(166)** which was variably obtained in 35-95% yield, with results tending to be poorly reproducible on scale. Although the use of iodoacetonitrile gave a better ratio of the C-alkylated product **(167)**, the overall yields were significantly lower, therefore it was sought to generate the iodoacetonitrile *in situ* using Finkelstein type conditions.[84] Consistent with previous observations the *in situ* Finkelstein conditions resulted in the most favourable distribution of products. Results were similar regardless of which halide was used as a starting material, leading to use of the cheaper chloroacetonitrile reagent **(164)** (Table 3.1, Scheme 3.17).



Scheme 3.17

Conditions	X	Yield (C)*	Yield (O)
DMSO, TBAI, K_2CO_3, rt, 16 h	Cl	3	95
DMSO, TBAI, K_2CO_3, rt, 16 h	Br	15	82
DMSO, K_2CO_3, rt, 16 h	I	13	22
MeCN, KI, K_2CO_3, 82 °C, 16 h	Cl	24	62
MeCN, KI, K_2CO_3, 82 °C, 16 h	Br	28	67
Acetone, KI, K_2CO_3, 56 °C, 16 h	Cl	28	53
Acetone, NaI, Na_2CO_3, 56 °C, 16 h	Cl	72	17
Acetone, NaI, Na_2CO_3, 56 °C, 16 h (5g scale)	Cl	32	40

Table 3.1. (* yields are a crude estimate of the C-alkylated fraction: see experimental)

Although the *O*-alkylated product **(166)** was easily obtained, frustratingly the C-alkylated system **(167)** could not be well characterised or purified. Evidence suggests that it exists as a tautomeric mixture with the enol **(168)** that may be slowly and reversibly interconverting with the cyclic form **(169)** which is also tautomeric with the aminofuran **(170)**, identified by certain characteristic peaks in the ^1H NMR spectrum. A key aromatic singlet appears at 5.95 ppm, corresponding to the furan form, in addition to peaks at approximately 3.0-3.5 ppm corresponding to tautomeric forms of the acetonitrile derived methylene and a pair of broad singlets at 5.5 and 6.5 ppm identified as the NH protons of the aromatic form. All of these peaks disappeared on addition of D_2O indicating the protons were readily exchangeable (Figure 3.4).

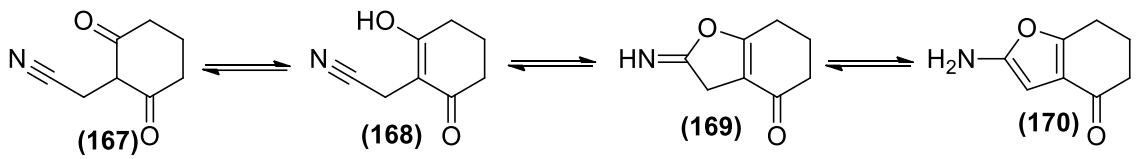
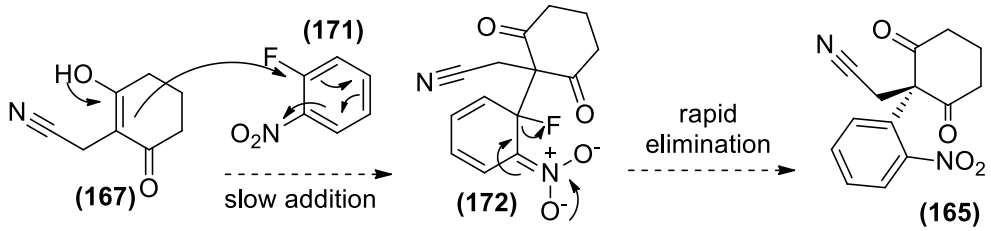


Figure 3.4: Suggested tautomeric equilibrium

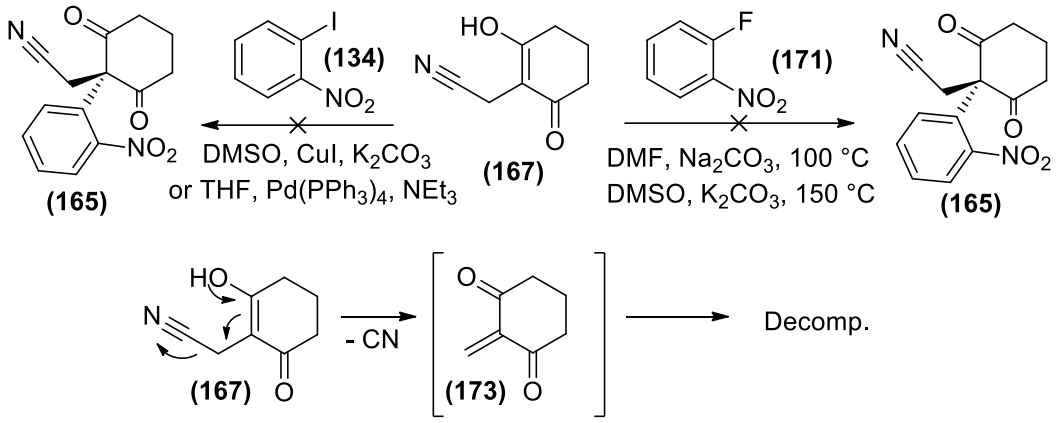
This was supported by significant cross peaks and streaking in the two dimensional TLC analysis, poor reproducibility and reversible solvent dependent changes in relative NMR peak intensities. The material obtained was used directly in subsequent steps in the hope that the equilibrium mixture would be funnelled through the most reactive individual species consistent with the Curtin-Hammett principle.[115]

Installation of the quaternary centre was initially proposed *via* a nucleophilic aromatic substitution process with 2-fluoronitrobenzene **(171)**. This proceeds by addition of an appropriate nucleophile to an aromatic ring bearing an electron withdrawing group and leaving group. Addition occurs *ipso* to the leaving group resulting in a formal build of negative charge and a loss of aromaticity, forming a Meisenheimer complex[114] **(172)**. This system is mesomerically stabilised by the electron withdrawing groups and the use of a fluorine as the leaving group results in an additional stabilisation through inductive effects.[114] (Scheme 3.18).



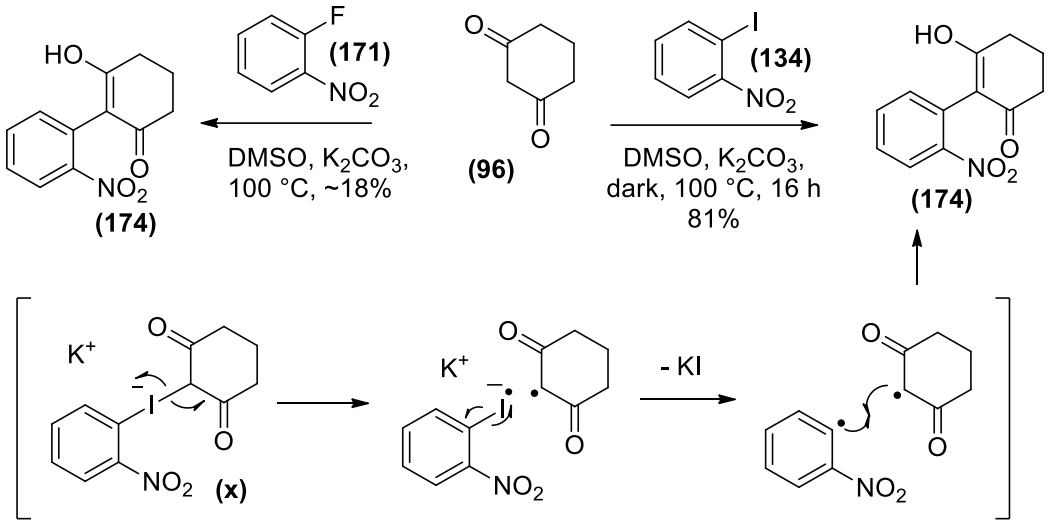
Scheme 3.18

Disappointingly subsequent exposure of the nitrile dione mixture to the typical conditions used to facilitate nucleophilic aromatic substitution with fluoro nitrobenzene **(171)** (DMSO or DMF, K_2CO_3, 80-150 °C, etc.)[114] failed to yield any usable material as decomposition of the starting material seemed to predominate at the higher temperatures employed, with recovery of the nitroarene. Additional attempts at a transition metal catalysed process with 2-iodonitrobenzene **(134)** (CuI, $Pd(PPh_3)_4$) were likewise unsuccessful. It is theorised that at higher temperatures the nitrile moiety may be lost as cyanide in an E_1cB elimination, resulting in a transient 2-exomethylene intermediate **(173)**; such an intermediate would be extremely reactive and is presumed to be the cause of the very large number of observed side products (Scheme 3.19). The additional tautomerism of the dione starting material (see Figure 3.4) with multiple electrophilic and nucleophilic positions further complicates the situation.



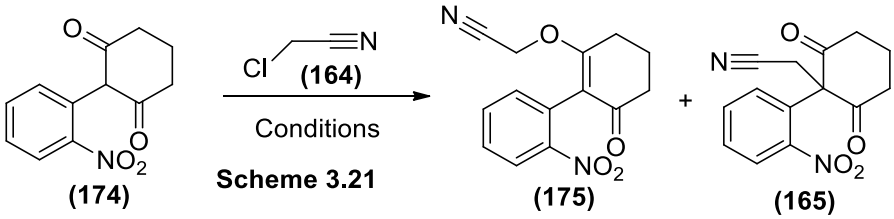
Scheme 3.19

To investigate the alternative order of events whereby the dione **(96)** is arylated then alkylated, the known[116] aryl dione **(174)** was synthesised. Use of the literature conditions with fluoronitrobenzene **(171)** resulted in an unsatisfactory yield of less than 20% involving laborious separations. Utilising the conditions developed by Bonjoch *et al*.[117] iodonitrobenzene **(134)** was subjected to essentially similar nucleophilic aromatic substitution conditions with the strict exclusion of light, resulting in a much improved yield of 81%. The isolated nitroenone **(174)** exists solely as the enol form by ^{1}H NMR and the diketo proton is not observed. Without the fluoro group the electronics of the substitution process make an S_NAr process untenable. When using the iodide it is proposed that the reaction instead occurs *via* a non-chain radical nucleophilic substitution.[118] Initial association of the nucleophile to the aromatic system, potentially through the iodine atom results in a single electron transfer event to form a radical anion, concomitant loss of iodide results in a radical pair which recombine to give the product after tautomerisation. This is favoured by high viscosity DMSO which prevents diffusion of the reactive intermediates out of the solvent cage[119] (Scheme 3.20).



Scheme 3.20

With the nitroarylenone tautomer **(174)** in hand, conditions for formation of the quaternary centre were sought. As the best results of previous alkylation efforts were observed upon exposure to Finkelstein like conditions,[84] this was the first resort. In performing the reaction, two products were observed by crude NMR, of which one could be cleanly separated. This was tentatively identified as the desired symmetric product **(165)** based on a desymmetrisation of the aliphatic ring protons in ^{1}H NMR including clearly identifiable ddd signals, with high coupling constants (18 Hz) consistent with geminal coupling that had not been observed in the enol starting material. This was further supported by the presence of a nitrile group in the IR spectra. The other major product was identified as the *O*-alkylated product **(175)** due to a characteristic AB system present at 4.6 ppm in the ^{1}H NMR, corresponding to the methylene directly attached to oxygen. This AB system seemed to indicate that the *o*-nitro group was preventing free rotation about the aryl-cyclohexenone bond. In varying the metal counter-ion used in the Finkelstein alkylation the proportion of *O*-alkylated product was higher going down the group 1 metals. This was assessed by crude NMR analysis, comparing two distinct aromatic protons. When the lithium counter ion was used with an excess of LiI (2.2 equivalents), what was thought to be the C alkylated product **(165)** predominated (Table 3.2, Scheme 3.21).



Conditions	%Yield	% **(165)**	% **(175)**
Acetone, LiI (cat), Li_2CO_3, 56 °C, 16 h	63	48	52
Acetone, NaI (cat), Na_2CO_3, 56 °C, 16 h	83	35	65
Acetone, KI (cat), K_2CO_3, 56 °C, 16 h	81	29	71
Acetone, LiI (2.2 eq.), Li_2CO_3, 56 °C, 16 h	72	81*	19

Table 3.2 % O or C product calculated from discrete aromatic proton NMR integrals after quench and extraction, * 58% isolated yield.

After laborious purification it was possible to isolate and then crystallise some of what was assumed to be the C-alkylated product **(165)**, however the *O*-alkylated product could not be cleanly isolated. Surprisingly an X-ray crystal analysis revealed what was assumed to be the C alkylated product of the Finkelstein reaction not to be the desired symmetric system but an unexpected atropisomeric compound **(176)** resulting from overall substitution of the enol hydroxyl group by cyanide (Figure 3.5). The crystal structure shows a significant dihedral angle of 63° between the planes of the two ring systems and a 33° out of plane deformation of the nitro group with respect to the aromatic ring.

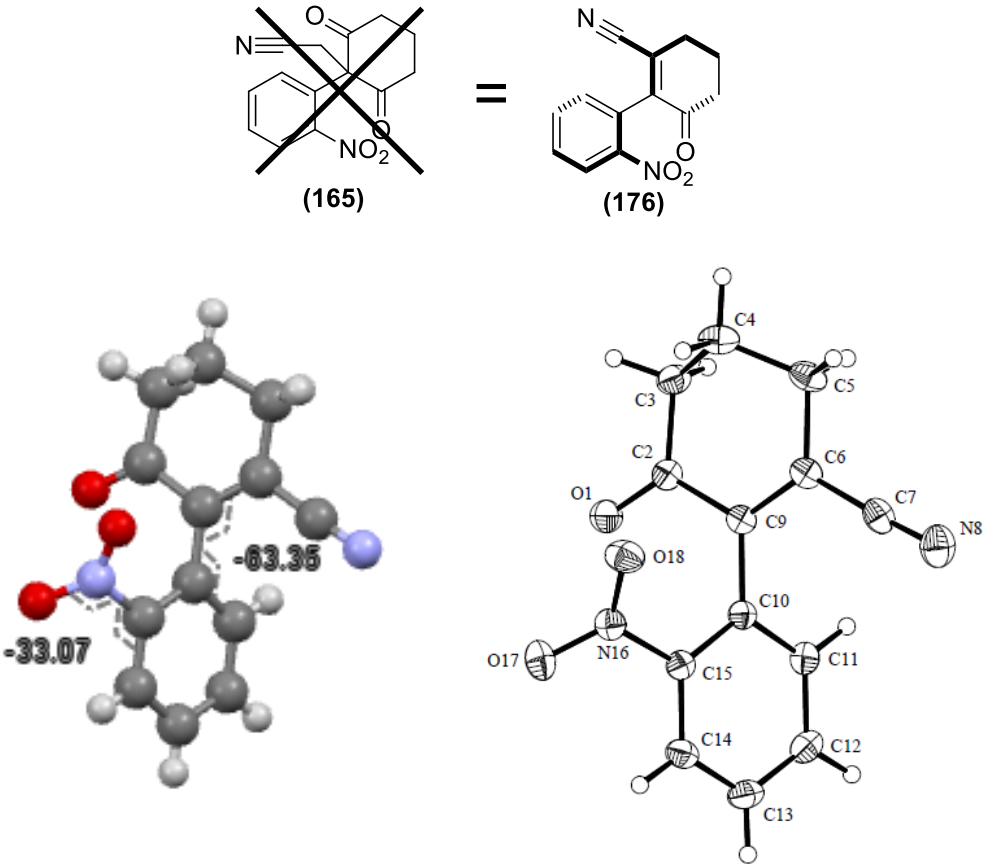
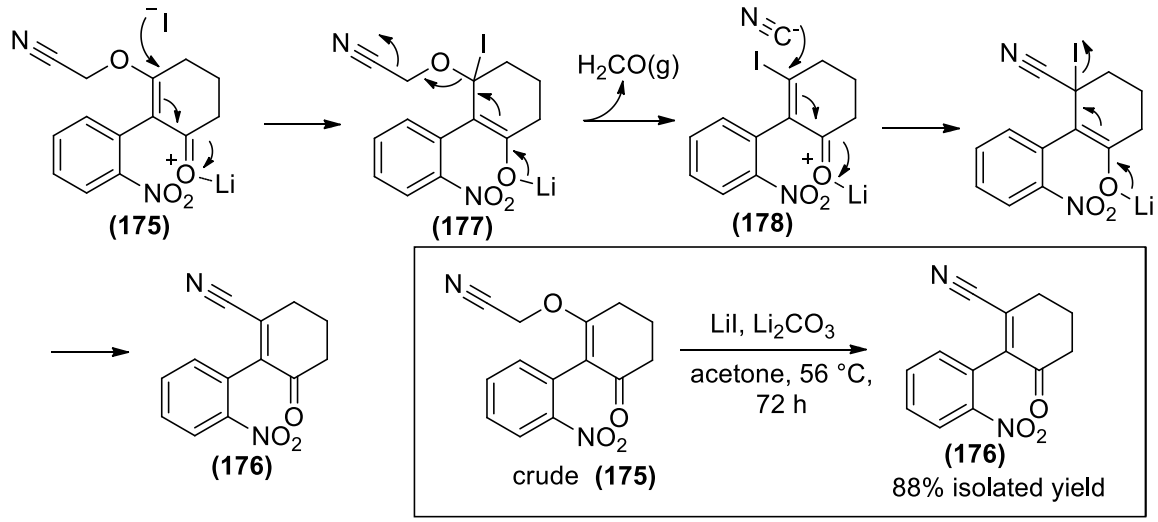


Figure 3.5 Left: Ball and stick model derived from the X-ray crystal structure of **(176)** with selected dihedral angles (modelled using Mercury 3.7). Right: Structure of $C_{13}H_{10}N_2O_3$ **(176)** with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Presumably the high nucleophilicity of the iodide anion[115] and the Lewis acidity of the lithium counter-ion facilitate a conjugate addition of iodide to the *O*-alkylated product **(175)**. This intermediate **(177)** could then eliminate glyconitrile to give the highly electrophilic iodoenone **(178)**. Glyconitrile decomposes under basic conditions[120] into formaldehyde and lithium cyanide, in a process which may be concerted with the elimination from the intermediate **(177)** as shown in scheme 3.22. The loss of formaldehyde as a gas under the refluxing temperatures would thus drive the reaction forward.[115] The cyanide anion could in turn undergo Michael addition to the highly electrophilic iodoenone **(178)** which can be seen as a vinylogous acyl iodide. This intermediate would then eliminate iodide to yield the observed product **(176)**.. As evidence for this mechanism the reaction the impure *O*-alkylated material **(175)** obtained from using the potassium counter-ion was then resubjected to prolonged

heating under the lithium iodide Finkelstein conditions in the absence of electrophile, after which almost complete conversion of the *O*-alkylated material **(175)** was observed and the atropisomeric product **(176)** was obtained in 88% yield (Scheme 3.22). In addition to iodide this transformation could also conceivably be catalysed by initial hydrolysis of **(175)** by adventitious water to give **(174)** and a population of cyanide anions. The cyanide anions could then serve as a catalyst to effect the direct transformation of **(175)** to **(176)** in an analgous fashion without the intermediate iodoenone **(178)**.

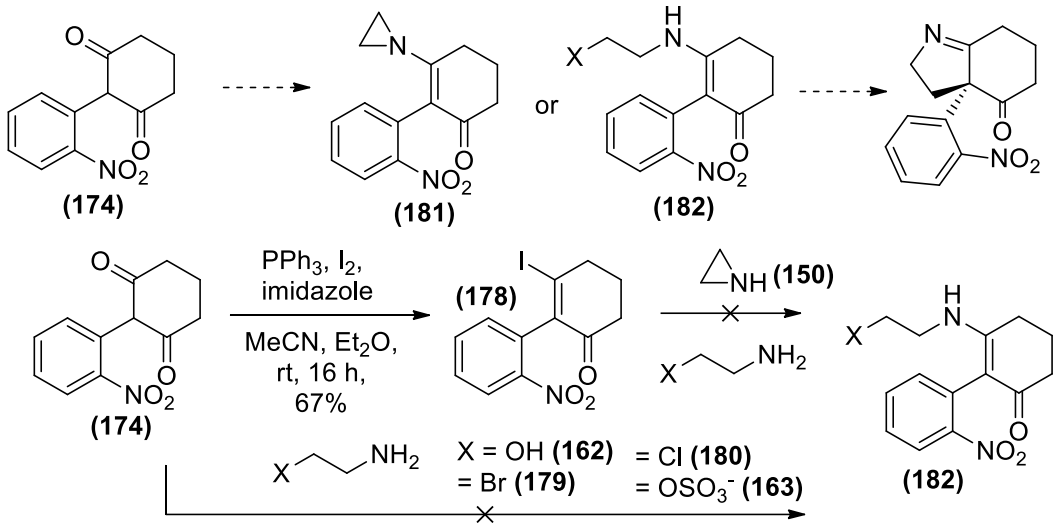


Scheme 3.22

On the basis of this result it was determined that direct intermolecular alkylation of the dione **(174)** was not feasible. In a return to the previously explored chemistry, it was theorised that an intramolecular alkylation may be possible either through addition of aziridine **(150)** in a fashion similar to that attempted previously (see Scheme 3.15) or *via* an ethylamine bearing an appropriate leaving group. Unfortunately attempts to condense the dione **(174)** directly with aziridine **(150)**, chloroethylamine **(179)**, bromoethylamine **(180)**, zwitterion **(163)**, or even ethanolamine **(162)** were unsuccessful and no vinylogous amides **(181)** or **(182)** were observed despite their reported ease of synthesis.[117] A range of conditions were attempted featuring various acids (AcOH, TMSCl, $Ti(OEt)_4$), dehydrating agents (4 Å sieves, TMOF, etc.), solvents and temperatures.

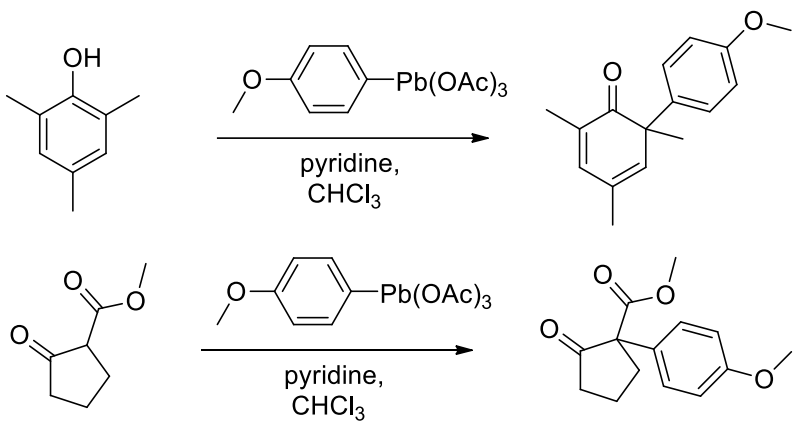
Hoping to take advantage of the previous discovery it was decided to synthesise iodoenone **(178)**; the proposed intermediate in the formation of the side product

(176). Exposure of the dione **(176)** to Appel-like conditions,[121] afforded the moderately unstable iodoenone **(178)** in relatively good yield. The system showed similar evidence of atropisomerism in the ^{1}H NMR spectra with discrete diastereotopic splitting of the protons in the aliphatic ring. The iodoenone **(178)** proved somewhat capricious resulting in either decomposition or complete recovery of starting material when attempts were made introduce aziridine **(150)**, bromoethylamine **(179)**, chloroethylamine **(180)**, ethanolamine **(162)** or zwitterion **(163)** (Scheme 3.23).



Scheme 3.23

Disillusioned by the observed results, the overall synthetic strategy was reassessed and a less conventional approach was taken based on some related organolead chemistry developed by Pinhey. The Pinhey reaction exploits the high oxidation potential of an aryl substituted Pb(IV) compound to effect electrophilic arylation of activated carbon acids or electrophilic dearomatisation of substituted phenols, creating a quaternary carbon centre alpha to an aromatic ring[122] (Scheme 3.24).



Scheme 3.24

The required aryl organolead compounds can be accessed *in situ* by a mercury catalysed transmetallation of the organoboron or organotin compounds.[122] Although less well established in the realm of natural product synthesis; this approach features a powerful transformation with a demonstrated capacity to establish highly functionalised and sterically demanding quaternary centres, from fairly easily accessible starting materials. The literature suggests a fairly broad substrate scope, with electron donating and withdrawing functionalities tolerated[123] on the aromatic ring of the aryl lead species and varying substitution patterns.[124] It has even been used recently in a total synthesis of maeocrystal V **(183)** utilising a sterically hindered *ortho*-MOM protected aryl lead species[125] (Figure 3.6).

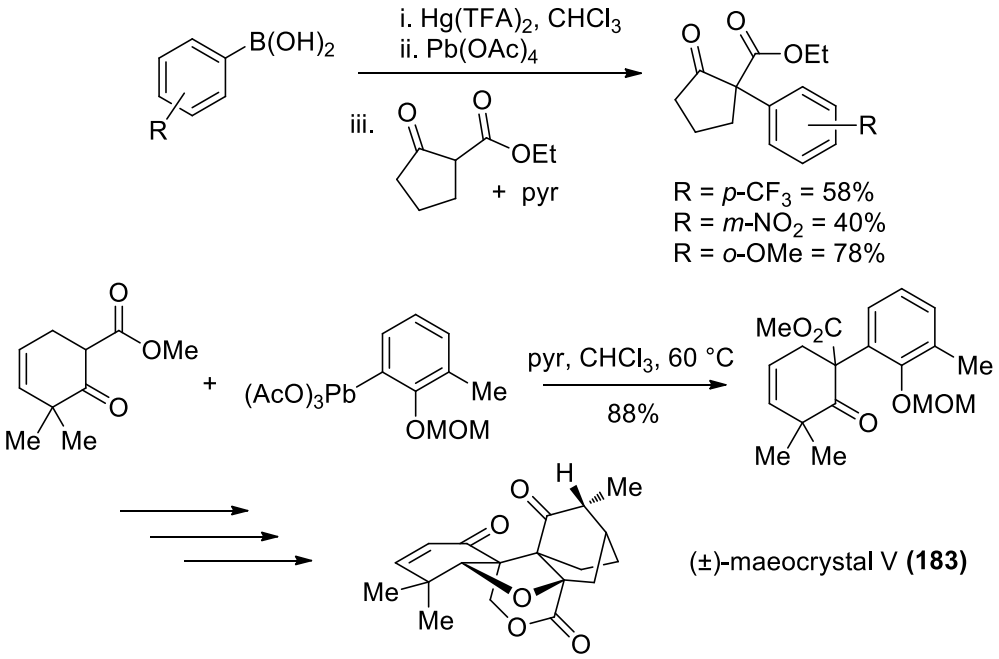
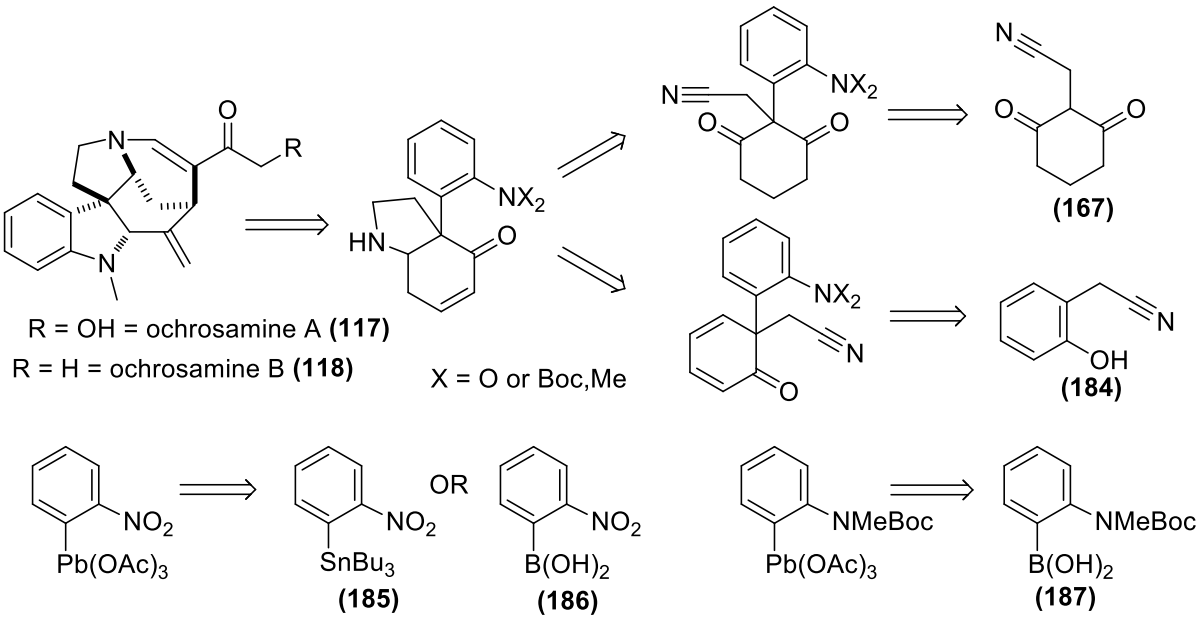


Figure 3.6: Substrate scope and exemplar synthesis of Pinhey electrophilic arylation

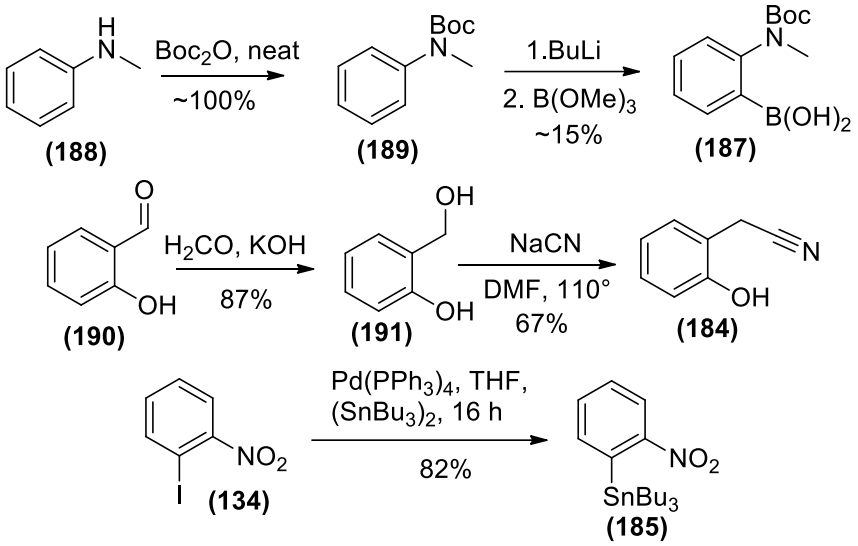
Applying this transformation in the context of the ochrosamine system yielded some distinct possibilities for variation, tying into the original A,C,E ring system (see Scheme 3.11) in the hope of still using the earlier proposed diketene chemistry. Disconnection by electrophilic arylation, results in the previously synthesised nitrile dione **(167)**; and by dearomatisation, results in the known phenol[126] **(184)**. The nitrile functionality was seen as a relatively good candidate to introduce the nitrogen of the C ring, as it is resistant to oxidative conditions and has particularly low steric demand. These options would then be complemented by an appropriate nitrogen bearing, aryl lead system derived from the corresponding stannane or boronic acid. The nitrostannane **(185)** was known[127] and the nitroboronate **(186)** was commercially available, however identifying that the sterically demanding and highly electron withdrawing nitro group as potentially problematic;[128] a protected methylaniline **(187)** was also investigated (Scheme 3.25).



Scheme 3.25

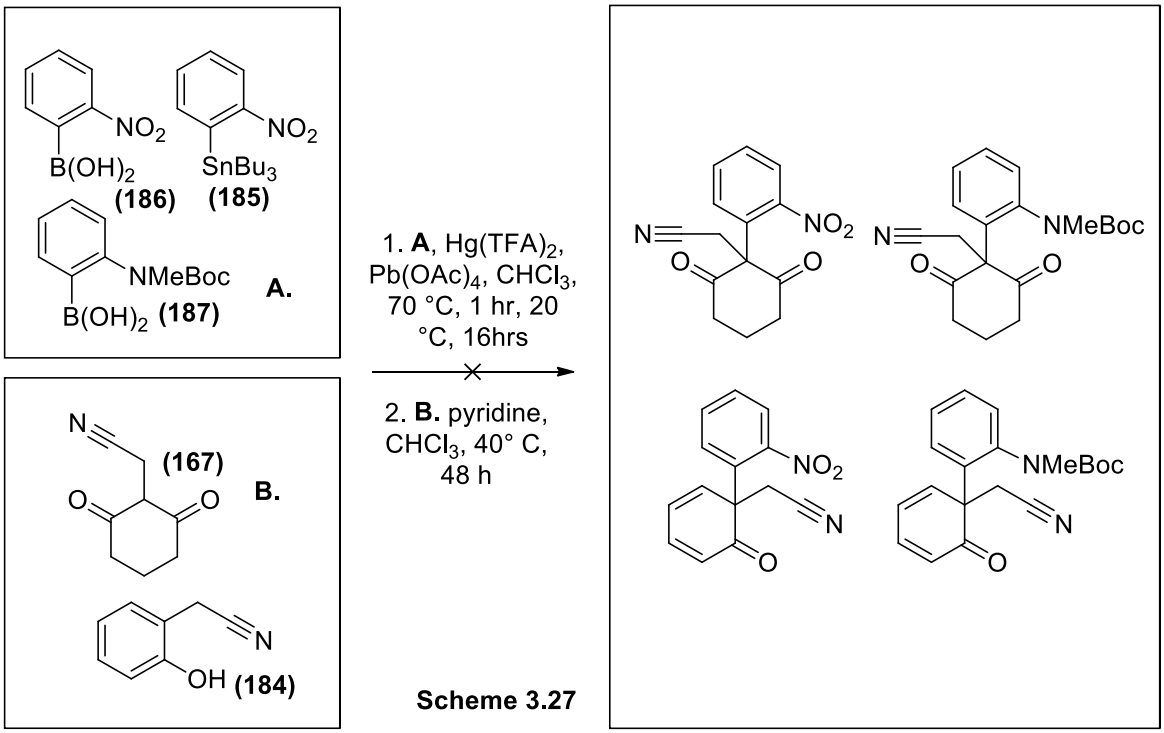
N-methylaniline **(188)** was protected with a *t*-butoxycarbonyl group[129] to give the carbamate **(189)** which was then deprotonated in a directed ortho-metallation with *n*-butyl lithium. Quenching of the anion with trimethoxyborane[130] resulted in the formation of the crude boronic acid **(187)** in low yet sufficient yield which was used without purification. Following literature conditions salicylaldehyde **(190)** was reduced *via* a crossed Cannizaro reduction[131] to the alcohol **(191)** which was subjected to sodium cyanide in hot dimethylformamide.[126] This results in the

transient formation of a quinone methide which acts as a strong Michael acceptor to form the desired 2-(cyanomethyl)phenol **(184)**.[132] Stille coupling of iodonitrobenzene **(134)** with hexabutylditin afforded the corresponding nitrophenylstannane **(185)**[127] (Scheme 3.26).



Scheme 3.26

With the required materials in hand, attempts were made to effect the desired Pinhey coupling. In order to assess the feasibility of the reaction, the nitrostannane **(185)** was subjected to transmetallation with $Pb(OAc)_4$ and catalytic $Hg(TFA)_2$ using standard conditions used to isolate aryl lead triacetates.[122] Although some material did crystallise during the course of the reaction, indicating successful transmetallation, it decomposed upon attempts to isolate and characterise it. Encouraged by this result, each combination of the Pinhey chemistry was attempted *in situ*. Unfortunately despite an exhaustive analysis of each of the possible combinations of starting materials, no Pinhey reaction product could be isolated (Scheme 3.27).



Scheme 3.27

Although both moderately electron poor substrates[123] and ortho substituted aromatic systems[133] have been used in the Pinhey arylation it is possible that the combination of both may inhibit either, substitution of the phenol **(184)** or dione **(167)** at the lead centre, or the ensuing reductive elimination through steric crowding. The reaction is likely further complicated by the complex nature of the nitrile dione **(167)** which might not be reacting through the desired enol form; recall Figure 3.4.

It was therefore required to re-evaluate the overall synthetic strategy. One of the common ways of overcoming problems encountered with *O*-alkylation of enolate systems is to employ an appropriate 3,3-sigmatropic rearrangement.[115] This approach has been used successfully in the same nitrodione system by Bonjoch *et al*. *via* an allylation;[117] therefore a more original approach was sought. Due to ongoing problems with the ortho nitro group it was alternatively decided to attempt an interrupted Fischer indole synthesis to establish the quaternary carbon centre. Traditionally the Fischer indole synthesis occurs *via* 3,3-sigmatropic rearrangement of a tautomerised phenylhydrazone **(192)**, subsequent ring closure and elimination of ammonia then results in the formation of an indole **(193)**.[134] In the interrupted version of the same reaction, the enamine position of the phenylhydrazone **(192)** is disubstituted so that the sigmatropic rearrangement results in the formation of a quaternary centre preventing aromatisation to the indole[135] (Figure 3.7).

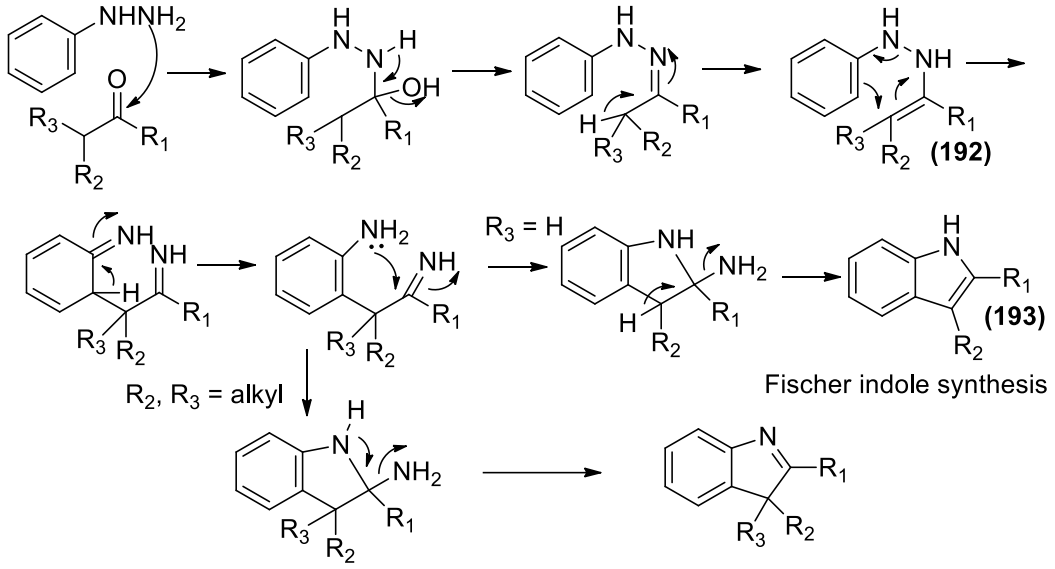
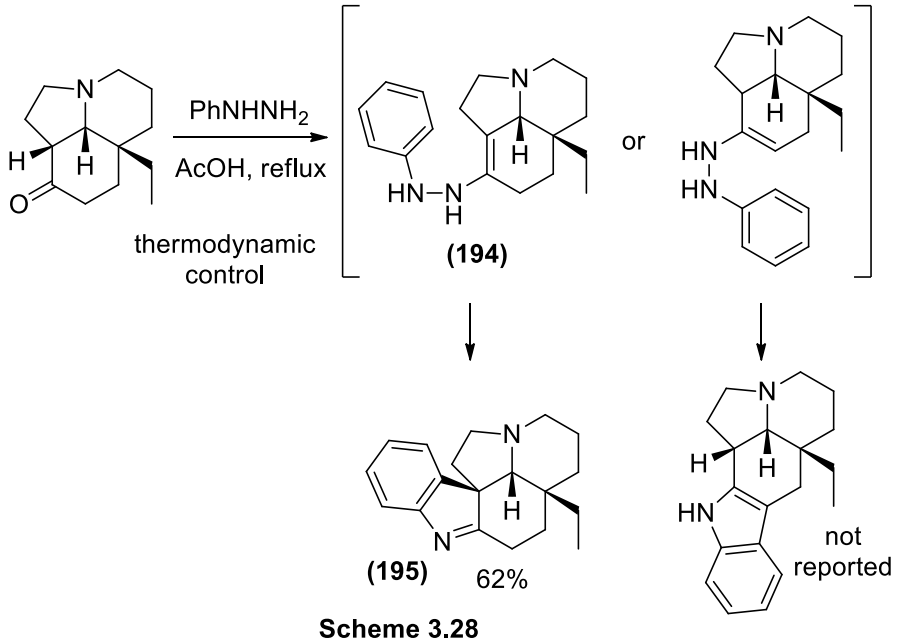


Figure 3.7: Interrupted Fischer indole synthesis

The challenge then becomes in selectively forming the desired enamine, as illustrated below in a synthesis of aspidospermidine **(132)** by Zard *et al*.[136] In this case regioselectivity was achieved *via* the formation of the more stable substituted enamine **(194)** under thermodynamic conditions with only the desired product **(195)** reported in 62% yield (Scheme 3.28).



Scheme 3.28

More generally, the selectivity of this process is known to be quite low and highly substrate dependent.[135] Often this has been overcome by controlling the substrate in way that only one single enamine form is possible such as with aldehydes[137] or those with bridgehead carbons in the alpha position.[138] As a more versatile approach

to constructing the desired alpha aryl quaternary centre, it was suggested that the regioselectivity of the enamine formation could be controlled through electronic effects using a 1,3-dione. In this case any formed hydrazone should easily tautomerise to the stabilised vinylogous amide which could then undergo the interrupted Fischer cyclisation. This is supported by the literature in that the Fischer indole synthesis with 1,3-cyclohexanedione **(96)** is known and regioselectively cyclises onto the 2 position[139] to give the indole **(196)** (Figure 3.8).

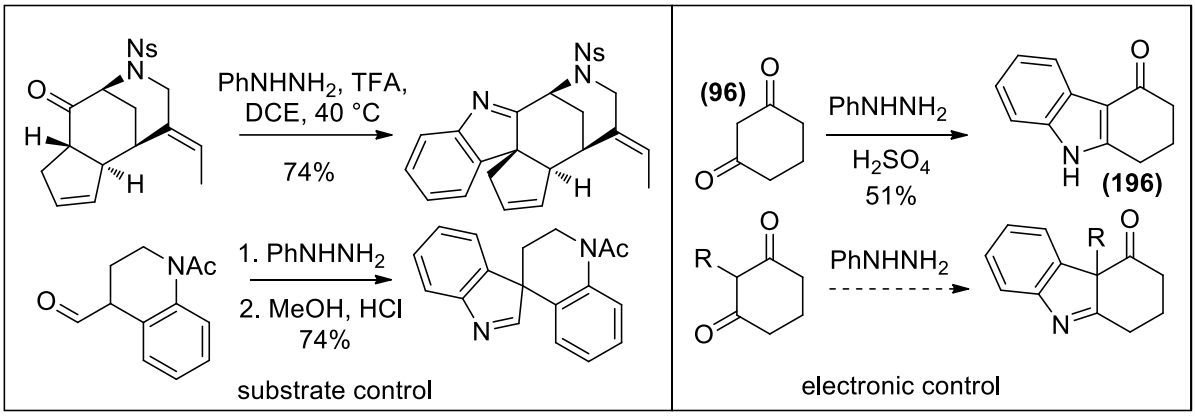
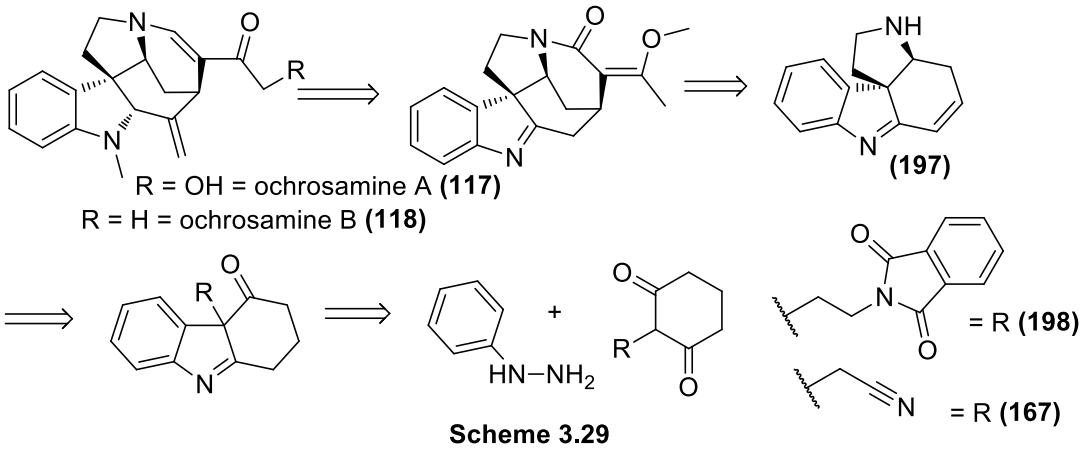


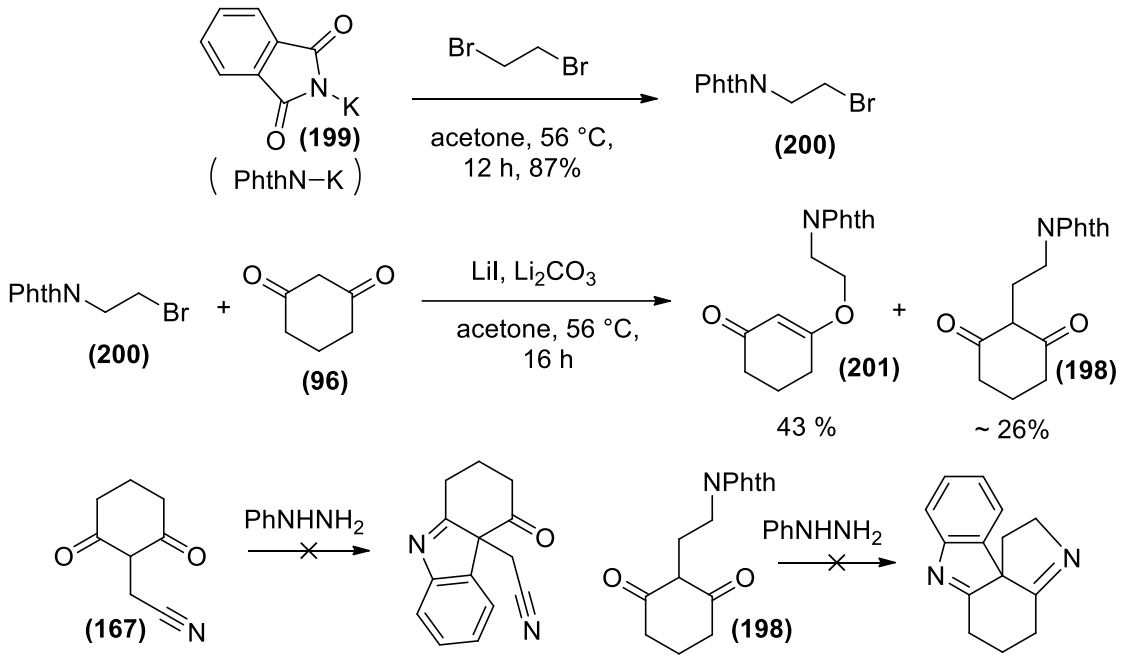
Figure 3.8: Controlling regioselectivity in the interrupted Fischer indole synthesis

This strategy removes the effectively removes the troublesome nitro group and establishes the B-ring at a much earlier stage of the synthesis, however the remaining diketene chemistry should still be feasible. Disconnection in this case follows a similar pattern to that proposed earlier, now *via* the imine **(197)**. In applying this particular strategy to the system at hand requires an appropriately substituted 1,3-dione to create the intermediate vinylogous amide. The ideal substitution at the 2 position was a relatively inert two carbon fragment containing nitrogen. In addition to the previously synthesised nitriledione **(167)**, a phthalyl protected ethylamine **(198)** was suggested.[140] The idea being that treatment with phenylhydrazine would cause both the desired 3,3-sigmatropic rearrangement and simultaneously deprotect the nitrogen moiety (Scheme 3.29).



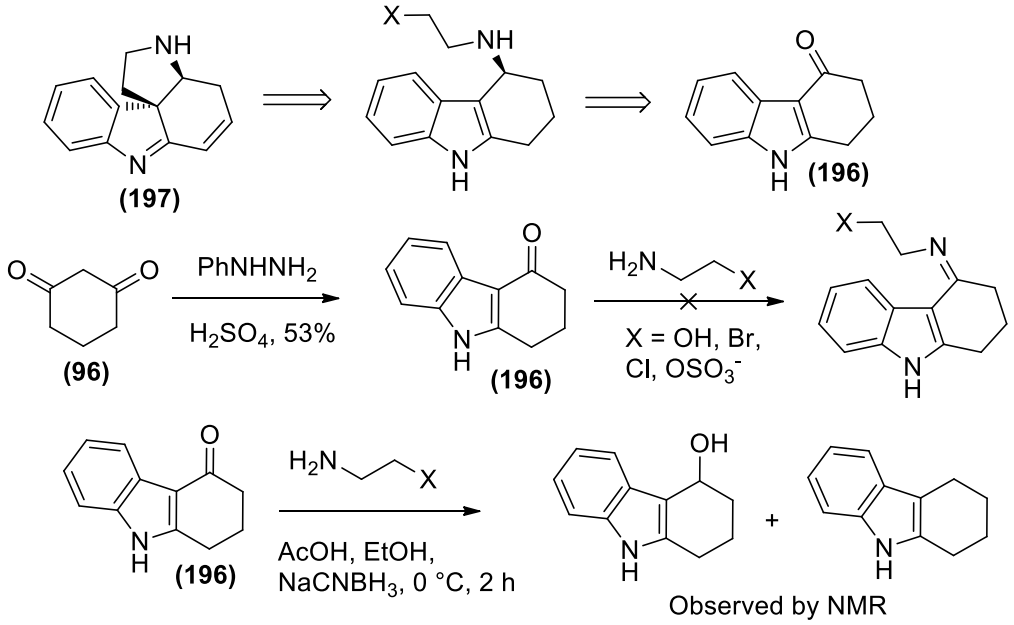
Scheme 3.29

Potassium phthalimide **(199)** was therefore alkylated with 1,2-dibromoethane under literature conditions[141] to yield the required two carbon electrophilic fragment **(200)**. Alkylation of 1,3-cyclohexanedione **(96)** once again proved troublesome, with significant *O*-alkylated product **(201)** isolated and an inability to cleanly isolate the desired tautomeric mixture corresponding to dione **(198)** which as a result, remains poorly characterised (see experimental). Incorporation of the phthalyl ethyl amine was clearly evident in the ^{1}H NMR by the presence of two distinct apparent doublets at 7.79 ppm and 7.68 ppm corresponding to the aromatic ring in addition to the aliphatic signals. However between the mixture of tautomers and impurities from self-condensation of the starting material, the ^{13}C NMR could not be adequately resolved from the multitude of signals. Unfortunately exposure of this material to various conditions[135] featuring phenylhydrazine resulted only in complex or intractable mixtures, with only limited NMR evidence of the 3,3-sigmatropic reaction having taken place from minor signals corresponding to desymmetrisation of the aliphatic ring protons and a lack of clear signals corresponding to the cyclised aromatic ring. Similarly treatment of nitriledione **(167)** with phenylhydrazine resulted only in decomposition (Scheme 3.30).



Scheme 3.30

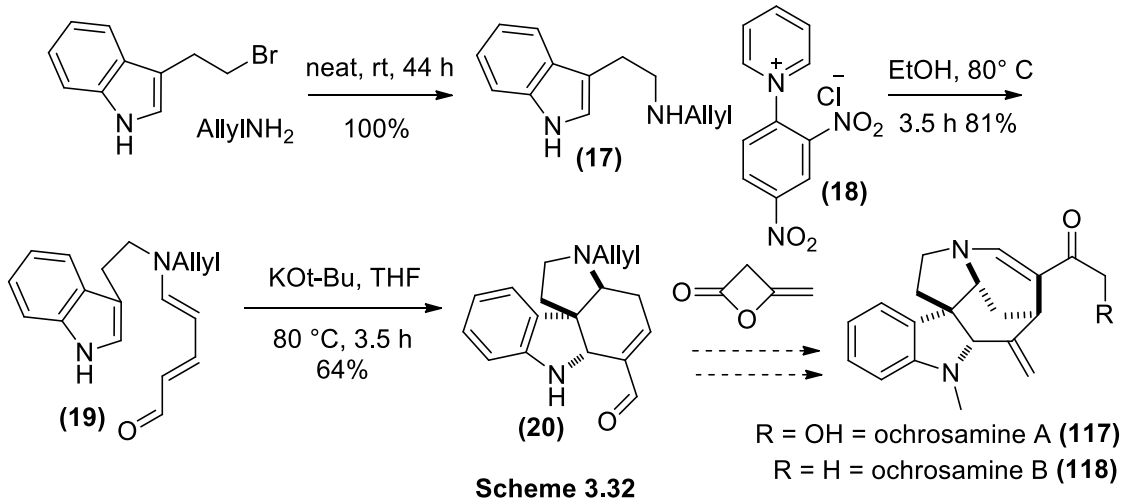
Further revision suggested elaboration of a preformed ABE indole core **(196)** which could be further elaborated to tie in to the existing plan for synthesis. From the oxo indole **(196)** reductive amination would install the required nitrogen allowing for an internal alkylation onto the indole which has good literature precedence[96, 142]. Following the literature procedure for the Fischer indole synthesis, 1,3-cyclohexanedione **(96)** was converted into the corresponding known[139] indole **(196)**. Unfortunately all attempts at reductive amination or imine formation[143] with substituted aminoethyl systems failed. It is assumed that the indole nitrogen significantly deactivates the ketone, acting as a vinylogous amide and preventing imine condensation. This is further evidenced by the overreduction observed using hydridic reagents such sodium cyanoborohydride, a phenomena previously observed in the literature[144] (Scheme 3.31).



Scheme 3.31

3.6. Future Work

At this point the project was placed on hiatus to pursue more rewarding endeavours, as potential future work it may be worth utilising some of the existing synthetic methods to access advanced intermediates in order to attempt the proposed diketene chemistry. One such recently developed method by Vanderwal *et al.*[145] would allow very direct access to the required ABCE core **(20)** in just three steps (see Chapter 1 for overview). From such a system it would only require a few minor functional group interconversions to attempt the key diketene chemistry and thus further elaborate the system to form the natural product (Scheme 3.32).

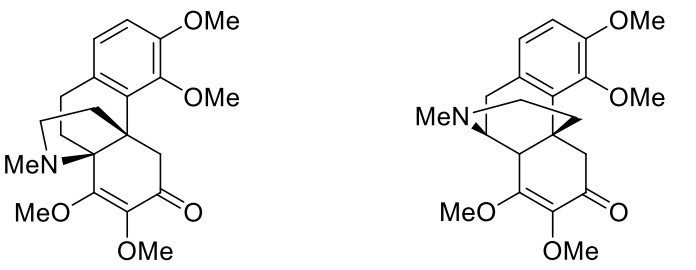


Scheme 3.32

Chapter 4 - Hasubanans

4.1 Introduction

The hasubanan class of alkaloids; named after the originally isolated hasubanonine, are a complex class of alkaloids that have been thoroughly investigated with respect to their biological significance.[146] When the first alkaloid of the family was isolated in 1951 by Kondo *et al*. it was originally misidentified as being part of the well-known morphinan class **(202)** due to limited spectroscopic data. Further analysis[147] established that hasubanonine **(203)** was a novel linkage isomer of the morphinan system with antipodal stereochemistry,[148] comprising an independent class of alkaloids found to be widespread amongst the genus *Stephania* (Figure 4.1).



(-)-hasubanonine **(203)**

(-)-hasubanonine originally reported **(202)**

Figure 4.1: Structural revision of hasubanonine

Over the course of the following 60 years the hasubanan class of alkaloids has become well populated with more than 40 different alkaloids all bearing the characteristic benzo fused aza[4.4.3]propellane core in the depicted absolute configuration **(204)**. This is complemented by a wide range of differing oxygenation patterns and formation of accessory rings, resulting in a high degree of both diversity and complexity within the class of alkaloids[149] (Figure 4.2). Many of the plants in the *Stephania* genus have been used in traditional folk medicine for centuries. The flowers, berries, leaves or roots have been used to treat a broad range of ailments from diarrhoea to asthma and even leprosy.[150] In traditional Chinese medicine alone, analgesic properties have been attributed to more than 25 different species in the *Stephania* genus.[151] This is of particular interest given the salient similarities

between the hasubanan framework and that found in morphine, a common opiate pain-killer.[28]

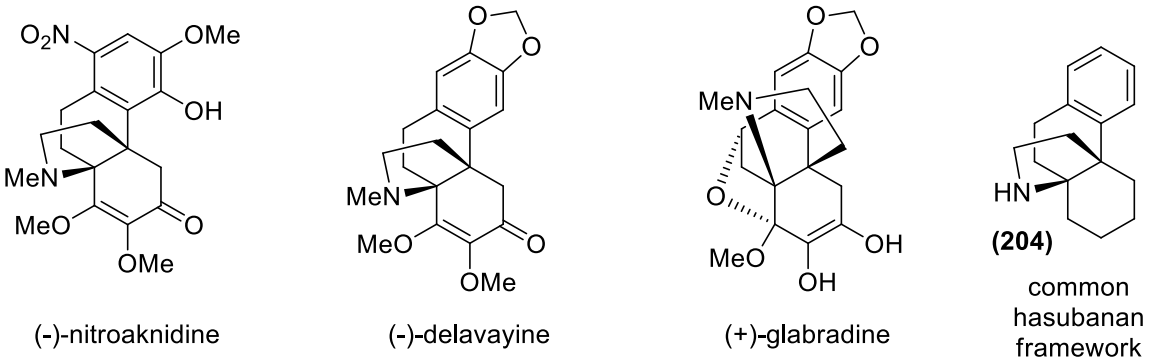


Figure 4.2: Structural diversity in the hasubanan class of alkaloids

Although hasubanan alkaloids have been tested for activity upon various opioid receptors,[152] they have relatively modest activity.[153] The relative orientation of the heterocycle is thought to a significant factor in determining biological activity which led to a hypothesis by Schultz and Wang[154] that the unnatural enantiomers of the hasubanan alkaloid framework may possess powerful opiate like activity. This is further supported by the distinct structural similarities between the unnatural enantiomer of the hasubanan framework **(205)** and that of the naturally occurring morphinans **(206)**. As can be seen in Figure 4.3 the two systems each bear a core tetracyclic ring system bearing a characteristic T-shape that directs the amine functionality perpendicular to the generalised plane of the ABC ring system shared by both systems.

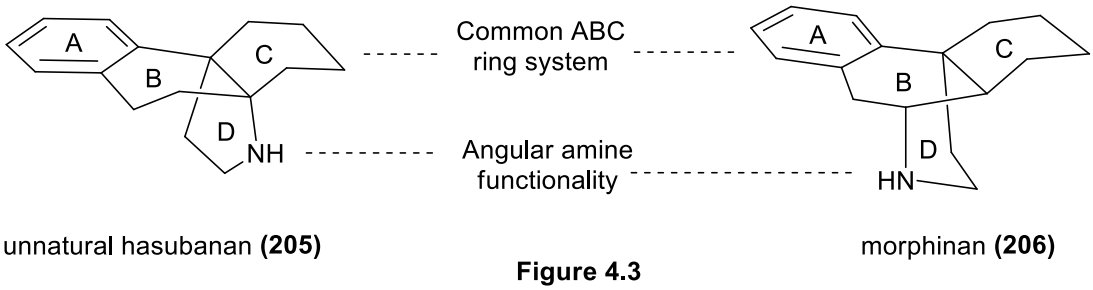
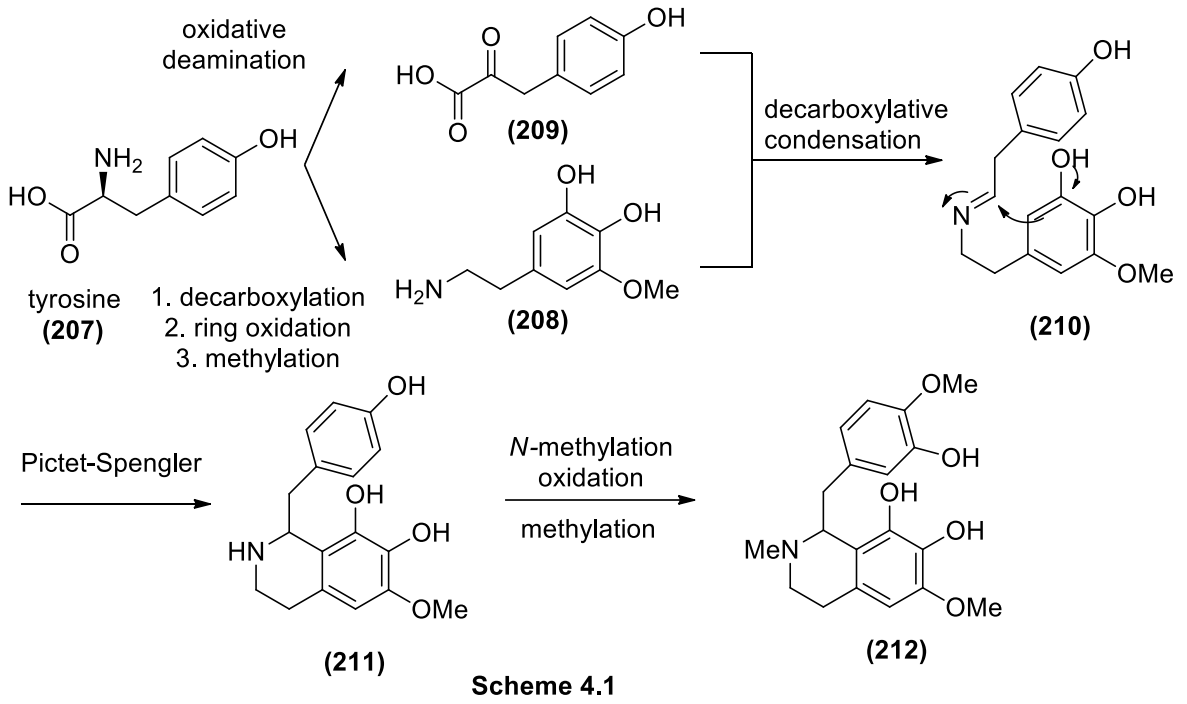


Figure 4.3

4.2 Biogenesis.

Although the complete biogenesis of the hasubanan alkaloids has yet to be fully elucidated, the best known member is hasubanonine **(203)** itself which can be seen

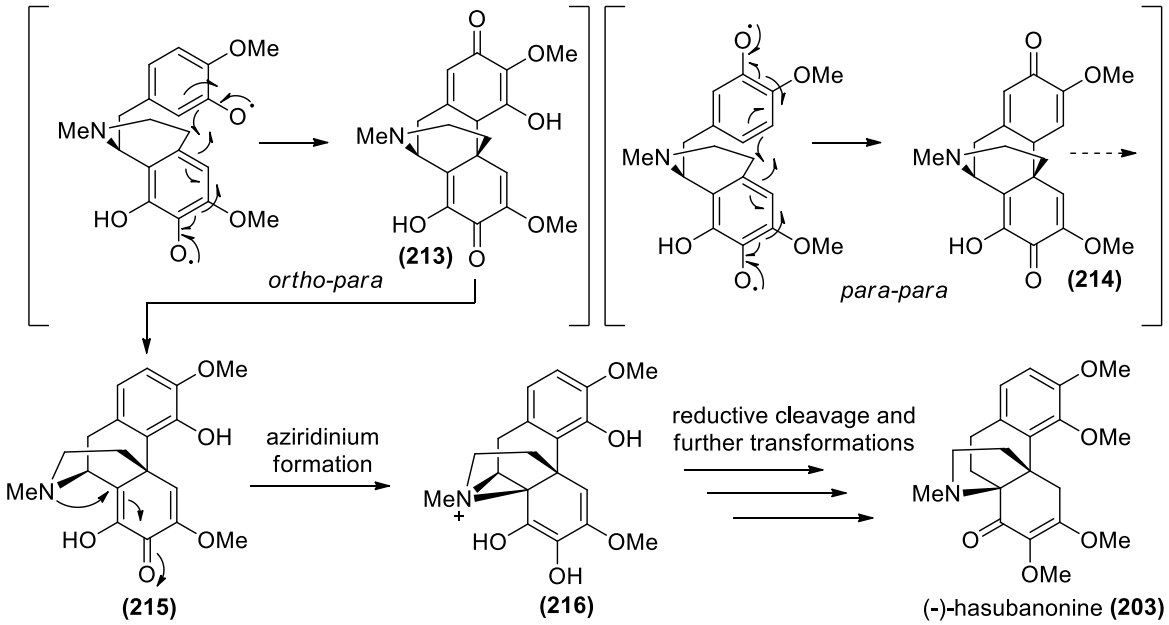
as representative of the class.[155] The core structures of hasubanan alkaloids are thought to be ultimately derived from two molecules of the amino acid, tyrosine **(207)** that diverge early in the biosynthesis.[156] One molecule of tyrosine undergoes enzymatic decarboxylation to yield the intermediate tyramine which undergoes further oxidation and methylation to the identified intermediate **(208)** which was confirmed by isotopic feeding studies.[157] The other molecule of tyrosine is oxidatively deaminated to give 4-hydroxyphenylpyruvate **(209)**. Decarboxylative condensation results in the imine **(210)** followed by the enzymatic equivalent of an intramolecular Pictet-Spengler reaction.[158] This generates a key benzylisoquinoline **(211)** which is further oxidised and methylated to yield a bis-phenol **(212)** (Scheme 4.1).



Scheme 4.1

This benzylisoquinoline system is then well set up to undergo oxidative coupling to form the enantiomorphic morphinan alkaloid system. Structural differences between ortho-para **(213)** and para-para **(214)** coupling products most likely generates some of the diversity found in the ring oxygenation patterns.[147] The intermediacy of the morphinan **(215)** has been conclusively proved by isotopic feeding studies,[157] although the mechanism of the rearrangement of the morphinan system to that of the hasubanans has yet to be conclusively established. It has been proposed that the enone in the now dearomatised C ring acts as an electrophile for the nucleophilic tertiary amine.[157] The resulting aziridinium intermediate[159] **(216)** would then eliminate

or be reduced enzymatically,[160] followed by further functional group transformation to yield hasubanonine **(203)**. Changes in the oxidation and methylation states at various points in the biosynthesis in turn generate the observed diversity in oxygenation patterns found throughout the hasubanan class of alkaloids[156] (Scheme 4.2).



Scheme 4.2

4.3 Applicable syntheses

Interest in this particular class of alkaloids was piqued in part due to the prior research and successful synthesis of the structurally similar natural product, hamayne.[161] The three A, C and D rings of the tetracyclic core system in hamayne are found in the hasubanans with the structural difference coming from the connectivity of the B ring. Hamayne attaches *via* a single methylene between the aromatic ring and the nitrogen atom, whereas the hasubanans attach *via* an ethyl linkage between the aromatic ring and one of the carbons alpha to the nitrogen atom. As the hamayne synthesis introduces the B ring at a late stage[161] it was envisioned that a similar approach could be taken that would intersect with much of the chemistry used in the hamayne project (Figure 4.4).

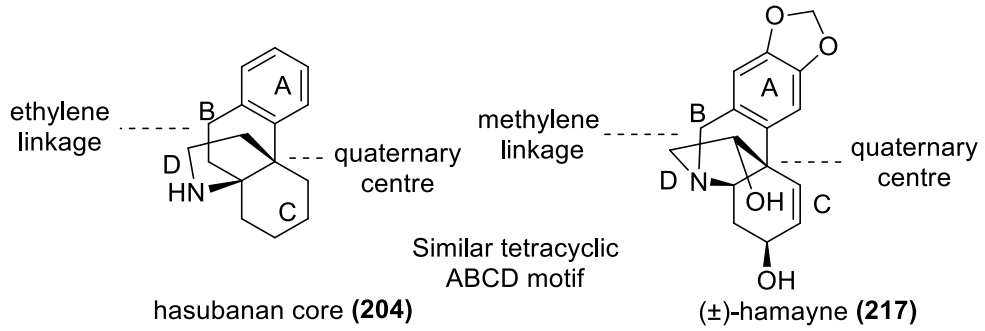
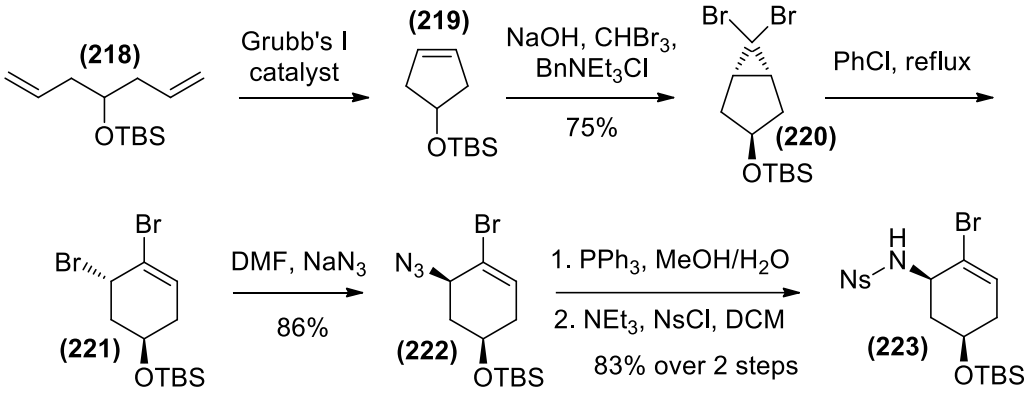


Figure 4.4

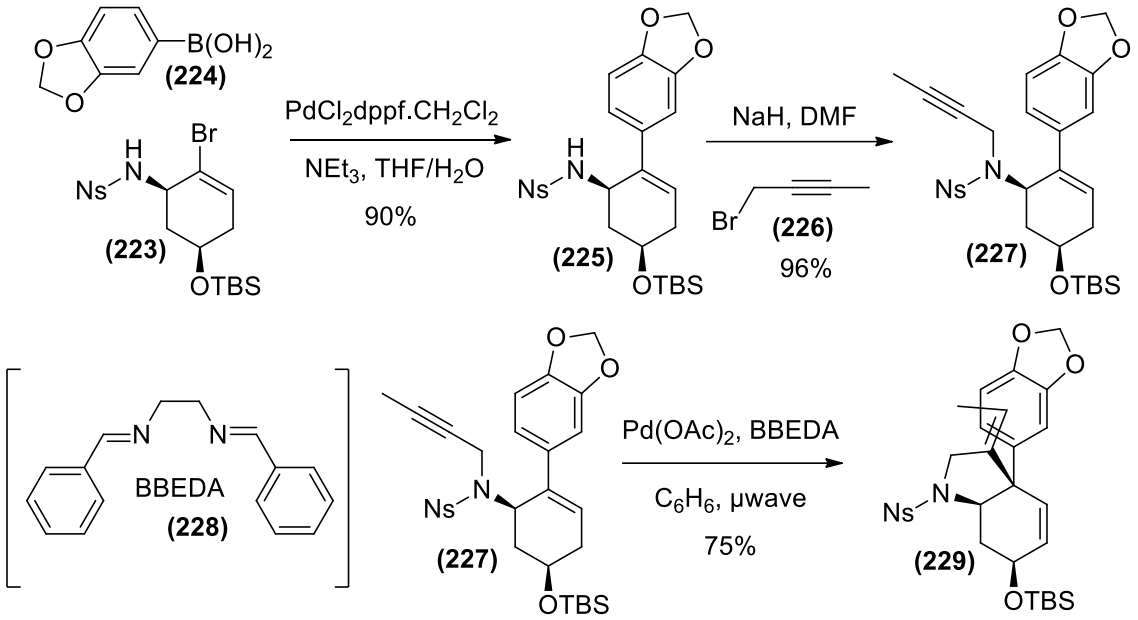
The synthesis of hamayne begins from the known[162] TBS protected alcohol **(218)** which is subjected to a ring closing metathesis to generate the cyclopentene derivative **(219)**. Subjection of this system to bromoform and base in the presence of a phase transfer catalyst results in the isolation of the dibromocyclopropane **(220)** resulting from addition of dibromocarbene. Thermally induced electrocyclic ring opening and direct functionalization of the resulting dibromide **(221)** with sodium azide affords the highly functionalised cyclohexane ring **(222)**. Staudinger reduction of the azide followed by protection with nosyl chloride affords the corresponding derivative **(223)**.[161] This strategy rapidly introduces the amine found in the natural product replete with a bromo alkene that allows easy access to cross coupling chemistry (Scheme 4.3).



Scheme 4.3

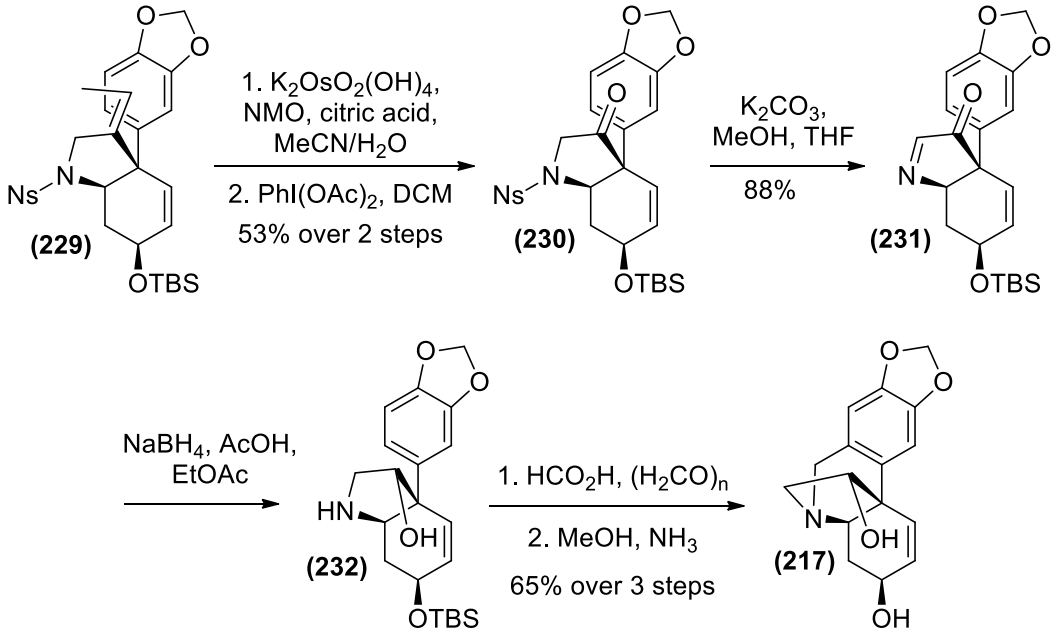
As such the compound **(223)** was subjected to Suzuki conditions with boronic acid **(224)** smoothly resulting in the cross coupled product **(225)**. The protected amine was then alkylated with 1-bromo-2-butyne **(226)** to give an appropriate substrate **(227)** for a palladium catalysed Alder-ene reaction. Indeed, exposure of this compound to $Pd(OAc)_2$ and the BBEDA ligand **(228)** under microwave irradiation[163]

yielded the desired product **(229)**,[161] forming the key quaternary carbon centre (Scheme 4.4).



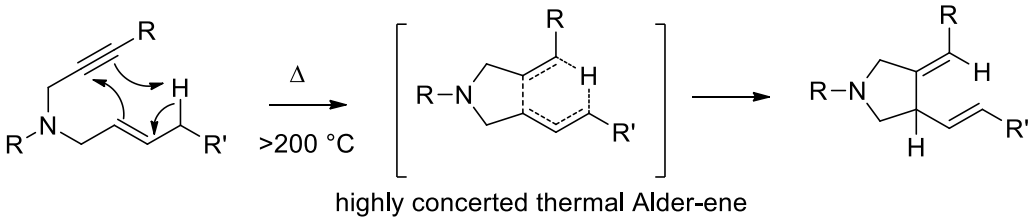
Scheme 4.4

Chemoselective oxidative cleavage of the more substituted alkene was achieved *via* an Upjohn dihydroxylation followed by a phenyliodonium diacetate mediated cleavage of the resulting diol to give ketone **(230)**. The protecting nosyl group was removed *via* E_1cB elimination to give the ketoimine **(231)** which was reduced with sodium triacetoxyborohydride to give the free amine **(232)** with the C11 alcohol in the desired configuration. Under the Pictet-Spengler conditions using paraformaldehyde and formic acid, the final desired ring was formed and this was accompanied by deprotection of the TBS group, resulting in the formate diester which was then deprotected with methanolic ammonia to afford the racemic natural product (±)-hamayne **(217)**.[161]



Scheme 4.5

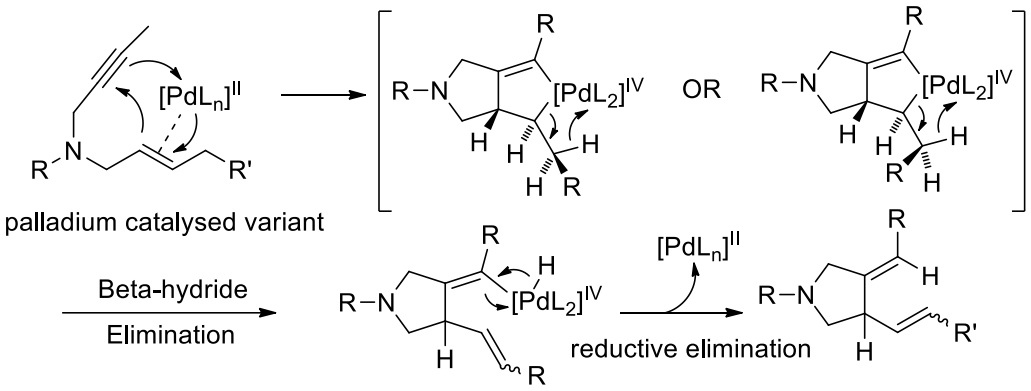
Essentially the most important step in the synthetic sequence as it applies to the hasubanan skeleton is the Pd mediated Alder-ene reaction[164] as it is used to form the pivotal quaternary carbon centre. The Pd mediated Alder-ene reaction actually proceeds through a significantly different mechanism than that of its non-catalysed namesake and renders them truly distinct at a mechanistic level.[165] The original Alder-ene reaction[166] is pericyclic; proceeding *via* a concerted 6-membered transition state in what is essentially a sigmatropic shift involving the carbon hydrogen bond of the ene. This often requires harsh conditions in the absence of strongly activating steric or electronic effects.[167] The concerted process conserves stereochemical information and can be highly selective.[168]



Scheme 4.6

Comparatively the Pd catalysed version originally developed by Trost proceeds at much lower temperatures.[164] The Pd catalyst coordinates to both the alkene and alkyne, thereby facilitating the formation of an intermediary palladacycle in an oxidative process. This palladacycle then undergoes beta hydride elimination to give

the alkenyl palladium hydride species which undergoes reductive elimination to yield the product.[165] The key difference is that the beta hydride elimination is not concerted and occurs in a *syn*-fashion with the most readily available hydrogen. This can ultimately lead to mixtures of alkene diastereomers (Scheme 4.7). In the hamayne synthesis, the use of a cyclic alkene substrate and the small ring tether conserves stereochemistry and prevents the formation of side products as the intermediate palladacycle can only eliminate in one direction.[161]

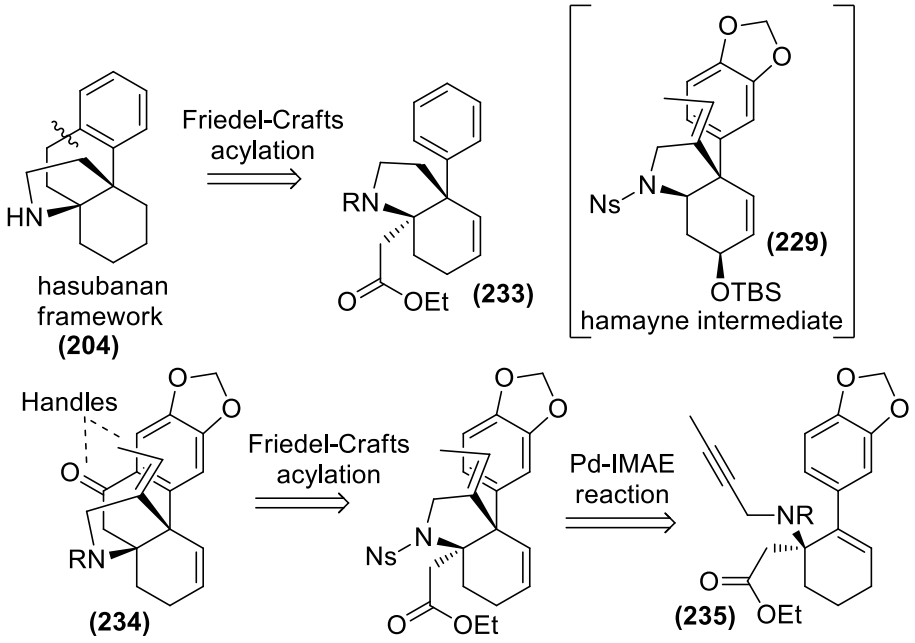


Scheme 4.7

4.4 Retrosynthesis

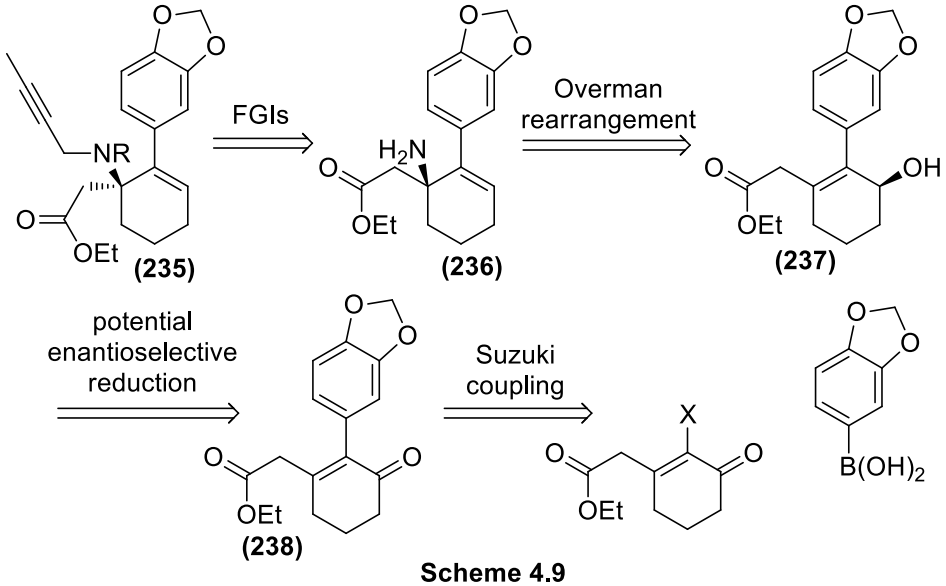
As such an analogous retrosynthetic analysis of the hasubanan skeleton featuring the Pd-mediated Alder-ene reaction as a key step was devised for a project originally researched by Jeremy Nugent in the pursuit of his honours dissertation.[169]

The hasubanan framework **(204)** was first disconnected *via* a late stage Friedel Crafts acylation to the corresponding arylindoline system **(233)** which would be favoured by the relatively electron rich aromatic ring systems common in the hasubanans.[170] This arylindoline bears striking resemblance to intermediate **(229)** in the hamayne synthesis. It was hoped that this intermediate could then be reached by the key Pd catalysed Alder-ene chemistry that had been so successful in synthesising the key features of the hamayne skeleton.[161] It was envisioned that the accessory functionality in **(234)** resulting from these disconnections could then be either removed in a fashion similar to the hamayne synthesis or used as handle to introduce further diversity in exploring the hasubanan system (Scheme 4.8).



Scheme 4.8

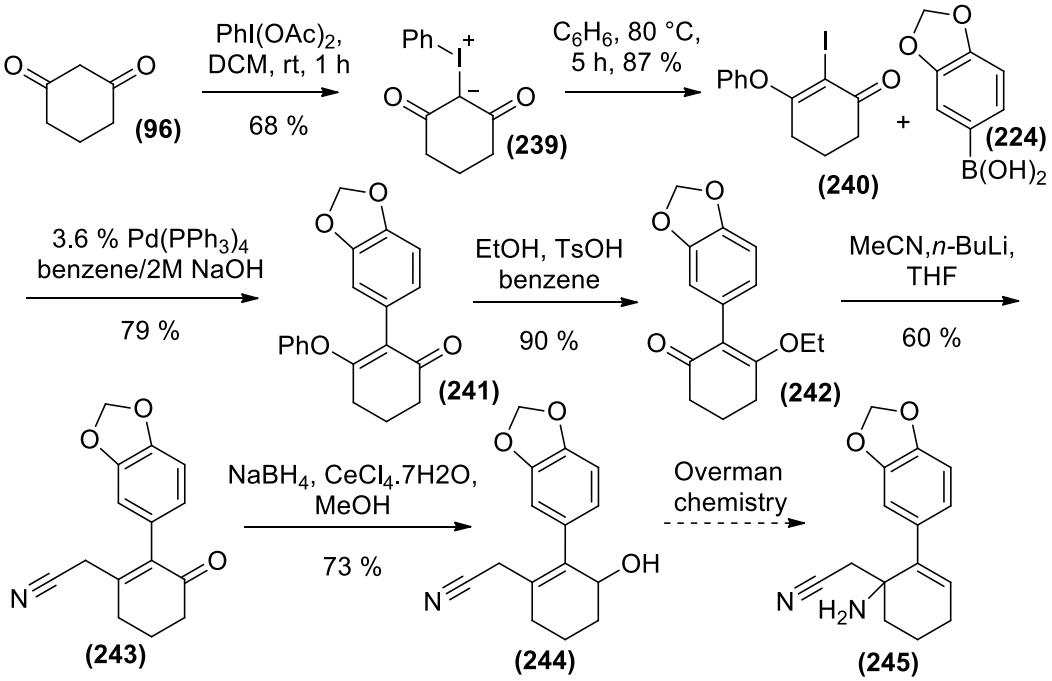
The required propargylic amine **(235)** could then be accessed by alkylation and protection of the alpha aryl amine **(236)** which would be available through an Overman rearrangement[171] of the trichloroacetimidate derived from the corresponding allylic alcohol **(237)**. Disconnection of the aryl carbon-carbon bond through Suzuki cross coupling chemistry similar to that used in the hamayne synthesis thus reveals simple starting materials. Enantioselective reduction of the enone **(238)** would then allow selective access to the unnatural enantiomeric series of the hasubanan system; thereby allowing the investigation of its biological potential[154] (Scheme 4.9).



Scheme 4.9

4.5 Prior Work

As a generalised summary, the following progress had been achieved by J. Nugent in his honours year.[169] Following literature precedent the Iodonium ylid **(239)** of cyclohexanedione **(96)** was subjected to thermal rearrangement to generate the iodo substituted phenoxyenone **(240)**. This underwent Suzuki cross coupling with the methylenedioxy substituted aryl boronic acid **(224)** to generate the key aryl linkage **(241)**. Transesterification of the phenoxy group to the ethoxy group **(242)** allowed nucleophilic addition of the anion of acetonitrile to generate the desired enone **(243)**. The enone was then reduced under Luche[172] conditions to give the allylic alcohol **(244)**, which could be used as a substrate for trichloroacetimidate formation and subsequent Overman rearrangement to give the desired amine **(245)** (Scheme 4.10). Initial experiments regarding the rearrangement chemistry had indicated that it might not be a suitable substrate for trichloroacetimidate formation.[169]

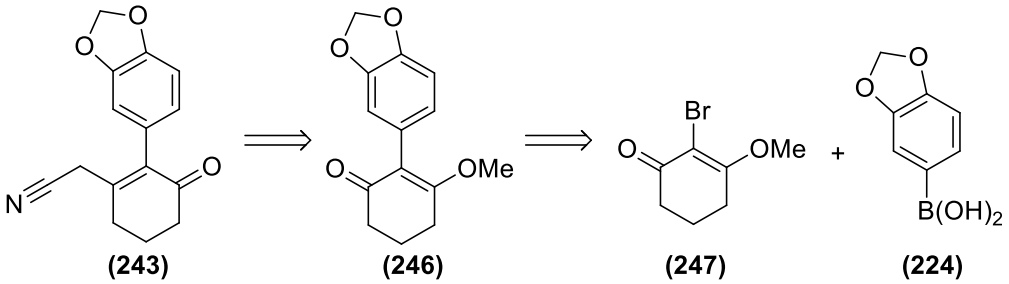


Scheme 4.10

4.6 Results and Discussion

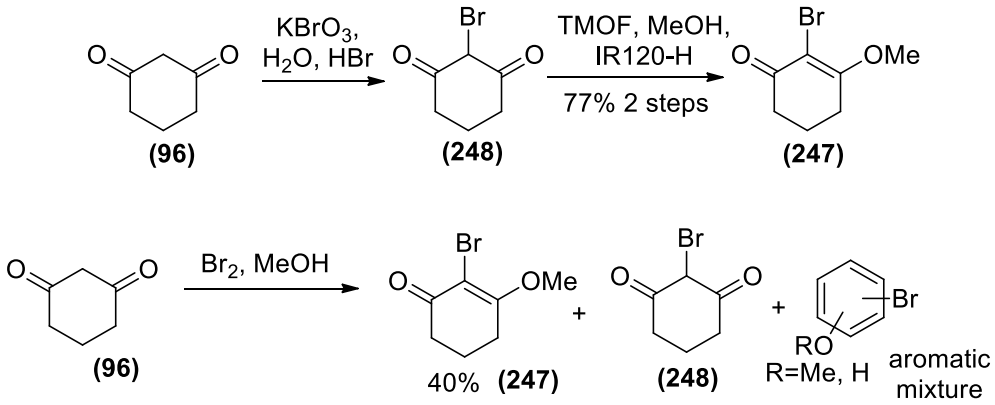
As such the initial objectives were to replicate or improve on the existing synthetic scheme and further investigate the trichloroacetimidate formation and subsequent Overman chemistry. In an initial attempt to reduce the step count and address some minor supply issues, it was decided to disconnect the nitrile **(243)** *via* the Suzuki

coupling product **(246)** to the corresponding known bromomethoxyenone[173] **(247)**. This obviates the need for transesterification of the vinylogous ester at the cost of using the somewhat less activated bromo functionality. Some encouragement was provided by literature precedence that the bromomethoxyenone **(246)** was a competent coupling partner in the Suzuki-Miyaura reaction[174] (Scheme 4.11).

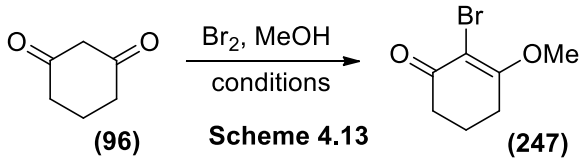


Scheme 4.11

Following the literature protocol, initial bromination of cyclohexanedione **(96)** under comproportionating conditions affords the bromo dione **(248)** in good yield. Subsequent esterification with trimethylorthoformate in MeOH with a solid supported acid catalyst then affords the desired bromomethoxyenone[173] **(247)**. As a further effort to streamline the synthesis, research was conducted into the possibility of telescoping the two reactions. Gratifyingly when 1,3-dione **(96)** was dissolved in methanol and treated with a single equivalent of bromine at 0 °C in the absence of light, the desired methoxyenone **(247)** could be isolated in 40% yield. Presumably initial electrophilic bromination of the dione moiety generates hydrobromic acid which acts as the required acid catalyst for the formation of the methoxyenone (Scheme 4.12).



Scheme 4.12



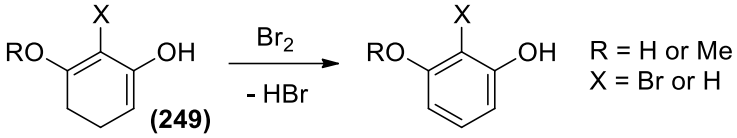
(96) **Scheme 4.13** (247)

Table 4.1: Optimisation of tandem bromination, esterification reaction.

Entry	Light	Additive	T in °C	Comment	Yield
1	no	none	0	incomplete esterification, aromatisation	40 %
2	yes	none	0	decomposition, multiple products	~5 %
3	no	none	25	complete aromatisation	0 %
4	no	none	- 10	less aromatisation	45 %
5	no	none	- 40	low aromatisation, poor esterification	52 %
6	no	none	- 78	reaction sluggish, poor esterification	23 %
7	no	TMOF	- 40	higher aromatisation observed	63 %
8	no	pyridine	- 40	poor esterification, no aromatisation	55 %
9	**no**	**TMOF + Pyridine**	**- 40**	**minimal dibromination also observed**	**87%**

Isolated yields reported, 1 eq. Br_2

Careful analysis of the reaction mixture revealed partial aromatisation to the corresponding resorcinolic systems and incomplete esterification of the bromo dione **(248)**. Efforts made in the optimisation of this reaction are summarised in Table 4.1 Strict exclusion of light was found to be necessary to isolate appreciable quantities of product. The observed aromatisation is a transformation that is known to occur upon treatment of the same system with iodine[71] and showed some temperature dependence, with – 40 °C identified as an optimum (entry 5). In the context of this reaction, this was thought to be in part due to the high acidity of HBr in methanol forming the easily aromatised bis-enolic tautomers **(249)** of the corresponding diones *in situ*[170] (Scheme 4.14).

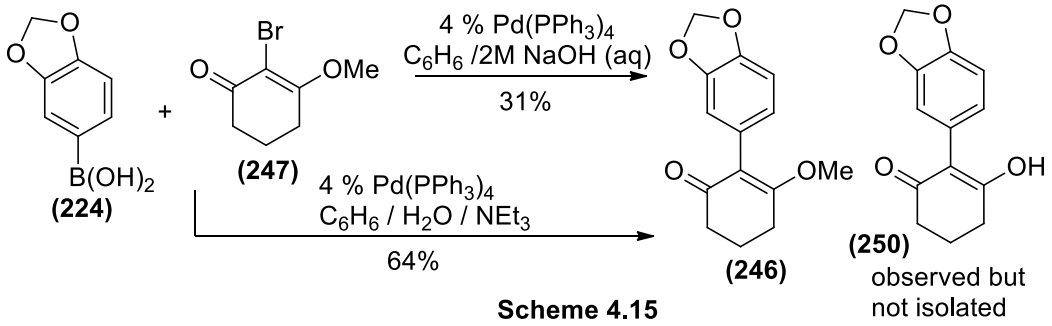


(249)

Scheme 4.14

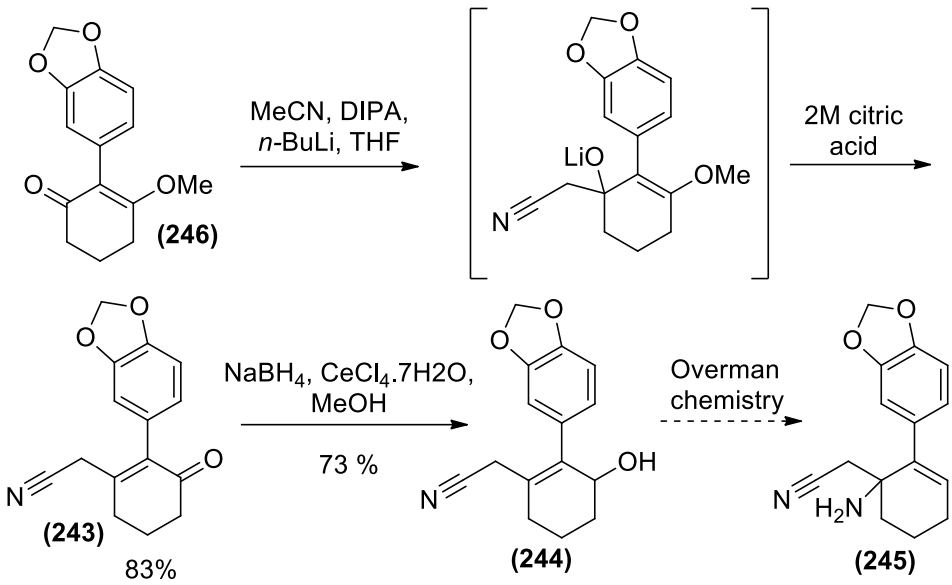
Inclusion of pyridine as a weak base to the reaction mixture attenuated the acidity and substantially reduced formation of aromatised byproducts by NMR; however the sluggish methoxyenolisation still limited yields. As the methoxyenolisation produces water as a side product, it was decided to exploit this under the reaction conditions. After addition of bromine, an equivalent of trimethylorthoformate (TMOF) was added; this helped drive the esterification to completion but seemed to promote aromatisation. By utilising both TMOF and pyridine a respectable yield of 87% was achieved (entry 9).

Exposure of the bromoethoxyenone **(247)** to the previously developed[169] Suzuki coupling conditions resulted in a disappointing yield of 31% for the cross coupled product **(246)**. Upon inspection it was revealed that there was competing hydrolysis of the vinylogous ester to form the enol **(250).** This can be attributed to the relative instability of the methoxy group to the quite basic conditions employed. By changing from potassium carbonate to the organic base, triethylamine, the yield improved remarkably to a functional 64% isolated yield with minimal hydrolysis (Scheme 4.15).



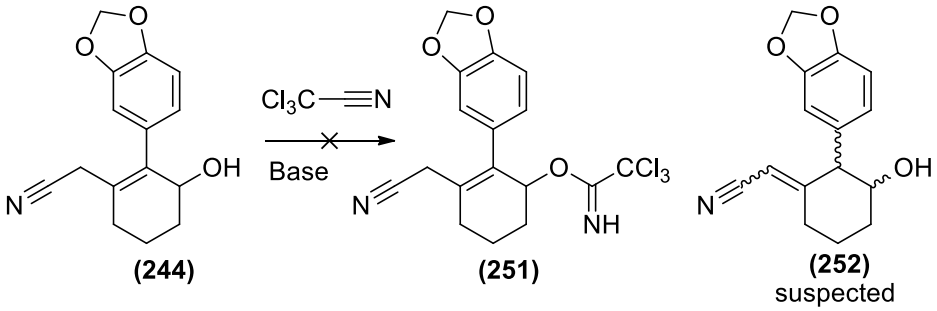
Scheme 4.15

Gratifyingly, subjection of cross coupled material **(246)** to modified conditions for acetonitrile addition, occurred smoothly and upon addition of aqueous hydrochloric acid cleanly afforded the desired nitrile adduct **(243)** in superior yield. Nucleophilic addition occurs at the ketone forming an alcohol enol ether intermediate, which upon exposure to mildly acidic conditions hydrolyses the enol ether and eliminates water to give the product. Luche reduction again proceeded smoothly in a manner consistent to that observed by Nugent.[169] With significant quantities of the required allylic alcohol **(244)** in hand attention was then turned toward fully investigating the acetimidate formation and subsequent Overman rearrangement[175] to give the requisite amine **(245)** (Scheme 4.16).



Scheme 4.16

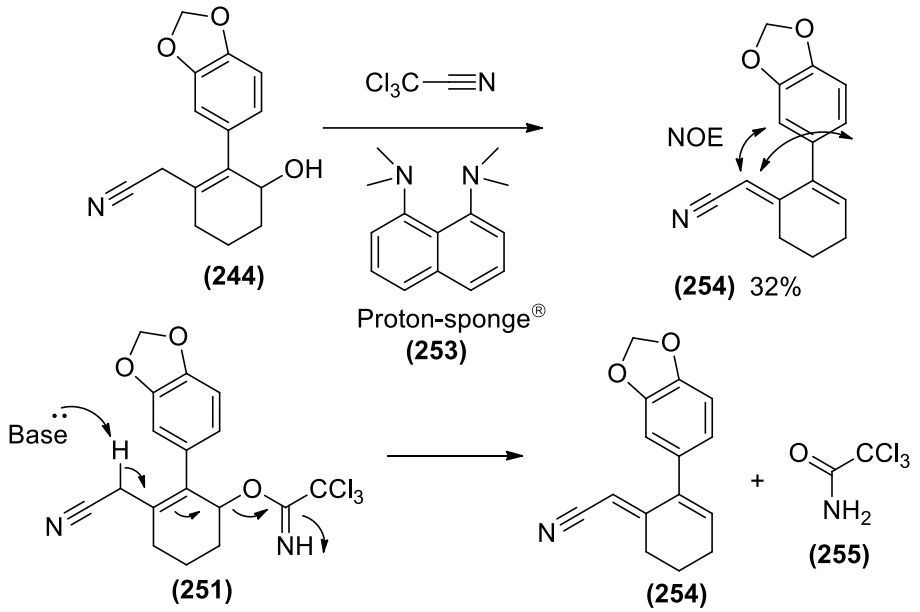
Trichloroacetimidates are invariably formed under basic conditions from trichloroacetonitrile.[51, 171, 175-176] As the basicity of the acetimidate anion is quite high, only catalytic base is generally required. Frustratingly, subjection of the allylic alcohol **(244)** and trichloroacetonitrile to the usual conditions prevalent in the literature (NaH, KH, DBU)[51] resulted only in recovery of starting material or a variety of complex and intractable mixtures without any isolation of the desired imidate product **(251)**. Although isolation and characterisation of side products proved futile, analysis of mixed chromatographic fractions by ^{1}H NMR revealed the presence of characteristic doublets at around 3.4 ppm corresponding to the benzylic position. This was interpreted as evidence that acidic protons alpha to the nitrile were being deprotonated and the double bond was shifting out of conjugation with the aromatic ring, thus resulting in a mixture of diastereomers **(252)** (Scheme 4.17).



Scheme 4.17

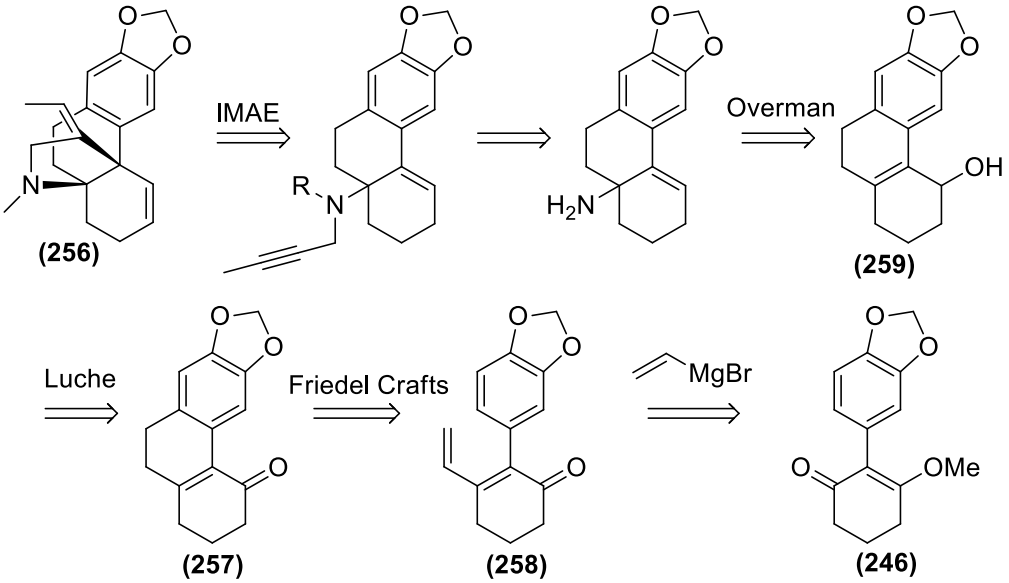
To address this issue, the strong hindered base, Proton-sponge® **(253)** was used which is known for its slow deprotonation.[177] It was theorised that this would favour

the kinetic deprotonation of the alcohol over the methylene. Intriguingly, treatment of the allylic alcohol **(244)** under these conditions led only to the isolation of the diene **(254)** which could be fully characterised. The *E*-stereochemistry of which was confirmed by NOE spectroscopy showing positive correlations between the nascent olefinic singlet and the aromatic system. It was postulated that the trichloroacetimidate **(251)** does form but the basic conditions facilitate vinylogous E_1cB elimination. The imidate activates the alcohol into becoming a good leaving, group driven by exothermic formation of trichloroacetamide **(255)** upon elimination[170] (Scheme 4.18).



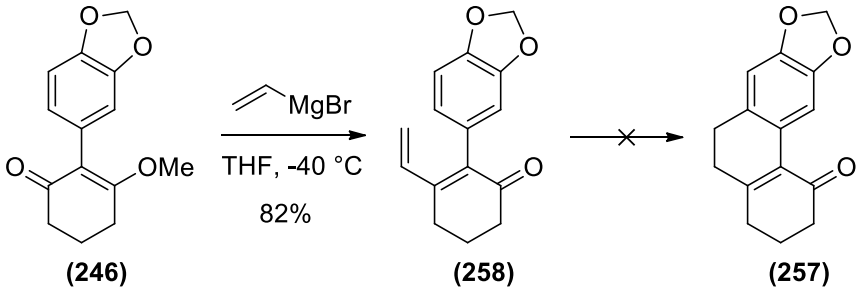
Scheme 4.18

As a way of circumnavigating this difficulty the order of steps for the synthetic strategy was altered. In this case the late stage Friedel Crafts reaction, planned to close the last ring of the synthesis, was instead brought forward. The hasubanan skeleton **(256)** was disconnected *via* the Alder-ene and Overman chemistry to the tricyclic structure **(257)**. Following literature precedence[178] this could be prepared *via* an intramolecular Friedel Crafts reaction from an appropriate diene **(258)**. After Luche reduction to form the allylic alcohol **(259)**, it was envisioned that this would be an appropriate substrate for the Overman chemistry, abrogating the possibility of E_1cB elimination. The necessary material could then be easily accessed from the previously synthesised vinylogous ester **(246)** (Scheme 4.19).



Scheme 4.19

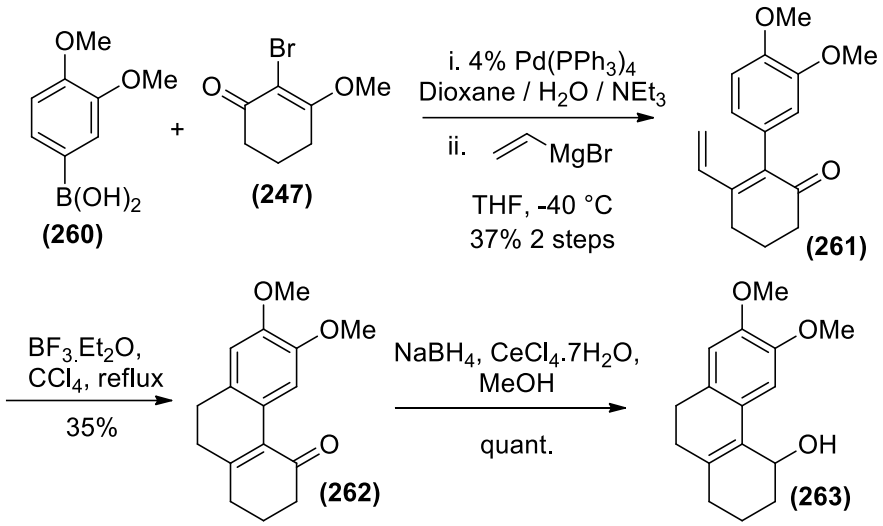
Indeed, upon subjection of the vinylogous ester **(246)** to vinylmagnesium bromide in a manner similar to the previous acetonitrile addition; the corresponding vinyl enone **(258)** was obtained in good yield. Unfortunately when subjected to the literature conditions for cyclisation and after screening a number of other Lewis acids, no product was observed. Upon close inspection it became obvious that the methylenedioxy group was incompatible with the harsh Lewis acid conditions required for the Friedel Crafts chemistry.[51] As the methylenedioxy group itself is not of vital importance to the hasubanan alkaloids it was substituted for the corresponding similar, yet substantially more acid stable dimethoxybenzene derivative (Scheme 4.20).



Scheme 4.20

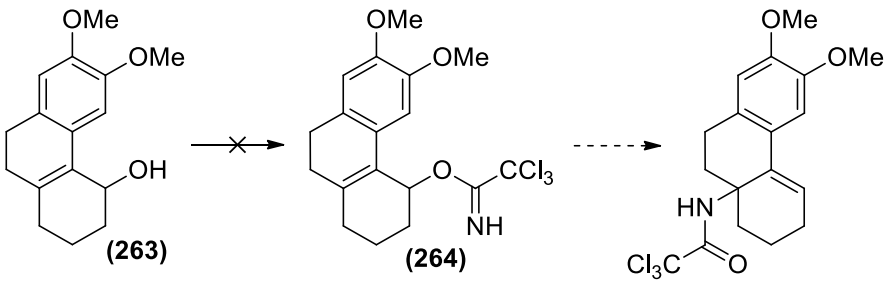
Interestingly, when the corresponding dimethoxyphenylboronic acid **(260)** was substituted in the existing synthetic scheme, the yield of the Suzuki reaction plummeted and significant problems were encountered with the solubility and polarity of the product; which could not be separated from other impurities. In this case the

Suzuki coupling reaction mixture was carried through crude and had to be separated after the addition of vinylmagnesium bromide, in a combined yield of only 37% across two steps for product **(261)**. Subjection of this material to the Friedel Crafts conditions resulted in the isolation of the desired tricyclic compound **(262)** in a modest 35% yield, not dissimilar to that reported in the literature.[178] Material was brought through the synthetic scheme nonetheless and Luche reduction resulted in quantitative isolation of the requisite allylic alcohol **(263)** suitable for trichloroacetimidate formation (Scheme 4.21).



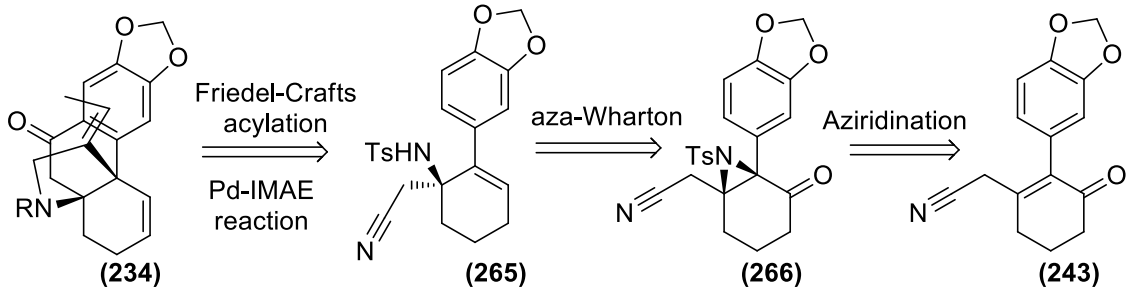
Scheme 4.21

Unfortunately, once again despite screening a wide range of conditions common in the literature,[51] the trichloroacetimidate **(264)** could not be isolated. It is thought that the steric environment directly surrounding the allylic alcohol is too crowded to allow for the formation of the bulky trichloroacetimidate functionality (Scheme 4.22). This was taken as clear evidence that the Overman rearrangement approach was not suitable for this system, requiring a rethink of the original synthetic strategy.



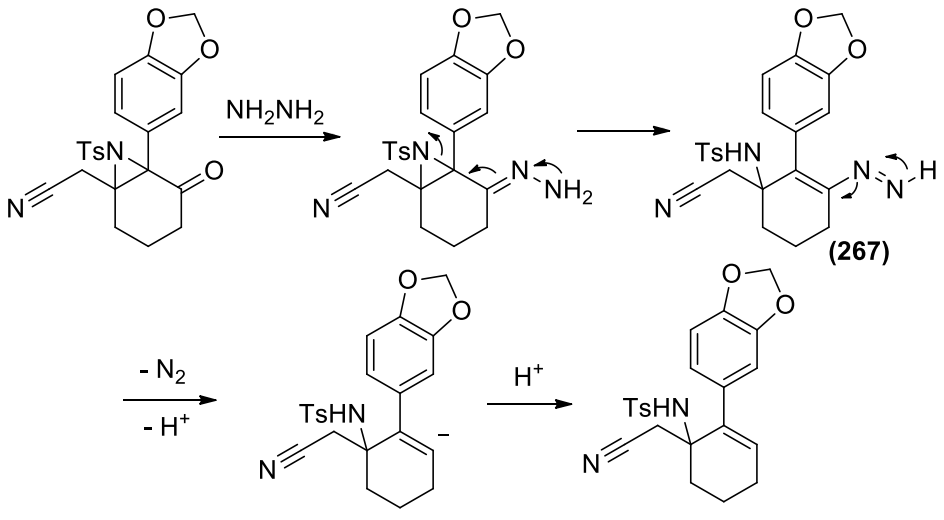
Scheme 4.22

Aiming to retain most of the existing synthesis to form **(234)**, it was proposed that the requisite amine **(265)** could be installed *via* a two-step process from the existing enone intermediate **(243)**. First by direct aziridination[179] of the cross coupled product **(243)** to form a highly substituted aziridine **(266)**, followed by an aza-Wharton rearrangement to generate the allylic amine **(265)** for which there is some literature precedence[180] (Scheme 4.23).



Scheme 4.23

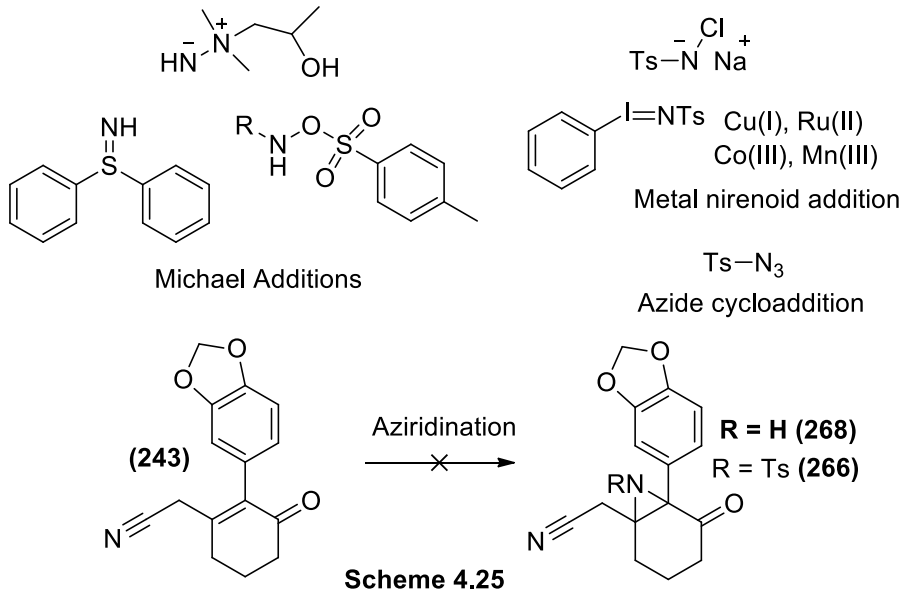
The aza-Wharton reaction proceeds *via* an initial hydrazone condensation which then pushes electrons into the system, opening the aziridine ring forming an unstable vinyl diazene **(267)** which fragments with release of dinitrogen to generate the product. The reaction itself is driven by the formation of the strong dinitrogen triple bond, the release of a gas and the relief of the aziridine ring strain[180c] (Scheme 4.24).



Scheme 4.24

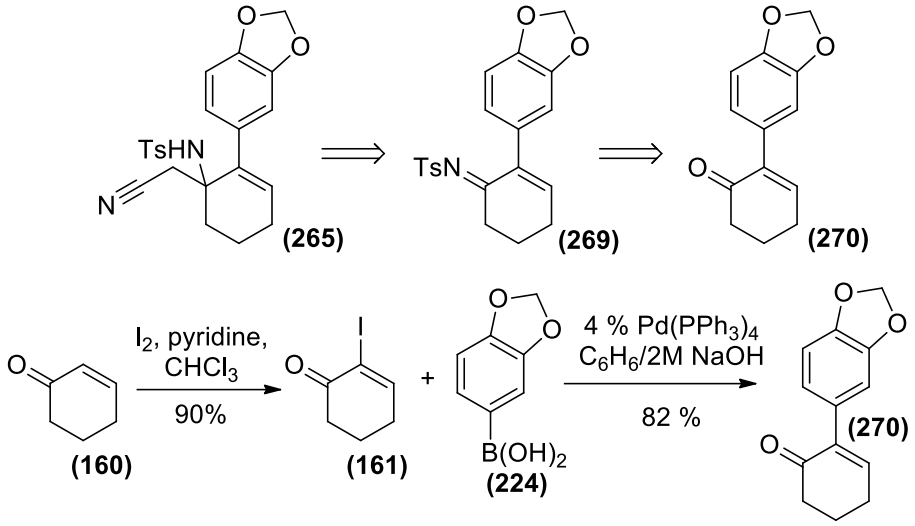
By comparison to the oxygen analogue, epoxidation; direct aziridination of olefins is far less common.[179] A review of the literature revealed three main categories of

direct aziridination methods. Either by direct addition of a metal nitrenoid to the olefin,[179, 181] azide cycloaddition with accompanying loss of nitrogen,[182] or by a Michael type addition of a nitrogen centre bearing a leaving group.[183] In order to maximise the potential for success, representative examples from each category were attempted however no desired product either with **(266)** or without **(268)** the tosyl protecting group was ever observed, with the reactions leading variously to recovery of starting material **(243)** or decomposition under more forcing conditions. This is in keeping with literature precedent, in that outside of intramolecular cases, no examples exist of direct aziridination of tetrasubstituted electron poor olefins[96, 179, 180c, 181d] (Scheme 4.25).



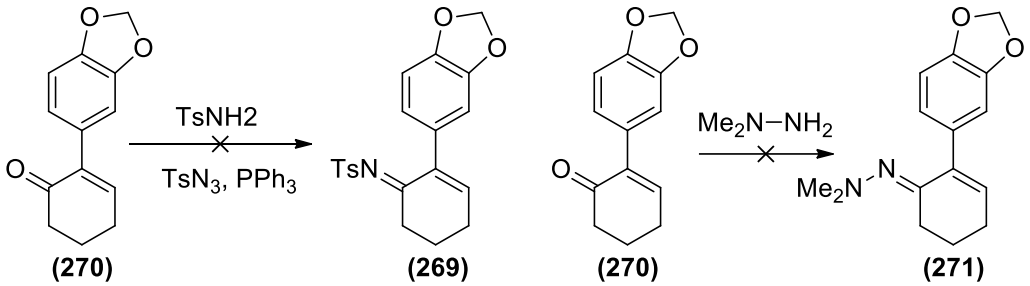
Scheme 4.25

Given the previous success with the acetonitrile anion, an alternate pathway was envisioned whereby the amine **(265)** could be formed from a nucleophilic addition to an appropriately substituted imine **(269)**. This imine could then in turn be formed from the known enone **(270)**. Following the literature protocols, the Johnson iodination[101] of cyclohexenone **(160)** proceeds smoothly to give the iodoenone **(161)**, followed by Suzuki coupling with the previously featured boronic acid[169] **(224)** (Scheme 4.26).



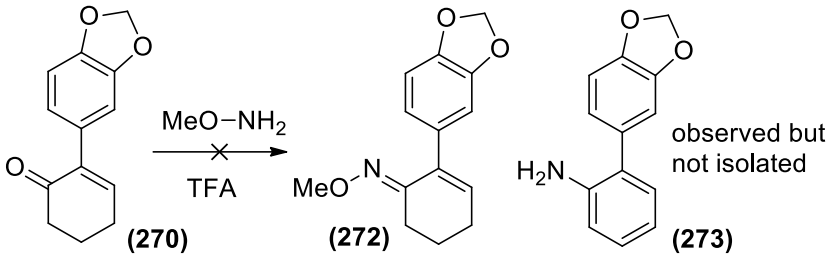
Scheme 4.26

Direct condensation of the aryl enone **(270)** with tosylamine, was remarkably unsuccessful under all attempted conditions,[143] resisting even the aza-Wittig / Staudinger ligation of tosyl azide in the presence of triphenylphosphine.[184] The lack of success in this endeavour was generally attributed to the high steric strain of the alpha aryl group leading to excessive steric strain and therefore easy hydrolysis of the resulting imine **(269)**. However, even upon attempted condensation with the much smaller and more nucleophilic dimethylhydrazine, the system failed to yield stable hydrazone adducts **(271)** (Scheme 4.27).



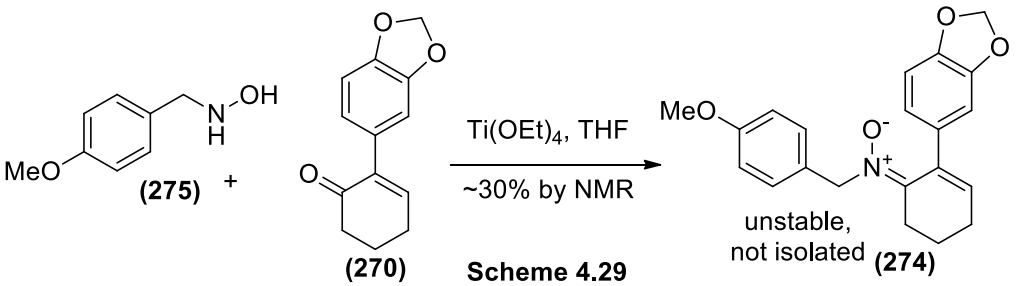
Scheme 4.27

In an attempt to synthesise *O*-methyloxime **(272)**, under more forcing conditions with methoxyamine and trifluoroacetic acid, additional aromatic signals were observed in the ^{1}H NMR corresponding to what was believed to be a Semmler-Wolff aromatisation[185] product **(273)**. Although this compound was not characterised, it was taken as encouragement that the imine formation is possible, although the product was likely unstable (Scheme 4.28).



Scheme 4.28

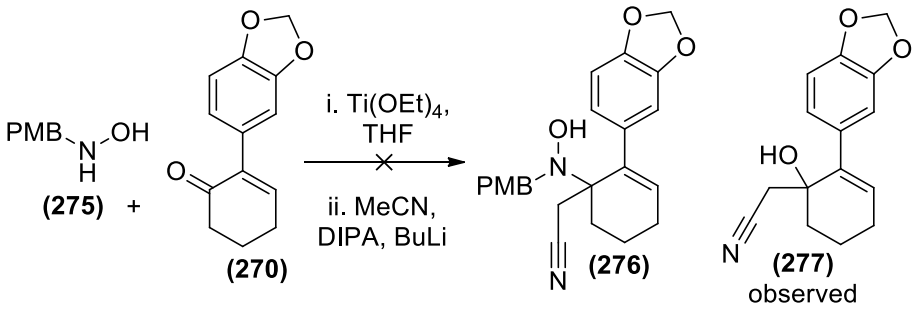
The low boiling point and relative instability of methoxyamine[186] limited the scope of available reaction conditions. As such it was decided that an appropriately substituted nitrone **(274)** would be synthesised. The known *N*-PMB hydroxylamine **(275)** was selected as the PMB group could later be orthogonally deprotected under oxidative conditions.[51] It was viewed that the use of the nitrone offered multiple advantages.[187] Not only would the Semmler-Wolff aromatisation no longer be feasible, as the nitrone would no longer a leaving group on nitrogen; but also the electronic features would attenuate the possibility of Michael addition in the subsequent step.[115, 170] When exposed to most standard conditions (Dean-Stark, 4Å sieves, $MgSO_4$, TMOF etc.)[143] no evidence could be obtained that condensation was successful. Fortuitously subjection of the system to two equivalents of titanium ethoxide as a combined Lewis acid and dehydration agent[188] resulted in the observation of the nitrone adduct **(274)** through identification of the corresponding M+H peak by LCMS and careful ^1H NMR analysis of the unpurified product, particularly a strong upfield shift in the alkene triplet. Disappointingly the nitrone adduct itself could not be chromatographically isolated and the titanium impurities were difficult to remove without hydrolysing the nitrone. This was further supported by 2D TLC which confirmed decomposition of the product on silica (Scheme 4.29).



Scheme 4.29

Confident that nitrone formation was taking place in the reaction system and in light of the isolation difficulties; it was decided to investigate a single pot reaction. It was

envisioned that the excess titanium ethoxide could perhaps further facilitate the nucleophilic addition process as a Lewis acid.[170] After 48 hours at reflux to ensure maximal formation of the nitrone **(274)**, lithiated acetonitrile was generated in 4 fold excess then added *via* cannula. This excess is necessary due to the formation of ethanol as a reaction side product. Unfortunately no corresponding product **(276)** was observed; even by mass spectroscopy. The major observation was recovery of the enone **(270)** and minor formation of a product corresponding to nucleophilic addition to the ketone, which was not further characterised **(277)**. A pair of coupled protons at 2.64 ppm and 2.46 ppm with a coupling constant of 16.4 Hz was observed, accompanied by transformation of the previously clear aliphatic ring protons into complex multiplets without incorporation of the desired nitrogen substituents. It was interpreted from this that there was a persistent equilibrium present in the reaction system and that addition of the basic nucleophile resulted in selective addition to the substantially more electrophilic ketone (Scheme 4.30).



Scheme 4.30

Nitrones are also well known as 1,3-dipoles that are capable of undergoing Huisgen dipolar cycloadditions[189] with a range of electron rich and electron poor dipolarophiles.[134] Application of this reactivity to the formed nitrone would result in a spirocyclic product and would proceed without the need for basic conditions. It was perceived that the resulting spirocyclic system had the potential to offer an additional kinetic benefit to the envisioned Alder-ene cyclisation. The rigidity of the spirocyclic system orthogonal to the plane of the cyclohexane ring, would force the alkyne to occupy a position that would be optimal for the rearrangement to occur (Figure 4.5).

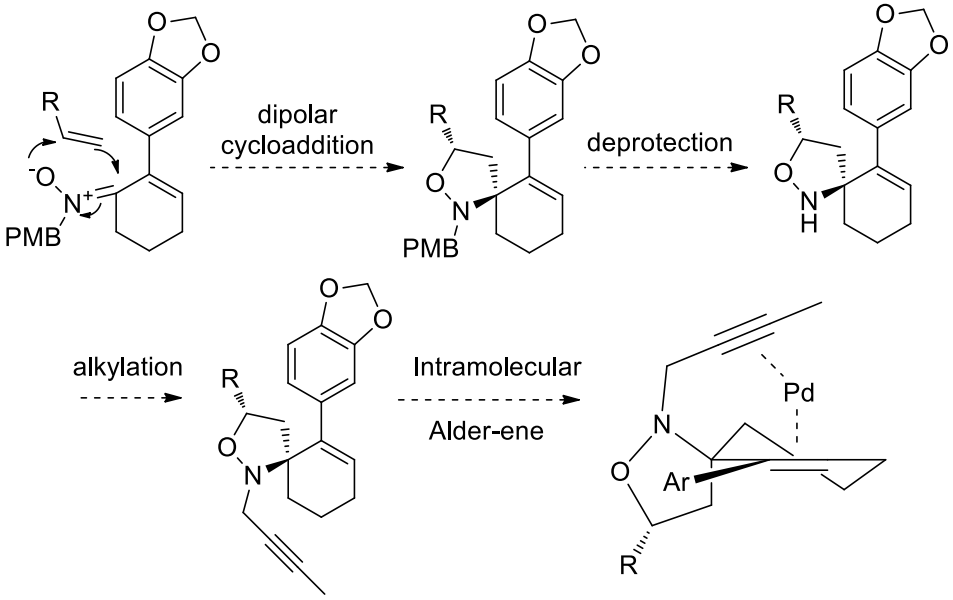
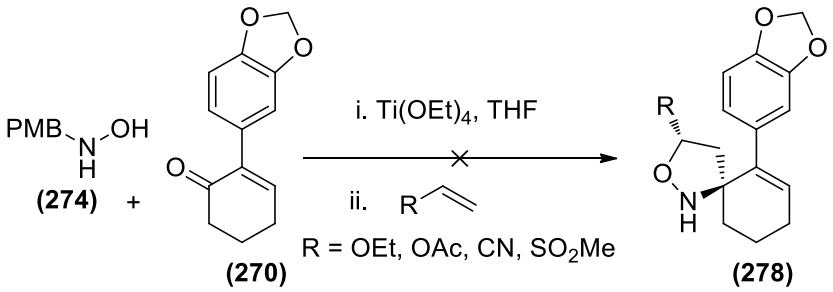


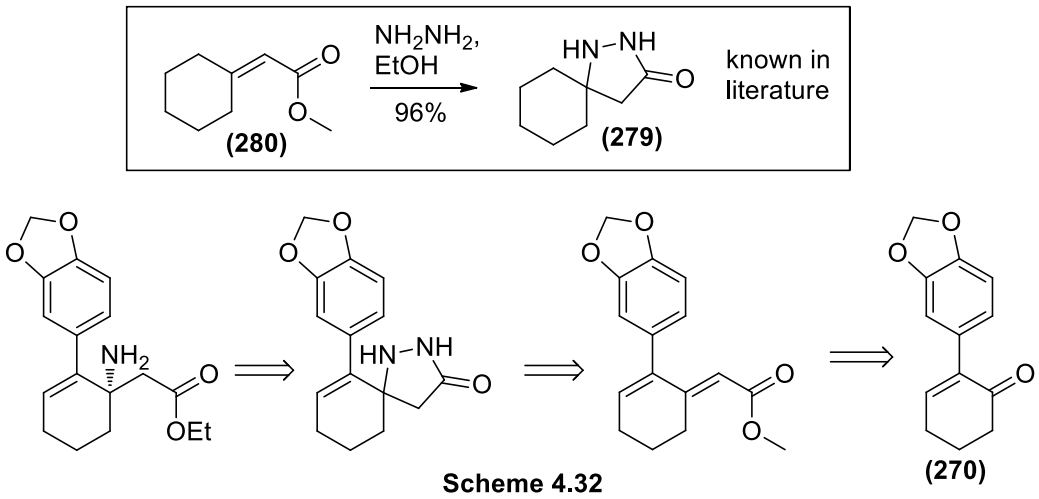
Figure 4.5: Kinetic advantages of incorporating a spirocyclic system

As the regioselectivity of the cycloaddition would most likely be controlled by steric factors,[190] four suitable dipolarophiles were selected that could be converted into the desired aldehyde or ester functionality upon eventual cleavage of the isoxazolidine ring **(278)**. Ethyl vinyl ether and vinyl acetate provided good examples of electron rich dipolarophiles;[191] whereas methyl vinyl sulfone and acrylonitrile were selected as good electron poor dipolarophiles.[190, 191b] In all cases, reductive cleavage of the isoxazolidine reveals the same aldehyde. Disappointingly and despite numerous attempts, this approach proved fruitless, resulting in only complex mixtures from which little information could be gleaned. It is inferred that the strong Lewis acidity of the titanium ethoxide results in decomposition of the dipolarophiles, potentially involving the ethanol side product. It is worth noting that the inability to isolate the nitrone **(274)** makes it difficult to reach strong conclusions regarding reactivity (Scheme 4.31).



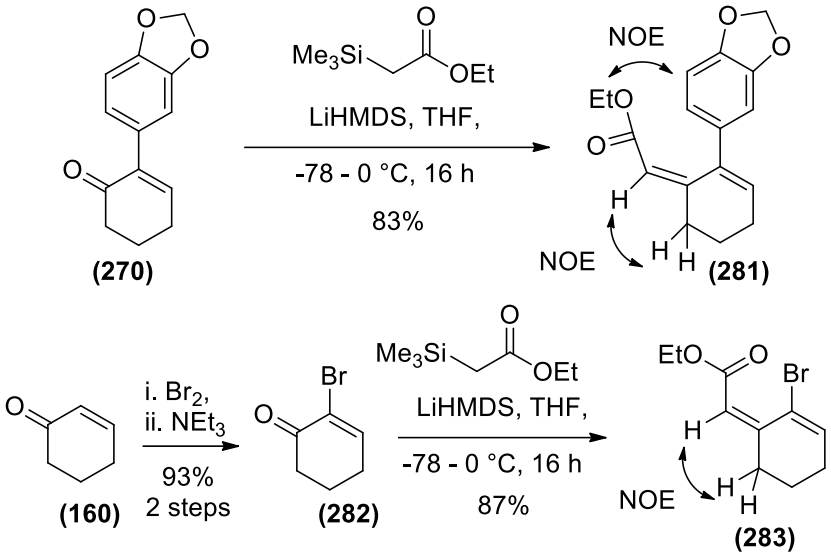
Scheme 4.31

Disaffected by these results, a further reimagining of the synthetic sequence was sought. Enthralled by the potential of a spirocyclic intermediate to facilitate the desired Alder-ene chemistry, it was incorporated into the overall synthetic strategy. Further encouragement was provided in the form of literature precedence as the related [6,5]-spirocyclic pyrazolidinone **(279)** had been synthesised from the corresponding exo alkene[192] **(280)**. Transposing these ideas onto the chemistry at hand results in a simple disconnection to the previously established alpha arylenone **(270)** *via* an appropriate olefination protocol (Scheme 4.32).



Scheme 4.32

In practice olefination proved to be modestly difficult as 1,4-addition provided a competing pathway problematic, resulting in mixtures of products under Doebner-Knoevenagel or Horner-Wadsworth-Emmons conditions.[134] In order to prevent conjugate addition, conditions were sought that featured a harder nucleophilic species.[115] Satisfyingly, utilisation of a Peterson olefination protocol[193] resulted in the smooth isolation of a single product **(281)**. Interestingly on full characterisation it was revealed to possess the higher energy *Z*-double bond stereochemistry, which was confirmed by NOE spectroscopy. It was hoped that the additional steric strain would activate the system to Michael addition. In order to fully probe the reaction possibilities the alpha bromo cyclohexenone[194] **(282)** was synthesised from cyclohexanone **(160)** and also converted to its diene ester **(283)**, this proceeded smoothly under the same conditions again affording only the *Z*-stereoisomer.



Scheme 4.33

It has been established that the enolate formed under these conditions tends to feature the lithium oxide *trans* with respect to the trimethylsilyl group.[195] Application of the Zimmerman-Traxler model for the addition of the *Z*-esterenolate, results in two possible transition states.[170] Upon inspection there is a clear steric interaction between the ethyl group of the ester enolate and the alpha aryl system. The resulting silyl alkoxide **(284)** then rapidly eliminates lithium trimethylsiloxide in an exclusively *syn*-fashion, resulting in the observed product **(281)**[195] (Figure 4.6).

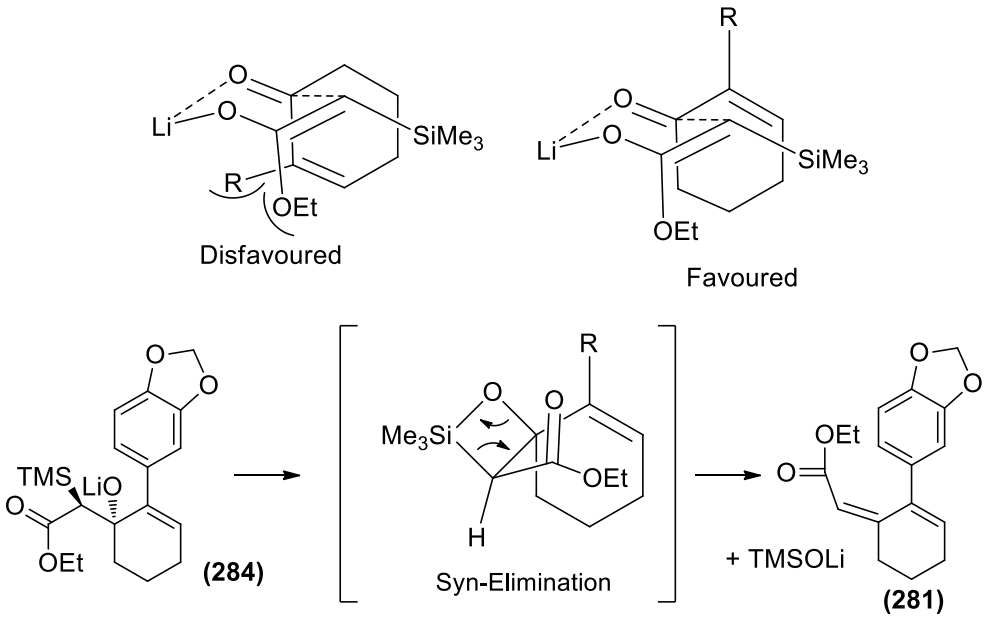
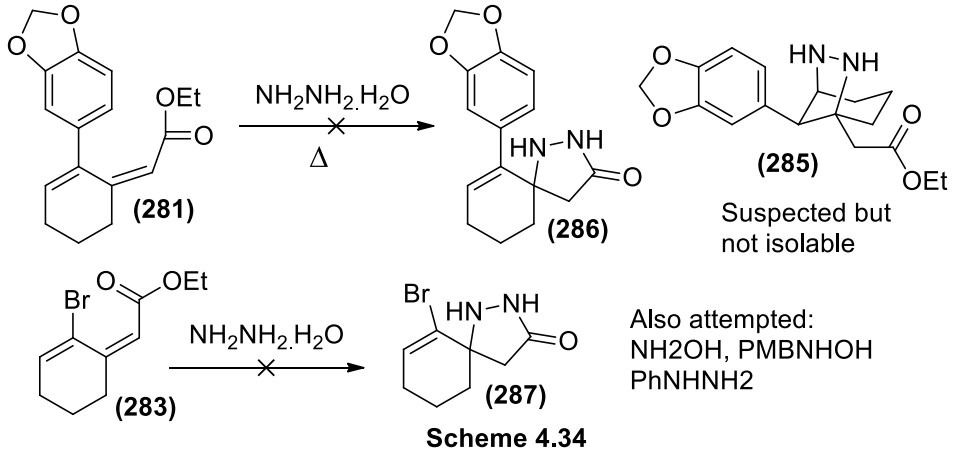


Figure 4.6: Mechanistic rational for the observed regioselectivity in the Peterson olefination

Disappointingly, when the ester diene was subjected to the literature conditions for pyrazolidinone formation;[192] multiple products were observed by NMR. The major identifiable product retained the ethyl group and featured both an isolated doublet at 2.8 ppm and a characteristic AB system, which with loss of both of the alkene signals, indicated desymmetrisation. Although not isolated, based on this information it was believed that a stepwise double Michael addition process was occurring, resulting in a bicyclic product **(285)** which could also be detected by ESI mass spectrometry with an *m/z* mass peak at 319.2 corresponding to the proton adduct. Unfortunately due to the high polarity the product was lost on silica, when attempts were made to purify it. In the hope of isolating a more tractable product, attempts were also made to form the isoxazolidinone with hydroxylamine or PMB hydroxylamine but to no avail with primarily return of starting material. When similar conditions were trialled on the bromoalkene **(283)**, starting material was returned, with the usually unstable haloalkene showing remarkably little reactivity. Unfortunately none of the desired products **(286, 287)** were isolated (Scheme 4.34).



Scheme 4.34

4.7 Future Work

Although a number of avenues were explored, none of them proved to be ultimately fruitful. As such, further extensions of the approaches featured herein will be the subject of “future work”. Of particular interest could be the reapplication of the bromoenone to pre coupling formation of the desired allylic amine system using the imine based methodology. Although attempts were made using the iodoenone, these were thwarted by the photosensitivity of the resulting products. Given the surprising comparative stability of the related bromide derivatives observed late in the project,

this may be worth further investigation. As a furtherance to the development of the Pd catalysed Alder-ene reaction it may also be worthwhile forming the butynyl ethers of the various allyl alcohols synthesised during the project to investigate their activity and provide additional structural novelty (Figure 4.7).

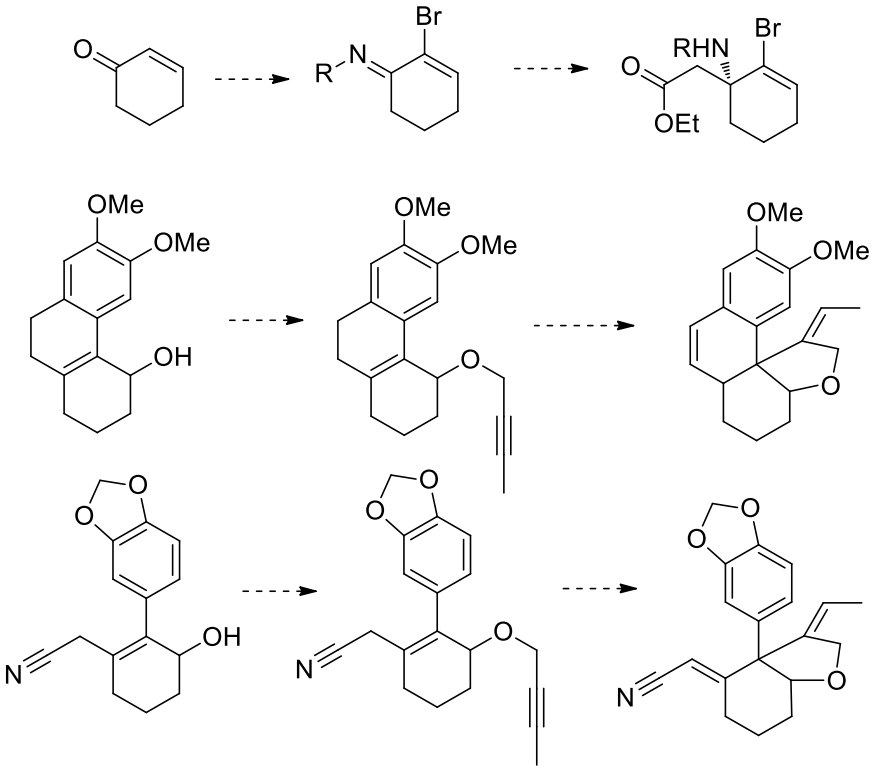
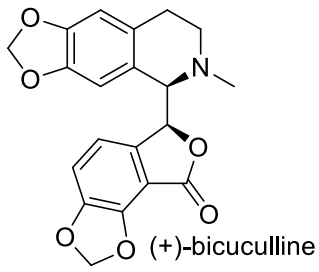


Figure 4.7: "Future Work"

Chapter 5 – Bicuculline

5.1 Introduction

The phthalide isoquinoline natural product bicuculline **(288)** was first isolated in 1932, from *Dicentra bicucullaria*, commonly known as Dutchman's breeches.[196] It has since been detected in a range of different species within the Papaverae (Poppy) family of which it is a member.[197] It was determined shortly thereafter to be a powerful and toxic convulsant[198] which can be used to model epilepsy. In 1970 there was an explosion of interest in the compound after it was shown to be a relatively selective antagonist of gamma aminobutyric acid (GABA) induced inhibition at neuronal synapses, providing some of the first evidence of GABA as a neurotransmitter.[199] In the intervening 45 years, bicuculline **(288)** has played a key role in the investigation of GABA receptors, featuring in hundreds of publications as a biological probe[200] (Figure 5.1).



(+)-bicuculline
(288)

Figure 5.1

It has since been determined that bicuculline has lower selectivity than originally thought, with reports stating that it may also have some indirect antagonistic effect on other neurotransmitters such as glutamate, glycine and 5-hydroxytryptamine.[201] The major additional activity that has proven to result from administration of bicuculline, is antagonism of nicotinic acetylcholine receptors (nAChRs).[202] The nAChRs are pentameric complexes that form a ligand gated ion pore through the cell membrane. These pentameric complexes can consist of multiple different protein subtypes that determine the varying physiological roles of the receptors[28] (Figure 5.2). Following an in depth investigation using isolated oocyte receptor expression, Demuro *et al*. determined that the degree of antagonism by bicuculline on nAChRs was moderately subtype selective with the order of potency being

α7>α2β4>α4β2>αβγδ with IC50s ranging from 6.8 to 34 μM. This led to the conclusion that bicuculline has potential as a lead compound in the development of selective anticholinergics for possible medical use.[203]

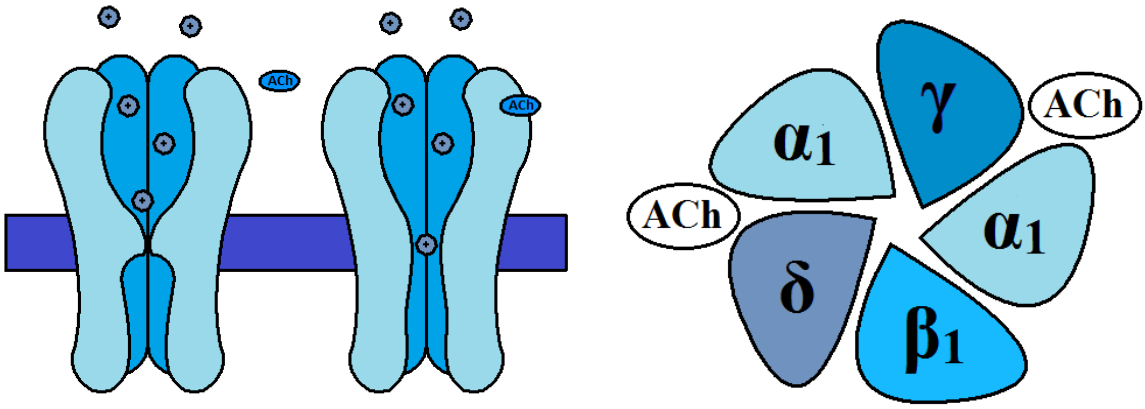
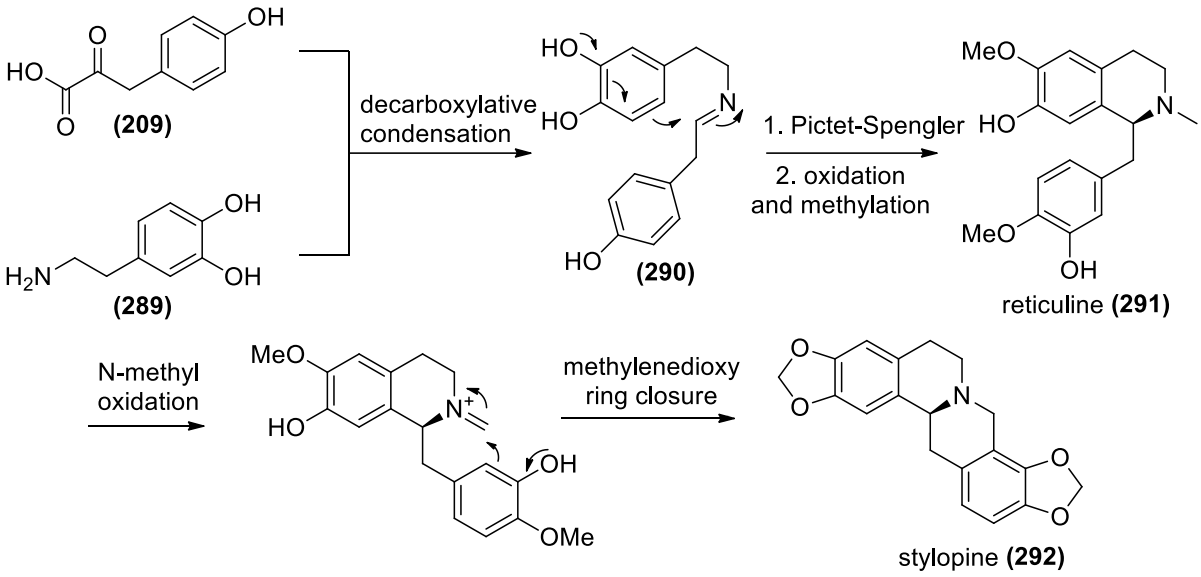


Figure 5.2 Left: Ligand gated ion channel cross sectional view. Right: Top down view of a muscular αβγδ type nicotinic acetylcholine receptor showing the different subunits and binding sites.[28]

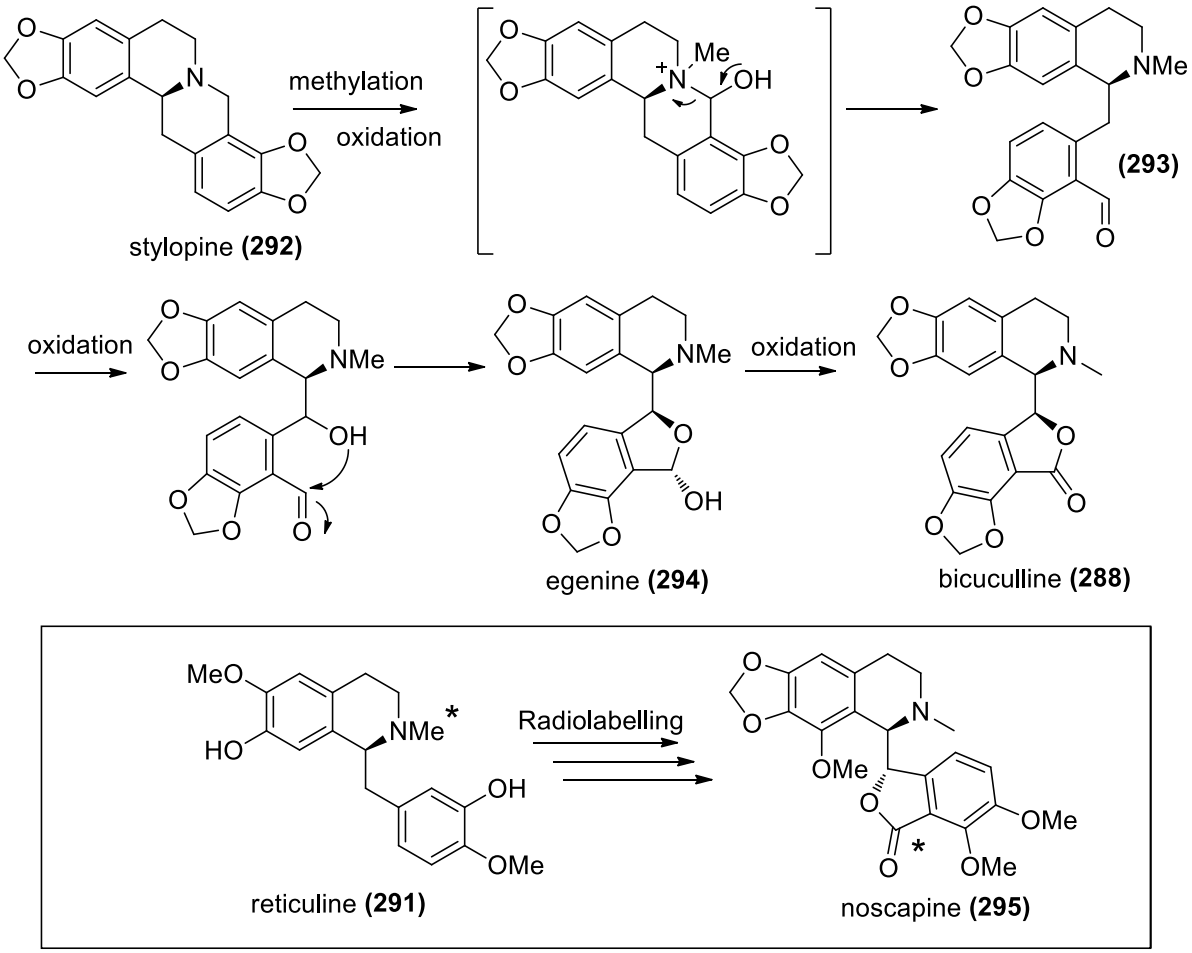
5.2 Biosynthesis

As a phthalide isoquinoline alkaloid the biogenesis of bicuculline **(288)** is remarkably similar to that of the initial stages in the biosynthesis of hasubanan (see Chapter 4). Here a molecule of dopamine **(289)** and 4-hydroxyphenyl pyruvate **(209)** undergo the analogous enzymatic Pictet-Spengler type reaction via imine **(290)**, which after further oxidation and methylation generates the intermediate reticuline **(291)**.[204] Interestingly, oxidation of the *N*-methyl group results in an intramolecular electrophilic aromatic substitution, forming an additional ring. Oxidation of the *O*-methyl groups of the aromatic rings then furnishes the methylenedioxy systems to yield the natural product stylopine **(292)**[205] (Scheme 5.1).



Scheme 5.1

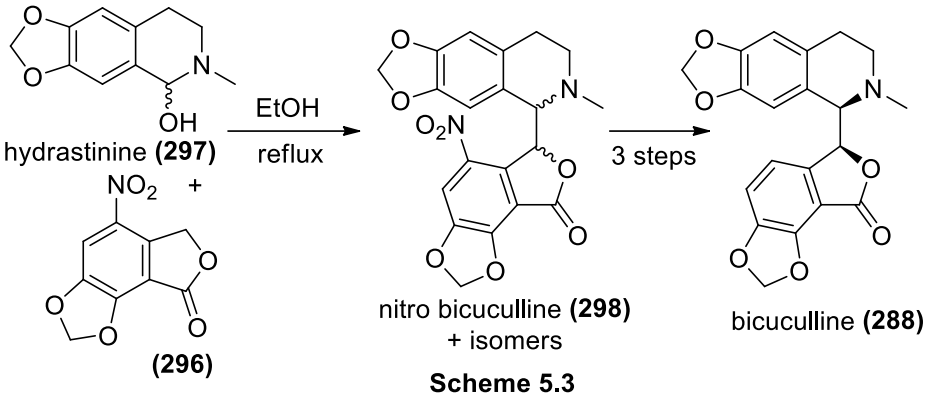
It is believed that from stylopine **(292)**, further *N*-methylation results in the quaternary ammonium salt which then undergoes oxidation at the methylene group to give an aldehyde **(293)**. Further oxidation at the unsubstituted benzyl position gives the known hemiacetal egenine **(294)** which is readily converted into bicuculline **(288)**.[206] This is supported by radiolabelling studies of the related phthalide isoquinoline natural product noscapine **(295)**, which determined that the lactone carbonyl originated from the *N*-methyl group of reticuline **(291)**[207] (Scheme 5.2).



Scheme 5.2

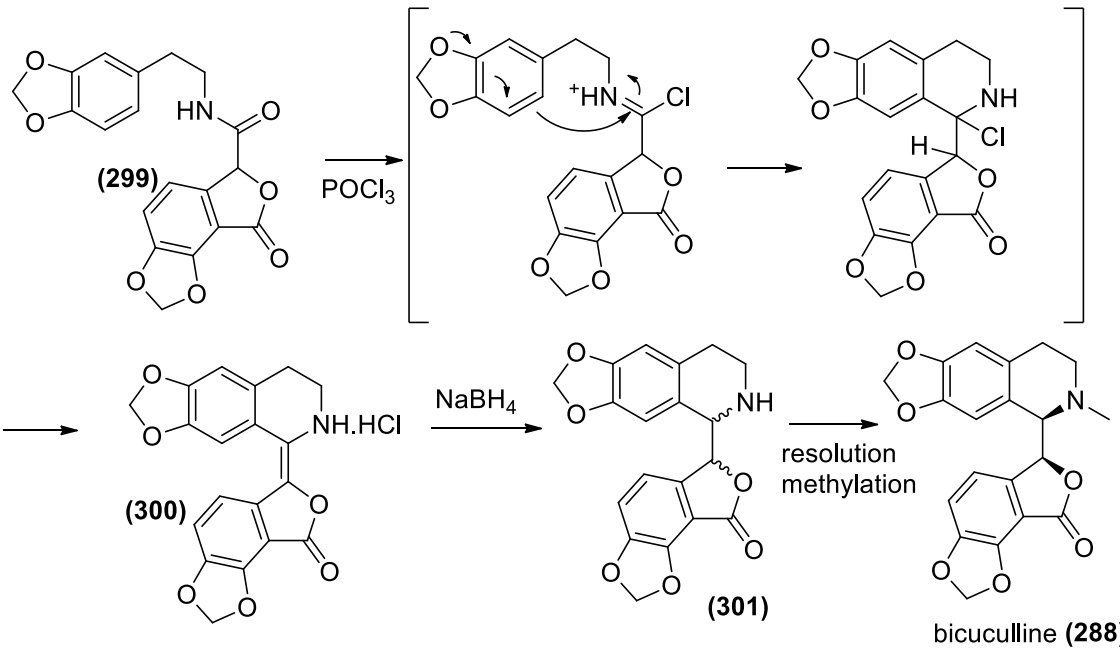
5.3 Prior Art

Bicuculline **(288)** has been the subject of multiple syntheses, with the first completed by Groenewoud and Robinson in 1936.[208] In this approach the two separate ring systems were disconnected to give a nitro phthalide **(296)** and the known hydrastinine **(297)**. A three step protocol was then used to remove the aromatic nitro group from **(298)** with later resolution of the natural product by crystallisation as the tartrate salts (details unavailable).[208] Several variants of this iminium addition approach have since been published[209] (Scheme 5.3).



Scheme 5.3

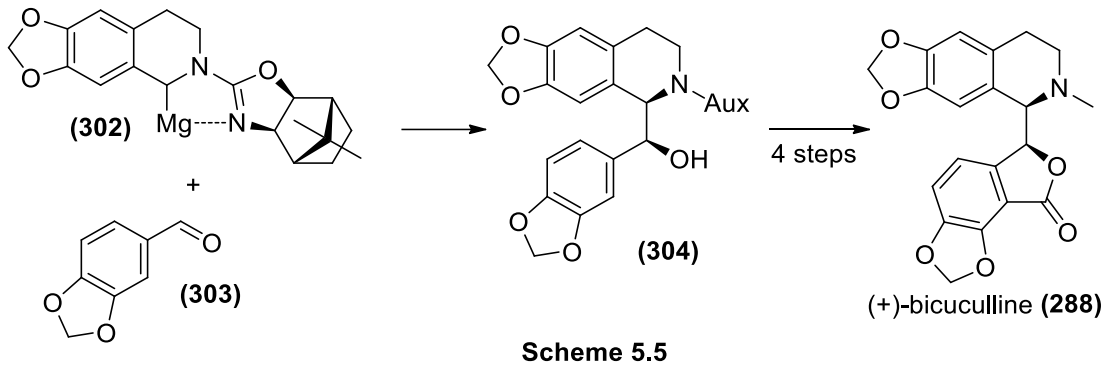
Another strategy that has been employed in the synthesis of bicuculline **(288)** follows a more biosynthetic approach.[210] Here the disconnection was made in the isoquinoline ring to give a linear amide **(299)** which was cyclised under Bischler-Napieralski conditions to give the enamine hydrochloride salt **(300)**. This can be seen as the amide equivalent of the enzymatic Pictet Spengler reaction that forms the isoquinoline ring in nature.[134] Upon reduction this gave a racemic mixture of norbicuculline diastereomers **(301)** from which bicuculline **(288)** had to be labouriously purified by crystallisation as the tartrate salt followed by methylation[210] (Scheme 5.4).



Scheme 5.4

One of the few enantioselective approaches employed in the synthesis of bicuculline **(288)** and related phthalide isoquinolines has utilised the reversed polarities to that of Groenewoud and Robinson with the same disconnection between rings. This

strategy instead generated a benzylisoquinoline anion bearing a chiral auxiliary **(302)** which was then added to piperonal **(303)**.[211] The most notable of these approaches is that by Gawley and Zhang, wherein the desired adduct could be formed with 80% diastereoselectivity (other isomers not reported), albeit in 62% yield[212]. This was achieved by using a magnesium counterion in combination with a camphor derived chiral auxiliary. The major diastereomer **(304)** could be isolated chromatographically and converted in a further 4 steps to (+)-bicuculline **(288)** (Scheme 5.5).

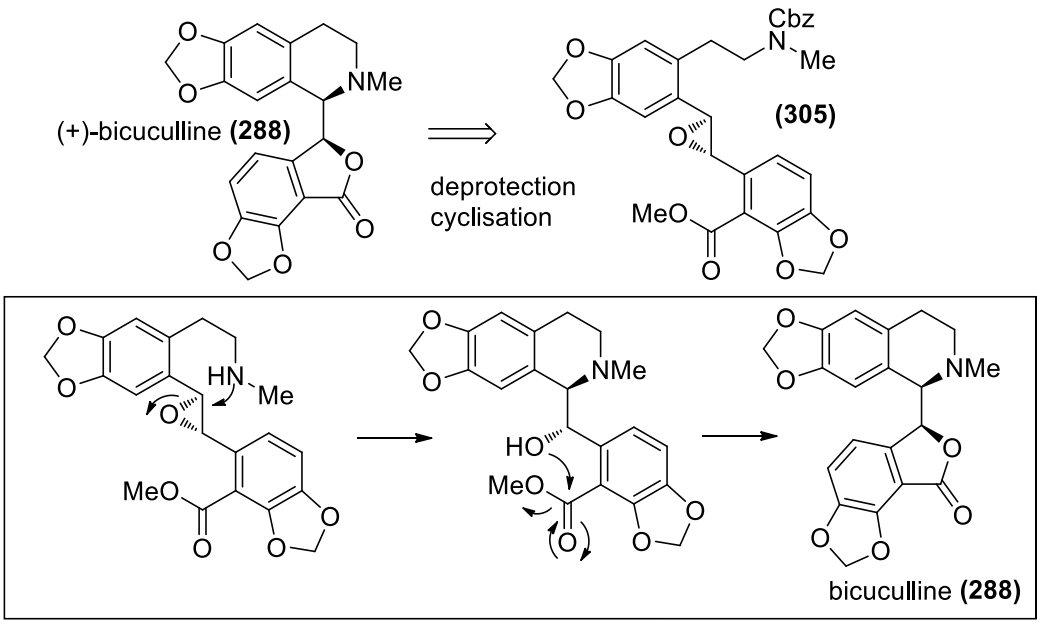


Scheme 5.5

The major disadvantage of these approaches is that they invariably result in mixtures of diastereomers that have proven difficult to control and require substantial further effort to separate and resolve to afford enantiomerically pure bicuculline.[210] This is particularly incompatible with the synthesis of analogues as each new compound would require the development of new conditions. In order to investigate the structure activity relationship of bicuculline in the various receptor subtypes, a synthetic scheme was desired that could reliably form the desired diastereomer in an ideally modular approach that would favour the ready synthesis of derivatives.[7] In this respect it was envisioned that the carbon skeleton could be formed *via* stereoselective synthesis of the corresponding stilbene, followed by oxidative functionalization in a stereocontrolled manner. Initial efforts in this regard focused around the ring opening of an epoxide and were the subject of an honours dissertation within the research group by Lucy McPherson, which is summarised below.[213]

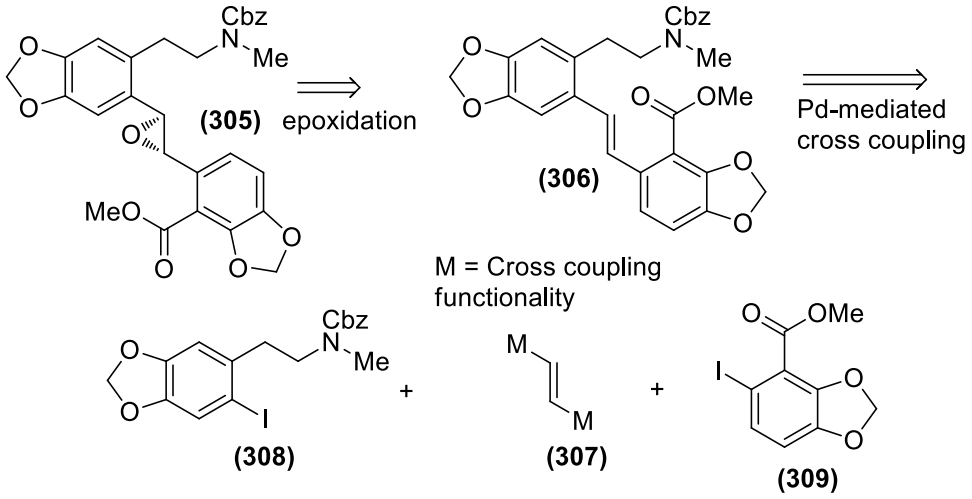
Retrosynthetically, bicuculline **(288)** was disconnected to an appropriately protected epoxide **(305)**. A carboxybenzyl (Cbz) group was chosen to protect the nitrogen functionality, which could be deprotected under hydrogenative conditions.[51] Conceptually, initial deprotection would reveal the nucleophilic amine which would

then undergo ring opening of the epoxide, accompanied by esterification of the resulting alcohol to give the natural product **(288)**. As epoxide ring opening proceeds with inversion, the *trans*-epoxide was required give the desired stereochemistry (Scheme 5.6).



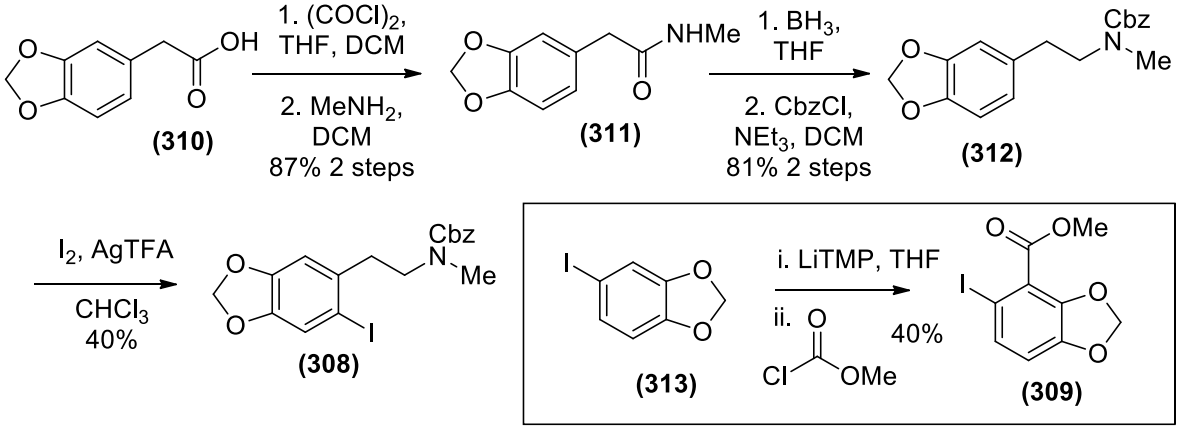
Scheme 5.6

The highly functionalised epoxide **(305)** in turn could then be accessed by *syn*-selective epoxidation of the corresponding *trans*-stilbene **(306)**. Using the established Shi epoxidation protocol[77] it would then be possible to carry this out enantioselectively. The stilbene itself could then be synthesised by sequential cross coupling chemistry of a corresponding bis-functionalised vinyl equivalent **(307)** and two aromatic iodides **(308)** and **(309)** (Scheme 5.7).



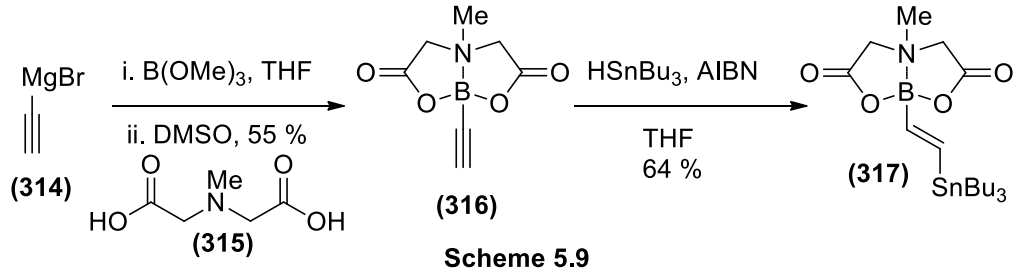
Scheme 5.7

The first of the required coupling partners was synthesised from the commercially available 3,4-methylenedioxyphenylacetic acid **(310)**. Oxalyl chloride mediated formation of the acid chloride, followed by quenching with methylamine furnished the corresponding methylamide **(311)** in good yield. Borane mediated reduction of the secondary amide followed by acid hydrolysis of the resulting amine-borane complex resulted in isolation of the free secondary amine which was protected under standard conditions to give protected material **(312)**.[51] Subsequent iodination under silver trifluoroacetate promoted conditions then gave the requisite coupling partner **(308)**. The second coupling partner **(309)** was known within the group and could be accessed *via* directed orthometallation[214] of the commercially available 4-iodo-1,2-methylenedioxybenzene **(313)** followed by quenching with methyl chloroformate (Scheme 5.8).



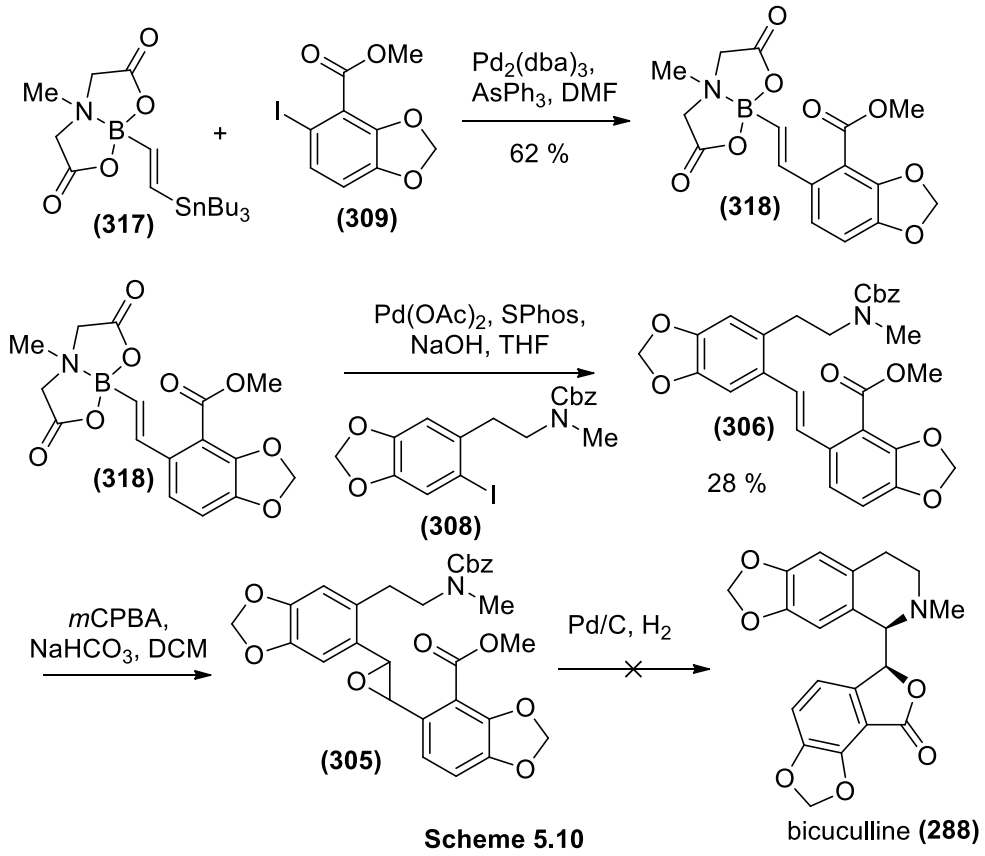
Scheme 5.8

Owing to their relatively high stability, a methyliminodiacetyl (MIDA) boronate was selected as an appropriately functionalised coupling partner, for which there were multiple options.[215] After some optimisation the stannyl substituted system was deemed the most appropriate as the stannane is more reactive to cross coupling conditions in the absence of base. Following literature procedures[215] ethynylmagnesium bromide **(314)** was quenched with trimethylborate to give the crude ethynylboronic acid which was immediately condensed with methyliminodiacetic acid **(315)** to give the stable MIDA derivative **(316)**. Radical mediated hydrostannylation with tributyltin hydride then afforded the desired stannane **(317)** in moderate yield (Scheme 5.9).



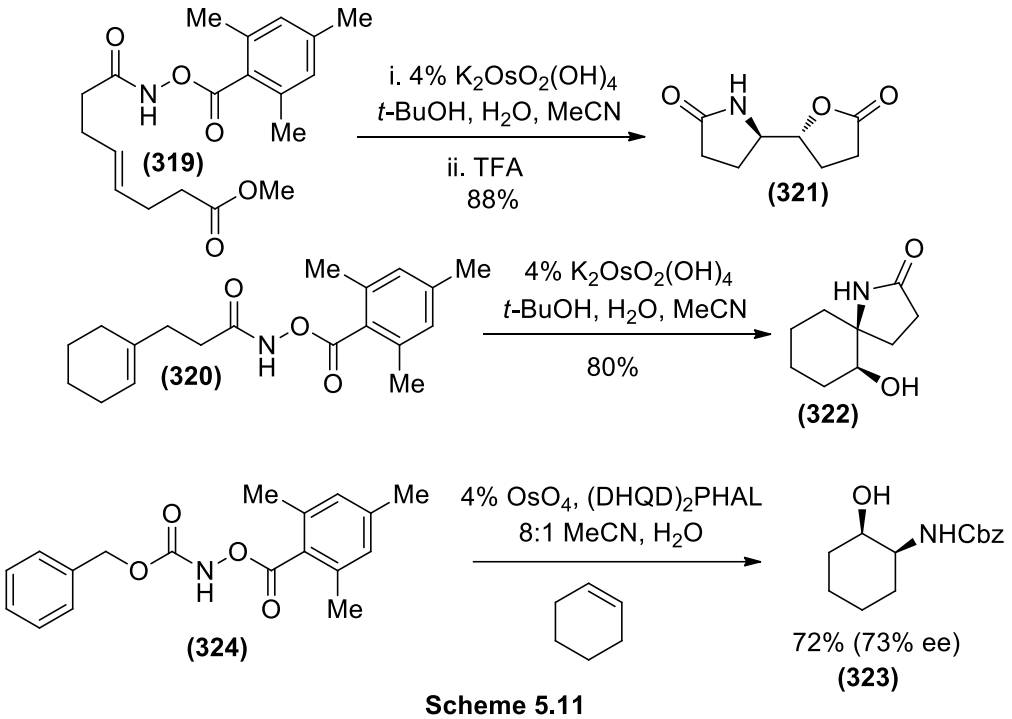
Scheme 5.9

Subjection of the synthesised stannane **(317)** to Stille coupling conditions with the iodo ester **(309)** allowed isolation of the selectively cross coupled MIDA protected product **(318)** in moderate yield. Subsequent exposure of this material to the second cross coupling partner **(308)** then afforded the desired *trans*-alkene **(306)** in an unoptimised yield of 28%. Upon treatment of the *trans*-alkene with *m*-CPBA to effect peracid mediated epoxidation, the product epoxide **(305)** was found to be somewhat chromatographically unstable.[213] As such it was subjected directly to deprotection conditions in the hope of isolating the natural product **(288)** directly. Unfortunately the stilbene epoxide proved unstable to the hydrogenative conditions and only decomposition was observed (Scheme 5.10).



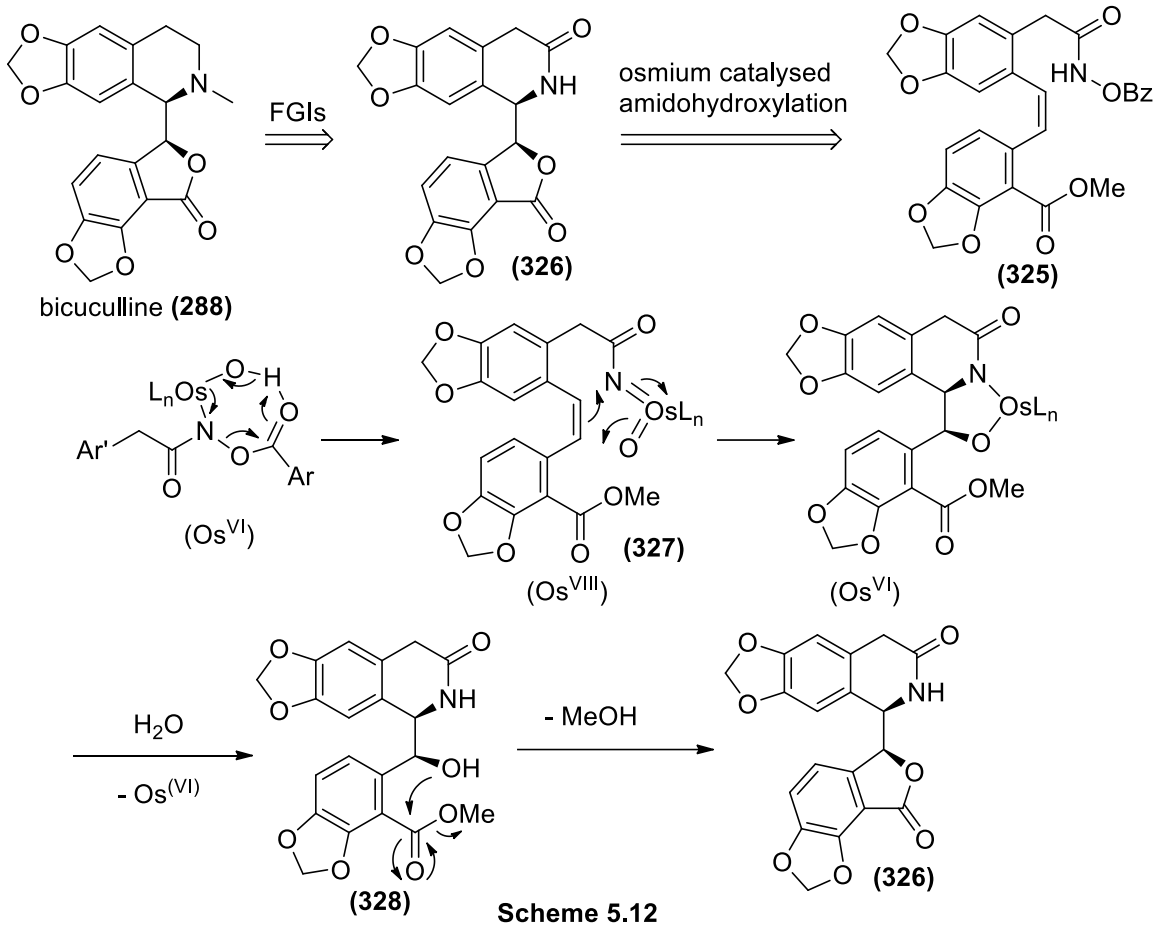
Scheme 5.10

The project was then taken over by Luke Pasfield as part of his PhD thesis.[216] Key yields were optimised however isolation of the desired epoxide proved elusive. Limited ^{1}H NMR, and MS evidence was obtained for the formation of the natural product under Lewis acid mediated conditions however it could not be cleanly isolated. Owing to the difficulties in handling of the stilbene epoxide system, it was decided that another approach be taken whereby the functionalisation of the alkene could be achieved *via* an osmium catalysed intramolecular aminohydroxylation reaction.[217] This was spurred on in part by the recent publication by Donohoe *et al*. which demonstrated that *O*-benzoylated hydroxamic acids **(319, 320)** were viable substrates for the reaction that can even be used with accompanying esterification[218] **(321, 322)**. Although not known in an intramolecular fashion, enantioselectivity has been achieved **(323)** in the intermolecular variant with benzyl carbamate substrates[219] **(324)**. With further research this may allow for a potentially enantioselective synthesis of bicuculline **(288)** (Scheme 5.11).



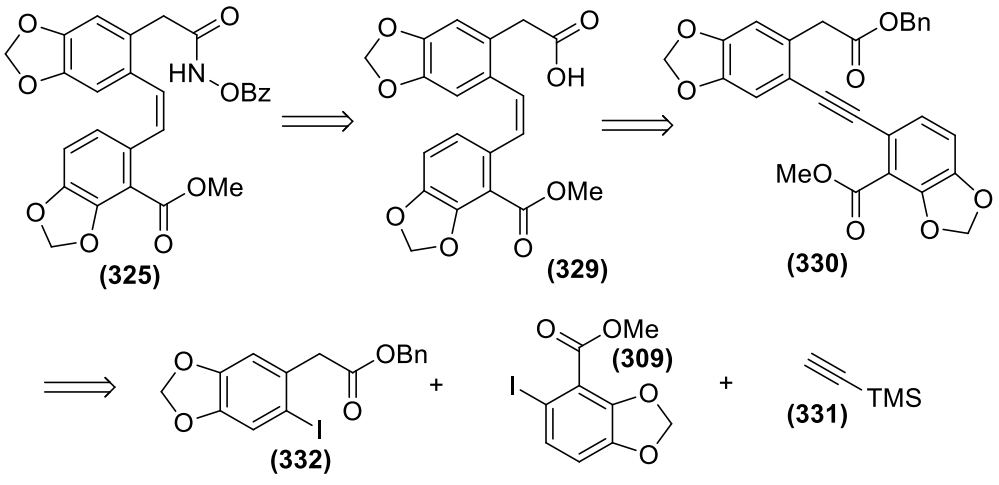
Scheme 5.11

In applying this methodology to the synthesis of bicuculline **(288)** it is apparent that the *cis*-stilbene **(325)** is required to achieve the desired stereochemical outcome. The resulting amide **(326)** could then be methylated and reduced to afford the natural product. The required *O*-benzoylated hydroxamic acids can be readily synthesised in a few steps from the corresponding carboxylic acid,[218] revealing the mono protected stilbene as a key intermediate. It is believed that the mechanism of the reaction proceeds *via* initial binding to the amide nitrogen by the osmium(VI) centre which reduces nitrogen-oxygen bond to give an imido osmium(VIII) intermediate **(327)** which can then undergo *syn*-selective [3+2] cycloaddition with an olefin. It was hoped that the resulting amide alcohol **(328)** would then cyclise to give the ester **(326)**[217] (Scheme 5.12).



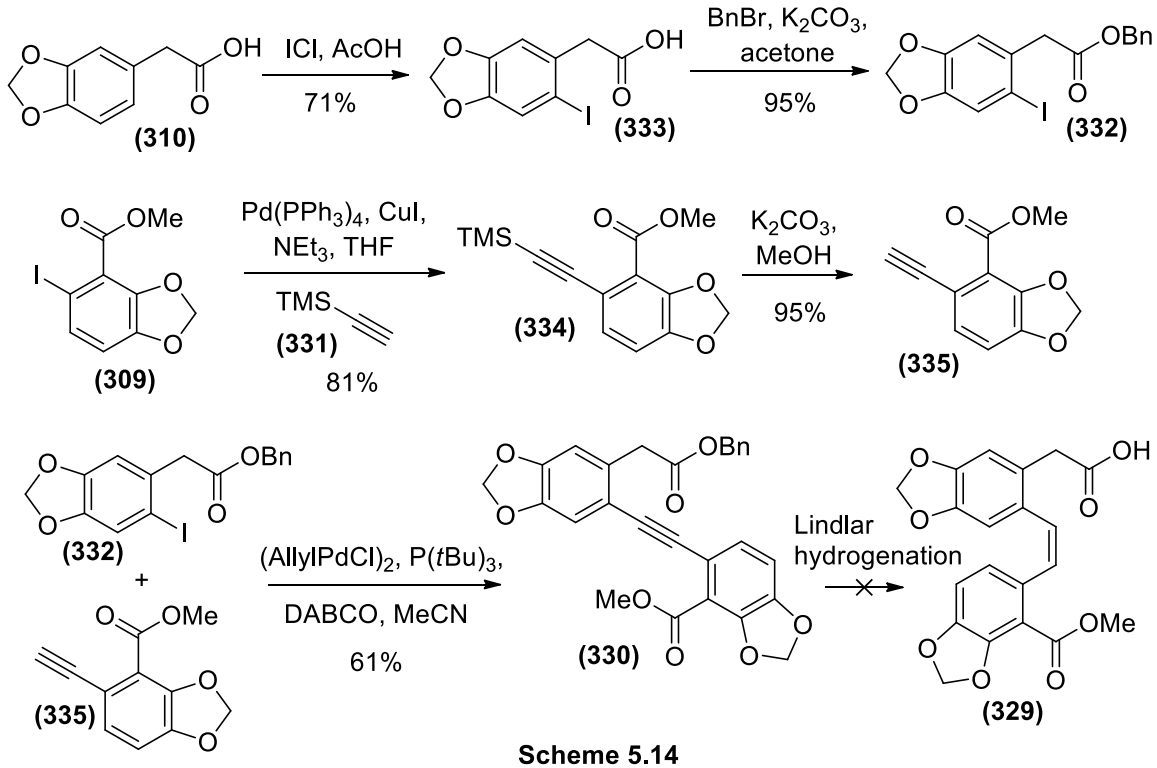
Scheme 5.12

It was proposed that the stilbene intermediate **(329)** could be formed by Lindlar reduction of the tolane benzyl ester **(330)**, itself available by sequential Sonogashira type coupling of trimethylsilylacetylene **(331)** with two appropriate aromatic fragments **(332, 309)** (Scheme 5.13). A summary of progress made by Pasfield in this approach follows.



Scheme 5.13

3,4-(Methylenedioxy)phenylacetic acid **(310)** was iodinated under literature conditions[220] with iodine monochloride to afford the corresponding iodide **(333)** which was then protected as the benzyl ester **(332)**. Initial cross coupling of methyl ester **(309)** (previously obtained by McPherson) with trimethylsilylacetylene **(331)** proceeded smoothly to give the alkyne product **(334)**, followed by a facile deprotection of the TMS group in potassium carbonate and methanol. The subsequent cross coupling between the terminal alkyne **(335)** and the benzyl ester **(332)** proved to be troublesome and was achieved in moderate yield by resorting to a copper free Sonogashira protocol.[216] Unfortunately the Lindlar semihydrogenation of the tolane **(330)** proved to be highly challenging, with incomplete removal of the benzyl protecting group and competing over reduction of the resulting stilbene, preventing isolation of the desired product **(329)** (Scheme 5.14).

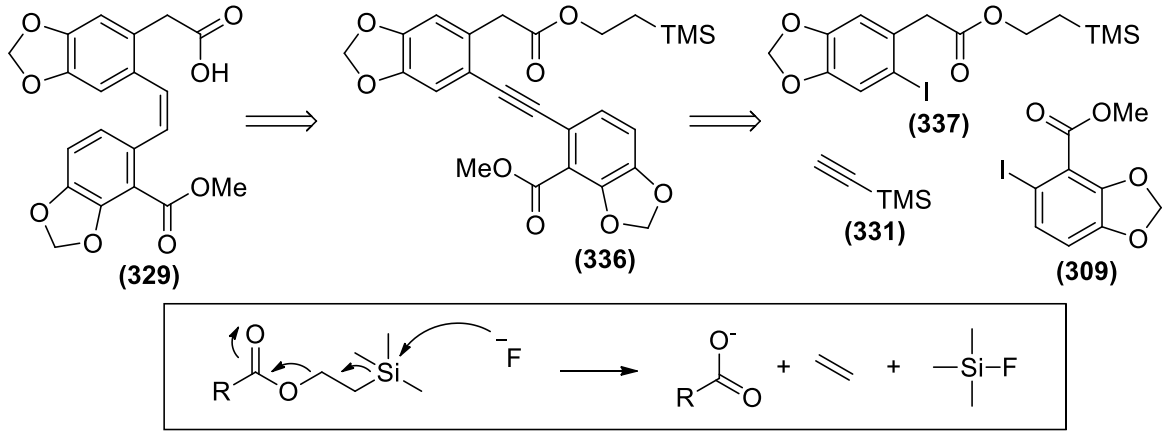


Scheme 5.14

5.4 Results and Discussion

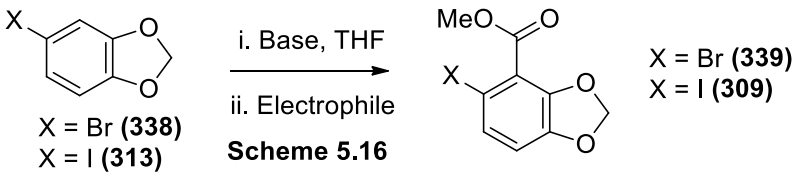
Upon receiving the project it was decided to continue with the proposed aminohydroxylation strategy. The benzyl protecting group was identified as being unsuitable owing the difficulties in its orthogonal removal during the Lindlar semihydrogenation. As such a strategic decision was made to switch to the use of the moderately stable trimethylsilyl ethyl group (TMSE) to reach the key mono

protected stilbene **(329)**. The advantage of this is that TMSE groups can be selectively cleaved in the presence of fluoride *via* a Grob like fragmentation, driven by the formation of ethylene gas.[51] This preserves most of the key synthetic elements of the progress made by Pasfield, instead going through the corresponding TMSE protected intermediates **(336)** and **(337)** (Scheme 5.15).



Scheme 5.15

Initial work focused on addressing inefficiencies in obtaining the second coupling partner **(309)**; although there was precedence within the group,[213, 216] yields were inconsistent. As such a quick methodological screen *via* ^{1}H NMR was conducted (see Table 5.1, Scheme 5.16). Using the brominated material **(338)** it was thereby established that LDA and dimethyl carbonate were superior reagents for effecting the desired transformation forming bromide **(339)** in good yield. Despite similar pKa values the LiHMDS used did not seem to undergo deprotonation; use of LiTMP resulted in similar product distribution to that of LDA but there may have been some problems in the purity of the TMP base. When the iodinated starting material **(313)** was used the yield dropped in a fashion that was consistent with the literature.[214] In this case freshly distilling the TMP allowed formation of the desired product **(309)** in the same yield as that obtained with brominated material.



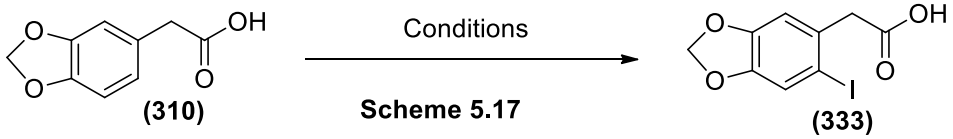
Scheme 5.16

X	Base	Electrophile	Yield, Comment
Br	LiHMDS	MeOCOCl	0%, Starting material fully recovered

Br	LiHMDS	MeOCOOMe	1%, Starting material recovered
Br	LiHMDS	MeOCOCN	5%, Starting material recovered
Br	LDA	MeOCOCl	62%, multiple side products observed
Br	**LDA**	**MeOCOOMe**	**81%, clean with some starting material**
Br	LDA	MeOCOCN	70%, starting material recovery, side products
Br	LiTMP	MeOCOCl	44%, starting material recovery, side products
Br	LiTMP	MeOCOOMe	40%, starting material recovery
Br	LiTMP	MeOCOCN	32%, starting material recovery
I	LDA	MeOCOOMe	55%, multiple side products
I	**LiTMP**	**MeOCOOMe**	**81%, some side products, distilled TMP used**

Table 5.1. Optimisation of orthometallation chemistry

Similarly speaking, the first step in the formation of iodo acid **(333)** was investigated to increase yields but also due to the practical undesirability of working with the highly reactive and sludge like iodine monochloride (Scheme 5.17, Table 5.2). A range of conditions were screened that cover the various ways of activating iodine for electrophilic iodination.[221] Interesting all of the trialled conditions resulted in the formation of some product, however the only viable non ICl alternative seems to be base induced disproportionation. This may be worth further investigation as the conditions are unoptimised. It is assumed that the carboxy group may be providing some anchimeric assistance.[170]



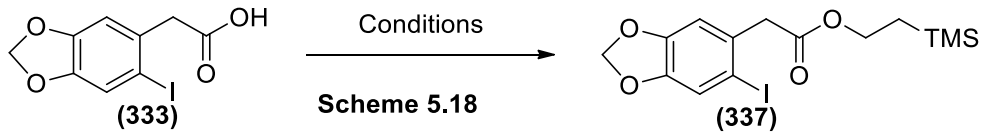
(310) **Scheme 5.17** (333)

Iodine source	Conditions	Yield
ICl	AcOH	68%
ICl	AcOH (anhydrous)	72%
ICl	AcOH, AgOAc, (silver assisted)	65%
ICl	TFA. AcOH had to be added ICl insoluble in TFA	14%
I_2	**NaOH, NaI, H_2O/THF (basic, disproportionation)**	**71%**
I_2	K_2CO_3, H_2O_2, H_2O/THF (basic, oxidative)	26%
NaI	Oxone, H_2O/THF (Acidic, oxidative)	12%

NaI	*N*-chlorosuccinimide, Acetone (NIS *in situ*)	21%

Table 5.2. Optimisation of initial iodination

After encountering some difficulties, a scalable procedure for TMSE protection was developed (Table 5.3, Scheme 5.18). Early attempts using acid chlorides were inefficient, resulting in a number of side products that were not easily separable by standard techniques. TMSCl assisted esterification looked promising[222] but was ultimately not amenable to scale with 4-chlorobutanol being observed as a major side product arising from solvent reactivity. Utilisation of the Steglich esterification protocol[51] with DCC and DMAP proved most amenable to use and could be directly purified without need for chromatography.

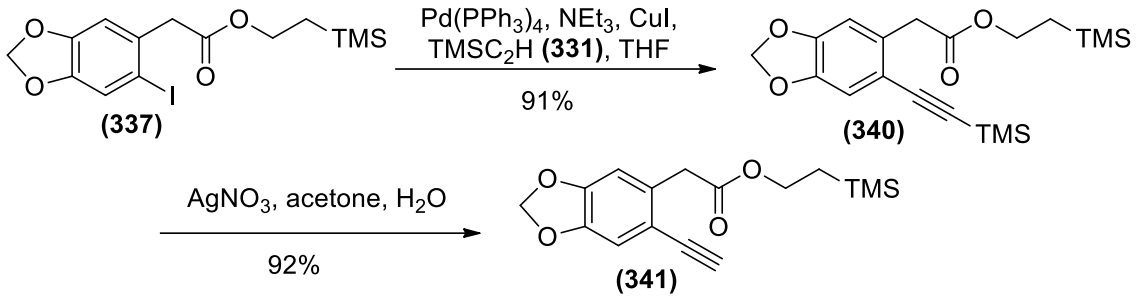


(333) Scheme 5.18 (337)

Conditions	Yield
i. Oxalyl chloride, DMF, DCM ii. TMSEOH, pyr, DCM.	60%
i. Oxalyl chloride, DMF, DCM ii. TMSEOH, NEt_3, DCM.	86%
i. $SOCl_2$ reflux neat ii. TMSEOH, NEt_3, DCM.	43%
TMSCl, TMSEOH, THF	94%
TMSCl, TMSEOH, THF, large scale	30%
TMSEOH, DCC, DMAP, DCM	89%
TMSEOH, DCC, DMAP, MeCN - scalable	**91%**

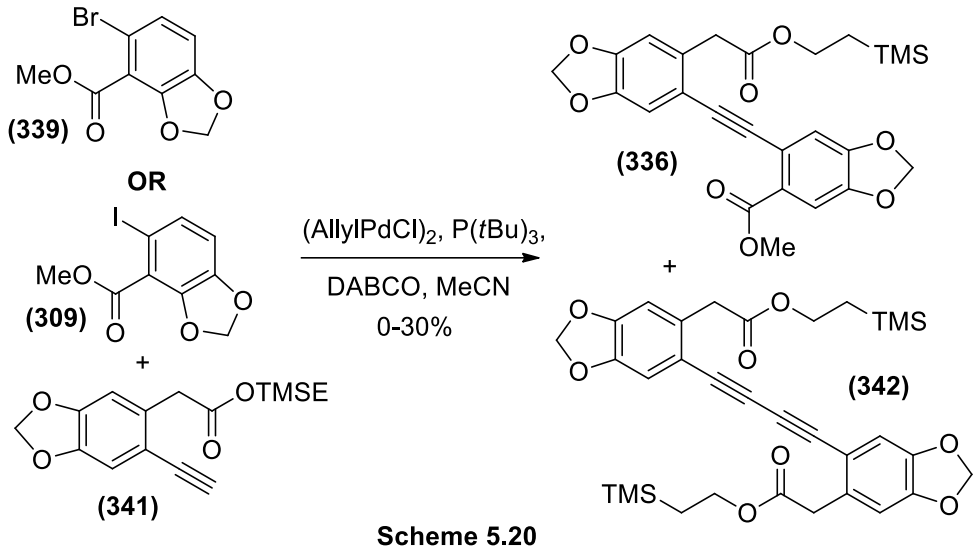
Table 5.3. Optimisation of TMSE esterification

The initial Sonogashira coupling smoothly afforded the cross coupled product **(340)** in good yield using conditions earlier described by Pasfield.[216] The use of catalytic silver nitrate in aqueous acetone allowed for the selective deprotection of the acetylenic TMS group in the presence of the TMSE ether to give the terminal alkyne **(341)**. It is believed that the silver salt acts as a π acid, activating the acetylenic TMS to nucleophilic attack by water, potentially forming a silver acetylide that is then rapidly protonated[223] (Scheme 5.19).



Scheme 5.19

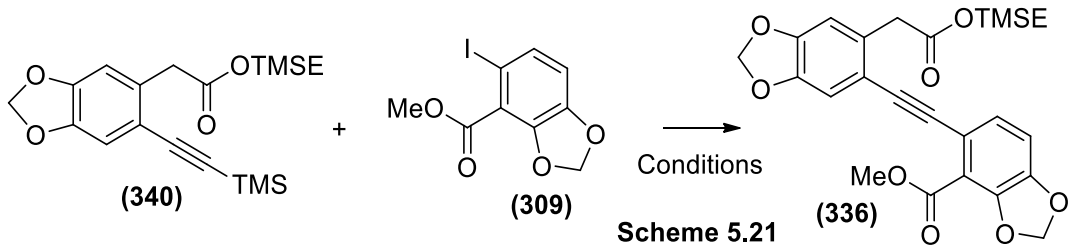
Owing to the difficulties previously observed by Pasfield,[216] efforts continued with the optimisation using the initial coupling copper free Sonogashira protocol.[224] Although initially promising, difficulties were encountered with relatively poor reproducibility, particularly on increasing scale. Multiple side products were generated in various quantities without recovery of the alkyne, primarily through a Glaser type dimerization,[225] the product of which **(342)** could be isolated and characterised. Slow addition of the alkyne to minimise homocoupling proved ineffective, and similar results were obtained with either the iodinated **(309)** or brominated **(339)** starting material. Due to the limiting yields and capricious nature of the reaction, other conditions were investigated (Scheme 5.20).



Scheme 5.20

One of the known methods of reducing Glaser-type homocoupled products is to use the TMS protected alkyne **(340)** directly in what is known as a sila-Sonogashira reaction.[226] This has an added advantage of decreasing the overall step count. Unfortunately, using a variety of literature based conditions; this methodology was

ineffective, providing only low yields of the desired product (Scheme 5.21, Table 5.4).

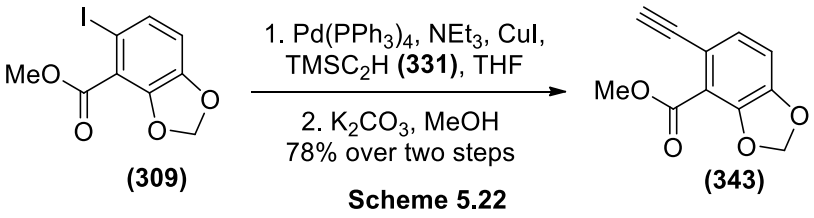


Scheme 5.21

Conditions	Yield	Comment
$Pd(PPh_3)_4$, 50% CuCl, DMF, 80° C	0%	Recovery of starting materials
$Pd(PPh_3)_4$, Ag_2O, TBAB, THF, 65° C	5%	Homocoupling, loss of TMS
$Pd(PPh_3)_4$, AgOAc, THF, 65° C	12%	Homocoupling, loss of TMS

Table 5.4. Sila-Sonogashira attempts

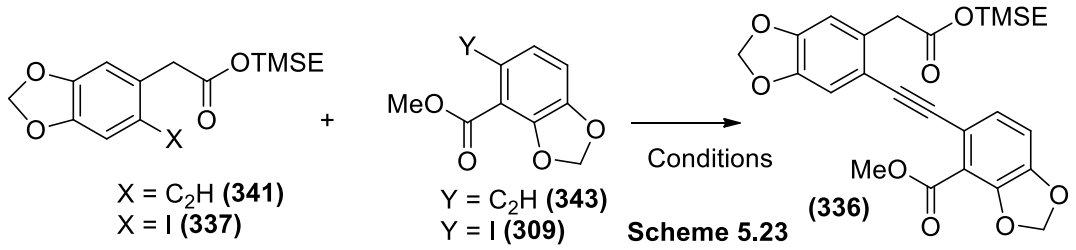
In order to fully explore the potential conditions for the Sonogashira coupling the alternative coupling order was also investigated. Using conditions developed by Pasfield, methyl ester **(309)** was coupled with trimethylsilylacetylene **(331)** directly followed by deprotection of the crude material with potassium carbonate in methanol. This afforded the alternate coupling partner **(343)** in good yield over two steps[216] (Scheme 5.22).



Scheme 5.22

After reviewing the original attempts made by Pasfield, it was decided to return to a copper promoted methodology. One of the common conditions originally developed for the Sonogashira reaction is to use a free amine as a solvent, which helps to solubilise and activate the copper catalyst.[227] This was originally overlooked due to the possibility of amidation; however with diisopropylethylamine, the large steric bulk of amine prevents the formation of amide side products. This immediately led to an improvement in yield. As the Glaser coupling is oxidative, switching to the preformed Pd(0) catalyst $Pd(PPh_3)_4$ substantially increased yields (entry 3).[227] By altering the order of addition and adding the alkyne last, dropwise over one minute, at 60° the

reaction proceeds almost instantly with visible precipitation of diisopropylammonium iodide and without significant side products (entries 4 and 7). Presumably the higher rate of the reaction helps prevent the build-up of larger concentrations of the free alkyne, thus helping to minimise homocoupling. Under optimised conditions the order of the Sonogashira couplings made minimal difference to the overall yield (entries 4 and 7) (Table 5.5, Scheme 5.23).

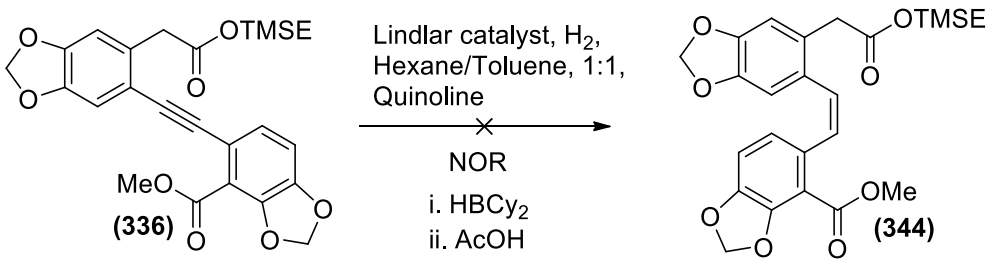


Scheme 5.23

No.	X	Y	Conditions	Yield
1	I	C_2H	DIPA, CuI, $P(tBu)_3$, $Pd(MeCN)_2Cl_2$	36%
2	I	C_2H	DIPA, CuI, PCy_3, $Pd(MeCN)_2Cl_2$	52%
3	I	C_2H	DIPA, CuI, $Pd(PPh_3)_4$	71%
4	I	C_2H	**DIPA, CuI, $Pd(PPh_3)_4$**	**92%**
5	C_2H	I	DIPA, CuI, $P(tBu)_3$, $Pd(MeCN)_2Cl_2$	25%
6	C_2H	I	DIPA, CuI, PCy_3, $Pd(MeCN)_2Cl_2$	23%
7	C_2H	I	**DIPA, CuI, $Pd(PPh_3)_4$**	**96%**

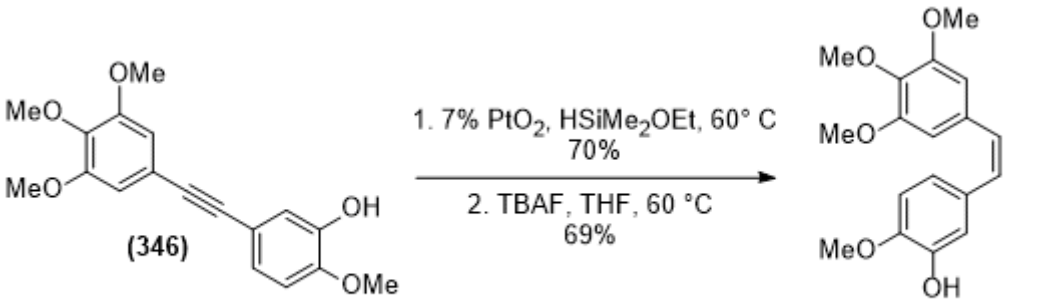
Table 5.5. 5% Pd catalyst loading, 10% CuI loading.

In contrast to the results reported by Pasfield,[216] initial investigations with Lindlar catalyst[228] did not afford any reduction but resulted in the recovery of unchanged starting material **(336)**. Likewise, a two-step process of hydroboration with dicyclohexylborane, followed by protodeboration with acetic acid[229] only resulted in the return of starting material and no isolation of the desired stilbene **(344)** (Scheme 5.24).



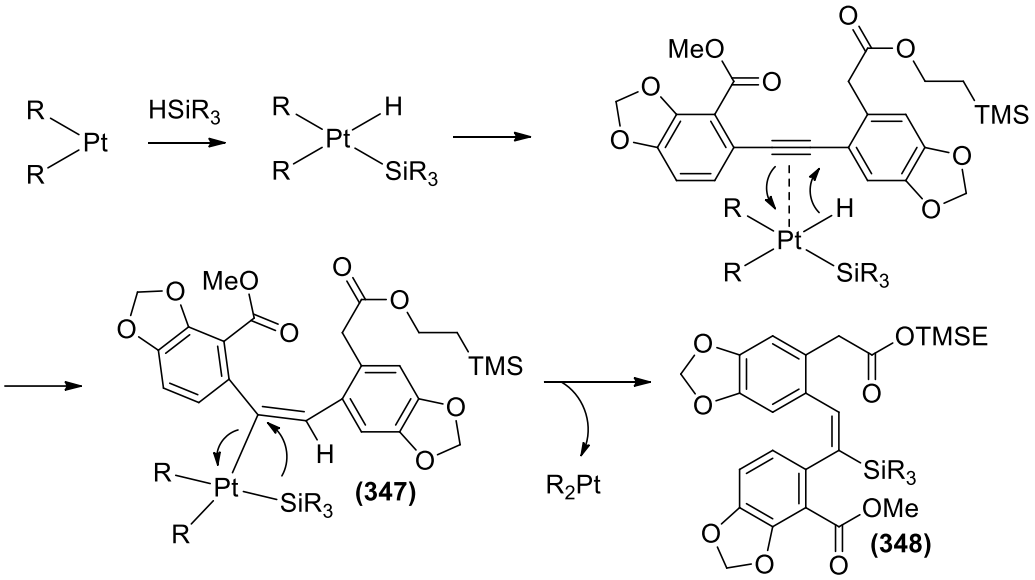
Scheme 5.24

A third and ultimately more productive option was explored whereby the triple bond undergoes a platinum oxide catalysed hydrosilylation followed by addition of TBAF which both fluorodesilylates the double bond and simultaneously removes the TMSE protecting group. This was adapted from a reported procedure used in the synthesis of the stilbene moiety of combretastatin A-4 **(345)** where other semihydrogenation attempts of the tolane **(346)** had resulted in modest yields or selectivities[230] (Scheme 5.25).



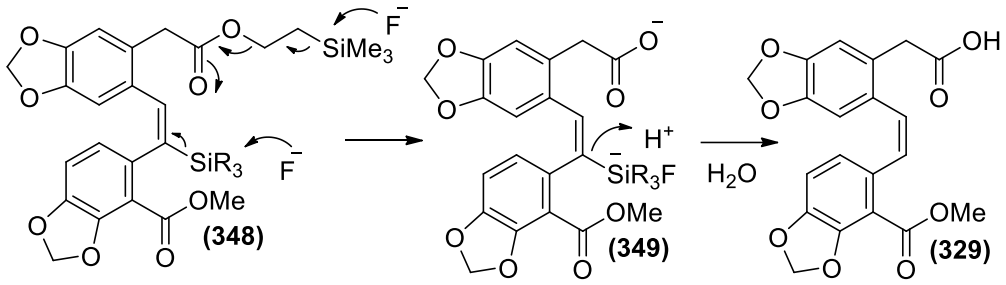
Scheme 5.25

The precise role of platinum oxide in this particular reaction has not been directly evaluated and likely proceeds through reduction by the silane to form platinum black as the active catalyst.[231] The generally accepted mechanism for hydrosilylation is the Chalk-Harrod mechanism, depicted here for a single regioisomeric addition. This invokes initial oxidative addition of the silane to a platinum centre followed by association of the alkyne. Migratory insertion of the hydride occurs in a *cis*-selective fashion to give an intermediate organoplatinum species **(347)** which undergoes reductive elimination with the silyl group with retention of configuration to give the observed *cis*-silyl stilbene[232] **(348)**. The exact speciation of the platinum centre is difficult to ascertain given the heterogeneous nature of the reaction (Scheme 5.26).



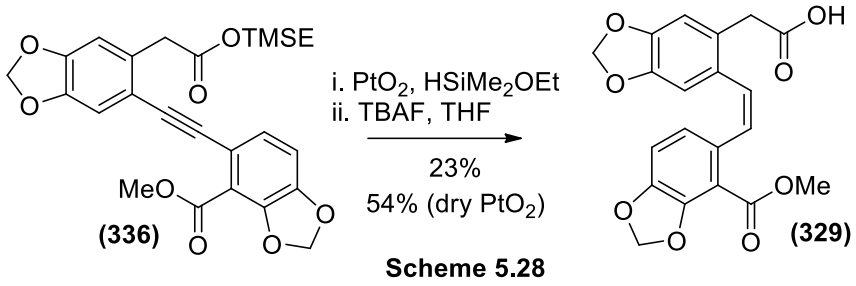
Scheme 5.26

The resulting silyl *cis*-stilbenes **(348)** undergo nucleophilic attack by fluoride at the silicon centre resulting in a transient ate complex **(349)** that is protonated by water present in the TBAF reagent[233] with deprotection of the TMSE group occurring *via* the previously mentioned Grob like fragmentation[51] to give the desired product **(329)** (Scheme 5.27).



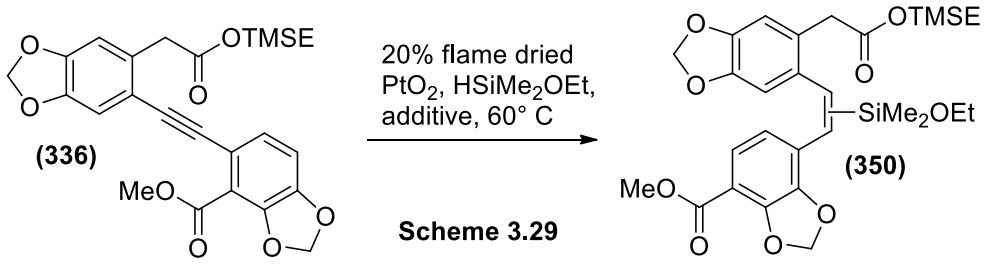
Scheme 5.27

Initial attempts at this two step protocol resulted in an unoptimised 23% yield of the key intermediate **(329)**, which was increased to 54% on flame drying of the catalyst under vacuum before use. This was supported by the appearance of two additional signals in the ^{1}H NMR at 6.82 and 6.53 ppm with a coupling constant of 12 Hz, characteristic of the *Z*-stilbene[234] (Scheme 5.28).



Scheme 5.28

In order to better assess the situation the reaction was carried out in two separate steps and on a larger scale, with yields of the silylated material **(350)** estimated by ^{1}H NMR (see Table 5.6, Scheme 5.29). Recrystallisation of the starting material after significant quantities were obtained, identified solubility problems with the neat reaction conditions. This was thought to be a limiting factor in conversion, particularly on a larger scale. Addition of a small volume of DCM equal to that of the silane reagent resulted in observable dissolution of the starting material and a noticeable exotherm however a lower yield was obtained, presumably due to the lower reflux temperature of the reaction mixture. Switching to chloroform resulted in a better conversion but also the observation of additional side products, possibly due to acidic impurities. Acetonitrile proved to be immiscible with the silylating agent, whereas THF was eventually identified as an ideal solvent, resulting in full conversion of starting material.

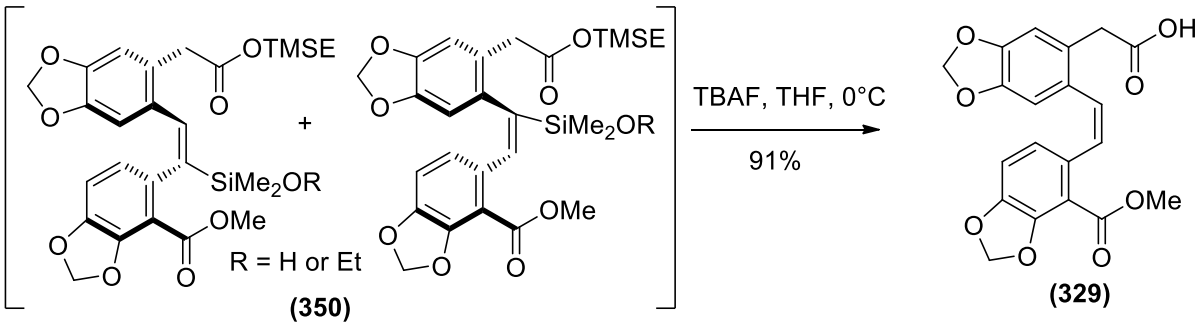


Scheme 3.29

Additive	**Yield**	**Comment**
None	42%	Solubility problems, SM recovery
DCM	32%	Dissolved, SM recovery, lower reflux temperature
$CHCl_3$	60%	Side products observed, SM recovery
MeCN	0%	Solvent immiscible with silane, SM recovery
THF	82%	Full conversion

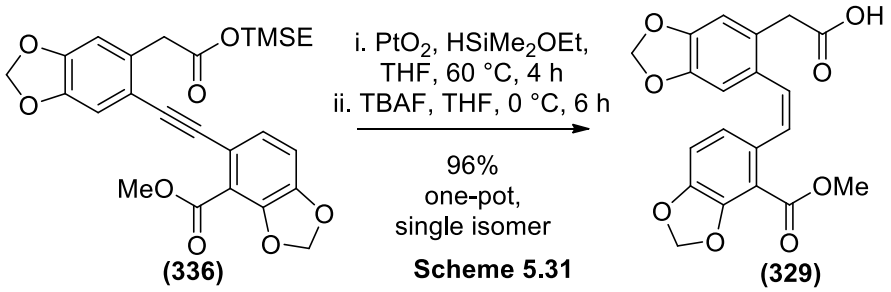
Table 5.6. Silylation optimisation

When attempts were made to isolate and characterise the intermediates **(350)**, the ethoxy group on the silane was observed to be moderately unstable to chromatography. Both regioisomers were observed along with partial hydrolysis of the vinylethoxysilane. The ^{1}H NMR of individual fractions indicated that the silylated stilbenes were atropisomeric resulting in characteristic diastereotopic splitting in the two silyl methyl groups and all three methylenes, which significantly complicated analysis. Fortuitously, these isomers converged upon deprotection with TBAF to give the desired product **(329)** in good yield (Scheme 5.30).



Scheme 5.30

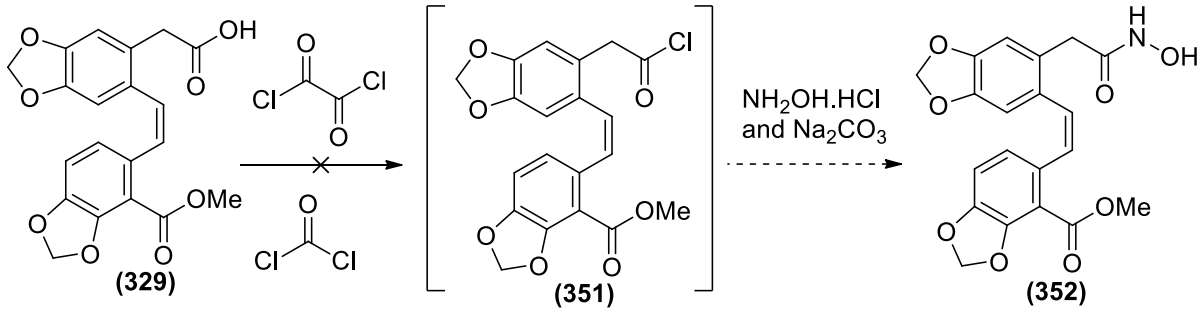
By switching to a newer bottle of anhydrous platinum oxide, with dry THF as a solvent, the hydrosilylation reaction could be monitored directly by TLC. After full conversion to the two regioisomers, TBAF could be added directly in excess to the reaction mixture resulting in a 96% yield of the deprotected stilbene acid **(329)** as a single diastereomer in one pot from tolane **(336)** (Scheme 5.31).



Scheme 5.31

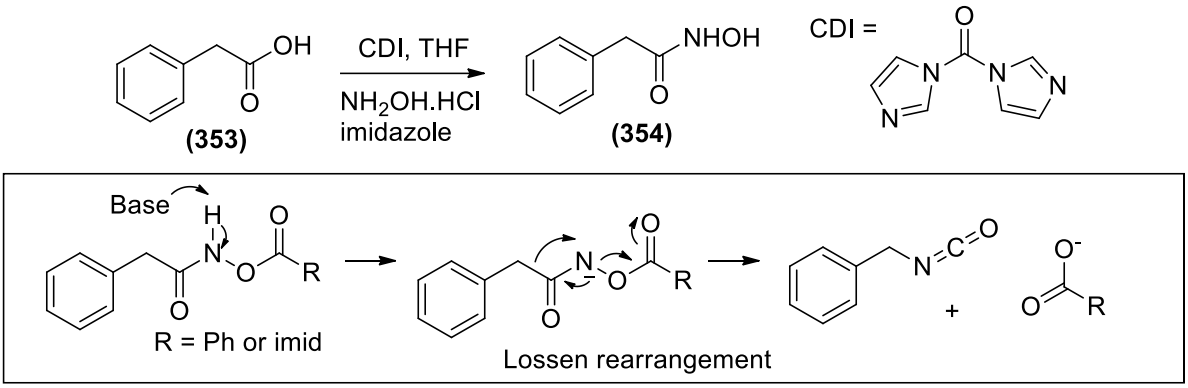
With an established route to the free acid **(329)**, efforts were undertaken to synthesise the hydroxamate ester **(325)** in order to attempt the pivotal osmium catalysed intramolecular aminohydroxylation step. Investigation of the various literature sources had primarily indicated formation of the corresponding acid chloride **(351)** which is subsequently reacted with hydroxylamine to form the hydroxamic acid **(352)**.[217-219] Initial reaction with oxalyl chloride or thionyl chloride

and catalytic DMF consumed starting material, however multiple products formed. This included characteristic ^{1}H NMR peaks for the trans stilbene[234] with coupling constants of ~16 Hz and additional peaks around 9 ppm, characteristic of an aldehyde. A possible explanation for this is that the Vilsmeier like intermediate formed by DMF[115] is undergoing electrophilic aromatic substitution. Based on this information it was presumed that the starting material of this reaction featured considerable acid sensitivity (Scheme 5.32).



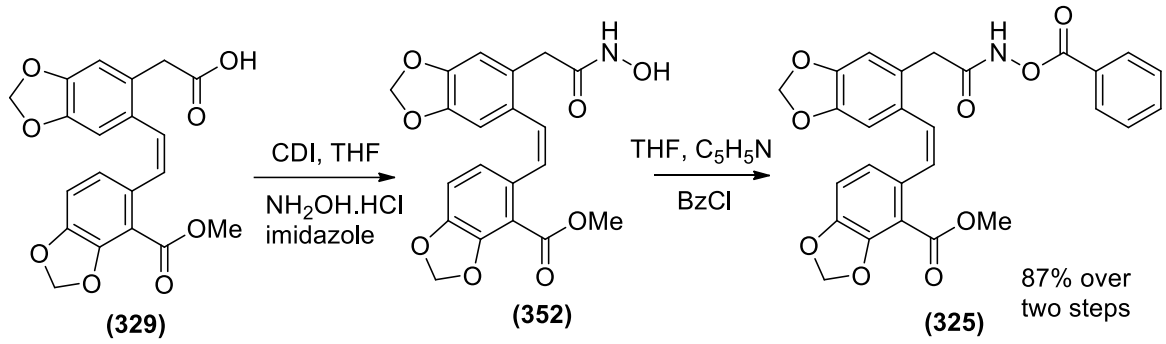
Scheme 5.32

Given the relatively precious nature of the advanced intermediate, a simple model was chosen to identify milder conditions for the formation of the hydroxamic acid and to establish the proof of concept. As such phenylacetic acid **(353)** was treated with CDI in an attempt to generate the imidazoloyl system *in situ* under basic conditions which would then be displaced by hydroxylamine[235] to give the hydroxamic acid **(354)**. Under the initial conditions found in the literature using 1.5 equivalents of CDI in refluxing tetrahydrofuran followed by addition of an excess of hydroxylamine hydrochloride, only moderate conversions were observed. Investigation of the crude ^{1}H NMR spectra revealed that a Lossen rearrangement[134] had likely taken place to generate a number of side products, indicated by additional distinct peaks between 4 and 4.5 ppm characteristic of benzylic amine derivatives which were not further analysed. By altering the order of addition, temperature and stoichiometry this was avoided. The side product seemed to arise from the hydroxamic acid reacting with remaining CDI reagent, a reaction known in the literature.[236] After formation of the imidazoloyl system, the reaction was cooled to room temperature and an excess of imidazole (ground to a fine powder) was added prior to addition of hydroxylamine hydrochloride. This then allowed any excess CDI reagent to be consumed by free hydroxylamine, minimising the possibility of side products (Scheme 5.33).



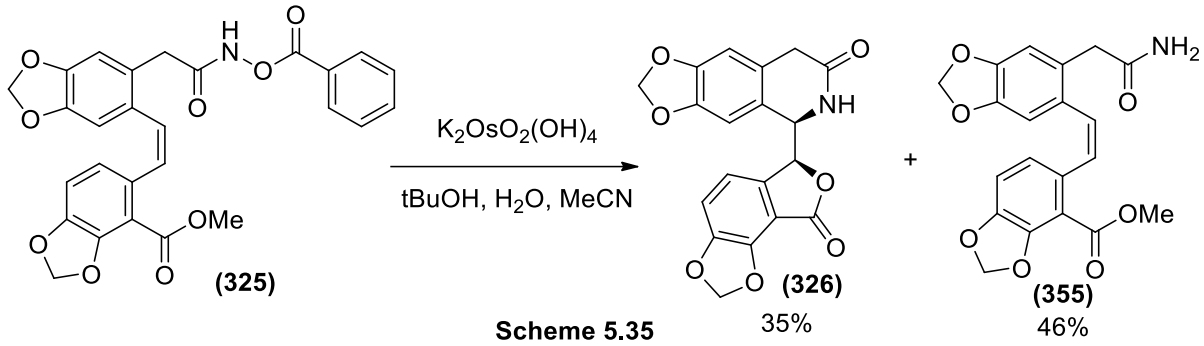
Scheme 5.33

Taking heed of the lessons learnt in the model system, the developed methodology was applied to the synthesised stilbene acid **(329)**. Treatment with CDI and hydroxylamine hydrochloride under optimised conditions cleanly afforded the desired hydroxamic acid **(352)**. When subjecting the crude hydroxamic acid to the benzoylation conditions, pyridine was used as a weaker base in place of triethylamine to help prevent the previously observed Lossen rearrangement. Thankfully, the *O*-benzoylated derivative **(325)** was obtained in high purity with an overall yield of 87% over two steps (Scheme 5.34).



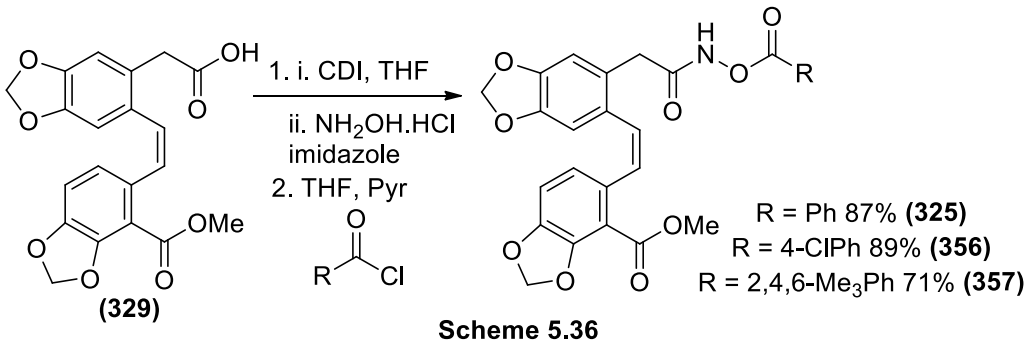
Scheme 5.34

With the critical benzoylated hydroxamate **(325)** in hand it was finally possible to attempt the key late stage amidohydroxylation reaction. Simple treatment of the system with 10% potassium osmate in a 1:1:1 mixture of t-BuOH, MeCN and water resulted in complete consumption of starting material and the isolation of the desired product **(326)** as a single diastereomer in 35% yield with the majority of the remaining mass balance accounted for by the reduced amide **(355)** which could be isolated and characterised (Scheme 5.35).



Scheme 5.35

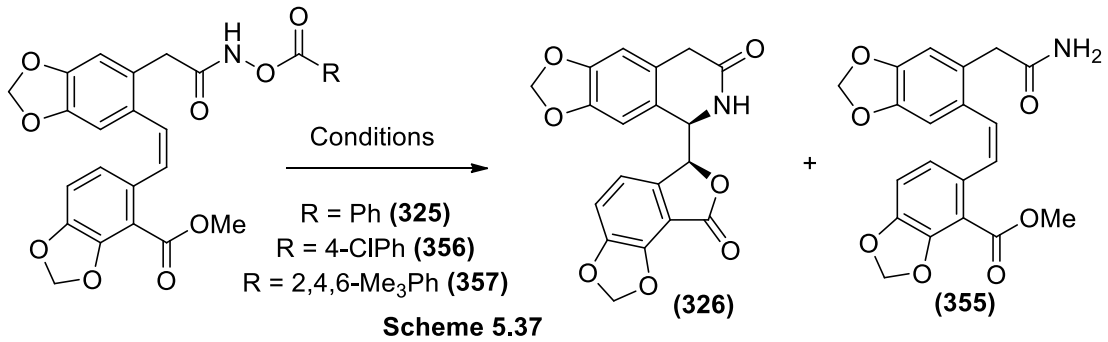
The mechanism for the formation of the reduced amide product is unknown but had also been observed in the literature for certain other leaving groups, most notably the pivalate ester.[237] It is intriguing as cleavage of the *N-O* bond is an inherently reductive process yet only a catalytic quantity of osmate is used without the observation of any other oxidised products. In addition to the benzoate **(325)**, the mesitoate **(356)** and 4-chlorobenzoate **(357)** derivatives were also synthesised in comparable yield from their corresponding acid chlorides. These examples were selected as they had been the groups of choice in previous literature studies[218-219] (Scheme 5.36).



Scheme 5.36

Optimisation of the aminohydroxylation protocol is summarised in Table 5.7 (Scheme 5.37). Interestingly, under identical conditions the differing benzoyl leaving groups had practically no effect on the isolated yield, with results falling easily within experimental error (entries 1-3). As such the remainder of the optimisation work was carried out with the 4-chloro derivative **(356)** as the ^{1}H NMR peaks were the most clearly identifiable in the spectrum of the crude reaction mixture, allowing for a direct approximation of yield. It was later discovered that the product could be cleanly isolated from crude reaction mixtures dissolving the crude mixture in hot tetrahydrofuran then adding an equivalent volume of hexane to selectively precipitate the product. A quick screen of solvents (entries 4-9) identified THF and dioxane as

the most suitable, in most cases the mass balance was accounted for by the reduced amide side product **(355)**. Changing the catalyst to osmium tetroxide[219] resulted in a modest reduction in yield and additional uncharacterised side products presumably due to dihydroxylation (entry 11). Attempts to change the pH of the reaction medium (entries 12-15) to see if it was having an effect on yield resulted in a modest increase in yield using sodium bicarbonate, but almost complete loss of activity in the presence of sodium carbonate or acetic acid. Interestingly the addition of triethylamine to the reaction medium seemed to have no deleterious or beneficial effect. The best yield of 63% was obtained by reducing the concentration of water in the reaction medium (entry 17), however too little water resulted in a decrease in the observed yield.



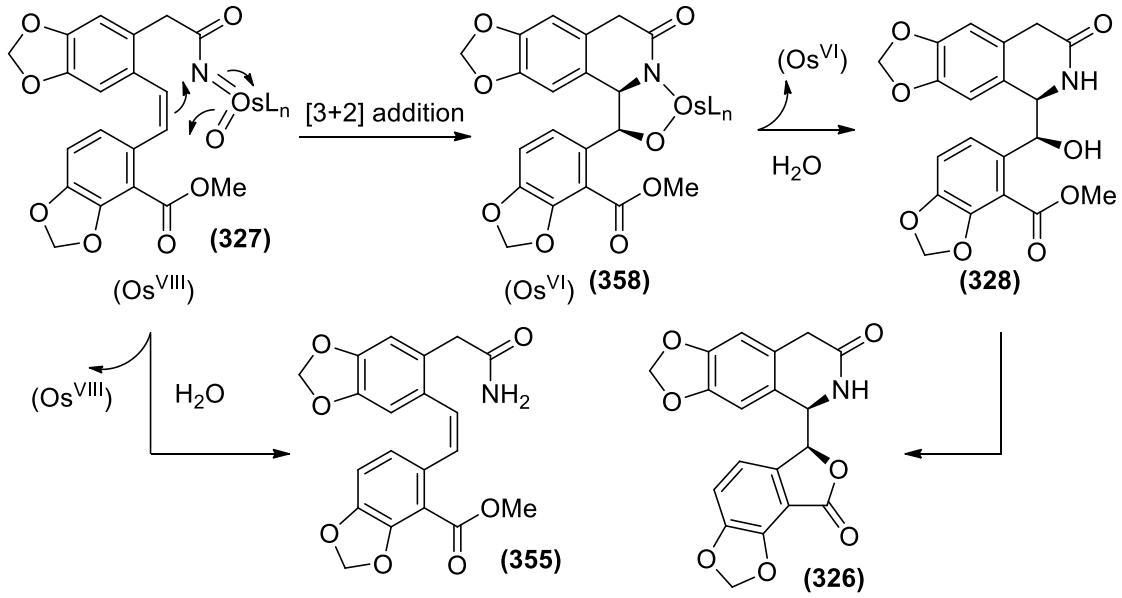
Scheme 5.37

No.	R	Solvent	Ratio	Catalyst	Additive	Yield (%)
1*	Ph	*t*BuOH, MeCN, H_2O	1:1:1	$K_2OsO_2(OH)_4$ 10%	none	35
2*	4-ClPh	*t*BuOH, MeCN, H_2O	1:1:1	$K_2OsO_2(OH)_4$ 10%	none	32
3*	Mes	*t*BuOH, MeCN, H_2O	1:1:1	$K_2OsO_2(OH)_4$ 10%	none	31
4*	4-ClPh	MeCN, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	none	30
5*	4-ClPh	Dioxane, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	none	38
6	4-ClPh	*t*BuOH, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	none	10
7	4-ClPh	*n*BuOH, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	none	5
8	4-ClPh	Acetone, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	none	8
9*	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	none	42

10	4-ClPh	THF, H_2O	1:1	$K_2OsO_2(OH)_4$ 10%	none	27
11	4-ClPh	THF, H_2O	4:1	OsO_4 10%	none	21
12	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	citric acid	0
13*	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	$NaHCO_3$	51
14	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	NEt_3	38
15	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 2%	Na_2CO_3	6
16	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 20%	$NaHCO_3$	12
17*	4-ClPh	THF, H_2O	4:1	$K_2OsO_2(OH)_4$ 10%	$NaHCO_3$	53
18*	**4-ClPh**	**THF, H_2O**	**9:1**	$K_2OsO_2(OH)_4$ 10%	**$NaHCO_3$**	**63**
19*	4-ClPh	THF, H_2O	40:1	$K_2OsO_2(OH)_4$ 10%	$NaHCO_3$	42 %

Table 5.7 Entries marked with * correspond to isolated yields.

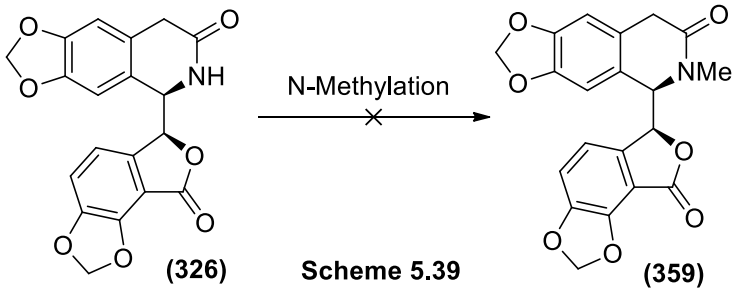
The water itself is required for the catalytic cycle to maintain higher turnover as the cyclic osmium intermediate **(358)** must be hydrolysed to regenerate active osmium(VI) and free the nascent benzylic alcohol to cyclise with the ester.[217] However water may also be problematic in the formation of reduced amide side product **(355)** by hydrolysis of the intermediate imido osmium species **(327)**. The initial activation step produces an equivalent of the corresponding benzoic acid which will lower the pH as the reaction proceeds, use of $NaHCO_3$ to buffer the reaction system may be what resulted in the modest increase in yield if the lower pH promotes imido osmium hydrolysis (Scheme 5.38).



Scheme 5.38

Formation of the desired product was supported by experimental evidence and could be fully characterised. Strong diastereotopic splitting of the amide alpha protons are indicative of incorporation into a ring and a clear coupling could be observed between the amide NH signal at 8.30 ppm and the aminomethine at 4.95 ppm. A correct mass of *m/z* 390 for the sodium adduct ([M+Na]$^+$), and loss of the methyl ester signal by NMR gave additional evidence that lactone formation had also occurred. The relative stereochemistry is not easily determined from the experimental data but inferred based on the mechanism of the amidohydroxylation[217] and the isolation of a single diastereomer.

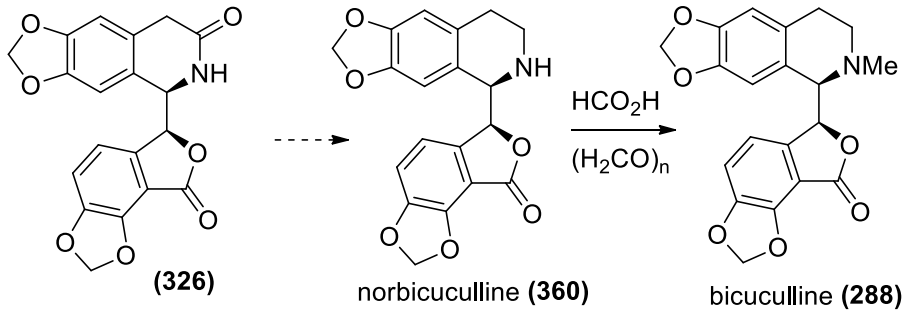
After successful development of the key osmium catalysed transformation, attention was turned to methylating and then reducing the amide. Initial efforts focused around direct formation of the methylamide **(359)**. Unfortunately, despite attempting a number of conditions this was found to be unsuccessful. With kinetic deprotonation with LDA in THF, quenched with methyl iodide or dimethyl sulfate a complex mixture of seemingly inseparable products was obtained, the use of diisopropylethylamine at higher temperatures yielded similar results. This is presumed to be due to the highly similar pKa values of the amide nitrogen and the acidic methylene protons alpha to the amide which makes both C and *O*-methylation possible in addition to the desired *N*-alkylated product. Additional singlet peaks were observed in ^{1}H NMR around 3.8, 3.5, 3.4, 2.4, 1.7 and doublets at 1.2, which along with other signals indicated formation of at least 4 different products. Further investigation of this approach was therefore determined to be a waste of valuable material.



(326) **Scheme 5.39** **(359)**

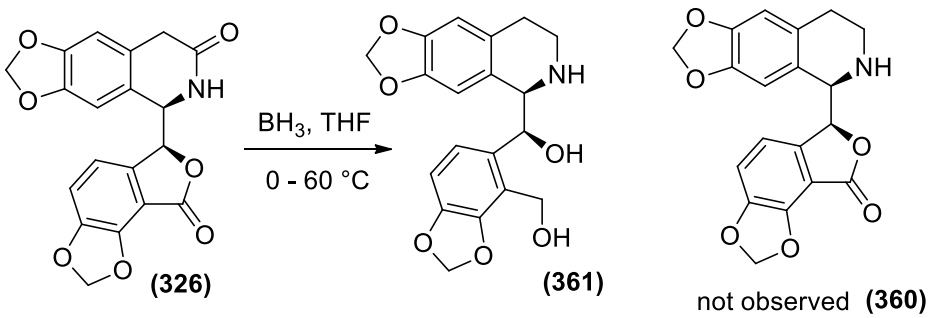
The primary focus was therefore shifted to chemoselective reduction of the secondary amide in the presence of the ester carbonyl. This in turn would produce the natural product norbicuculline **(360)**, which can be converted to bicuculline itself *via* an Eschweiler-Clarke reaction under literature conditions.[210] If successful this

would constitute a total synthesis of norbicuculline and a formal synthesis of bicuculline itself (Scheme 5.40). In general, conditions for the selective reduction of amides in the presence of esters exploit the higher nucleophilicity of the amide carbonyl and require the use of the electrophilic reducing agents.[238]



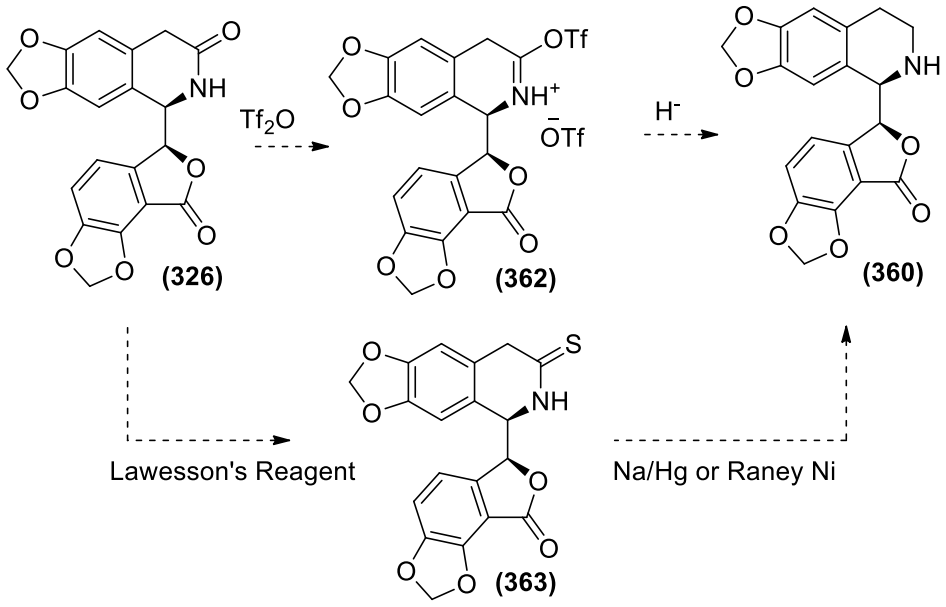
Scheme 5.40

When the system was subjected to the most prototypical electrophilic reducing agent, borane,[238a] over reduction was observed spectroscopically but the product was not isolated. This was supported by the appearance of an addition AB system in the ^{1}H NMR at 5.1 ppm corresponding to the protons of the benzylic alcohol. The reaction proceeded *via* initial formation of a borane adduct accompanied by production of hydrogen gas, this was supported by initial ^{1}H NMR of the crudely obtained material which featured the same signals as the starting material without the amide NH accompanied by a distinct broadening and change in solubility.[238a] Upon heating only over reduction to the amino alcohol was observed, presumably facilitated by internal hydride delivery. Attempts to form an amide formaldehyde adduct and reduce directly with borane to give bicuculline were likewise unsuccessful, with none of the key literature peaks being identifiable in the ^{1}H NMR (Scheme 5.41).



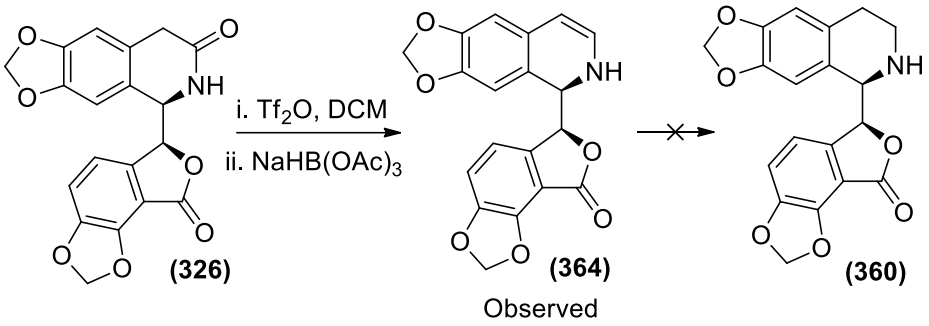
Scheme 5.41

Two alternative approaches were therefore investigated to selectively activate the amide carbonyl to reduction.[239] It was thought that this could be achieved by either selective transformation with triflic anhydride to the iminoyl triflate **(362)** followed by nucleophilic reduction *in situ*; or in a two-step process featuring selective formation of the thioamide **(363)** with Lawesson's reagent,[240] the sulphur atom could then be reductively removed with an appropriate thiophilic reducing agent[241] such as sodium mercury amalgam or Raney nickel (Scheme 5.42).



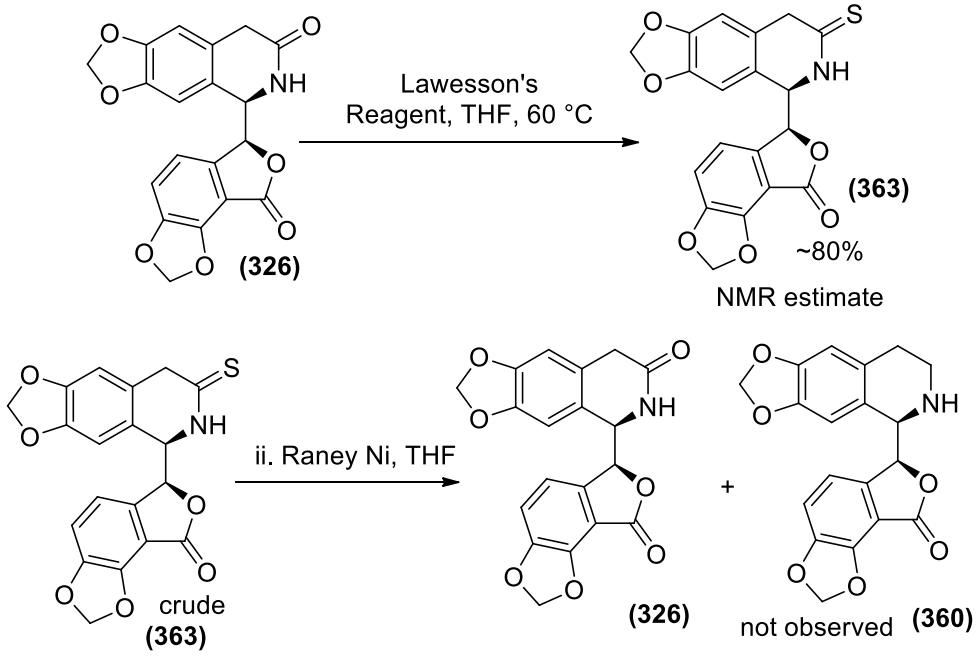
Scheme 5.42

In general, selective activation of the amide carbonyl with triflic anhydride was successful, however subsequent addition of sodium triacetoxyborohydride resulted in incomplete reduction, forming characteristic peaks identified as the enamine **(364)** in the ^{1}H NMR of the crude reaction product, forming a pair of doublets at 7.6 and 6.3 ppm with a coupling constant of 12 Hz (Scheme 5.43). When the crude material was further exposed to $NaCNBH_3$ and acetic acid in an attempt to isolate the desired product, only decomposition was observed. Use of triethylsilane or diludine following literature precedence[242] resulted only in formation of complex mixtures.



Scheme 5.43

Using the thioamide approach with Lawesson's reagent in refluxing tetrahydrofuran, the thioamide product **(363)** was clearly observable as the major product by TLC with a characteristic decrease in polarity. Direct treatment of the crude thioamide **(363)** with Raney Ni resulted in recovery of the starting amide **(326)**, however it is known in the literature that this may be due to poor reagent quality.[240b] Owing to time and safety constraints it was not possible to prepare freshly activated reagent (Scheme 5.44).

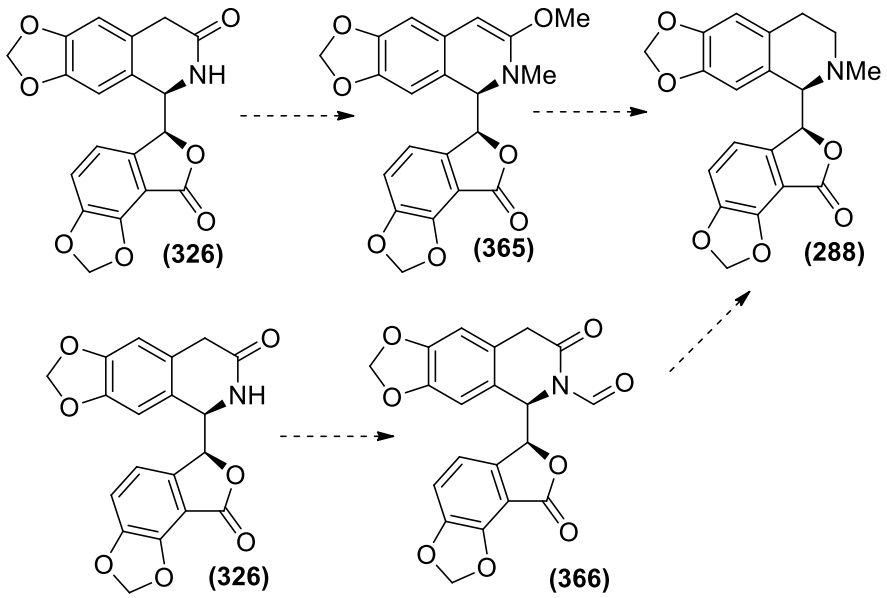


Scheme 5.44

5.5 Future work

At this point research was discontinued due to time constraints. Both the thioamide and imidoyl triflate approaches warrant further investigation as the final step of the synthesis, as each are promising. Another option that was considered but not

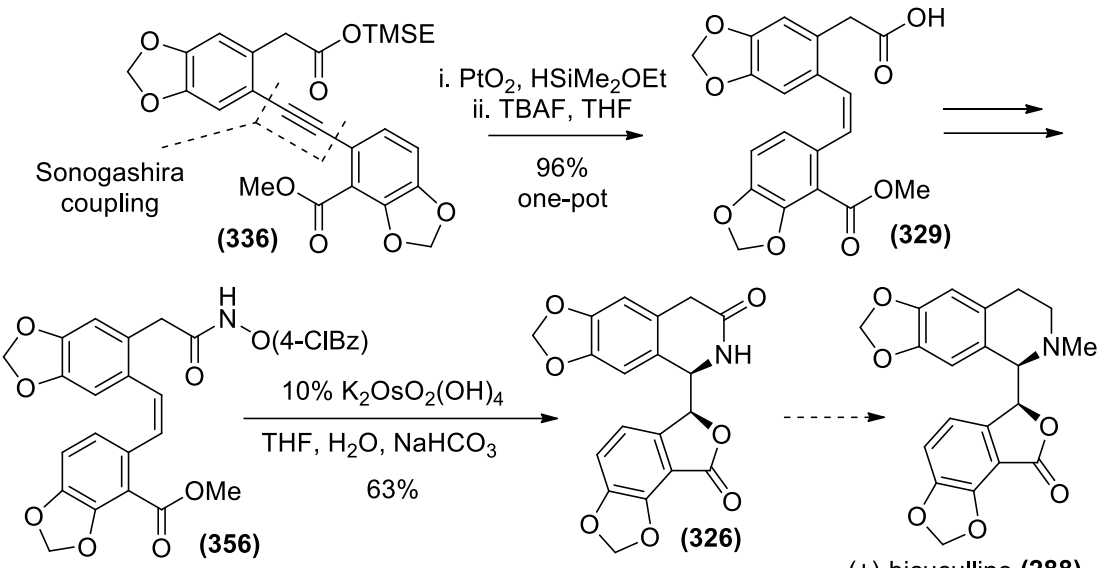
attempted is to *N,O-bis*-methylate **(365)** with Meerwein's salt[243] or methyl triflate then reduce; or to alkylate the nitrogen with something that can be subsequently reduced to a methyl group for example a formyl substituted imide[51] **(366)** using formic acetic anhydride followed by borane reduction (Scheme 5.45). Additional work could then be undertaken to establish enantioselective conditions for the pivotal amidohydroxylation reaction, for which there is some literature precedence in the intermolecular case.[219]



Scheme 5.45

5.6 Conclusion

Overall the synthetic procedure came tantalisingly close to the synthesis of the natural product norbicuculline **(360)**, which should be achievable with further effort. The required carbon framework **(336)** was rapidly accessed utilising a twinned Sonogashira coupling of readily accessible starting materials. Following which a key stereoselective hydrosilylation /protodesilylation/deprotection transformation was effected in high yield, in a one pot reaction **(329)**. This then set the stage for a *syn*-selective osmium catalysed intramolecular amidohydroxylation reaction, establishing two new rings with the desired relative configuration present in the natural product. This key polycyclic framework **(326)** was synthesised in a completely diastereoselective fashion in an impressive 31.5% overall yield in a shortest linear sequence of 8 steps (Scheme 5.46).

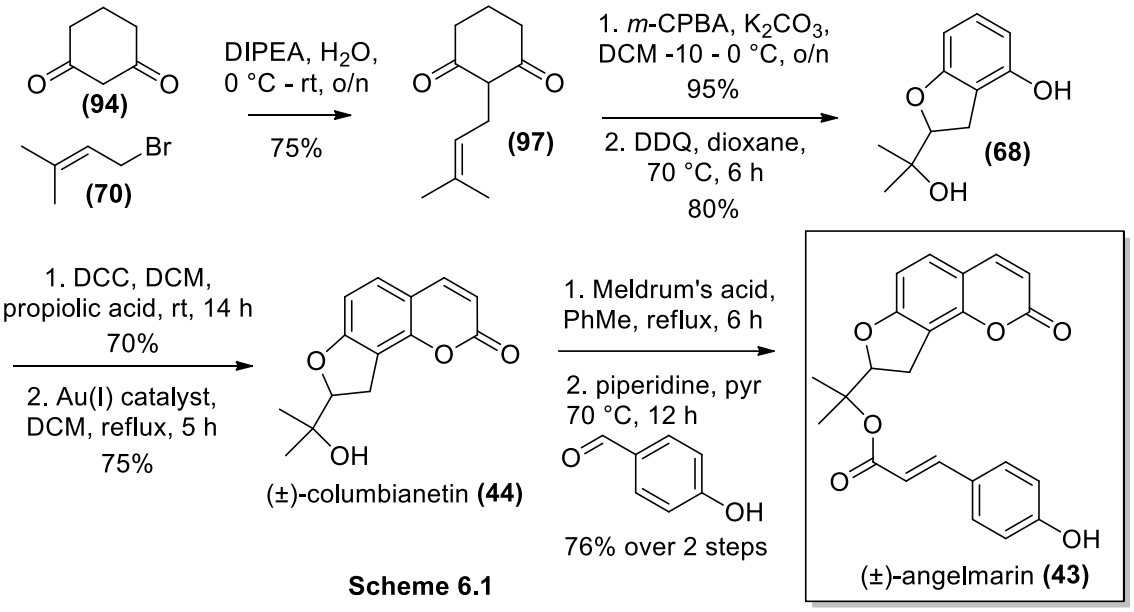

OTMSE
Sonogashira coupling
MeO
(336)
i. PtO2, HSiMe2OEt
ii. TBAF, THF
96%
one-pot
OH
OMe
(329)
H
N
O(4-ClBz)
OMe
(356)
10% K2OsO2(OH)4
THF, H2O, NaHCO3
63%
NH
(326)
NMe
(±)-bicuculline (288)

Scheme 5.46

Chapter 6 - Conclusion

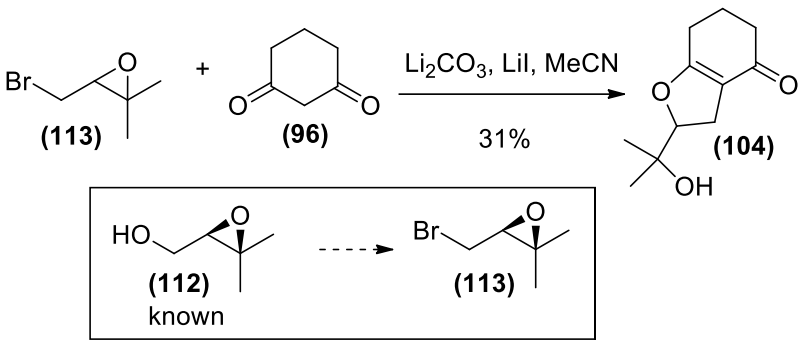
The preceding body of work covers a broad range of chemistry featuring diverse approaches to access a variety of complex molecular scaffolds. Attempts have been made to conduct a systematic investigation of the chemistry therein, grounded in the scientific method. Through this approach, guided by results and observations, progress was made towards the synthesis of the desired targets.

In chapter 2 careful analysis of side products revealed a facile 5-exo-tet cyclisation that was able to be incorporated into the synthetic scheme. Combined with the versatility and mild conditions of the gold(I) catalysed intramolecular hydroarylation this ultimately allowed for a protecting group free synthesis of the natural product angelmarin **(43)** in only 7 steps and 22% overall yield (Scheme 6.1).



Scheme 6.1

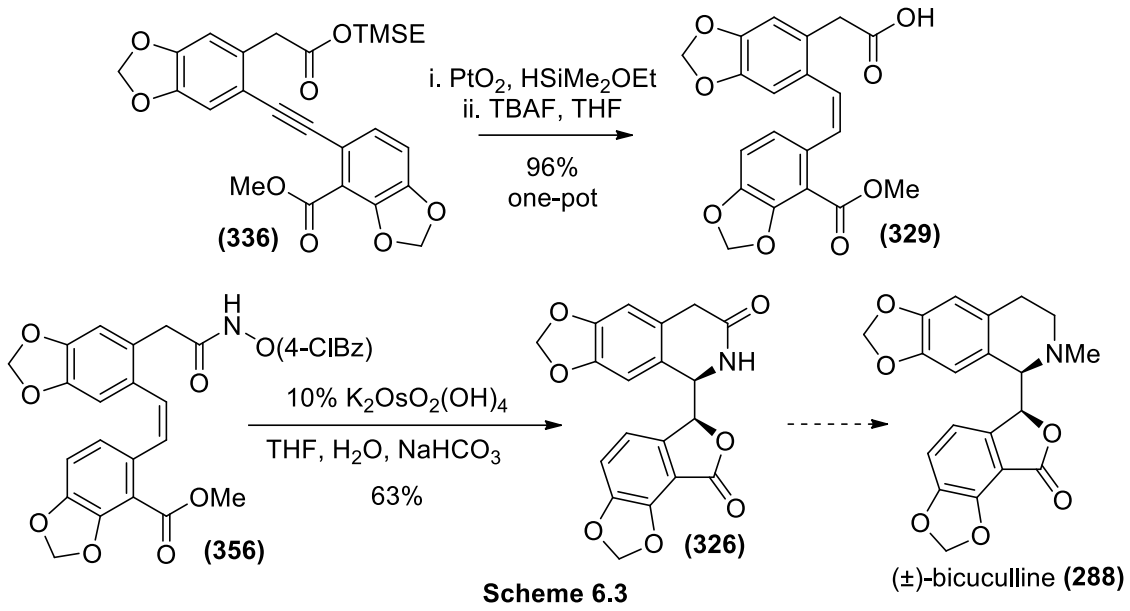
In comparison to the pre-existing syntheses, this one is particularly versatile, allowing for an easy synthesis of analogues. The possibility of an enantioselective synthesis was also investigated. In doing so a novel annulation reaction was discovered that has the potential to generate either enantiomer *via* a known Sharpless epoxidation procedure (Scheme 6.2).



Scheme 6.2

During investigations into the synthesis of ochrosamine B **(118)** in Chapter 3, an ambitious high risk, high reward plan was embarked upon to rapidly access the desired framework through novel chemical approaches. Despite exploration of a range of intriguing approaches, little progress was achieved. This is part of the reality of the research paradigm where the exploration of the unknown often correlates poorly with success. It remained, however a worthwhile investigation in the pursuit of good synthesis. Research towards the hasubanan framework **(204)** followed a similar pathway with efforts falling short of obtaining the desired α-tertiary amine framework that would have enabled the planned intramolecular Alder-ene reaction.

Finally in Chapter 5, significant progress was made towards a regioselective synthesis of bicuculline **(288)**. Key highlights were the developments of a highly efficient one pot stereoselective hydrosilylation/protodesilylation/deprotection transformation and the successful implementation of an osmium catalysed intramolecular amidohydroxylation reaction to simultaneously and diastereoselectively, install both of the remaining rings found in the natural product (Scheme 6.3).



Scheme 6.3

This sets the stage for reduction of the amide and subsequent methylation to form the natural product. The major advantage of the synthetic approach is that the inherent stereoselectivity of the reactions' mechanisms completely control the relative stereochemistry. Adaptation of existing research, regarding enantioselective amidohydroxylations, to the intramolecular version carries the possibility of achieving an enantioselective synthesis.

In terms of the overall goal of striving towards good synthesis, many aspects have been achieved. The successful development of a protecting group free synthesis of angelmarin is an excellent showcase of the powerful yet mild Au(I) catalysed intramolecular hydroarylation bolstered by the invention of a novel annulation reaction. This is again demonstrated in the research towards the synthesis of bicuculline, with a highly efficient and stereoselective synthesis of the desired polycyclic framework featuring one of the first applications of an amidohydroxylation towards the synthesis of a natural product.

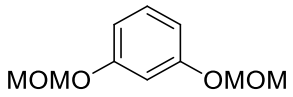
Chapter 7 – Experimental

7.1 General Experimental Procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian or Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei or on a Bruker spectrometer operating at 800 MHz for proton and 200 MHz for carbon nuclei. Unless otherwise specified, spectra were acquired at 25 °C in deuterochloroform ($CDCl_3$) that had been stored over anhydrous K_2CO_3. Chemical shifts are recorded as δ values in parts per million (ppm) downfield shift from tetramethylsilane (δ_{TMS} = 0), using residual solvent as an internal reference.[244] Infrared spectra (ν_{max}, cm^{-1}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on KBr plates. Low and high resolution ESI mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low and high-resolution EI mass spectra were recorded on a VG Fisons AUTOSPEC three-sector double focussing instrument. Melting points were measured using a Stanford Research Systems Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating.[245] Flash chromatographic separations were carried out following protocols defined by Still *et al*.[246] with silica gel 60 (40–63 μm) as the stationary phase and using the AR or HPLC-grade solvents indicated. Starting materials and reagents were generally available from Sigma–Aldrich, Merck, TCI, Strem or Lancaster chemical companies and were used as supplied. Solvents, drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab chemical companies. Solvents including THF, DMF, dichloromethane, benzene and toluene were dried using a Glass Contour solvent purification system that was based upon a technology originally described by Grubbs *et al*.[247] Methanol and ethanol were used as obtained from the above mentioned suppliers. Where necessary, reactions were performed under a nitrogen atmosphere. All X-Ray crystallographic analysis was performed by Dr. Tony Willis of the Australian National University.

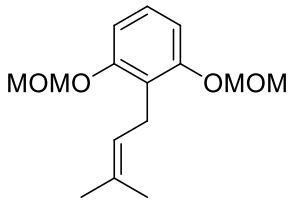
7.2 Angelmarin and Columbianetin.

1,3-Bis(methoxymethoxy)benzene **(71)**[49]



Sodium hydride 60% dispersion in mineral oil (872 mg, 36.3 mmol) was added portionwise over 5 minutes to a stirred solution resorcinol **(72)** (1.00 g, 9.08 mmol) in anhydrous *N*,*N*-dimethylformamide (25 mL) at 0 °C. After 30 minutes, methoxymethylchloride (2.76 mL, 36.3 mmol) was added as a single portion and the resulting solution was warmed to room temperature over 12 hours. The reaction was cooled to 0 °C, quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL), and then extracted with ethyl acetate (3 × 30 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was purified *via* silica gel chromatography using ethyl acetate : hexane (1:4) to afford 1,3-bis(methoxymethoxy)benzene **(71)** as a colourless oil (1.75 g, 97%);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 1H), 6.80 (t, J = 2.3 Hz, 1H), 6.75 (dd, J = 8.2, 2.4 Hz, 2H), 5.20 (s, 4H), 3.51 (s, 6H). Spectral data were in good agreement to that reported in the literature.[49]

1,3-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)benzene **(73)**[50]

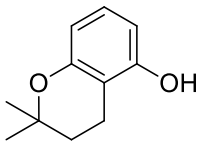


Butyllithium 1.6 M solution in hexane (7.50 mL, 12.0 mmol) was added to a stirred solution of 1,3-bis(methoxymethoxy)benzene **(71)** (2.00 g, 10.1 mmol) in dry tetrahydrofuran (10 mL) under nitrogen at -78 °C. This was warmed to 0 °C and stirred for 1 hour. Prenyl bromide (1.28 mL, 11.1 mmol) **(70)** was then added dropwise and the reaction allowed to warm to room temperature over a 14 hour period. The reaction was then diluted with water (25 mL) and the product extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography using ethyl acetate : hexane (1:9) to give 1,3-

bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yl)benzene **(73)** as a colourless oil (1.83 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, t, J = 8.5 Hz), 6.77 (2H, d, J = 8.5 Hz), 5.23 (1H, t, J = 7 Hz), 5.20 (4H, s), 3.49 (6H, s), 3.42 (2H, d, J = 7 Hz), 1.81 (3H, s), 1.68 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.9, 131.2, 127.0, 123.1, 120.4, 108.2, 94.7, 56.2, 26.0, 23.0, 18.0. Spectral data identical to that reported in the literature.[50]

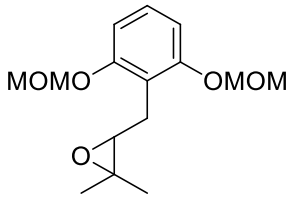
2,2-Dimethylchroman-5-ol **(74)**[52]



To a cooled (0 °C), stirred solution of 1,3-Bis(methoxymethoxy)-2-prenylbenzene **(73)** (1.33 g, 5 mmol) in tetrahydrofuran (4 mL), was added aqueous HCl (0.1 M, 1 mL). The solution was stirred, and monitored by thin layer chromatography. After 2 hours starting material had been consumed. The acidic solution was neutralised by careful addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was subjected to silica gel chromatography by gradient elution using ethyl acetate : hexane (1:10 – 1:0). Concentration of the resulting fractions led to the isolation of 2,2-dimethylchroman-5-ol as a colourless oil **(74)** (521 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (m, 1H), 6.43 (dd, J = 7.9, 1.0 Hz, 1H), 6.34 (dd, J = 7.9, 1.0 Hz, 1H), 4.7 (s, 1H), 2.68 (t, J = 6.8 Hz, 1H), 1.83 (t, J = 6.8 Hz, 2H), 1.35 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 154.2, 127.5, 110.3, 108.8, 106.3, 74.3, 32.5, 27.0, 17.2. Spectral data identical to that reported in the literature.[52]

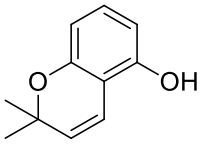
3-(2,6-Bis(methoxymethoxy)benzyl)-2,2-dimethyloxirane **(75)**



m-chloroperbenzoic acid (925 mg, 77%, 4.13 mmol) was added portionwise to a stirred, cooled (0 °C) solution of 1,3-bis(methoxymethoxy)-2-prenylbenzene **(73)** (1 g, 3.75 mmol) in dichloromethane (25 mL) over a period of 5 minutes. The reaction was stirred for a further 2 hours at 0 °C then quenched by addition of saturated aqueous Na_2SO_3 (20 mL). The ensuing mixture was then extracted with dichloromethane (3 x 20 mL) and the combined organic extracts washed with saturated aqueous Na_2CO_3 (2 x 20 mL). After drying over Na_2SO_4 and removal of solvent *in vacuo*, the resulting residue was purified by silica gel chromatography using ethyl acetate : hexane (1:9) to give 3-(2,6-bis(methoxymethoxy)benzyl)-2,2-dimethyloxirane **(75)** as a colourless oil (869 mg, 82%).

R_f = 0.76 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.23 (m, 4H), 3.51 (s, 6H), 3.15 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.01 (dd, *J* = 7.5, 4.5 Hz, 1H), 2.87 (dd, *J* = 13.6, 7.5 Hz, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 156.3, 127.8, 116.2, 107.8, 94.6, 63.8, 59.1, 56.1, 24.9, 23.3, 19.1; **IR** ν_{max} (neat) 2956, 1594, 1468, 1254, 1152, 1039, 922, 783 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 305.1 [(M + Na)+, 100%], 251 (22), 221 (43); **HRMS** [Found: $(M + Na)^+$, 305.1368. $C_{15}H_{22}O_5Na$ requires $(M + Na)^+$, 305.1365].

2,2-Dimethyl-*2H*-chromen-5-ol **(77)**[54]

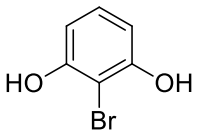


To a cooled (0 °C), stirred solution of 3-(2,6-bis(methoxymethoxy)benzyl)-2,2-dimethyloxirane **(75)** (421 mg, 1.49 mmol) in tetrahydrofuran (4 mL), was added 0.1M HCl (1 mL). The solution was stirred and monitored by thin layer chromatography. After 2 h starting material had been consumed. The acidic solution was neutralised by careful addition of saturated sodium bicarbonate solution (10 mL)

and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was subjected to silica gel chromatography by gradient elution using ethyl acetate : hexane (1:10 – 1:0) concentration of the resulting fractions led to the isolation of undesired 2,2-dimethyl-*2H*-chromen-5-ol **(77)** as a colourless solid (85 mg, 32%).

m.p. 114 °C, (lit 114-116° C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.92 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 10.2 Hz, 1H), 6.40 (d, *J*= 8.8 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 5.58 (d, *J* = 9.7 Hz, 1H), 4.83 (s, 1H), 1.41 (s, 6H). Spectral data identical to that reported in the literature.[54]

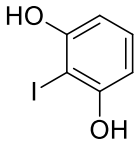
2-Bromoresorcinol **(79)**[248]



Bromine (3.83 mL, 74.4 mmol) was slowly added to resorcinol **(72)** (2.48 g, 22.5 mmol) in chloroform (40 mL) over 5 minutes at room temperature. After heating at reflux for 1 hour the solvent was removed by rotary evaporation and the residue dissolved in methanol (55 mL). To this a solution of sodium sulfite (5.67 g, 45.0 mmol) and sodium hydroxide (1.80 g, 45.0 mmol) in water (65 mL) was added and stirred for 18 hours at room temperature. The reaction was then acidified with 1 M hydrochloric acid followed by extraction with diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and then purified by silica gel chromatography using ethyl acetate : hexane (3:17) to give 2-bromoresorcinol **(79)** as pale orange crystals (3.66 g, 86%).

R_f = 0.22 (EtOAc:Hex, 3:7); **m.p.** 83-84 °C (lit 101-102 °C)[248]; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 2H), 5.48 (br s, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 152.9, 129.0, 108.1, 99.3; Spectral data identical to that reported in the literature.[248]

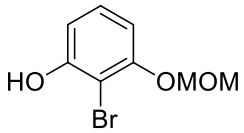
2-Iodoresorcinol **(80)**[56]



To a cooled (0 °C) suspension of resorcinol **(72)** (7.27 g, 66.0 mmol) and iodine (17.92 g, 70.6 mmol), in water (46 mL) was added sodium bicarbonate (6.16 g, 73.3 mmol) portionwise over 5 minutes. The mixture was warmed to room temperature and stirred for a further 30 minutes. The products were extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts successively washed with 10% aqueous sodium sulfite (50 mL) and brine (50 mL). After drying over Na_2SO_4 and removal of solvent *in vacuo*, the solid residue was triturated with cold (-10 °C) chloroform (20 mL) then dried under vacuum to give 2-iodoresorcinol **(80)** as a cream-coloured solid (9.43 g, 61%).

m.p. 98 °C (lit. 99-101 °C)[56]; **^{1}H NMR** (400 MHz, acetone-*d*6) δ 8.83 (s, 2H), 7.00 (t, *J* = 8.1 Hz, 1H), 6.46 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (100 MHz, acetone-*d*6) δ 158.8, 130.4, 107.1, 75.4. Spectral data identical to that reported in the literature.[56]

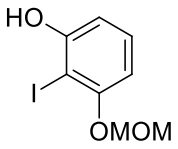
2-Bromo-3-(methoxymethoxy)phenol **(81)**[57b]



A solution of 2-bromoresorcinol **(79)** (1.00 g, 5.29 mmol) in dry N,N-dimethylformamide (5 mL) was slowly added to a suspension of sodium hydride (444 mg, 11.1 mmol, 60% in mineral oil, washed three times with pentane) in dry N,N-dimethylformamide (10 mL) at 0 °C. After stirring for 1 hour at room temperature, methoxymethyl chloride (0.4 mL, 5.27 mmol) was added dropwise at 0 °C and the solution stirred for a further 2 hours. The reaction was quenched by addition of saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the crude product was purified by silica gel chromatography using ethyl acetate : hexane (1:9) yielding 2-bromo-3-(methoxymethoxy)phenol **(81)** (653 mg, 53%).

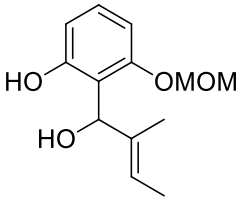
m.p. 55 °C (lit. 55-56 °C)[57b]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (m, 1H), 6.71 (m, 2H), 5.70 (s, 1H), 5.24 (s, 2H), 3.51 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.3 153.5, 128.7, 109.4, 107.4, 101.3, 95.5, 56.4. Spectral data identical to that reported in the literature.[57b]

2-Iodo-3-(methoxymethoxy)phenol **(82)**[55]



A solution of 2-Iodoresorcinol **(80)** (1.25 g, 5.29 mmol) in dry N,N-dimethylformamide (5 mL) was slowly added to a suspension of sodium hydride (444 mg, 11.1 mmol, 60% in mineral oil, washed three times with pentane) in dry N,N-dimethylformamide (10 mL) at 0 °C. After stirring for 1 hour at room temperature, methoxymethyl chloride (0.4 mL, 5.27 mmol) was added dropwise at 0 °C and the solution stirred for a further 2 hours. The reaction was quenched by addition of saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the crude product was purified by silica gel chromatography using ethyl acetate : hexane (1:9) yielding 2-Iodo-3-(methoxymethoxy)phenol **(82)** (723 mg, 49%).
R_f = 0.24 (EtOAc:Hex, 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (dd, J = 8.3, 8.1 Hz, 1H), 6.69 (dd, J1 = 8.3, 1.2 Hz, 1H), 6.62 (dd, J1 = 8.1, 1.2 Hz, 1H), 5.52 (s, 1H), 5.24 (s, 2H), 3.51 (s, 3H); Spectral data identical to that reported in the literature.[55]

(E)-2-(1-Hydroxy-2-methylbut-2-en-1-yl)-3-(methoxymethoxy)phenol **(84)**

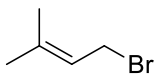


The following serves as a representative example for reactions of **81** or **82** with **70** or **73**. A solution of *t*BuLi 1.6M in pentane (1.9 mL, 3.0 mmol) was added dropwise to a

cooled (-78 °C), stirred solution of 2-Iodo-3-(methoxymethoxy)phenol **(82)** (280 mg, 1.0 mmol) in tetrahydrofuran (3 mL) over a period of 5 minutes, this was warmed to -40 °C and stirred for 1 h. At this temperature prenyl bromide **(70)** (0.13 mL, 1.1 mmol) was added dropwise as a solution in tetrahydrofuran (1 mL). The solution was stirred for a further 3 hours then quenched under nitrogen by addition of saturated aqueous ammonium chloride (10 mL). The ensuing mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts washed with brine (20 mL) then dried over Na_2SO_4. Following removal of solvent under reduced pressure the resulting residue was purified by silica gel chromatography using ethyl acetate:hexane (1:1) to give (E)-2-(1-hydroxy-2-methylbut-2-en-1-yl)-3-(methoxymethoxy)phenol **(84)** as a colourless solid (115 mg, 48%). The remaining mass balance was accounted for by compound **85** which was not further characterised. Evaporative crystallisation of the isolated product from ethyl acetate yielded crystals that were submitted for crystallographic analysis. Crystallographic data is available as supplementary information that accompanies the thesis.

m.p. = 75–79 °C; $\mathbf{R_f}$ = 0.18 (EtOAc:Hex); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.02 (t, *J* = 8.2 Hz, 1H), 6.51 (dd, *J* = 8.2, 0.7 Hz, 1H), 6.48 (dd, *J* = 8.1, 0.9 Hz, 1H), 5.70 (s, 1H), 5.54 (q, *J* = 6.7 Hz, 1H), 5.03–5.08 (m, 2H), 3.35 (s, 3H), 2.33 (s, 1H), 1.62 (s, 3H), 1.55 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 157.4, 154.6, 135.7, 129.0, 121.7, 114.2, 111.1, 105.2, 94.4, 75.2, 56.1, 13.3, 12.3; **IR** ν_{max} (neat) 3381, 3220, 2914, 1591, 1455, 1150, 1030, 1006, 907, 778 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 261.1 [(M + Na)+, 100%], 221 (22), 189 (90); **HRMS** [Found: $(M + Na)^+$, 261.1104. $C_{13}H_{18}O_4Na$ requires $(M + Na)^+$, 261.1103].

Prenyl bromide **(70)**[65]

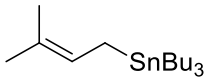


To a stirred, cooled (0 °C) solution of 2-methylbut-3-en-2-ol **(94)** (5 mL, 47.8 mmol) in dichloromethane (50 mL) was added acetyl bromide (5.3 mL, 71.7 mmol) dropwise over 5 minutes. The mixture was stirred at this temperature for a further 2 hours. After addition of water (50 mL), the mixture was extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed sequentially with saturated

aqueous $NaHCO_3$ (50 ml) and brine (50 ml), dried over Na_2SO_4 and concentrated to give prenyl bromide **(70)** (6.59 g, 92%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (tq, J = 2.6, 1.1, 1H), 3.99 (d, J = 8.4, 2H), 1.77 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.3, 121.0, 29.9, 26.0, 17.8. Spectral data identical to that reported in the literature.[65]

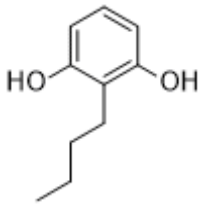
Tributyl(3-methyl-2-butenyl)tin **(93)**[249]



A suspension of magnesium turnings (305 mg,12.5 mmol) in tetrahydrofuran (10 mL) was immersed in an ice filled ultrasound bath and 1,2-dibromoethane (0.10 mL, 1.2 mmol) added. The mixture was sonicated for 10 minutes then tributyltin chloride (2.7 mL, 10 mmol) added. To this suspension a solution of prenyl bromide **(70)** (1.4 mL, 12 mmol) in 5 mL of THF was added dropwise, over 30 minutes, under sonication at 0 °C. After the addition was complete, sonication was continued for a further 30 minutes at 0 °C. The reaction mixture was poured onto ice water (50 mL) and the resulting mixture extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed sequentially with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and the solvent removed in vacuo to give tributyl(3-methyl-2-butenyl)tin **(93)** (2.6 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (t, *J* = 9 Hz, 1H), 1.67 (s, 3H), 1.64 (d, *J* = 9 Hz), 1.57 (s, 3H), 1.47 (m, 6H), 1.29 (m, 6H), 0.89 (t, *J* = 7 Hz, 9H), 0.83 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 125.3, 123.0, 29.3, 27.4, 25.5, 17.4, 13.7, 10.7, 9.4. Spectral data identical to that reported in the literature.[249]

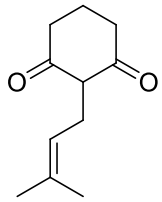
2-Butylresorcinol **(95)**



2-Iodoresorcinol **(80)** (236 mg. 1.0 mmol) was added to a stirred solution of tributyl(3-methyl-2-butenyl)tin **(93)** (540 mg, 1.5 mmol), palladium acetate (24 mg, 0.1 mmol), caesium fluoride (304 mg, 2.0 mmol), and copper iodide (36 mg, 0.2 mmol) in degassed toluene (5 mL). The resultant mixture was heated under reflux for 16 hours and the reaction quenched through addition of saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude mixture was subjected to silica gel chromatography using ethyl acetate : hexane (1:1) to yield 2-butylresorcinol **(95)** (18 mg, 11%) which was identified by ^{1}H NMR and discarded without further characterisation.

^{1}H NMR (400 MHz, $CDCl_3$) 7.01 (t, *J* = 8.1 Hz, 1H), 6.36 (d, *J* = 8.1 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 1.53 (m, 2H), 1.40 (m, 2H), 0.94 (t, *J* = 7.0 Hz, 3H).

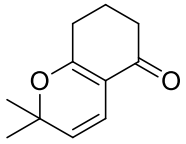
2-(3-Methylbut-2-en-1-yl)cyclohexane-1,3-dione **(97)**[69]



Diisopropylethylamine (14.6 mL) and prenyl bromide **(70)** (7.7 mL, 9.8 g, 0.07 mol) were added simultaneously, and dropwise, to a cooled (0° C) and magnetically stirred suspension of cyclohexane-1,3- dione **(96)** (11.3 g, 0.10 mol) in water (15 mL). The ensuing mixture was allowed to warm to 18 °C then stirred at this temperature for 16 h before being treated with aqueous sodium hydroxide (160 mL,1 M). The aqueous phase was washed with hexane (3 × 50 mL) then acidified with glacial acetic acid. The ensuing precipitate was collected by filtration and dried under reduced pressure to give the previously reported 2-(3-methylbut-2-en-1-

yl)cyclohexane-1,3-dione **(97)** (9.1 g, 75%) as an amorphous solid. This material was used without purification in the following steps.

2,2-Dimethyl-7,8-dihydro-2H-chromen-5(6H)-one **(99)**[54]

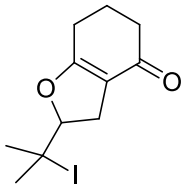


A magnetically stirred solution of compound 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **(97)** (450 mg, 2.5 mmol) in dry 1,4-dioxane (30 mL) was treated with 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (623 mg, 2.74 mmol) and the resulting mixture heated at reflux for 6 hours. The cooled reaction mixture was filtered and the filtrate treated with TLC-grade silica (1.5 g) then concentrated to dryness under reduced pressure. The resulting free-flowing solid was then purified by silica gel chromatography using ethyl acetate : hexane (1:1) to afford 2,2-dimethyl-7,8-dihydro-2H-chromen-5(6H)-one **(99)** as a light orange solid (325 mg, 73%).

m.p. 38 °C (lit 40–41 °C)[54]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.66 (s, 6H),1.85-1.95 (m, 2H), 2.26-2.36 (m, 4H), 5.17 (d, 1H, *J* = 9.6 Hz), 6.34 (d, 1H, *J* = 9.6 Hz). Spectral data identical to that reported in the literature.[54]

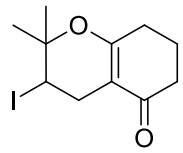
2-(2-Iodopropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **(100)** and 3-iodo-2,2-dimethyl-3,4,7,8-tetrahydro-2H-chromen-5(6*H*)-one **(102).**

Iodine (1.77 g, 7.0 mmol) was added to a solution of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **(97)** (630 mg, 3.5 mmol) in MeOH (10 mL) and stirred for 16 hours at room temperature. The solution was quenched by addition of saturated aqueous Na_2SO_3 (10 mL) and diluted with water (10 mL). The excess methanol was removed under reduced pressure and the resulting solution extracted with ethyl acetate (3 x 20 mL). The combined organic extracts washed with brine (20 mL) then dried over Na_2SO_4. Following removal of solvent under reduced pressure, the resulting residue was purified by silica gel chromatography using ethyl acetate : hexane (1:1) to give two isolated products.



The major product 2-(2-iodopropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **(100)** (662 mg, 62%) as a light yellow solid.

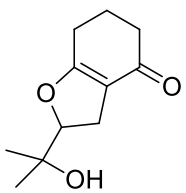
m.p. = 118 °C; $\mathbf{R_f}$ = 0.33 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 4.20 (m, 1H), 2.98 (dd, *J* = 14.9, 10.2 Hz, 1H), 2.76 (dd, *J* = 14.9, 7.7 Hz, 1H), 2.48 (m, 2H), 2.39 (m, 2H), 2.09 (m, *J* = 7.2, 1.6 Hz, 2H), 1.96 (s, 3H), 1.94 (s, 3H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 195.3, 176.8, 113.2, 92.9, 49.3, 36.4, 33.0, 32.5, 31.7, 23.8, 21.7; **IR** ν_{max} (neat) 2981, 2888, 1621, 1402, 1113, 952, 600, cm^{-1}; **LRMS** (ESI, +ve) *m/z* 307.0, [(M)+, 100%], 179 (20); **HRMS** [Found: $(M + Na)^+$, 329.0014. $C_{11}H_{15}O_2INa$ requires $(M + Na)^+$, 329.0015].



The minor product 3-iodo-2,2-dimethyl-3,4,7,8-tetrahydro-2H-chromen-5(6*H*)-one **(102)** (289 mg, 27%) as a light yellow oil.

$\mathbf{R_f}$ = 0.59 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 4.18 (dd, *J* = 8.9, 5.5 Hz, 1H), 2.96 (dd, *J* = 17.3, 5.4 Hz, 1H), 2.77 (dd, *J* = 17.3, 8.9 Hz, 1H), 2.32 (m, 4H), 1.93 (m, 2H), 1.47 (s, 3H), 1.41 (s, 3H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 197.0, 169.7, 109.9, 79.3, 36.4, 30.7, 30.3, 28.8, 27.0, 24.3, 20.8; **IR** ν_{max} (neat) 2980, 2946, 1617, 1379, 1274, 1126, cm^{-1}; **LRMS** (ESI, +ve) *m/z* 307.1 [(M)+, 100%], 171 (28); **HRMS** [Found: $(M)^+$, 307.0191. $C_{11}H_{15}O_2I_{127}$ requires $(M)^+$, 307.0195].

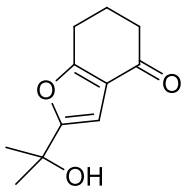
2-(2-Hydroxypropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one **(104)**



A solution of *m*-chloroperbenzoic acid (1.37 g, 77%, 6.11 mmol) in dichloromethane (25 mL) was added dropwise, to a magnetically stirred, cooled (–10 °C) mixture of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **(97)** (1.00 g, 5.55 mmol) and anhydrous K_2CO_3 (1.15 g, 8.32 mmol) in dichloromethane (25 mL). The ensuing mixture was allowed to stir at room temperature for 14 hours then diluted with water (30 mL). The separated aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic phases washed with saturated aqueous Na_2CO_3 (40 mL) and brine (20 mL) before being dried over Na_2SO_4 and concentrated under reduced pressure to give 2-(2-hydroxypropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **(104)** (1.03 g, 95%) as a white, crystalline solid. Evaporative crystallisation of the isolated product from ethyl acetate yielded crystals that were submitted for crystallographic analysis. Crystallographic data is available in the CCDC or as supplementary information that accompanies the thesis.

m.p. = 120–122 °C; **Rf** = 0.1 (EtOAc:Hex, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.60 (m, 1H), 2.76 (m, 1H), 2.67 (m, 1H), 2.43 (m, 2H), 2.33 (m, 2H), 2.04 (m, 2H),1.85 (broad s, 1H), 1.27 (s, 3H), 1.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.4, 177.2, 113.8, 91.7, 71.8, 36.3, 27.1, 25.5, 23.8, 23.7, 21.7; **IR** ν_{max} (KBr) 3400, 2943, 1619, 1405, 1233, 1182, 1062, 999, 944 cm^{-1}; **LRMS** (EI, 70 eV) m/z 196 (M+•, 82%), 181 (44), 163 (63), 138 (100), 137 (92), 110 (95), 82 (66). **HRMS** [Found: M+•, 196.1100. $C_{11}H_{16}O_3$ requires M+•, 196.1099]. This material was used without purification in the next step of the reaction sequence.

2-(2-Hydroxypropan-2-yl)-6,7-dihydrobenzofuran-4(5H)-one **(105)**

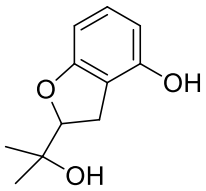


A solution of 2-(2-hydroxypropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one **(104)** (101 mg, 0.52 mmol) in dry dichloromethane (30 mL) was treated with freshly prepared MnO_2 (241 mg, 2.77 mmol) and the ensuing mixture stirred vigorously at room temperature for 48 hours. The suspension was then treated with TLC-grade silica (1.0 g) and concentrated to dryness under reduced pressure. The resulting free-flowing solid was purified by silica gel chromatography using ethyl acetate :

hexane (1:1) to give 2-(2-hydroxypropan-2-yl)-6,7-dihydrobenzofuran-4(5H)-one **(105)** (42 mg, 44%) as an unstable, pale-yellow oil.

R_f = 0.3 (EtOAc:Hex, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.46 (s, 1H), 2.87 (t, J = 6.0 Hz, 2H), 2.48 (m, 2H), 2.17 (p, J = 6.0 Hz, 2H), 1.59 (s, 6H) (signal due to OH group proton not observed); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.7, 166.5, 160.5, 121.6, 100.3, 100.2, 68.6, 37.6, 28.5, 23.4, 22.6; **IR** ν_{max} (KBr) 3403, 2977, 2941, 1663, 1599, 1455, 1358, 1217, 1181, 1126, 1003 cm^{-1}; **LRMS** (EI, 70 eV) m/z 194 (M+•, 100%), 180 (83), 179 (72), 151 (45), 137 (65). **HRMS** [Found: M+•, 194.0945.C11H14O3 requires M+•, 194.0943]

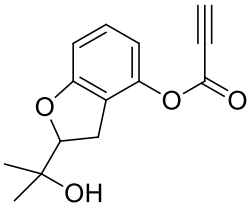
2-(2-Hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-ol **(68)**



A magnetically stirred solution of 2-(2-hydroxypropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one **(104)** (402 mg, 2.05 mmol) in dry 1,4-dioxane (30 mL) was treated with 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (426 mg, 1.88 mmol) and the resulting mixture heated at reflux for 6 hours. The cooled reaction mixture was filtered and the filtrate treated with TLC-grade silica (1.0 g) then concentrated to dryness under reduced pressure. The resulting free-flowing solid was purified by silica gel chromatography using ethyl acetate : hexane (1:1) to give an orange solid, recrystallisation (from ethyl acetate/hexane) of which afforded 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-ol **(68)** (318 mg, 80%) as pale-yellow crystals.

m.p. = 143–147 °C (lit. 150–152 °C). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (t, J = 8.4 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 4.80 (br s, 1H), 4.65 (t, J = 8.8 Hz, 1H), 3.10 (d, J = 8.8 Hz, 2H),1.92 (br s, 1H), 1.35 (s, 3H), 1.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.2, 152.9, 128.9, 112.7,107.9, 101.7, 89.7, 71.9, 27.9, 26.1, 23.8; **IR** ν_{max} (KBr) 3302, 2977, 1608, 1465, 1376, 1326, 1281, 1235,1152, 1041, 1003 cm^{-1}; **LRMS** (EI, 70 eV) *m/z* 194 (M+•, 76%), 161 (37), 136 (100), 135 (82), 107 (62). **HRMS** [Found: M+•, 194.0945 $C_{11}H_{14}O_3$ requires M+•, 194.0943]

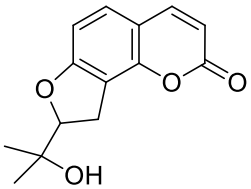
2-(2-Hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-yl propiolate **(67)**



A chilled (0 °C) suspension of 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-ol **(68)** (100 mg, 0.52 mmol) and propiolic acid (108 mg, 1.54 mmol) in acetonitrile (3 mL) was added, dropwise, to a magnetically stirred solution of DCC (160 mg, 0.78 mmol) in acetonitrile (3 mL). The resulting solution was stirred at room temperature for 4 hours then filtered to remove the precipitated dicyclohexylurea. The filtrate was concentrated under reduced pressure and the residue thus obtained subjected to silica gel column chromatography using ethyl acetate : hexane gradient elution (1:4–1:1) to yield 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-yl propiolate **(67)** (89 mg, 70%) as a pale-yellow oil.

R_f = 0.6 (EtOAc:Hex, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (t, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 4.65 (t, J = 8.8 Hz, 1H), 3.08 (d, J = 8.8 Hz, 2H), 3.08 (d, J =8.8 Hz, 2H), 3.08 (s, 1H), 1.90 (broad s, 1H), 1.32 (s, 3H), 1.21 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.3, 149.9, 146.3, 129.1, 119.6, 113.2, 107.6, 89.9, 76.9, 74.0, 71.7, 28.7, 25.9, 24.0; **IR** ν_{max} (KBr) 3441, 3268, 2977, 2934, 2123, 1732, 1622, 1600, 1481, 1464, 1246, 1201, 1003, 777 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 269 [(M + Na)+, 100%]. **HRMS** [Found: (M + Na)+, 269.0789 $C_{14}H_{14}O_4$ requires (M + Na)+, 269.0790]

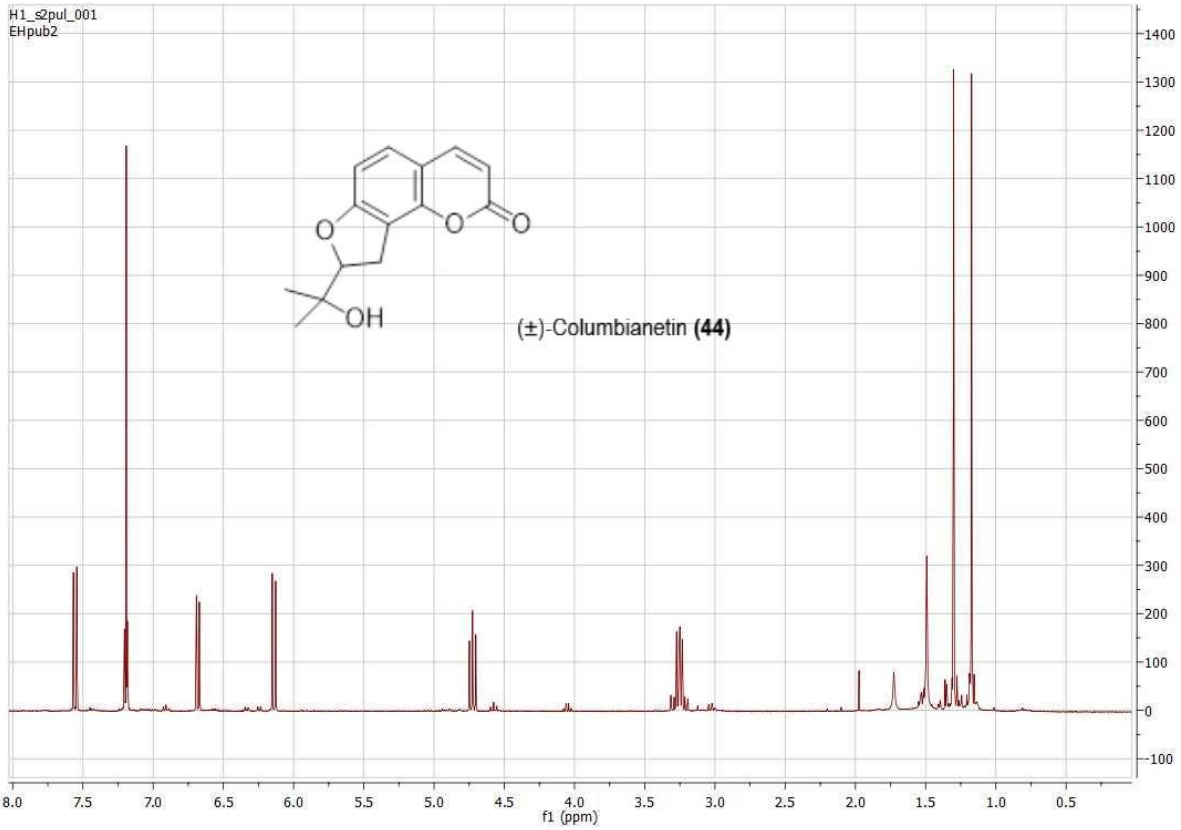
(±)-Columbianetin **(44)**[42]

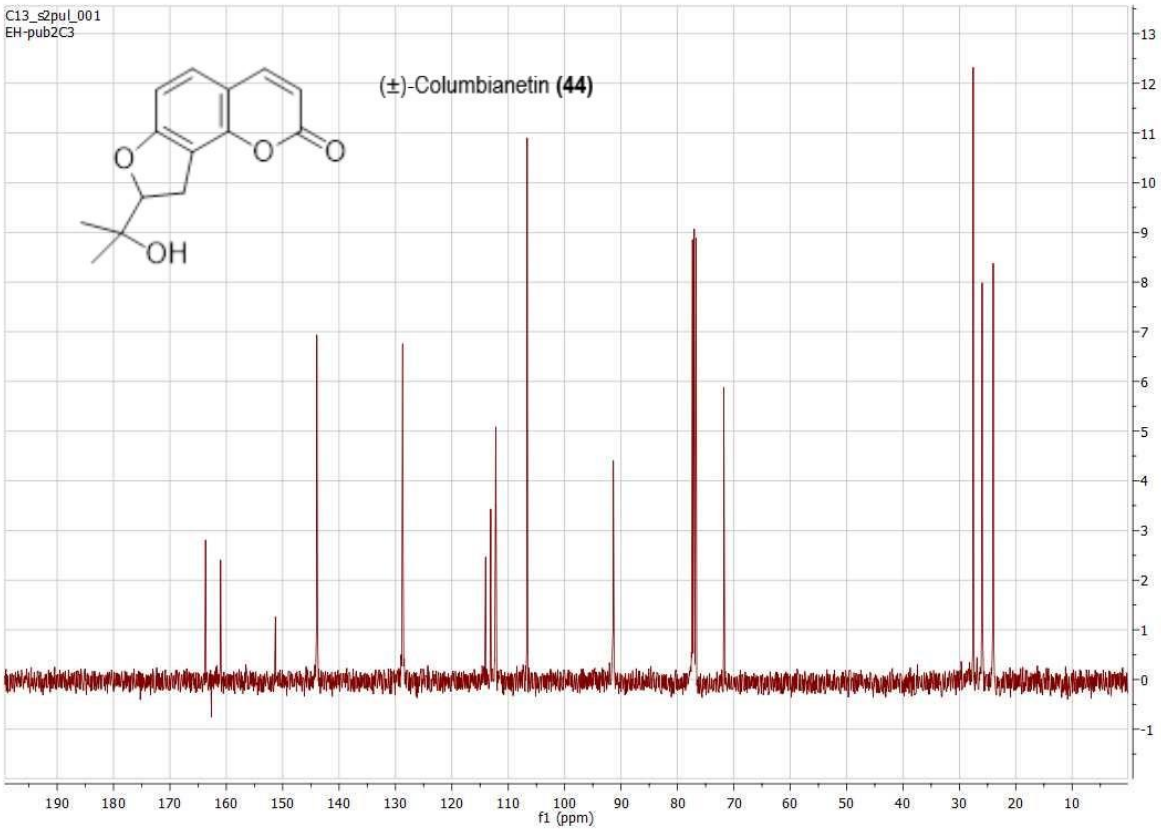


A magnetically stirred solution of 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-yl propiolate **(67)** (89 mg, 0.36 mmol) in dichloromethane (3 mL) was treated with acetonitrile[(2-biphenyl)di-tert-butylphosphine]gold(I)-hexafluoroantimonate (Echavarren's catalyst **(106)**, 5.5 mg, 2 mol %) and the resulting solution heated at

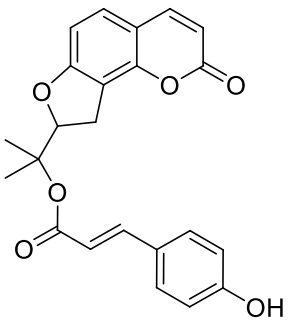
reflux for 16 hours. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to silica gel chromatography using ethyl acetate : hexane (1:1) to yield (±)-columbianetin **(44)** (66.5 mg, 75%) as a pale-yellow solid. Evaporative crystallisation of the isolated product from ethyl acetate yielded crystals that were submitted for crystallographic analysis. Crystallographic data is available in the CCDC or as supplementary information that accompanies the thesis.

m.p. 164–168 °C (lit.[42] 161–162 °C); $\mathbf{R_f}$ = 0.4 (EtOAc:Hex, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, J = 9.6 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.21 (d, J = 9.6 Hz, 1H), 4.80 (t, J = 8.8 Hz, 1H), 3.32 (m, 2H), 1.80 (br s, 1H), 1.37 (s, 3H), 1.24 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.7, 161.0,151.3, 144.0, 128.7, 114.0, 113.1, 112.2, 106.7, 91.3, 71.8, 27.6, 26.0, 24.0; **IR** ν_{max} (KBr) 3444, 2975, 1732,1716, 1615, 1461, 1262, 1115, 1066, 964, 833 cm^{-1}; **LRMS** (EI, 70 eV) *m/z* 246 (M+•, 42%), 188 (80), 187 (100), 160 (35), 136 (33). **HRMS** [Found: M+•, 246.0900. C14H14O4 requires M+•, 246.0892].





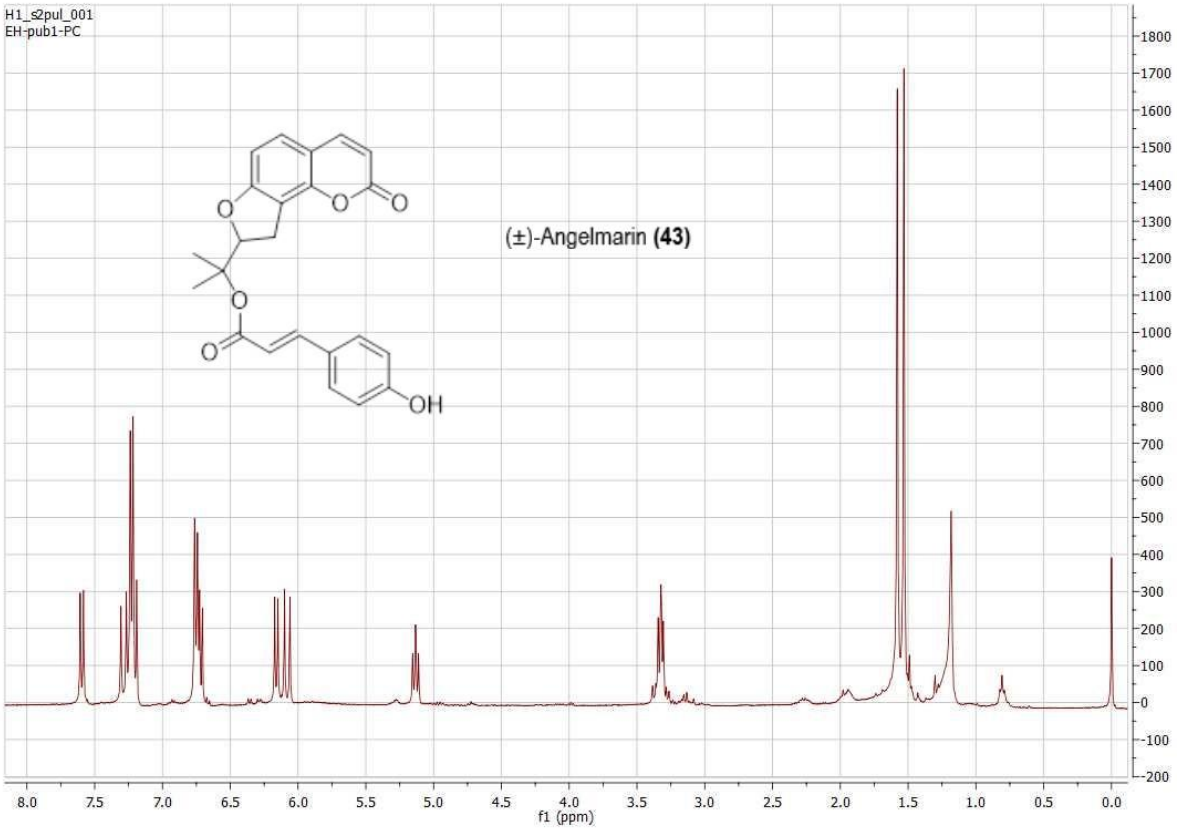
(±)-Angelmarin **(43)**[32]

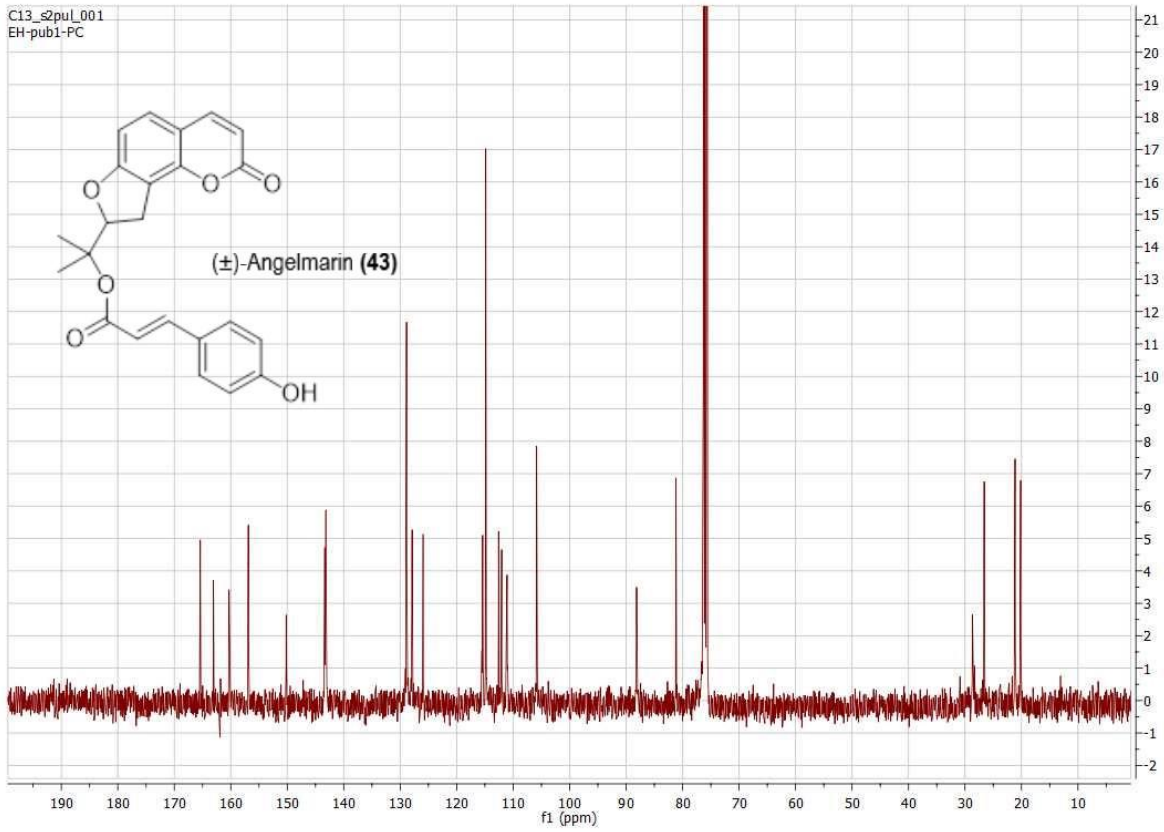


A magnetically stirred solution of (±)-columbianetin **(44)** (82 mg, 0.33 mmol) in toluene (4 mL) was treated with Meldrum's acid **(56)** (53 mg, 0.37 mmol). The resulting solution was heated at reflux for 6 hours then cooled and concentrated under reduced pressure. The ensuing yellow oil was dissolved in pyridine (4 mL) and the solution so-formed treated with piperidine (3 drops) and p-hydroxybenzaldehyde **(58)** (45 mg, 0.37 mmol) then heated at 70 °C for 16 hours. The cooled reaction mixture was diluted with ethyl acetate (10 mL) then washed with aqueous HCl (5 mL, 5% w/v), water (5 mL) and brine (5 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was

subjected to silica gel column chromatography using hexane : ethyl acetate (1:1) to yield (±)-angelmarin **(43)** (99 mg, 76%) as a white, amorphous solid.

R_f = 0.3 (EtOAc:Hex, 1:1), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 9.6 Hz, 1H), 7.36 (d, J = 15.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 1H), 6.23 (d, J = 9.6 Hz, 1H), 6.15 (d, J = 15.6 Hz, 1H), 5.20 (m, 1H), 3.37 (m, 2H), 1.65 (s, 3H), 1.60 (s, 3H) (signal due to phenolic group proton not observed); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 164.1, 161.3, 157.9, 151.2, 144.4, 144.2, 130.0, 128.9, 127.0, 116.4, 115.9, 113.6, 113.1, 112.1, 106.9, 89.2, 82.2, 27.6, 22.2, 21.2; **IR** ν_{max} (KBr) 3338, 2926, 1732, 1705, 1616, 1605, 1514, 1457, 1329, 1263,1168, 1134, 831 cm^{-1}; **LRMS** (EI, 70 eV) m/z 392 (M+•, 23%), 228 (73), 213 (100), 147 (95). **HRMS** [Found: M+•, 392.1261 $C_{23}H_{20}O_6$ requires M+•, 392.1260].

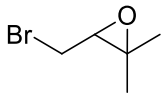




Shi epoxidation protocol for compound **104**

A solution of aqueous Oxone (1M, 10 mL) was added dropwise simultaneously with a solution of aqueous potassium hydroxide (2M, 10 mL) over 1 hour, to a magnetically stirred, cooled (0 °C) mixture of 2-(3-methylbut-2-en-1-yl)cyclohexane-1,3-dione **(97)** (1.00 g, 5.55 mmol) in acetonitrile (25 mL). The ensuing mixture was allowed to stir at room temperature for 6 hours then diluted with water (30 mL). The resultant solution was extracted with dichloromethane (3 × 50 mL) and the combined organic phases washed with saturated aqueous Na_2CO_3 (40 mL) and brine (50 mL) before being dried over Na_2SO_4. Concentration under reduced pressure yielded a light-yellow solid that was subjected to silica gel chromatography using hexane : ethyl acetate (1:1) to give 2-(2-hydroxypropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one **(104)** (195 mg, 18%) as a white, crystalline solid. Chiral HPLC analysis was performed with the use of a DAICEL chiralcel OJ-H column which features a tris p-toluate cellulose stationary phase; with a flow rate of 0.5 mL/min using a 5% solution of isopropanol and hexane. The enantiomeric excess was determined to be 15%.

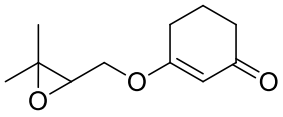
1-Bromomethyl-2,2-dimethyloxirane **(113)**[82]



To a stirred solution of aqueous KOH (29 g, in 100 mL) was slowly added bromine (28 g, 17.4 mmol) at 0 °C. The mixture was stirred for 15 minutes at the same temperature, then to this solution was added 2-methyl-3-buten-2-ol **(94)** (10 g, 11.61 mmol) at 0 °C and stirred for 20 hours. The mixture was diluted with hexane (50 mL) and the organic layer separated and evaporated under reduced pressure. Distillation of the resulting oil under reduced pressure afforded 1-Bromomethyl-2,2-dimethyloxirane **(113)** (16 g, 82.0%) as a colourless oil.

b.p. 53 °C (25 mmHg); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.48 (dd, J = 10.4, 6.0, 1H), 3.23 (dd, J = 10.4, 7.0, 1H), 3.05 (dd, J = 7.5, 6.0, 1H), 1.33 (s, 3H), 1.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 62.1, 60.5, 29.8, 24.3, 18.1. Spectral data identical to that reported in the literature.[82]

3-((3,3-Dimethyloxiran-2-yl)methoxy)cyclohex-2-enone **(114)**



1-Bromomethyl-2,2-dimethyloxirane **(113)** (485 mg, 2.94 mmol) was added to a magnetically stirred solution of cyclohexane-1,3-dione **(96)** (302 mg, 2.70 mmol), lithium iodide (40 mg, 0.29 mmol) and lithium carbonate (260 mg, 2.53 mmol) in acetonitrile (10 mL). The resulting suspension was heated to reflux and after 14 hours the reaction mixture was cooled to room temperature then treated with water (10 mL) and saturated aqueous Na_2CO_3 (5 mL) The ensuing solution was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were then washed with brine (20 mL) and dried over Na_2SO_4. Concentration under reduced pressure yielded a light-yellow solid that was subjected to silica gel chromatography using hexane : ethyl acetate (1:1) affording two fractions, A and B. Concentration of fraction A afforded 3-((3,3-dimethyloxiran-2-yl)methoxy)cyclohex-2-enone **(114)** (360 mg, 62%) as a white, crystalline solid. Evaporative crystallisation of the isolated

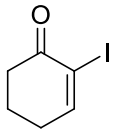
product from dichloromethane yielded crystals that were submitted for crystallographic analysis. Crystallographic data is available in the CCDC or as supplementary information that accompanies the thesis.

m.p. 59–63 °C, $\mathbf{R_f}$ = 0.3 (EtOAc:Hex, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.04 (dd, J = 10.8, 4.0 Hz, 1H), 3.83 (dd, J = 10.8, 4.0 Hz, 1H), 3.06 (dd, J = 6.4, 4.0 Hz, 1H), 2.44 (m, 2H), 2.35 (t, J = 6.4 Hz, 2H), 1.98 (p, J = 6.4 Hz, 2H), 1.36 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.5, 177.4, 103.1, 67.5, 60.2, 58.1, 36.7, 28.8, 24.5, 21.2, 19.0; **IR** ν_{max} (KBr) 3059, 2945, 1648, 1599, 1391, 1240, 1226, 1184, 1132, 998, 961, 877, 811 cm^{-1}; **LRMS** (EI, 70 eV) *m/z* 196 (M+•, 11%), 126 (70), 85 (100). **HRMS** (Found: M+•, 196.1096. $C_{11}H_{16}O_3$ requires M+•, 196.1099)

Concentration of fraction B afforded 2-(2-hydroxypropan-2-yl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one **(104)** (180 mg, 31% yield) that was identical, in all respects, with the material obtained earlier.

7.3 Ochrosamines

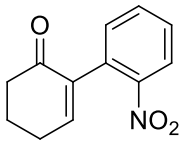
2-Iodocyclohex-2-enone **(161)**[101]



To a magnetically stirred solution of cyclohex-2-enone **(160)** (500 mg, 5.2 mmol) and pyridine (10 mL) in chloroform (10 mL) was slowly added a solution containing I_2 (5.23 g, 20.6 mmol) and pyridine (10 mL) in chloroform (10 mL). The reaction was stirred at room temperature for 30 minutes, before being diluted with diethyl ether and washed sequentially with 1 M aqueous HCl (30 mL), water (20 mL), saturated aqueous Na_2SO_3 (2 × 10 mL) and brine (10 mL). The organic phases were dried over $MgSO_4$, and concentrated *in vacuo* to afford 2-iodocyclohex-2-enone **(161)** (1.01 g, 90 %) as a yellow oil which was used without further purification

R_f = 0.5 (EtOAc:Hex, 1:3); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (t, *J* = 4.4 Hz, 1H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.47 (dt, *J* = 4.5, 6 Hz, 2H), 2.09 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.2, 159.5, 103.9, 37.3, 30.0, 22.9. Spectral data identical to that reported in the literature.[101]

2'-Nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(147)**[98]



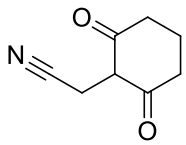
A magnetically stirred mixture of 2-iodonitrobenzene **(134)** (2.49 g, 10 mmol), 2-iodocyclohex-2-enone **(161)** (1.11 g, 5 mmol), copper powder (1.59 g, 25 mmol) and tris(dibenzylideneacetone)dipalladium (260 mg, 0.25 mmol) in DMSO (15 mL) was heated at 70 °C for 1 hour under a nitrogen atmosphere then cooled and diluted with diethyl ether (150 mL). The resulting mixture was then filtered through a pad of Celite which was then washed with ether (50 mL). The combined filtrates were washed with water (150 mL) and brine (150 mL) then dried over $MgSO_4$. The resulting solution was concentrated under reduced pressure to give a brown oil which was purified by

silica gel chromatography using ethyl acetate : hexane (3:7) to afford 2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(147)** (712 mg, 65%) as a yellow solid.
m.p. = 92–95 °C (lit. 96–98 °C)[98]; **1H NMR** (400 MHz, $CDCl_3$) δ 7.99 (dd, J= 8.1, 1.5 Hz, 1H), 7.58 (td, J= 7.5, 1.5Hz, 1H), 7.45 (td, J= 8.1, 1.5 Hz, 1H), 7.24 (dd, J= 7.5 and 1.5 Hz, 1H), 7.01 (t, J=4.2 Hz, 1H), 2.60–2.54 (m, 4H), 2.13 (p, J= 6.9 Hz, 2H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 196.4, 148.4, 146.8, 139.2, 133.2, 131.9, 131.5, 128.6, 123.9, 38.1, 26.1, 22.4. Spectral data identical to that reported in the literature.[98]

Aziridine **(150)**[107]

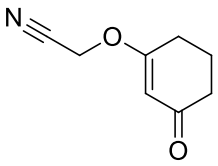
To a cooled (0 °C), stirred solution of ethanolamine **(162)** (6.10 g, 0.1 mol) in diethyl ether (1000 mL); chlorosulfonic acid (11.6 g, 10 mmol) was added dropwise over 20 minutes. The solution was stirred for a further 2 hours during which a precipitate forms. This was collected by filtration, washed with diethyl ether (3 x 100 mL) and dried under vacuum. To the resulting solid zwitterion **(163)** was added 6 M aqueous NaOH (80 mL) and the solution heated at 50 °C for 2 hours. The solution was then distilled at slightly reduced pressure until 10 mL of distillate had been collected. The cooled distillate was mixed with sodium hydroxide (10 g), and distilled at atmospheric pressure to give aziridine **(150)** as an unstable volatile liquid (450 mg, 10%), b.p. 55 °C (lit.[107] 56-57 °C). Owing to the toxicity and volatility it was used directly without further characterisation.

2-(2,6-Dioxocyclohexyl)acetonitrile **(167)**



Chloroacetonitrile **(164)** (0.62 mL, 9.8 mmol) was added to a magnetically stirred solution of cyclohexane-1,3-dione **(96)** (1 g, 8.9 mmol), sodium iodide (130 mg, 0.9 mmol) and sodium carbonate (1.04 g, 9.8 mmol) in acetone (50 mL). The resulting suspension was heated to reflux and after 5 hours the solvent volume was reduced

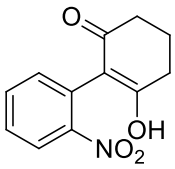
to 10 mL *in vacuo*. The suspension was then diluted with saturated aqueous Na_2CO_3 (50 mL) and water (30 mL). The ensuing solution was extracted with ethyl acetate (2 x 30 mL) at the organic fractions set aside. The aqueous phase was then acidified with 2M aqueous HCl to pH 3 then extracted with ethyl acetate (3 x 50 mL). The combined extracts from the acidified solution were then washed with brine (30 mL) and dried over Na_2SO_4. Concentration under reduced pressure gives a complex orange solid assigned as 2-(2,6-dioxocyclohexyl)acetonitrile **(167)** that was used without further purification.



Concentration of the combined organic extracts from the basified solution yields essentially pure 2-((3-oxocyclohex-1-en-1-yl)oxy)acetonitrile **(166)** (230 mg, 17%) as a colourless solid.

m.p. = 58–62 °C; $\mathbf{R_f}$ = 0.24 (EtOAc:Hex, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.63 (s, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.36 (t, *J* = 6.4 Hz, 2H), 2.01 (p, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.3, 175.5, 113.9, 103.8, 52.8, 36.5, 28.2, 20.8; **IR** ν_{max} (neat) 2980, 2889, 1655, 1610, 1383, 1175, 1137, 1012 $cm^{-}1$; **LRMS** (ESI, +ve) *m/z* 152.0 [(M)+, 100%]; **HRMS** [Found: $(M + Na)^+$, 174.0530. $C_8H_9NO_2Na$ requires $(M + Na)^+$, 174.0531].

6-Hydroxy-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(174)**[117]

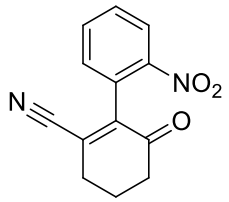


A mixture of 1,3-cyclohexanedione **(96)** (18 g, 160.6 mmol), anhydrous potassium carbonate (33.3 g, 241 mmol), and o-iodonitrobenzene **(134)** (20 g, 80.3 mmol) in dimethyl sulfoxide (250 mL) was heated to 90 °C for 4 h. After cooling the mixture was poured into water (1 L), the resulting solution was acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 x 400 mL). The combined organic extracts were washed with brine (250 mL), dried over Na_2SO_4 and

evaporated to give a brown foam, which was recrystallised from dichloromethane to give 6-hydroxy-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(174)** (15.1 g, 81%) as a tan powder.

m.p. = 204-208 °C (lit. 208-209 °C)[117] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (s, enol OH), 7.87 (d, J = 7.9 Hz, 1H), 7.49 (dd, J = 8.0, 7.1 Hz, 1H),7.33 (t, J = 8.1 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 2.35-2.5 (m, 4H), 1.9-2.1 (m, 2H). Spectral data in good agreement with that reported in the literature[117].

2'-Nitro-6-oxo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbonitrile **(176)**

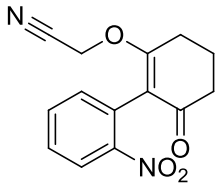


chloroacetonitrile (0.4 mL, 6.4 mmol) was added to a magnetically stirred solution of 6-hydroxy-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(174)** (1 g , 4.3 mmol), lithium iodide (1.26 g, 9.43 mmol) and lithium carbonate (475 mg, 6.4 mmol) in acetone (10 mL). The resulting suspension was heated to reflux and after 16 hours the solution was diluted with saturated aqueous Na_2CO_3 (50 mL) and water (30 mL). The ensuing solution was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were then washed with brine (30 mL) and dried over Na_2SO_4. Concentration under reduced pressure gave a crude brown solid that was purified by silica gel chromatography using gradient elution (EtOAc : Hexanes 4:1–1:1) to give 2'-nitro-6-oxo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbonitrile **(176)** as a tan solid (602 mg, 58%). A sample was crystallised from ethyl acetate and diethyl ether, and submitted to X-ray crystallographic analysis. Crystallographic data is available as supplementary information that accompanies the thesis.

m.p. = 96–101 °C; **R_f** = 0.57 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.67 (td, *J* = 7.5, 1.1 Hz, 1H), 7.57 (ddd, *J* = 7.5, 8.2, 1.3 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 2.76 (ddd, *J* = 18.4, 8.1, 5.0 Hz, 1H), 2.68 (m, 2H), 2.57 (ddd, *J* = 16.5, 7.8, 4.3 Hz, 1H), 2.26 (m, 1H), 2.12 (m, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 194.3, 148.6, 147.6, 134.2, 131.8, 130.8, 128.9, 125.1, 124.7, 116.5, 37.7, 28.7, 21.9. **IR** ν_{max} (neat) 2980, 2219, 1689, 1522, 1345, 1182, 747, 728 cm^{-1};

LRMS (ESI, +ve) *m/z* 265.0 [(M + Na)+, 100%], 185 (19); **HRMS** [Found: $(M + Na)^+$, 265.0589. $C_{13}H_{10}N_2O_3Na$ requires $(M + Na)^+$, 269.0589].

The O-alkylated product could also be identified by NMR from the same reaction mixture but not cleanly isolated. 2-((2'-nitro-6-oxo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)oxy)acetonitrile **(175)**

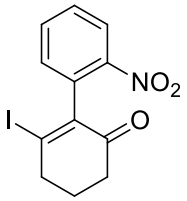


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.62 (tdd, *J* = 7.6, 1.3, 0.6 Hz, 1H), 7.48 (tdd, *J* = 7.5, 1.4, 0.6 Hz, 1H), 7.25 (m, 1H), 4.64 (d, *J* = 16.3 Hz, 1H), 4.56 (d, *J* = 16.3 Hz, 1H), 2.79 (m, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 2.21 (m, 2H).

Conversion of **(175)** to **(176)**

A crude mixture of **(176)** and **(175)** (212 mg, 3:7 ratio, see table Table 3.2. Entry 3.) was dissolved in acetone (5 mL), to this solution lithium iodide (630 mg, 4.71 mmol) and lithium carbonate (237 mg, 3.2 mmol) were added. The resulting suspension was heated to reflux and after 72 hours the solution was diluted with saturated aqueous Na_2CO_3 (30 mL) and water (15 mL). The ensuing solution was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were then washed with brine (30 mL) and dried over Na_2SO_4. Concentration under reduced pressure gave a crude brown solid that was purified by silica gel chromatography using gradient elution (EtOAc : Hexanes 4:1–1:1) to give 2'-nitro-6-oxo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbonitrile **(176)** as a tan solid (171 mg, 88%) identical in all respects to that obtained earlier.

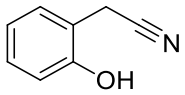
6-Iodo-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3*H*)-one **(178)**



Iodine (278 mg, 1.1 mmol) was added in small portions to a solution of triphenylphosphine (314 mg, 1.2 mmol) and imidazole (82 mg, 1.2 mmol) in a mixture of acetonitrile (3mL) and diethyl ether (1mL) then stirred for 1 hour at room temperature. To the resulting suspension was added 6-hydroxy-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3*H*)-one **(174)** (233 mg, 1 mmol) as a solution in acetonitrile (1mL). The flask was wrapped in tin foil and allowed to stir for a further 16 hours. The resulting suspension was filtered and then diluted with water (10 mL). The solution was then extracted with diethyl ether (3 x 10 mL) and the combined organic extracts washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the resulting residue purified by silica gel chromatography using ethyl acetate : hexane with gradient elution (1:4–1:1) to afford 6-iodo-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3*H*)-one **(178)** as a brown solid.

m.p. = 103 °C (decomposes); $\mathbf{R_f}$ = 0.70 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.5, 1.4 Hz, 1H), 7.17 (dd, *J* = 7.6, 1.4 Hz, 1H), 3.12 (m, 2H), 2.64 (ddd, *J* = 16.4, 10.4, 5.0 Hz, 1H), 2.56 (ddd, *J* = 16.4, 7.1, 4.5 Hz, 1H), 2.09 (m, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 191.9, 146.4, 135.8, 133.7, 132.3, 129.4, 126.3, 124.8, 115.8, 42.3, 37.7, 24.2. **IR** ν_{max} (neat) 2980, 1666, 1595, 1518, 1342, 1285, 1128, 980, 733, 566 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 366.0 [(M + Na)+, 100%], 217 (28), 161 (46); **HRMS** [Found: $(M + Na)^+$, 365.9604. $C_{12}H_{10}NIO_3Na$ requires $(M + Na)^+$, 365.9603].

2-(2-Hydroxyphenyl)acetonitrile **(184)**[126]

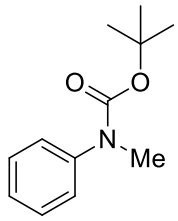


Aqueous potassium hydroxide (1.68 g, 30 mmol, in water 1.2 mL) was rapidly added to a solution of salicylaldehyde **(190)** (1.22 g, 10 mmol) in methanol (2 mL), and formalin (1 mL, 13 mmol). The reaction mixture was then heated to reflux for 2 hours. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed sequentially with water (10 mL) and brine (10 mL). The ensuing solution was dried over Na_2SO_4, and the solvent removed *in vacuo* to give the alcohol **(191)** as a white solid (1.08 g, 87%) used directly in the next step.

The previously obtained crude 2-hydroxybenzyl alcohol **(191)** (1.08 g, 8.7 mmol) and sodium cyanide (511 mg, 10.4 mmol) in N,N-dimethylformamide (10 mL) was stirred under nitrogen at 120 °C for 16 hours. The solution was cooled to room temperature, and water added (50 mL). The mixture was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were washed with water (10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residual orange oil was subjected to silica gel chromatrography by gradient elution using ethyl acetate : hexane (1:2–1:0) to afford 2-(2-hydroxyphenyl)acetonitrile **(184)** (810 mg, 67%) as an off white solid.

m.p. 115 °C (lit. 116–118 °C)[126]; **1H NMR** (400 MHz, $CDCl_3$) δ 7.21 (m, 2H), 6.82 (m, 2H), 3.58 (s, 2H). Spectral data identical to that reported in the literature.[126]

tert-Butyl methyl(phenyl)carbamate **(189)**[129]



To magnetically stirred molten *t*-butyldicarbonate (2.4 g, 11 mmol), *N*-methylaniline **(188)** (1.07 g, 10 mmol) was added portonwise over 10 minutes and stirred for 16 hours. The product was was then kept under vacuum (1 mmHg) at 40 °C to yield the essentially pure *tert*-butyl methyl(phenyl)carbamate **(189)** as a colourless oil (2.07 g, ~100%).

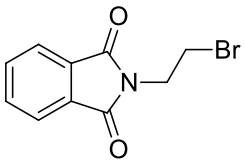
1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.31 (m, 5H), 3.21 (s, 3H), 1.43 (s, 9H); **13C NMR** (100 MHz, $CDCl_3$) δ 154.8, 143.8, 128.6. 125.6, 125.5, 80.2, 37.4, 28.3. Spectral data identical to that reported in the literature[129].

Tributyl(2-nitrophenyl)stannane **(185)**[127]

A stirred solution of hexabutylditin (8.7 g, 15 mmol), 2-iodonitrobenzene **(134)** (2.49 g, 10 mmol), and tetrakis(triphenylphosphine)palladium (115 mg, 0.1 mmol) in toluene (20 mL) was heated at 60 °C for 72 h under nitrogen. After removal of solvent *in vacuo*, the residue was dissolved in ethyl acetate (20 mL) and washed with aqueous potassium fluoride (10% w/w, 10 mL) then brine (10 mL). After drying over Na_2SO_4 and concentration under redued pressure, the resulting residue was purified by silica gel chromatography using hexane to yield tributyl(2-nitrophenyl)stannane **(185)** as a colourless oil.

1H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.68 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.61 (td, *J* = 7.2, 1.1 Hz, 1H), 7.49 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 1.49 (m, 6H), 1.31 (hx, *J* = 7.3, 7.3 Hz, 6H), 1.12 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H). Spectral data in good agreement with that reported in the literature.[127]

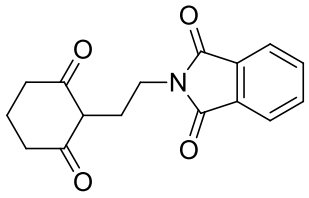
N-(2-Bromoethyl)phthalimide **(200)**[141]



Potassium phthalimide **(199)** (9.26 g., 50 mmol) was added in four equal portions over a 4 hour period to a refluxing solution of 1,2-dibromoethane (18.8 g, 100 mmol) in acetone (50 mL). The resulting mixture was heated at reflux for 24 hours, cooled to room temperature, and filtered. The filtrate was concentrated *in vacuo* and the crude residue was taken up in ethyl acetate (50 mL). This solution was washed with cold 2M sodium hydroxide (30 mL), and brine (30 mL) then dried over Na_2SO_4. Solvent was removed *in vacuo* and the crude solid thus obtained was recrystallised from ethanol to give *N*-(2-Bromoethyl)phthalimide **(200)** (11.0 g, 87%) as a colourless solid.

m.p. 80 °C (lit. 81 °C)[141]; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.88-7.83 (m, 2H), 7.76-7.70 (m, 2H), 4.09 (t, *J* = 6.9 Hz, 2H), 3.60 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) 167.8, 134.2, 131.7, 123.4, 39.2, 28.1. Spectral data identical to that reported in the literature.[141]

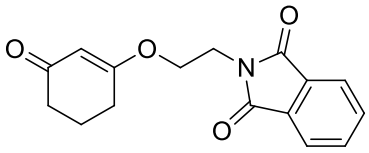
N-(2-(2,6-Dioxocyclohexyl)ethyl)phthalimide **(198)**



N-(2-Bromoethyl)phthalimide **(200)** (750 mg, 2.95 mmol) was added to a magnetically stirred solution of cyclohexane-1,3-dione **(96)** (800 mg , 7.13 mmol), lithium iodide (80 mg, 0.59 mmol) and lithium carbonate (436 mg, 5.9 mmol) in acetone (15 mL). The resulting suspension was heated to reflux and after 16 hours the solvent volume was reduced to ~5 mL *in vacuo* and diluted with saturated aqueous Na_2CO_3 (20 mL) and water (15 mL). The ensuing solution was extracted with ethyl acetate (2 × 30 mL) and the organic extracts set aside. The aqueous phase was then acidified with 2M aqueous HCl to pH 3 then extracted with ethyl acetate (3 x 20 mL). The combined extracts from the acidified solution were then washed with brine (30 mL) and dried over Na_2SO_4. Concentration under reduced pressure gives an impure crude orange solid **(198)** (521 mg, ~27% desired compound by NMR) used directly in the following steps.

R_f = 0.32 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.02 (m, 2H), 3.34 (m, 2H), 2.58-1.88 (m, 6H). **^{13}C NMR** not resolvable. **IR** ν_{max} (neat) 3199, 2951, 1729, 1588, 1377, 1353, 715, cm^{-1}; **LRMS** (ESI, +ve) *m/z* 308.1 [(M + Na)+, 100%].**HRMS** [Found: $(M + Na)^+$, 308.0897. $C_{16}H_{15}NO_4Na$ requires $(M + Na)^+$, 308.0899].

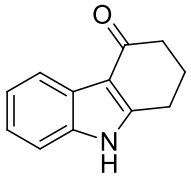
Concentration of the combined organic extracts from the basified solution yields essentially pure *N*-(2-((3-oxocyclohex-1-en-1-yl)oxy)ethyl)phthalimide **(201)** (361 mg, 43%) as a colourless solid.



m.p. = 171 °C; **R_f** = 0.18 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.37 (s, 1H), 4.12 (t, *J* = 5.3 Hz, 2H), 4.09 (t, *J* = 5.3 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.35 (t, *J* = 6.4 Hz, 2H), 1.98 (p,

J = 6.5 Hz, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 199.5, 177.1, 168.0, 134.2, 131.9, 123.5, 103.1, 65.0, 36.7, 36.6, 28.9, 21.1; **IR** ν_{max} (neat) 2950, 1774, 1712, 1650, 1604, 1393, 1184, 721 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 308.1 [(M + Na)+, 100%], 174 (20); **HRMS** [Found: $(M + Na)^+$, 308.0902 $C_{16}H_{15}NO_4Na$ requires $(M + Na)^+$, 308.0899].

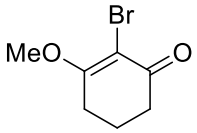
1,2-Dihydrocarbazol-4(3H)-one **(196)**[139]



A solution of phenylhydrazine (600 mg, 5.5 mmol) in 10% aqueous acetic acid (25 ml) was added to a solution of cyclohexane-1,3-dione **(96)** (600 mg, 5.3 mmol) in 10% aqueous acetic acid (25 mL). The mixture was warmed to 60 °C for 20 minutes and then allowed to cool to room temperature when a yellow- brown solid precipitated. This was filtered off and used directly in the next step. The crude brown solid was dispersed in aqueous sulphuric acid (20% v/v, 20 mL), and the mixture was heated to 110 °C for 3 hours. The resulting solution was poured into ice water (50 mL) to give a yellow solid which was filtered off and recrystallized from aqueous ethanol to afford 1,2-Dihydrocarbazol-4(3*H*)-one **(196)** as an orange solid (53%) **m.p.** 218 °C (lit. 221-223 °C)[139]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.22 (m, 1H), 7.30 (m, 3H), 2.98 (t, *J* = 6.2 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.25 (m, 2H). Spectral data identical to that reported in the literature.[139]

7.4 Hasubanans Framework

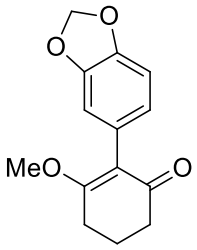
2-Bromo-3-methoxycyclohex-2-enone **(247)**[173]



Bromine (0.52 mL, 10 mmol) was added dropwise over 5 minutes to a stirred, cooled (-40 °C) solution of cyclohexane-1,3-dione **(96)** (1.12 g, 10 mmol) and pyridine (0.89 mL, 11 mmol) in methanol (25 mL). After addition was complete, trimethyl orthoformate (1.32 mL, 12 mmol) was added. The solution was stirred for 2 hours at -40 °C then slowly allowed to warm to room temperature and stirred for a further 16 h. The solution was then diluted with water (200 mL) and saturated aqueous Na_2SO_3 (10 mL) with vigorous stirring upon which a crystalline solid precipitated. This was collected by filtration and recrystallised from ethyl acetate and hexane to afford 2-bromo-3-methoxycyclohex-2-enone **(247)** (1.78 g, 87%) as colourless crystals.

m.p. 92-94 °C (lit. 94-95 °C)[173]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.34 (t, *J* = 6.3 Hz, 2H), 1.97 (p, J = 6.4 Hz, 2H). Spectral data in good agreement to that reported in the literature.[173]

2-(Benzo[d][1,3]dioxol-5-yl)-3-methoxycyclohex-2-enone **(246)**

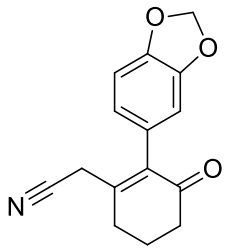


2-bromo-3-methoxycyclohex-2-enone **(247)** (3.08 g. 15.0 mmol) was added to a stirred solution of 3,4-(methylenedioxy)phenylboronic acid **(224)** (3.49 g, 21.0 mmol), tetrakis(triphenylphosphine)palladium (694 mg, 0.6 mmol) and triethylamine (10 mL) in degassed benzene/H2O (200 mL of an 4:1 v/v mixture). The resultant mixture was heated under reflux for 6 hours and the reaction quenched through addition of saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel

chromatography using ethyl acetate : hexane (2:1) to yield 2-(benzo[d][1,3]dioxol-5-yl)-3-methoxycyclohex-2-enone **(246)** (2.35 g, 64%) as a brown oil.

R_f = 0.66 (EtOAc:Hex, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 7.9 Hz, 1H), 6.64 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 3H), 5.92 (s, 2H), 3.72 (s, 3H), 2.69 (t, *J* = 6.2 Hz, 2H), 2.47 (t, *J* = 6.3 Hz, 2H), 2.08 (p, *J* = 6.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.6, 171.1, 145.9, 145.1, 125.9, 123.0, 119.3, 110.3, 106.8, 99.7, 55.8, 36.0, 25.6, 19.7; **IR** ν_{max} (neat) 2946, 2892, 1721, 1646, 1588, 1487 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 269.1 [(M + Na)+, 100%]; **HRMS** [Found: $(M + Na)^{+\cdot}$, 269.0793. $C_{14}H_{14}O_4Na$ requires $(M + Na)^{+\cdot}$, 269.0784].

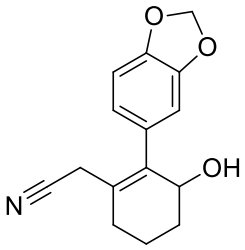
2-(2-(Benzo[d][1,3]dioxol-5-yl)-3-oxocyclohex-1-en-1-yl)acetonitrile **(243)**[169]



A magnetically stirred solution of diisopropylamine (0.78 mL, 5.5 mmol) in tetrahydrofuran (10 ml) was cooled to -78 °C under an atmosphere of nitrogen, to this *n*-BuLi (3.6 mL, 1.6M in pentane, 5.76 mmol) was added and the mixture warmed to 0 °C for 5 minutes. It was then cooled to -40 °C and to this solution acetonitrile (0.37 mL, 7 mmol) was then added and stirred for a further 1 hour. A solution of 2-(benzo[d][1,3]dioxol-5-yl)-3-methoxycyclohex-2-enone **(246)** (468 mg, 1.9 mmol) in THF (5 mL) was added over 2 minutes and the resultant mixture was stirred at -40 °C for 2 hours, then slowly warmed to room temperature and stirred for a further 16 hours. The reaction was quenched through addition of aqueous citric acid (10% w/w, 50 ml) and extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil that was purified by silica gel chromatography using ethyl acetate : hexane (1:2) to give 2-(2-(benzo[d][1,3]dioxol-5-yl)-3-oxocyclohex-1-en-1-yl)acetonitrile **(243)** as a brown oil (60 %).

R_f = 0.63 (EtOAc:Hex, 1:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 7.5 Hz, 1H), 6.51 (m, 2H), 5.98 (s, 2H), 3.22 (s, 2H), 2.67 (t, 6.0 Hz, 2H), 2.58 (t, 6.6 Hz, 2H), 2.15 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.1, 147.9, 147.6, 146.9, 140.4, 127.2, 122.9, 116.2, 109.9, 108.6, 101.3, 55.6, 29.7, 24.2, 21.8; Spectral data identical to that reported by Nugent.[169]

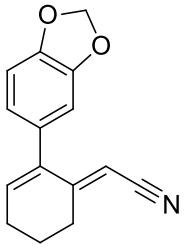
2-(2-(Benzo[d][1,3]dioxol-5-yl)-3-hydroxycyclohex-1-en-1-yl)acetonitrile **(244)**[169]



A magnetically stirred solution of 2-(2-(benzo[d][1,3]dioxol-5-yl)-3-oxocyclohex-1-en-1-yl)acetonitrile **(243)** (913 mg, 3.57 mmol) and $CeCl_3.7H_2O$ (1.48 g, 4.00 mmol) in MeOH (50 mL) was cooled to 0 °C, to this $NaBH_4$ (192.5 mg, 5.25 mmol) was added batchwise over 10 minutes. The solution was maintained at this temperature for 1 hour, at which point the reaction was quenched through addition of saturated aqueous NH_4Cl (50 mL). The reaction was diluted with ethyl acetate (150 ml) and washed with brine (50 mL), before being dried over Na_2SO_4. Concentration *in vacuo* gave a yellow oil which was purified by silica gel chromatography using ethyl acetate : hexane (1:1) to give 2-(2-(benzo[d][1,3]dioxol-5-yl)-3-hydroxycyclohex-1-en-1-yl)acetonitrile **(244)** (667 mg, 73%) as a yellow crystalline solid

m.p. = 87.2 – 88.5 °C; **R_f** = 0.63 (EtOAc:Hex, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.4 Hz, 1H), 6.65 (m, 2H), 5.99 (s, 2H), 4.35 (m, 1H), 2.98 (m, 2H), 2.23 (m, 4H), 1.78 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.0, 147.2, 140.1, 132.4, 127.1, 122.1, 117.8, 108.9, 108.6, 101.2, 68.4, 31.0, 29.0, 23.0, 17.8; Spectral data identical to that reported by Nugent.[169]

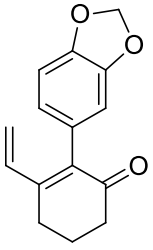
(E)-2-(2-(Benzo[d][1,3]dioxol-5-yl)cyclohex-2-en-1-ylidene)acetonitrile **(254)**



2-(2-(benzo[d][1,3]dioxol-5-yl)-3-hydroxycyclohex-1-en-1-yl)acetonitrile **(244)** (257 mg, 1 mmol) was added to a stirred solution of 1,8-bis(dimethylamino)naphthalene **(253)** (43 mg, 0.2 mmol), in freshly distilled trichloroacetonitrile (2 mL). The solution was then stirred at room temperature and monitored by TLC for consumption of starting material. After 4 hours the reaction was quenched by addition of saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (3 x 10 mL). Concentration *in vacuo* of the combined organic fractions yielded a black tar which was subjected to silica gel chromatography eluting with ethyl acetate : hexane (1:3). Concentration of the appropriate fractions led to the isolation of (E)-2-(2-(benzo[*d*][1,3]dioxol-5-yl)cyclohex-2-en-1-ylidene)acetonitrile **(254)** (76 mg, 32%) as a brown residue.

R_f = 0.83 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, DMSO) δ 6.90 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 1.2 Hz, 1H), 6.66 (dd, *J* = 7.9, 1.5 Hz, 1H), f 6.03 (s, 2H), 5.09 (s, 1H), 2.71 (t, *J* = 6 Hz, 2H), 2.37 (td, *J* = 5.7, 4.3 Hz, 2H), 1.79 (m, 2H). **^{13}C NMR** (200 MHz, DMSO) δ 159.0, 147.7, 147.2, 138.6, 138.2, 133.0, 122.7, 118.3, 109.7, 108.7, 101.5, 94.1, 29.9, 26.4, 22.0; **IR** ν_{max} (neat) 2924, 2210, 1718, 1607, 1485, 1232, 1035, 931,812 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 240.1 [(M + H)+, 100%], 227 (78); **HRMS** [Found: $(M + H)^+$, 240.1016 $C_{15}H_{14}NO_2$ requires $(M + H)^+$, 240.1025].

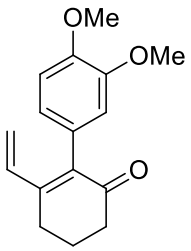
2-(Benzo[d][1,3]dioxol-5-yl)-3-vinylcyclohex-2-enone **(258)**



To a stirred solution of 2-(Benzo[d][1,3]dioxol-5-yl)-3-methoxycyclohex-2-enone **(246)** (246 mg, 1 mmol) in tetrahydrofuran (5 mL), cooled to -40 °C, was added vinylmagnesium bromide (4 mL, 1M in tetrahydrofuran, 4 mmol) dropwise. The solution was stirred at this temperature for 2 hours then slowly warmed to room temperature and stirred for a further 14 hours. The reaction was quenched through addition of 10% w/w citric acid (20 ml), stirred for a further 1 hour and extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil that was purified by silica gel chromatography using ethyl acetate : hexane (1:4) to give 2-(benzo[d][1,3]dioxol-5-yl)-3-vinylcyclohex-2-enone **(258)** (198 mg, 82%) as a colourless oil.

R_f = 0.9 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.80 (d, *J* = 7.9 Hz, 1H), 6.56 (d, *J* = 1.5 Hz, 1H), 6.51 (m, 2H), 5.96 (s, 2H), 5.65 (d, *J* = 17.6 Hz, 1H), 5.35 (d, *J* = 11.0 Hz, 1H), 2.64 (t, *J* = 6.1 Hz, 2H), 2.57 (t, *J* = 6.3 Hz, 2H), 2.11 (p, *J* = 6.3 Hz, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 199.0, 151.4, 147.3, 147.0, 138.1, 136.4, 128.6, 124.0, 120.4, 111.0, 108.0, 101.0, 38.4, 25.4, 21.8; **IR** ν_{max} (neat) 2937, 1716, 1663, 1485, 1239, 1037, 932 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 265.2 [(M +Na)+, 100%]; **HRMS** [Found: $(M + Na)^+$, 265.0837. $C_{15}H_{14}O_3Na$ requires $(M + Na)^+$, 265.0841].

3',4'-Dimethoxy-6-vinyl-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(261)**[178]

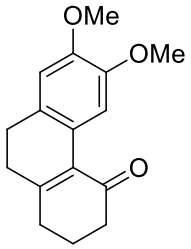


2-bromo-3-methoxycyclohex-2-enone **(247)** (3.08 g. 15.0 mmol) was added to a stirred solution of 3,4-(methylenedioxy)phenylboronic acid **(260)** (3.82 g, 21.0 mmol), tetrakis(triphenylphosphine)palladium (694 mg, 0.6 mmol) and triethylamine (10 mL) in degassed dioxane/water (200 mL of an 4:1 v/v mixture). The resultant mixture was heated under reflux for 6 hours and the reaction quenched through addition of saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (3 x 150 mL).

The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude orange solid was dissolved in tetrahydrofuran (50 mL) and cooled to -40 °C, then vinylmagnesium bromide (45 mL, 1M in tetrahydrofuran, 45 mmol) was added over 10 minutes. The solution was stirred at this temperature for 2 hours then slowly warmed to room temperature and stirred for a further 14 hours. Water (10 mL) was added and the reaction volume was then reduced to ~10 mL *in vacuo*. This was then diluted with 10% w/w citric acid (100 ml), stirred for a further 1 hour and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil that was purified by silica gel chromatography using ethyl acetate : hexane (1:4) to give 3',4'-dimethoxy-6-vinyl-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(261)** (1.43 g, 37%) as a colourless oil in 37% yield over two steps.

R_f = 0.37 (EtOAc:Hex, 1:2) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 7.9 Hz, 1H) 6.58-6.66 (m, 2H) 6.49 (dd, *J* = 17.5 Hz, 11.0 Hz, 1H) 5.64 (d, *J* = 17.5 Hz, 1H), 5.32 (d, *J* = 11.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.11 (p, *J* = 6.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.0, 151.2, 148.2, 138.1, 136.3, 127.5, 124.0, 122.9, 120.3, 113.6, 110.6, 55.7, 55.6, 38.3, 25.3, 21.7. Spectral data were in good agreement to that reported in the literature.[178]

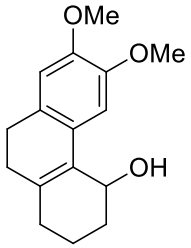
6,7-Dimethoxy-2,3,9,10-tetrahydrophenanthren-4(1H)-one **(262)**[178]



A solution of 3',4'-dimethoxy-6-vinyl-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one **(261)** (242 mg, 1 mmol) and boron trifluoride diethyl etherate (1.2 mL, 10 mmol) in carbon tetrachloride (10 mL) was refluxed for 16 hours. The reaction mixture was diluted with ether (50 mL) and neutralized with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with diethyl ether (2 x 20 mL) and the combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. Removal of solvent *in vacuo* resulted in a colourless oil which was purified by silica gel

chromatography with ethyl acetate : hexane (1:2), to give 6,7-dimethoxy-2,3,9,10-tetrahydrophenanthren-4(1H)-one **(262)** (90 mg, 35%) as a colourless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.66 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.56 (m, 4H), 2.40 (t, *J* = 7.7 Hz, 2H), 2.04 (p, *J* = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) 197.6, 158.6, 147.4, 147.1, 146.7, 128.1, 123.5, 110.9,110.4, 55.8, 55.7, 39.4, 32.1, 30.9, 26.9, 21.8. Spectral data in good agreement to that reported in the literature.[178]

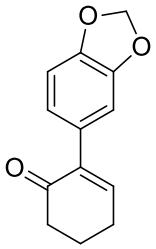
6,7-Dimethoxy-1,2,3,4,9,10-hexahydrophenanthren-4-ol **(263)**



A magnetically stirred solution of 6,7-dimethoxy-2,3,9,10-tetrahydrophenanthren-4(1H)-one **(262)** (258 mg, 1 mmol) and $CeCl_3.7H_2O$ (409 mg, 1.1 mmol) in MeOH (5 mL) was cooled to 0 °C, to this $NaBH_4$ (57 mg, 1.5 mmol) was added batchwise over 2 minutes. The solution was maintained at this temperature for 1 h, at which point the reaction was quenched through addition of saturated aqueous NH_4Cl (5 mL). The reaction was diluted with ethyl acetate (30 mL) and washed with brine (10 mL), before being dried over Na_2SO_4. Concentration *in vacuo* gave an oily residue that was purified by silica gel chromatography using ethyl acetate : hexane (1:1) to give 6,7-dimethoxy-1,2,3,4,9,10-hexahydrophenanthren-4-ol **(263)** (260 mg, ~100%) as a colourless oil.

R_f = 0.48 (EtOAc:Hex 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.53 (s, 1H), 4.58 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.76 (m, 2H), 2.61 (m, 2H), 1.35-1.80 (m, 6H) (OH not observed); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 147.5, 147.4, 136.5, 131.3, 128.1, 127.4, 112.6, 107.9, 67.0, 56.1, 55.8, 33.9, 32.6, 30.6, 29.6, 20.2; **IR** ν_{max} (neat) 3498, 2925, 2850, 1607, 1512, 1451, 1253, 1212, 1118, 728 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 283.2 [(M +Na)+, 100%], 245 (27); **HRMS** [Found: $(M + Na)^+$, 283.1314. $C_{16}H_{20}O_3Na$ requires $(M + Na)^+$, 283.1310].

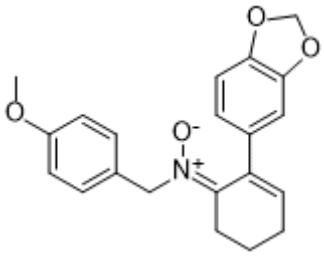
2-(Benzo[d][1,3]dioxol-5-yl)cyclohex-2-enone **(270)**[250]



A magnetically stirred solution of 2-iodocyclohex-2-enone **(161)** (3.33 g, 15 mmol) and 3,4-(methylenedioxy)phenylboronic acid **(224)** (3.48 g, 21 mmol) was treated with a degassed solution of benzene/2M Na_2CO_3 (200 mL 4:1), tetrakis(triphenylphosphine)palladium (693 mg, 0.6 mmol) was added and the resultant mixture was heated under reflux for 16 h. The reaction was quenched through addition of saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography using ethyl acetate : hexane (1:1) to give 2-(benzo[d][1,3]dioxol-5-yl)cyclohex-2-enone **(270)** (2.66 g, 82%) as a colourless crystalline solid.

m.p. = 103 °C (lit. 98-100 °C)[250], $\mathbf{R_f}$ = 0.47 (EtOAc:Hex, 1:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (t, *J* = 4.4 Hz, 1H), 6.68 (m, 3H), 5.95 (s, 2H), 2.55 (m, 4H), 2.09 (m, *2*H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.1, 147.3, 147.2, 147.1, 139.9, 130.5, 122.1, 109.4, 108.0, 101.0, 39.1, 26.6, 22.9; Spectral data identical to that reported in the literature.[250]

(Z)-N-(2-(benzo[d][1,3]dioxol-5-yl)cyclohex-2-en-1-ylidene)-1-(4-methoxyphenyl)methanamine oxide **(274)**

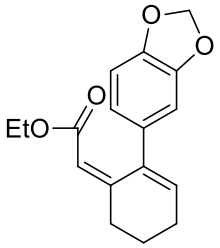


A magnetically stirred solution of 2-(benzo[d][1,3]dioxol-5-yl)cyclohex-2-enone **(270)** (216 mg, 1 mmol) and N-(4-methoxybenzyl)hydroxylamine (182 mg, 1.2 mmol) in tetrahydrofuran (5 mL) was treated with titanium(IV) ethoxide (556 mg, 2 mmol). The

mixture was heated at reflux for 16 hours. The reaction mixture was filtered through a plug of wet silica (prepared by evaporating a suspension of silica gel and 10 mL of a 9:1 tetrahydrofuran/water solution). The resulting filtrate was concentrated *in vacuo* to give crude product as a dark oil (351 mg) that was analysed directly by NMR. The key identifiable signals for **(274)** are given below in addition to the identification of the M+H signal by LCMS at 352 m/z. Signals in the aromatic portion of the NMR spectra could not be confidently assigned due to overlap with other impurities.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (t, *J* = 5.3 Hz, 1H), 5.97 (s, 2H), 4.64 (s, 2H), 3.77 (s, 3H), 2.93 (t, *J* = 6.4 Hz, 2H), 2.21 (td, *J* = 6,2 Hz, 5.3 Hz, 2H), 1.83 – 1.74 (tt, *J* = 6.4 Hz, 6.2 Hz, 2H). **LRMS** (ESI, +ve) *m/z* 352.0 [$(M + H)^+$, 72%]

(Z)-Ethyl 2-(2-(benzo[d][1,3]dioxol-5-yl)cyclohex-2-en-1-ylidene)acetate **(281)**

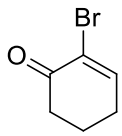


To a solution of ethyl trimethylsilylacetate (0.38 mL, 2.1 mmol) in tetrahydrofuran (2 mL), cooled to -78 °C, was added lithium bis(trimethylsilyl)amide (2.2 mL, 1M in tetrahydrofuran, 2.2 mmol). This was stirred for 1 hour at -78 °C, followed by the addition of 2-(benzo[d][1,3]dioxol-5-yl)cyclohex-2-enone **(170)** (432mg, 2 mmol) as a solution in THF (2 mL) this was warmed slowly to room temperature then stirred for a further 16 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. Removal of solvent *in vacuo* yielded a light yellow oil that was subjected to silica gel chromatography using ethyl acetate : hexane (1:3) to yield (Z)-ethyl 2-(2-(benzo[d][1,3]dioxol-5-yl)cyclohex-2-en-1-ylidene)acetate **(281)** (474 mg, 83%) as a light yellow oil.

R_f = 0.73 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.73 (d, *J* = 1.5 Hz, 1H), 6.69 (m, 2H), 5.94 (td, *J* = 4.0, 1.3 Hz, 1H), 5.90 (s, 2H), 5.69 (s, 1H), 3.61 (q, *J* = 7.1 Hz, 2H), 2.43 (m, 2H), 2.39 (td, *J* = 6.2, 4.2 Hz, 2H), 1.91 (m, 2H), 1.02 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 170.6, 166.9, 148.6, 147.4, 134.3, 129.8, 121.2,

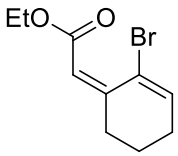
120.0, 116.7, 107.9, 107.7, 100.8, 60.1, 34.9, 26.7, 23.0, 13.9; **IR** ν_{max} (neat) 2940, 1744, 1711, 1486, 1240, 1192, 1035, 933, 912, 727 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 309.2 [(M + Na)+, 100%]; **HRMS** [Found: $(M + Na)^+$, 309.1102. $C_{17}H_{18}O_4Na$ requires $(M + Na)^+$, 309.1103].

2-Bromo-2-cyclohexen-1-one **(282)**[194]



To a stirred solution of 2-cyclohexen-1-one (**160**) (0.6 mL, 6.2 mmol) in dichloromethane (16 mL) at 0 °C was added a solution of bromine (0.32 mL, 6.3 mmol) in dichloromethane (16 mL) over 1 hour. Triethylamine (1.44 mL, 10.3 mmol) was then added and the resulting mixture was allowed to warm at room temperature then stirred for 2 hours before it was quenched with 1M aqueous HCl (10 mL). The layers were separated and the organic layer was washed with brine (100 mL), dried over Na_2SO_4) and concentrated *in vacuo* to afford 2-bromo-2-cyclohexen-1-one **(282)** (1.06 g, 98%) which was stored in the dark at 0 °C and used without further purification.

(Z)-Ethyl 2-(2-bromocyclohex-2-en-1-ylidene)acetate **(283)**



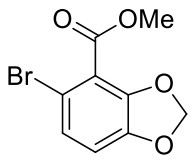
To a solution of ethyl trimethylsilylacetate (0.38 mL, 2.1 mmol) in tetrahydrofuran (2 mL), cooled to -78 °C, was added lithium bis(trimethylsilyl)amide (2.2 mL, 1M in tetrahydrofuran, 2.2 mmol). This was stirred for 1 hour at -78 °C, followed by the addition of 2-bromo-2-cyclohexen-1-one **(282)** (432mg, 2 mmol) as a solution in THF (2 mL) this was warmed slowly to room temperature then stirred for a further 16 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (20 mL)

and dried over Na_2SO_4. Removal of solvent *in vacuo* yielded a light yellow oil that was subjected to silica gel chromatography using ethyl acetate : hexane (1:3) to yield (Z)-ethyl 2-(2-bromocyclohex-2-en-1-ylidene)acetate **(283)** (480 mg, 87%) as a light yellow oil.

R_f = 0.85 (EtOAc:Hex, 1:1); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.68 (t, *J* = 4.6 Hz, 1H), 6.23 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.10 (m, 2H), 2.30 (q, *J* = 5.7 Hz, 2H), 1.77 (p, *J* = 6.1 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 166.8, 150.0, 140.9, 122.6, 118.5, 60.0, 28.5, 27.7, 21.6, 14.3; **IR** ν_{max} (neat) 2980, 2935, 1709, 1617, 1369, 1301, 1232, 1174,1033, 870 cm^{-1}; LRMS (ESI, +ve) *m/z* 245.1 [(M)+, 100%], 219 (65), 217 (69), 137 (53); **HRMS** [Found: $(M + Na)^+$, 268.9975. $C_{10}H_{13}O_2BrNa$ requires $(M + Na)^+$, 268.9976].

7.5 Bicuculline

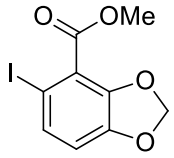
Methyl 5-bromobenzo[*d*][1,3]dioxole-4-carboxylate **(339)**[216]



Butyllithium (1.31 M in pentane, 7.02 mL, 9.13 mM) was dropwise over 5 minutes to a cooled (-78 °C) solution of diisopropylamine (1.40 mL, 9.95 mmol) in tetrahydrofuran (20 mL) under nitrogen. The mixture was warmed to 0 °C for 5 minutes then returned to -78 °C. 5-bromobenzo[d][1,3]dioxole **(338)** (1.00 mL, 8.30 mmol) was then added dropwise over 2 minutes at this temperature. After stirring for 45 minutes dimethyl carbonate (2.1 mL, 25 mmol) was added and the reaction then slowly warmed to room temperature over 2 hours. The solution was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed sequentially with 1M aqueous HCl (30 mL), saturated aqueous sodium carbonate (40 mL) and brine (40 mL). After drying over Na_2SO_4 the solution was concentrated under reduced pressure and the resulting oil purified by silica gel chromatography using ethyl acetate : hexane (1:9) to afford methyl 5-bromobenzo[*d*][1,3]dioxole-4-carboxylate **(339)** (1.78 g, 81%) as a pale yellow solid

R_f = 0.09 (Ether:Hex, 1:9); **m.p.** 58-59 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.05 (s, 2H), 3.94 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.0, 147.6, 147.4, 126.0, 115.9, 111.2, 110.9, 102.3, 52.4; **IR** ν_{max} (neat) 2953, 2905, 1733, 1626, 1451, 1342, 1276, 1137 cm^{-1}; **LRMS** (ESI^+) *m/z* = 281 ($[^{79}BrM+Na]^+$, 100%), 283 ($[^{81}BrM+Na]^+$, 98%); **HRMS** [Found 280.9425. $C_9H_7O_4{}^{79}BrNa$ requires (M+Na)+ 280.9425], [Found 282.9409. $C_9H_7O_4{}^{81}BrNa$ $(M+Na)^+$ requires 282.9405]. Data identical to that obtained by Pasfield.[216]

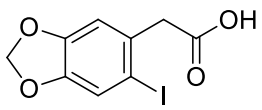
Methyl 5-iodobenzo[d][1,3]dioxole-4-carboxylate **(309)**[216]



Butyllithium (1.3M in pentane, 28.2 mL, 42.4 mmol) was added dropwise over 5 min to a cooled (-78 °C) solution of 2,2,6,6-tetramethylpiperidine (7.86 mL, 46.2 mmol) in tetrahydrofuran under nitrogen and the reaction warmed to 0°C. After stirring for 10 minutes the reaction was returned to -78°C followed by the dropwise addition of 5-iodobenzo[*d*][1,3]dioxole **(313)** (5.00 mL, 38.5 mmol) over 5 minutes. The solution was stirred for a further 45 minutes at -78 °C and dimethyl carbonate (12 mL, 142 mmol) was then added dropwise over 5 minutes. The reaction was then slowly warmed to room temperature over 2 hours, then quenched with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed sequentially with 1M aqueous HCl (30 mL), saturated aqueous sodium carbonate (40 mL) and brine (40 mL). After drying over Na_2SO_4 the solution was concentrated under reduced pressure and the resulting oil purified by silica gel chromatography using ethyl acetate : hexane (1:9) to afford methyl 5-iodobenzo[*d*][1,3]dioxole-4-carboxylate **(309)** (1.78 g, 81%) as a yellow oil.

R_f = 0.19 (Ether:Hex, 1:9); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.04 (s, 2H) 3.94 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 165.0, 148.5, 147.4, 133.3, 119.0, 112.0, 102.2, 81.4, 52.6; **IR** ν_{max} (neat) 2951, 2903, 1729, 1619, 1448, 1273, 1239, 1041 cm^{-1}; **LRMS** (EI^+) *m/z* = 306 ($M^{+\bullet}$, 100%); **HRMS** (Found 305.9393.$C_9H_7O_4I$ ($M^{+\bullet}$) requires 305.9389). Data identical to that obtained by Pasfield.[216]

2-(6-Iodobenzo[*d*][1,3]dioxol-5-yl)acetic acid **(333)**[251]

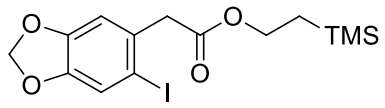


Iodine (7.9 g, 31.1 mmol) was added in small portions over 1 hour to a vigorously stirred solution of 2-(benzo[d][1,3]dioxol-5-yl)acetic acid **(310)** (4.00 g, 22.2 mmol), NaOH (2.66 g, 66.6 mmol) and NaI (3.33 g, 22.2 mmol) in tetrahydrofuran (15 mL) and water (30 mL). After addition was complete the reaction was then allowed to stir for 16 hours at room temperature and the reaction quenched by addition of a saturated aqueous Na_2SO_3 (20 mL). The resulting solution was poured into water (100 mL) and the reaction stirred under a stream of nitrogen for 3 hours, resulting in

the formation of a precipitate. The solids were collected by filtration and washed with water (3 x 30 mL) and dried under vacuum to afford 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetic **(333)** as a white solid (6.11 g, 71%).

R_f (EtOAc:Hex ; 1:1) 0.05; **m.p.** 179-186 °C (lit 180-181 °C)[251]; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.26 (s, 1H), 6.87 (s, 1H), 5.97 (s, 2H), 3.71 (s, 2H); **^{13}C-NMR** (100 MHz, CD_3OD) δ 174.5, 150.0, 149.0, 132.9, 119.3, 111.7, 103.2, 89.5, 46.6; **IR** ν_{max} (neat) 3317, 3012, 2910, 1697, 1484, 1407, 1226, 1034 cm^{-1}; **LRMS** (ESI^+) *m/z* = 329 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_9H_7O_4Na$ ($[M+H]^+$) 328.9287, found 328.9286. Data in good agreement with the literature.[251]

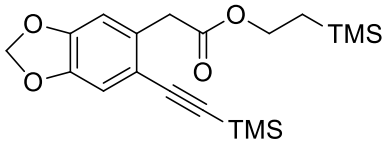
2-(Trimethylsilyl)ethyl 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetate **(337)**



A solution of 2-(trimethylsilyl)ethanol (2.87 mL, 20 mmol) and 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetic **(333)** (6.00 g, 19.6 mmol) in acetonitrile (30 mL) was added over 5 minutes to a stirred, cooled (0 °C) mixture of N,N'-dicyclohexylcarbodiimide (4.25 g, 20.58 mmol) and 4-(dimethylamino)pyridine (240 mg, 1.96 mmol) in acetonitrile (30 mL). The resulting solution was stirred at room temperature for a further 16 hours, cooled to 0 °C then filtered. The filtrate was concentrated under reduced pressure and the residue treated with hexane and sonicated. The resulting solution was cooled to 0 °C and filtered a second time. Concentration *in vacuo* afforded the essentially pure 2-(trimethylsilyl)ethyl 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetate **(337)** (7.25 g, 91%) as a colourless oil.

R_f = 0.72 (EtOAc:Hex, 1:4); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.80 (s, 1H), 5.96 (s, 2H), 4.21 (m, 2H), 3.69 (s, 2H), 1.01 (m, 2H), 0.03 (s, 9H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 170.8, 148.5, 147.6, 131.0, 118.6, 110.5, 101.7, 88.9, 63.4, 46.2, 17.3, -1.5; **IR** ν_{max} (neat) 2890, 1728, 1478, 1227, 1150, 1036, 831, 694 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 429.0 [(M +Na)+, 100%], 379 (20), 252 (38); **HRMS** [Found: $(M + Na)^+$, 428.9993. $C_{14}H_{19}IO_4Si_2Na$ requires $(M + Na)^+$, 428.9995].

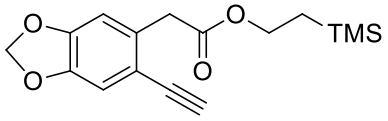
2-(Trimethylsilyl)ethyl 2-(6-((trimethylsilyl)ethynyl)benzo[d][1,3]dioxol-5-yl)acetate **(340)**



To a stirred solution of 2-(trimethylsilyl)ethyl 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetate **(337)** (3.12 g, 7.68 mmol), tetrakis(triphenylphosphine)palladium (443 mg, 0.38 mmol) and copper iodide (146 mg, 0.77 mmol) in tetrahydrofuran (50 mL) was added triethylamine (3.12 mL, 22.4 mmol) followed by ethynyltrimethylsilane **(331)** (1.59 mL, 11.1 mmol). The reaction was stirred for 16 hours at room temperature and then quenched with saturated aqueous NH_4Cl (75 mL). The resulting solution was extracted with ethyl acetate (3 x 30 mL), the combined organic layers washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residual orange oil was purified by silica gel chromatography using ethyl acetate : hexane (1:9) to give 2-(trimethylsilyl)ethyl 2-(6-((trimethylsilyl)ethynyl)benzo[d][1,3]dioxol-5-yl)acetate **(340)** (2.63 g, 91%) as a tan solid.

m.p. = 72 °C; $\mathbf{R_f}$ = 0.75 (EtOAc:Hex, 1:4); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.74 (s, 1H), 5.95 (s, 2H), 4.19 (m, 2H), 3.73 (s, 2H), 0.99 (m, 2H), 0.23 (s, 9H), 0.02 (s, 9H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 171.3, 148.2, 146.4, 131.8, 116.5, 111.7, 110.1, 103.2, 101.4, 97.3, 63.1, 39.8, 17.4, 0.0, -1.5; **IR** ν_{max} (neat) 2890, 2152, 1728, 1483, 1247, 1156, 830, 758 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 399.2 [(M +Na)+, 100%], 349 (55); **HRMS** [Found: $(M + Na)^+$, 399.1425. $C_{19}H_{28}O_4Si_2Na$ requires $(M + Na)^+$, 399.1424]

2-(Trimethylsilyl)ethyl 2-(6-ethynylbenzo[d][1,3]dioxol-5-yl)acetate **(341)**

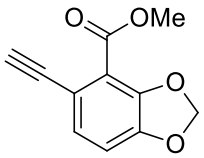


Aqueous silver nitrate (90 mg, 0.53 mmol, 5 mL water) was added to a solution of 2-(trimethylsilyl)ethyl 2-(6-((trimethylsilyl)ethynyl)benzo[d][1,3]dioxol-5-yl)acetate **(340)** (2.00 g, 5.31 mmol) in acetone (15 mL) and stirred for 16 hours at room temperature

under nitrogen. Brine (20 mL) was added and the solution filtered. The filtrate was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts washed with brine (30 mL) and dried over Na_2SO_4. Removal of solvent *in vacuo* gave a colourless oil that was purified by silica gel chromatography using ethyl acetate : hexane (1:9) to give 2-(trimethylsilyl)ethyl 2-(6-ethynylbenzo[d][1,3]dioxol-5-yl)acetate **(341)** (1.47g, 91%) as a colourless oil.

R_f = 0.67 (EtOAc:Hex, 1:4); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.74 (s, 1H), 5.94 (s, 2H), 4.18 (m, 2H), 3.73 (s, 2H), 3.15 (s, 1H), 0.97 (m, 2H), 0.00 (s, 9H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 171.3, 148.4, 146.5, 131.9, 115.3, 112.4, 110.1, 101.5, 81.8, 80.1, 63.2, 39.7, 17.3, -1.5; **IR** ν_{max} (neat) 3290, 2972, 2103, 1728, 1482, 1380, 1248, 1152, 1036, 939, 833 cm^{-1}; LRMS (ESI, +ve) *m/z* 327.1.4 [(M +Na)+, 100%], 277 (33); **HRMS** [Found: $(M + Na)^+$, 327.1030. $C_{16}H_{20}O_4SiNa$ requires $(M + Na)^+$, 327.1029]

Methyl 5-ethynylbenzo[d][1,3]dioxole-4-carboxylate **(343)**



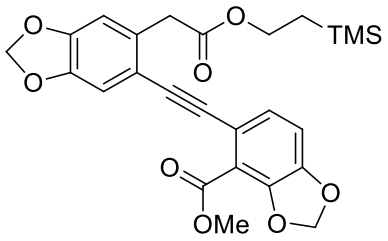
To a solution of methyl 5-iodobenzo[d][1,3]dioxole-4-carboxylate **(309)** (2.27 g, 7.42 mmol), tetrakis(triphenylphosphine)palladium (428 mg, 0.37 mmol), and copper iodide (140 mg, 0.74 mmol) in tetrahydrofuran (50 mL) was added triethylamine (3.12 mL, 22.4 mM) followed by ethynyltrimethylsilane **(331)** (1.6 mL, 11.1 mmol) and the reaction stirred for 16 hours at room temperature. The reaction was then quenched by addition of saturated aqueous NH_4Cl (75 mL) followed by extraction with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. Concentration under reduced pressure gave an orange oil that was used directly in the next step.

The previously obtained oil was dissolved in methanol (50 mL) and anhydrous potassium carbonate (102 mg, 0.74 mmol) added. The resulting suspension was then stirred at room temperature for 3 hours. The reaction was then diluted with

water (50 mL) followed by extraction with dichloromethane (3 x 40 mL) and washing with brine (50 mL). The combined organic layers were evaporated on to TLC grade silica (3 g) and evaporated to dryness. The compound was then purified by silica gel chromatography using ethyl acetate : hexane (1:4) to afford methyl 5-ethynylbenzo[d][1,3]dioxole-4-carboxylate **(343)** (775 mg, 95%) as a tan solid.

R_f (Ether:Hex ; 3:7) 0.18; **m.p.** 96 °C (decomp); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.09 (s, 2H), 3.94 (s, 3H), 3.20 (s, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.3, 148.7, 147.8, 129.1, 115.6, 114.9, 110.7, 102.3, 81.5, 79.7, 52.2; **IR** ν_{max} (neat) 3248, 2956, 2919, 1713, 1449, 1243, 1054, 921 cm^{-1}; **LRMS** (EI^+) *m/z* = 204 ($M^{+\bullet}$, 100%); **HRMS** [Found 204.0426. $C_{11}H_8O_4$ requires ($M^{+\bullet}$) 204.0423]

Methyl 5-((6-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)benzo[d][1,3]dioxol-5-yl)ethynyl)benzo[d][1,3]dioxole-4-carboxylate **(336)**

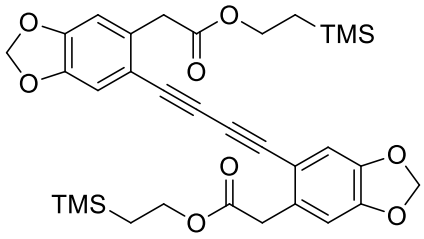


To a stirred, heated (60 °C) solution of 2-(trimethylsilyl)ethyl 2-(6-iodobenzo[d][1,3]dioxol-5-yl)acetate **(337)** (5.2 g, 12.8 mmol), copper iodide (230 mg, 1.26 mmol), and tetrakis(triphenylphosphine)palladium (700 mg, 0.61 mmol) in diisopropylamine (40 mL) was added methyl 5-ethynylbenzo[d][1,3]dioxole-4-carboxylate **(343)** (2.61 g, 12.8 mmol) as a solution in DIPA (10 mL) over a period of one minute. The solution was stirred for a further 30 minutes resulting in a voluminous precipitate. The reaction mixture was diluted with water (100 mL) and acidified to pH 4 with 2M aqueous HCl. The resulting solution was then extracted with ethyl acetate (3 x 70 mL) and the combined organic extracts washed with brine then dried over Na_2SO_4. Removal of solvent *in vacuo* yields a crude orange solid that was purified by silica gel chromatrography using ethyl acetate : hexane (1:4) to

afford methyl 5-((6-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)benzo[d][1,3]dioxol-5-yl)ethynyl)benzo[d][1,3]dioxole-4-carboxylate **(336)** (5.68 g, 92%) as a beige solid.

m.p. = 126 °C; **R_f** = 0.31 (EtOAc:Hex, 1:4); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 6.10 (s, 2H), 5.98 (s, 2H), 4.18 (m, 2H), 3.96 (s, 3H), 3.85 (s, 2H), 0.95 (m, 2H), -0.01 (s, 9H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 171.5, 164.4, 148.2, 148.1, 147.9, 146.5, 131.3, 128.1, 116.7, 116.4, 114.9, 111.5, 110.8, 110.1, 102.3, 101.5, 90.6, 90.3, 63.1, 52.3, 39.8, 17.3, -1.6; **IR** ν_{max} (neat) 2890, 2201, 1715, 1611, 1467, 1450, 1375, 1234, 1035, 840, 488 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 505.2 [(M +Na)+, 100%], 455 (24); **HRMS** [Found: $(M + Na)^+$, 505.1286. $C_{25}H_{26}O_8SiNa$ requires $(M + Na)^+$, 505.1295].

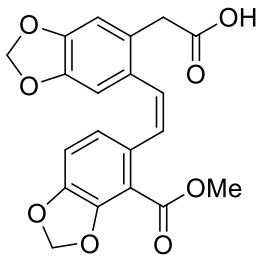
Bis(2-(trimethylsilyl)ethyl) 2,2'-(6,6'-(buta-1,3-diyne-1,4-diyl)bis(benzo[d][1,3]dioxole-6,5-diyl))diacetate **(342)**



After pooling of unsuccessful Sonogashira reactions and purification of the resulting residue by column chromatography with gradient elution using ethyl acetate : hexane (1:9 – 1:0) it was possible to isolate the homocoupled side product for characterisation.

m.p. = 120-130 °C, **R_f** = 0.5 (EtOAc:Hex, 1:4); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.94 (s, 2H), 6.78 (s, 2H), 5.98 (s, 4H), 4.22 (m, 4H), 3.76 (s, 4H), 1.02 (m, 4H), 0.02 (s, 18H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 171.1, 148.9, 146.6, 133.1, 115.1, 112.2, 110.2, 101.7, 80.4, 76.8, 63.3, 39.7, 17.4, -1.5; **IR** ν_{max} (neat) 2889, 2144, 1727, 1613, 1482, 1270, 1250, 1153, 1033, 831, 694, 519 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 629.4 [(M +Na)+, 100%], **HRMS** [Found: $(M + Na)^+$, 629.2003. $C_{32}H_{38}O_8Si_2Na$ requires $(M + Na)^+$, 629.2003].

(Z)-2-(6-(2-(4-(Methoxycarbonyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxol-5-yl)acetic acid **(329)**



Ethoxydimethylsilane (1 mL, 7.2 mmol) was added under nitrogen to a solution of Methyl 5-((6-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)benzo[d][1,3]dioxol-5-yl)ethynyl)benzo[d][1,3]dioxole-4-carboxylate **(336)** (1.01 g, 2.07 mmol) dissolved in tetrahydrofuran (1 mL), to this solution was added anhydrous platinum oxide (50 mg, 0.22 mmol). The resulting suspension was heated to 60 °C for 6 hours then the solvent removed *in vacuo*. The oily black residue was resuspended in tetrahydrofuran (3 mL) and cooled to -10 °C, followed by addition of a solution of tetrabutylammonium fluoride (10 mL of a 1M solution in THF, 10 mmol) over a period of 2 minutes, during which gas was evolved. The solution was slowly warmed to room temperature and stirred for a further 14 hours. The reaction was quenched by addition of 10% $CaCl_2$ solution (10 mL) and stirred for a further 1 hour. The resulting grey suspension is then filtered through Celite and the solids washed with diethyl ether (3 x 5 mL) and water (2 x 5 mL). The collected filtrates were extracted with diethyl ether (3 x 10 mL) and the combined organic extracts washed with brine (20 mL) then dried over Na_2SO_4. Solvent was removed *in vacuo* and the resulting grey solid was purified by silica gel chromatography using ethyl acetate : hexane : acetic acid (24:75:1) to give (Z)-2-(6-(2-(4-(methoxycarbonyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxol-5-yl)acetic acid **(329)** (771 mg, 96%) as a light orange solid.

m.p. = 153 °C; $\mathbf{R_f}$ = 0.34 (EtOAc:Hex, 3:2); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.82 (d, *J* = 11.8 Hz, 1H), 6.68 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 12.0 Hz, 1H), 6.48 (s, 1H), 6.03 (s, 2H), 5.87 (s, 2H), 3.90 (s, 3H), 3.60 (s, 2H), COOH not observed; **^{13}C NMR** (200 MHz, $CDCl_3$) δ 177.5, 165.4, 148.0, 147.3, 146.8, 146.7, 131.0, 130.6, 130.6, 127.3, 125.2, 124.3, 113.0, 111.0, 110.3, 110.0, 101.9, 101.1, 52.1, 38.4; **IR** ν_{max} (neat) 3658, 2889, 1711, 1497, 1459, 1266, 1230,

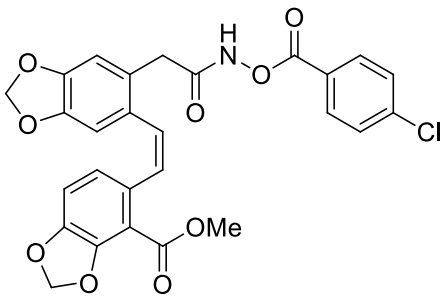
1035, 872 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 407.2 [(M +Na)+, 100%], 335 (16); **HRMS** [Found: $(M + Na)^+$, 407.0743. $C_{20}H_{16}O_8Na$ requires $(M + Na)^+$, 407.0743].

General procedure for formation of hydroxamate esters:

To a stirred solution of (Z)-2-(6-(2-(4-(methoxycarbonyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxol-5-yl)acetic acid **(329)** (1.01 g, 2.65 mmol) in THF (25 mL) was added freshly powdered imidazole (1.02 g, 15 mmol) and carbonyl dimidazole (670 mg, 4.13 mmol). The resulting solution was heated to reflux for 16 hours then cooled to room temperature. At this temperature powdered hydroxylamine hydrochloride (1.01 g, 14.5 mmol) was added in a single portion at room temperature. The solution was stirred for a further 16 hours, then diluted with water (100 mL) and acidified to pH 3 with 2M HCl. The resulting solution was extracted with ethyl acetate (3 x 70 mL) and the combined organic fractions washed with brine (50 mL) and dried over Na_2SO_4. Removal of solvent *in vacuo* yielded a beige solid (1.01 g) that was used without further purification.

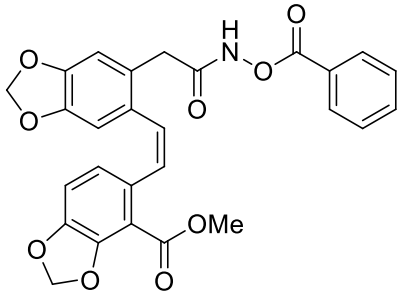
The crude hydroxamic acid (1.01 g, 2.5 mmol) was dissolved in THF (25 mL) and cooled to 0 °C, Pyridine (0.25 mL, 3.1 mmol) was added, followed by dropwise addition of the corresponding acid chloride (2.7 mmol). The reaction mixture was slowly warmed to room temperature and stirred for a further 16 hours. The reaction mixture was quenched by addition of 10% aqueous citric acid (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and the solvent removed *in vacuo* to give a beige solid that was purified by silica gel chromatography using ethyl acetate : hexane (1:1) to give the corresponding hydroxamate ester.

(Z)-Methyl 5-(2-(6-(2-(((4-chlorobenzoyl)oxy)amino)-2-oxoethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxole-4-carboxylate **(356)**



89% yield, **m.p.** 119 (decomp); **R_f** = 0.73 (EtOAc:Hex, 3:2); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 11.8 Hz, 1H), 6.76 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.63 (m, 2H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H), 5.92 (s, 2H), 3.93 (s, 3H), 3.41 (s, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 166.1, 165.4, 163.9, 148.0, 147.5, 147.1, 147.0, 140.7, 131.4, 131.0, 130.8, 130.3, 129.1, 127.9, 125.3, 124.5, 124.3, 112.6, 111.1, 111.1, 109.8, 102.0, 101.2, 52.6, 38.0; **IR** ν_{max} (neat) 2917, 1766, 1715, 1683, 1483, 1465, 1228, 1038, 1009, 908, 728 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 560.1 [(M +Na)+, 100%], 404 (12), 350 (11), 335 (11); **HRMS** [Found: $(M + Na)^+$, 560.0723. $C_{27}H_{20}{}^{35}ClNO_9Na$ requires $(M + Na)^+$, 560.0724].

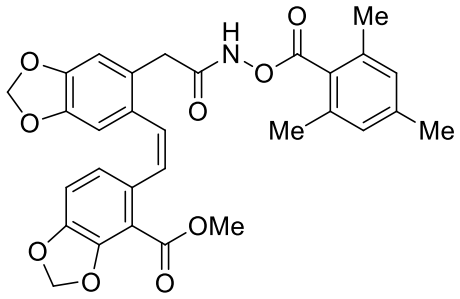
(Z)-Methyl 5-(2-(6-(2-((benzoyloxy)amino)-2-oxoethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxole-4-carboxylate **(325)**



87% yield; **m.p.** 121 (decomp); **R_f** = 0.69 (EtOAc:Hex, 3:2); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.01 (m, 2H), 7.54 (m, 1H), 7.39 (m, 2H), 6.73 (d, *J* = 11.8 Hz, 1H), 6.71 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 12.0 Hz, 1H), 6.54 (s, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 5.96 (s, 2H), 5.85 (s, 2H), 3.86 (s, 3H), 3.38 (s, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$) δ 165.8, 165.4, 164.7, 148.0, 147.4, 147.1, 147.0, 134.1, 131.9, 131.4, 131.0, 130.8, 130.4, 130.0, 128.7, 124.6, 124.3, 112.6, 111.1, 111.0, 109.8, 101.9, 101.2, 52.3, 38.7; **IR** ν_{max} (neat) 3195, 2924, 1768, 1714, 1667, 1450,

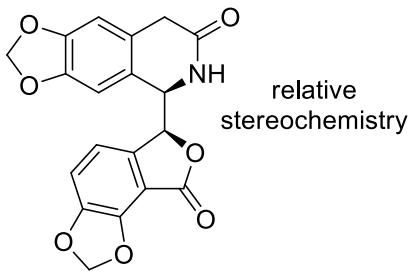
1229, 1039, 907, 728, 728 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 526.1 [(M +Na)+, 100%], 404 (12), 350 (17), 335 (16); **HRMS** [Found: $(M + Na)^+$, 526.1115. $C_{27}H_{21}NO_9Na$ requires $(M + Na)^+$, 526.1141].

(Z)-Methyl 5-(2-(6-(2-oxo-2-(((2,4,6-trimethylbenzoyl)oxy)amino)ethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxole-4-carboxylate **(357)**



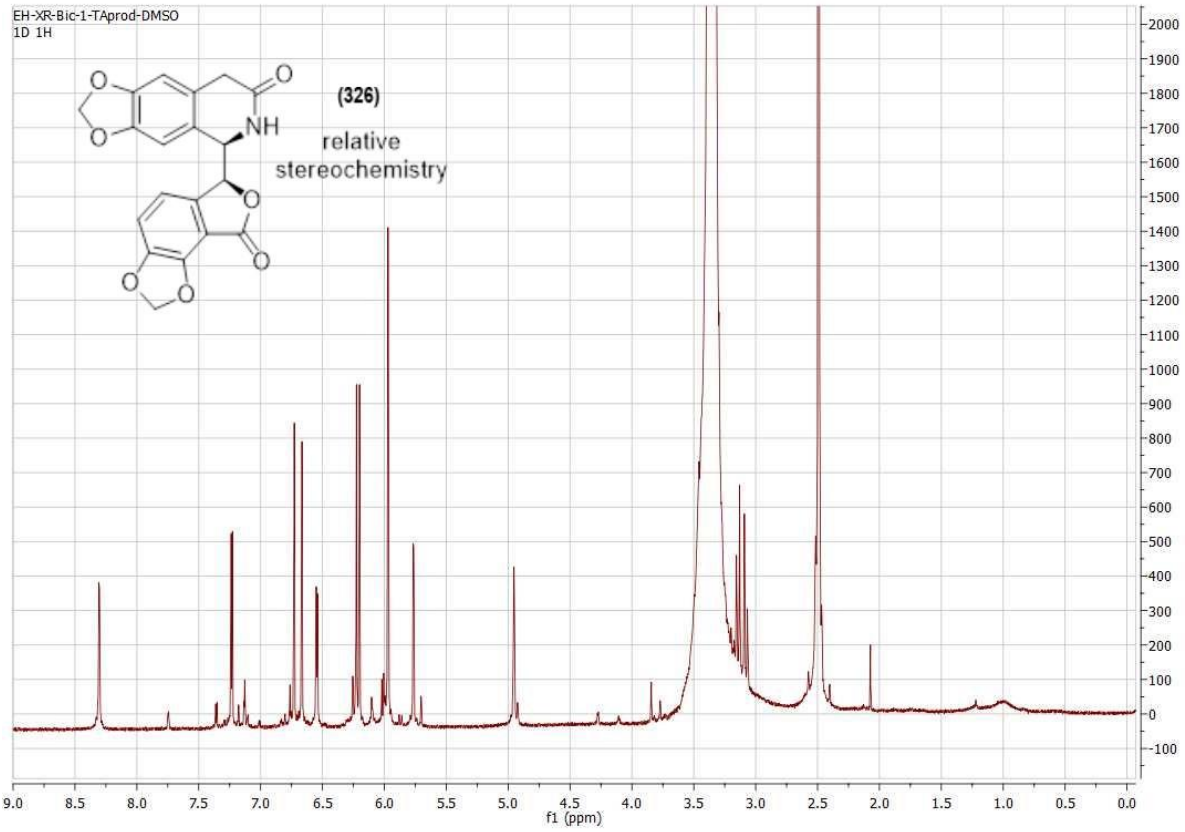
79% yield; **m.p.** 121 (decomp); $\mathbf{R_f}$ = 0.71 (EtOAc:Hex, 3:2); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 9.58 (s, 1H), 6.79 (s, 2H), 6.70 (s, 1H), 6.69 (d, *J* = 11.9 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 12 Hz, 1H), 6.55 (s, 1H), 6.50 (d, *J* = 8.1 Hz, 1H), 5.92 (s, 2H), 5.86 (s, 2H), 3.86 (s, 3H), 3.34 (s, 2H), 2.30 (s, 6H), 2.21 (s, 3H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 168.8, 167.8, 166.3, 147.9, 147.4, 147.1, 147.0, 140.5, 136.6, 130.8, 130.51, 130.3, 128.6, 128.5, 128.0, 124.6, 124.2, 112.6, 111.2, 111.1, 109.7, 101.9, 101.2, 52.5, 38.1, 21.2, 19.8; **IR** ν_{max} (neat) 3182, 2920, 1769, 1716, 1668, 1611, 1481, 1448,1227, 1036 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 568.2 [(M +Na)+, 100%], 147 (35); **HRMS** [Found: $(M + Na)^+$, 568.1586. $C_{30}H_{27}NO_9Na$ requires $(M + Na)^+$, 568.1584].

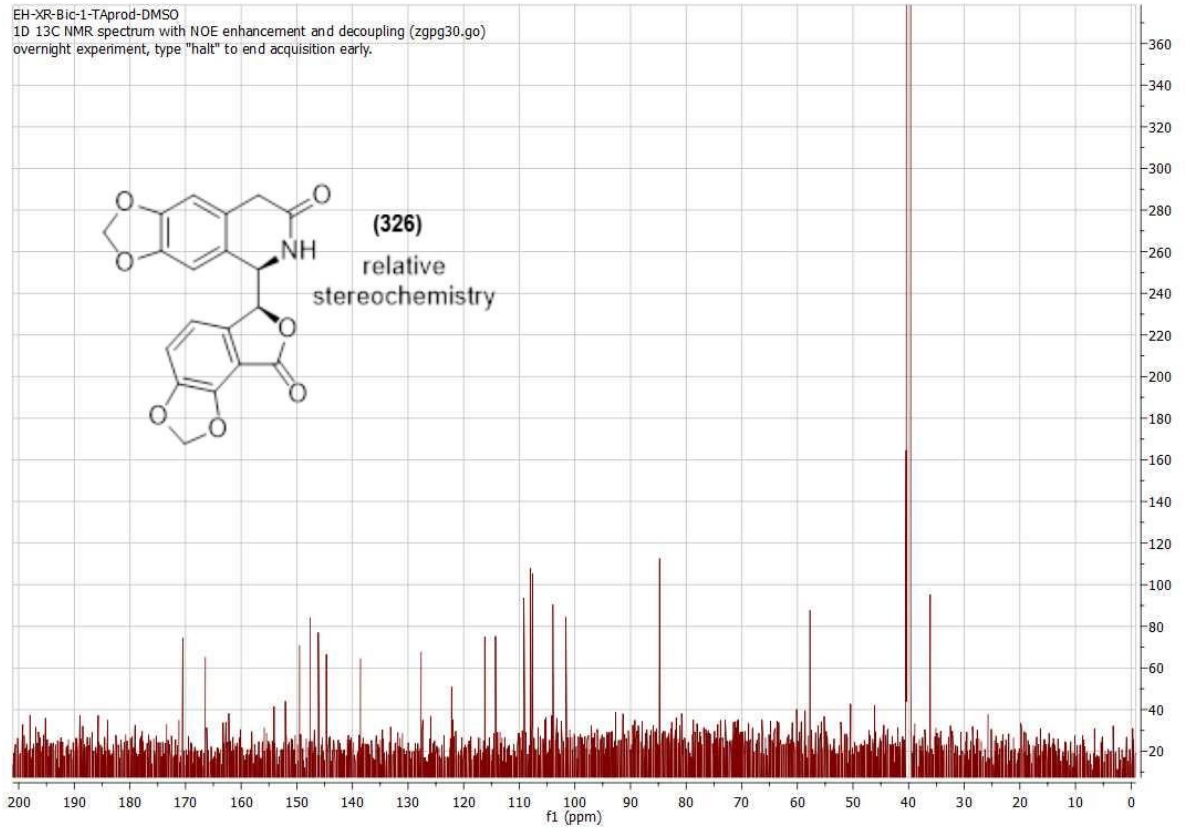
(±)-(R)-5-((S)-8-Oxo-6,8-dihydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-yl)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-7(8H)-one **(326)**



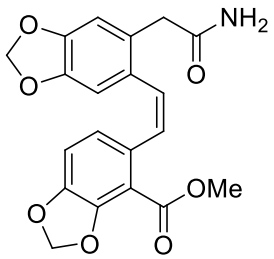
Potassium osmate(VI) dihydrate (30 mg, 0.09 mmol) was sonicated into a suspension in degassed milliQ water (0.5 mL) which was then added to a mixture of (Z)-methyl 5-(2-(6-(2-(((4-chlorobenzoyl)oxy)amino)-2-oxoethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxole-4-carboxylate **(356)** (500 mg, 0.93 mmol) and ground NaHCO3 (120 mg, 1.43 mmol) in degassed tetrahydrofuran (4.5mL) under nitrogen. The mixture slowly darkened and was stirred for 16 hours at room temperature. The reaction was quenched by addition of saturated aquoues Na_2SO_3 (5 mL) and filtered through Celite. The solids were washed with tetrahydrofuran (3 x 2 mL) and the combined filtrates extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (15 mL) and dried over Na_2SO_4. Removal of the solvent *in vacuo* gives a dark grey residue which was dissolved in hot tetrahydrofuran (10 mL), then diluted with hexane (10 mL). The resulting precipitate was filtered and washed with hexane to give (±)-(R)-5-((S)-8-oxo-6,8-dihydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-yl)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-7(8H)-one **(326)** (214 mg, 63%) as an off white solid.

m.p. = 243 °C; $\mathbf{R_f}$ = 0.07 (EtOAc:Hex, 3:2); **^{1}H NMR** (800 MHz, DMSO) δ 8.30 (d, *J* = 3.4 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 6.21 (m, 2H), 5.97 (s, 2H), 5.76 (d, *J* = 3.4 Hz Hz, 1H), 4.95 (t, *J* = 3.4 Hz, 1H), 3.14 (d, *J* = 20.3 Hz, 1H), 3.08 (d, *J* = 19.6 Hz, 1H); **^{13}C NMR** (200 MHz, DMSO) δ 170.5, 166.4, 149.5, 147.6, 146.1, 144.7, 138.5, 127.6, 122.2, 116.20, 114.3, 109.2, 108.0, 107.6, 104.0, 101.6, 84.8, 57.7, 36.1; **IR** ν_{max} (neat) 2980, 2914, 1762, 1716, 1666, 1475, 1239, 1037,732 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 390.1 [(M +Na)+, 100%], 280 (14), 228 (13), 206 (14), 164 (24); **HRMS** [Found: $(M + Na)^+$, 390.0587. $C_{19}H_{13}NO_7Na$ requires $(M + Na)^+$, 390.0590].


EH-XR-Bic-1-TAprod-DMSO
1D 1H
(326)
relative
stereochemistry
f1 (ppm)

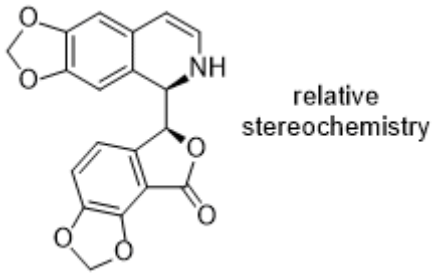

EH-XR-Bic-1-TAprod-DMSO
1D 13C NMR spectrum with NOE enhancement and decoupling (zgpg30.go)
overnight experiment, type "halt" to end acquisition early.
(326)
relative
stereochemistry
f1 (ppm)

Purification by column chromatography using gradient elution with ethyl acetate : hexane : methanol (4:1:0 – 1:0:0 – 19:0:1) allows for isolation of the other major side product, (Z)-methyl 5-(2-(6-(2-amino-2-oxoethyl)benzo[d][1,3]dioxol-5-yl)vinyl)benzo[d][1,3]dioxole-4-carboxylate **(355)** as a light orange solid.



m.p. = 172 °C; $\mathbf{R_f}$ = 0.16 (EtOAc:Hex, 3:2); **^{1}H NMR** (800 MHz, $CDCl_3$) δ 6.73 (d, *J* = 11.9 Hz, 1H), 6.64 (s, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.47 (m, 3H), 5.99 (s, 2H), 5.83 (s, 2H), 5.67 (s, 1H), 5.39 (s, 1H), 3.84 (s, 3H), 3.36 (s, 2H). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 173.22, 165.62, 148.05, 147.40, 147.07, 146.82, 131.02, 130.65, 130.24, 127.33, 126.54, 124.11, 112.90, 111.00, 110.60, 110.03, 101.94, 101.14, 52.28, 41.17; **IR** ν_{max} (neat) 3438, 3314, 3199, 2919, 2855, 1711, 1660, 1595, 1466, 1448, 1255, 1037, 1010, 923, 570 cm^{-1}; **LRMS** (ESI, +ve) *m/z* 406.1 [$(M + Na)^+$, 100%]; **HRMS** [Found: $(M + Na)^+$, 406.0902. $C_{20}H_{17}NO_7Na$ requires $(M + Na)^+$, 406.0903].

(±)- (S)-6-((R)-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-[1,3]dioxolo[4,5-e]isobenzofuran-8(6H)-one **(364)**



To a cooled (-40 °C), stirred suspension of (±)-(R)-5-((S)-8-oxo-6,8-dihydro-[1,3]dioxolo[4,5-e]isobenzofuran-6-yl)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-7(8H)-one **(326)** (100 mg, 0.27 mmol) in dicloromethane (2 mL) was added trifluoromethanesulfonic anhydride (92 mg, 0.32 mmol). The solution was stirred for 2 hours at the same temperature then tetrahydrofuran added (2 mL), followed by

sodium triacetoxyborohydride (86 mg, 0.40 mmol). The solution was allowed to warm to room temperature over 2 hours then quenched by addition of a saturated solution of ammonium chloride (5 mL). The resulting solution was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and the solvent removed *in vacuo* to give a beige oil that was analysed directly by ^{1}H NMR and LCMS.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 12.2 Hz, 1H), 6.27 (d, *J* = 12.2 Hz, 1H). **LRMS** (ESI, +ve) *m/z* 406.1 [$(M + H)^+$, 100%]

Chapter 8 - Bibliography

1. (a) Editorial, All natural. *Nature Chemical Biology* **2007,** *3*, 351-351; (b) Colegate, S. M.; Molyneux, R. J., *Bioactive Natural Products: Detection, Isolation, and Structural Determination*. CRC Press: 2007.
2. Wöhler, F., Ueber künstliche bildung des harnstoffs. *Annalen der Physik* **1828,** *88* (2), 253-256.
3. Nicolaou, K. C.; Montagnon, T., *Molecules That Changed The World*. Wiley-VCH Weinheim: 2008.
4. Nicolaou, K. C.; Chen, J. S., *Classics in total synthesis III*. Wiley Online Library: 2010.
5. Gershenzon, J.; Dudareva, N., The function of terpene natural products in the natural world. *Nature Chemical Biology* **2007,** *3* (7), 408-414.
6. Demain, A. L.; Fang, A., The natural functions of secondary metabolites. In *History of Modern Biotechnology I*, Springer: 2000; pp 1-39.
7. Foye, W. O.; Lemke, T. L.; Williams, D. A., *Foye's principles of medicinal chemistry*. Lippincott Williams & Wilkins: 2008.
8. Baker, D. D.; Chu, M.; Oza, U.; Rajgarhia, V., The value of natural products to future pharmaceutical discovery. *Natural Product Reports* **2007,** *24* (6), 1225-1244.
9. Dias, D. A.; Urban, S.; Roessner, U., A historical overview of natural products in drug discovery. *Metabolites* **2012,** *2* (2), 303-336.
10. Maplestone, R. A.; Stone, M. J.; Williams, D. H., The evolutionary role of secondary metabolites—a review. *Gene* **1992,** *115* (1-2), 151-157.
11. Stone, M.; Williams, D., On the evolution of functional secondary metabolites (natural products). *Molecular Microbiology* **1992,** *6* (1), 29-34.
12. (a) Schatz, P. F., Indigo and Tyrian purple—in Nature and in the Lab. *Journal of Chemical Education* **2001,** *78* (11), 1442; (b) Eisner, T.; Nowicki, S.; Goetz, M.; Meinwald, J., Red cochineal dye (carminic acid): its role in nature. *Science* **1980,** *208* (4447), 1039-1042.
13. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T., Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. *Journal of the American Chemical Society* **1971,** *93* (9), 2325-2327.
14. Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P., Highly efficient, practical approach to natural taxol. *Journal of the American Chemical Society* **1988,** *110* (17), 5917-5919.
15. De Marcano, D. P. D. C.; Halsall, T. G., Structures of some taxane diterpenoids, baccatins-III,-IV,-VI, and-VII and 1-dehydroxybaccatin-IV, possessing an oxetan ring. *Journal of the Chemical Society, Chemical Communications* **1975,** (9), 365-366.
16. Armaly, A. M.; DePorre, Y. C.; Groso, E. J.; Riehl, P. S.; Schindler, C. S., Discovery of Novel Synthetic Methodologies and Reagents during Natural Product Synthesis in the Post-Palytoxin Era. *Chemical Reviews* **2015,** *115* (17), 9232-9276.
17. Nicolaou, K.; Snyder, S., *Classics in Total Synthesis II*, Wiley Online Library: 2003
18. Suh, E. M.; Kishi, Y., Synthesis of palytoxin from palytoxin carboxylic acid. *Journal of the American Chemical Society* **1994,** *116* (24), 11205-11206.
19. Armstrong, R. W.; Beau, J. M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W. H.; Hawkins, L. D.; Jin, H.; Kang, S. H., Total synthesis of palytoxin carboxylic acid and palytoxin amide. *Journal of the American Chemical Society* **1989,** *111* (19), 7530-7533.
20. Nicolaou, K.; Snyder, S. A., The essence of total synthesis. *Proceedings of the National Academy of Sciences of the United States of America* **2004,** *101* (33), 11929-11936.
21. Martin, D. B.; Nguyen, L. Q.; Vanderwal, C. D., Syntheses of strychnine, norfluorocurarine, dehydrodesacetylretuline, and valparicine enabled by intramolecular cycloadditions of Zincke aldehydes. *The Journal of Organic Chemistry* **2011,** *77* (1), 17-46.

22. Trost, B. M., The Atom Economy—A Search for Synthetic Efficiency, *Science* **1991,**. *254*, 1471-1477.
23. Trost, B. M., Atom economy—a challenge for organic synthesis: homogeneous catalysis leads the way. *Angewandte Chemie International Edition in English* **1995,** *34* (3), 259-281.
24. Woodward, R.; Cava, M. P.; Ollis, W.; Hunger, A.; Daeniker, H.; Schenker, K., The total synthesis of strychnine. *Journal of the American Chemical Society* **1954,** *76* (18), 4749-4751.
25. Woodward, R.; Cava, M. P.; Ollis, W.; Hunger, A.; Daeniker, H.; Schenker, K., The total synthesis of strychnine. *Tetrahedron* **1963,** *19* (2), 247-288.
26. Paquette, L. A.; Geng, F., Applications of the squarate ester cascade to the expeditious synthesis of hypnophilin, coriolin, and ceratopicanol. *Journal of the American Chemical Society* **2002,** *124* (31), 9199-9203.
27. Wender, P.; Howbert, J., Synthetic studies on arene-olefin cycloadditions: total synthesis of (+)-α-cedrene. *Journal of the American Chemical Society* **1981,** *103* (3), 688-690.
28. Tortora, G. J.; Derrickson, B. H., *Principles of Anatomy and Physiology*. John Wiley & Sons: 2008.
29. Semenza, G. L., Targeting HIF-1 for cancer therapy. *Nature Reviews Cancer* **2003,** *3* (10), 721-732.
30. Esumi, H.; Lu, J.; Kurashima, Y.; Hanaoka, T., Antitumor activity of pyrvinium pamoate, 6-(dimethylamino)-2-[2-(2, 5-dimethyl-1-phenyl-1H-pyrrol-3-yl) ethenyl]-1-methyl-quinolinium pamoate salt, showing preferential cytotoxicity during glucose starvation. *Cancer Science* **2004,** *95* (8), 685-690.
31. Brown, J. M.; Giaccia, A. J., The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. *Cancer Research* **1998,** *58* (7), 1408-1416.
32. Awale, S.; Nakashima, E. M.; Kalauni, S. K.; Tezuka, Y.; Kurashima, Y.; Lu, J.; Esumi, H.; Kadota, S., Angelmarin, a novel anti-cancer agent able to eliminate the tolerance of cancer cells to nutrient starvation. *Bioorganic & Medicinal Chemistry Letters* **2006,** *16* (3), 581-583.
33. Willette, R. E.; Soine, T. O., Coumarins II. structures of columbianadin and columbianin. *Journal of Pharmaceutical Sciences* **1964,** *53* (3), 275-279.
34. Magolan, J.; J Coster, M., Targeting the resistance of pancreatic cancer cells to nutrient deprivation: anti-austerity compounds. *Current Drug Delivery* **2010,** *7* (5), 355-369.
35. Awale, S.; Lu, J.; Kalauni, S. K.; Kurashima, Y.; Tezuka, Y.; Kadota, S.; Esumi, H., Identification of arctigenin as an antitumor agent having the ability to eliminate the tolerance of cancer cells to nutrient starvation. *Cancer Research* **2006,** *66* (3), 1751-1757.
36. Ueda, J.-y., autophagic Panc-1 pancreatic cancer cell death. *Drug Design, Development and Therapy* **2014,** *8*, 39-47.
37. Khan, M. A.; Wood, P. J.; Lamb-Guhren, N. M.; Caggiano, L.; Kociok-Köhn, G.; Tosh, D.; Lewis, S. E., The enone motif of (+)-grandifloracin is not essential for 'anti-austerity'antiproliferative activity. *Bioorganic & Medicinal Chemistry Letters* **2014,** *24* (13), 2815-2819.
38. Yang, Z. J.; Chee, C. E.; Huang, S.; Sinicrope, F. A., The role of autophagy in cancer: therapeutic implications. *Molecular Cancer Therapeutics* **2011,** *10* (9), 1533-1541.
39. Esumi, H.; Owada, S.; Fujioka, R.; Tsuchihara, K.; Ohtsu, A.; Sato, A.; Ikeda, M.; Mochizuki, N.; Kishino, S.; Kawashima, T., Abstract CT213: Arctigenin, an antiausterity agent shows high safety and promising clinical response in phase I clinical trial in patient with gemcitabine-refractory pancreatic cancer. *Cancer Research* **2014,** *74* (19 Supplement), CT213-CT213.
40. (a) Shipchandler, M.; Soine, T.; Gupta, P., Coumarins XI: A total synthesis of (±)-columbianetin. *Journal of Pharmaceutical Sciences* **1970,** *59* (1), 67-71; (b) Bohlmann, F.; Franke, H., Natürlich vorkommende Cumarin-Derivate, VII Synthese von racemischen Lomatin, Columbianetin, Angenomalin und Samidin. *Chemische Berichte* **1971,** *104* (10), 3229-3233; (c) Steck, W., New synthesis of columbianetin and related coumarins. *Canadian Journal of Chemistry* **1971,** *49* (8), 1197-1201.

41. Magolan, J.; Coster, M. J., Total synthesis of (+)-angelmarin. *The Journal of Organic Chemistry* **2009,** *74* (14), 5083-5086.
42. Jiang, H.; Hamada, Y., Highly enantioselective synthesis of angelmarin. *Organic & Biomolecular Chemistry* **2009,** *7* (20), 4173-4176.
43. Tu, Y.; Wang, Z.-X.; Shi, Y., An efficient asymmetric epoxidation method for *trans*-olefins mediated by a fructose-derived ketone. *Journal of the American Chemical Society* **1996,** *118* (40), 9806-9807.
44. Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G., The Au (I)-catalyzed intramolecular hydroarylation of terminal alkynes under mild conditions: application to the synthesis of 2 H-chromenes, coumarins, benzofurans, and dihydroquinolines. *The Journal of Organic Chemistry* **2009,** *74* (22), 8901-8903.
45. Gagosz, F. In *Organogold Catalysis: Homogeneous Gold-Catalyzed Transformations for a Golden Jubilee*, Advances in Organometallic Chemistry and Catalysis: The Silver/Gold Jubilee International Conference on Organometallic Chemistry Celebratory Book, Wiley Online Library: 2013; pp 207-225.
46. Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F., Synthesis, structure and reactivity of organogold compounds of relevance to homogeneous gold catalysis. *Journal of Organometallic Chemistry* **2009,** *694* (4), 592-597.
47. Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F., Total synthesis of pawhuskin C: a directed ortho metalation approach. *Tetrahedron Letters* **2005,** *46* (8), 1321-1324.
48. Nevado, C.; Echavarren, A. M., Transition metal-catalyzed hydroarylation of alkynes. *Synthesis* **2005,** (2), 167-182.
49. Marshall, L. J.; Cable, K. M.; Botting, N. P., Iridium-catalyzed C–H activation/borylation/oxidation for the preparation of bis-protected phloroglucinol derivatives. *Tetrahedron Letters* **2010,** *51* (20), 2690-2692.
50. Grealis, J. P.; Müller-Bunz, H.; Ortin, Y.; Casey, M.; McGlinchey, M. J., Synthesis of Isobavachalcone and Some Organometallic Derivatives. *European Journal of Organic Chemistry* **2013,** *2013* (2), 332-347.
51. Wuts, P. G.; Greene, T. W., *Greene's protective groups in organic synthesis*. John Wiley & Sons: 2006.
52. Prado, S.; Janin, Y. L.; Saint-Joanis, B.; Brodin, P.; Michel, S.; Koch, M.; Cole, S. T.; Tillequin, F.; Bost, P.-E., Synthesis and antimycobacterial evaluation of benzofurobenzopyran analogues. *Bioorganic & Medicinal Chemistry* **2007,** *15* (5), 2177-2186.
53. Scopton, A.; Kelly, T. R., Synthesis of Azacridone A. *Organic Letters* **2004,** *6* (21), 3869-3871.
54. Rawat, M.; Prutyanov, V.; Wulff, W. D., Chromene chromium carbene complexes in the syntheses of naphthopyran and naphthopyrandione units present in photochromic materials and biologically active natural products. *Journal of the American Chemical Society* **2006,** *128* (34), 11044-11053.
55. Lüning, U.; Abbass, M.; Fahrenkrug, F., A Facile Route to Aryl-Substituted 1, 10-Phenanthrolines by Means of Suzuki Coupling Reactions between Substituted Areneboronic Acids and Halogeno-1, 10-phenanthrolines. *European Journal of Organic Chemistry* **2002,** *2002* (19), 3294-3303.
56. Tsujiyama, S.; Suzuki, K., Preparation of Benzocyclobutenone Derivatives Based on an Efficient Generation of Benzynes. *Organic Syntheses* **2007**, 272-284.
57. (a) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K., Total synthesis of the gilvocarcins. *Journal of the American Chemical Society* **1994,** *116* (3), 1004-1015; (b) Lüning, U.; Fahrenkrug, F., Synthesis of Concave 1, 10-Phenanthrolines by a Combination of Suzuki Coupling, Ring Closing Metathesis and Hydrogenation. *European Journal of Organic Chemistry* **2004,** *2004* (14), 3119-3127.
58. Neumann, H.; Seebach, D., Stereospecific preparation of terminal vinyllithium derivatives by Br/Li-exchange with t-butyllithium. *Tetrahedron Letters* **1976,** *17* (52), 4839-4842.

59. Worsfold, D. J.; Bywater, S., Anionic polymerization of isoprene. *Canadian Journal of Chemistry* **1964,** *42* (12), 2884-2892.
60. Garst, J. F.; Pacifici, J. A.; Felix, C. C.; Nigam, A., Intramolecular 1, 4 proton transfer in the 5-hexenyl anion. The 5-hexenyl probe as a detector of both alkyl radical and anion intermediates. *Journal of the American Chemical Society* **1978,** *100* (18), 5974-5975.
61. Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C.; Trabada, M., On the reactivity of *o*-lithioaryl ethers: tandem anion translocation and wittig rearrangement. *Organic Letters* **2002,** *4* (9), 1587-1590.
62. Fraenkel, G.; Qiu, F., Partially Delocalized Allylic Lithium Compounds: Dynamics of Inversion, 1, 3 Li Shift, and C-Li Bond, Exchange Influence of the Stereochemistry of Solvation. *Journal of the American Chemical Society* **1997,** *119* (15), 3571-3579.
63. Takaoka, S.; Takaoka, N.; Minoshima, Y.; Huang, J.-M.; Kubo, M.; Harada, K.; Hioki, H.; Fukuyama, Y., Isolation, synthesis, and neurite outgrowth-promoting activity of illicinin A from the flowers of Illicium anisatum. *Tetrahedron* **2009,** *65* (40), 8354-8361.
64. Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D., Formal 2+ 2 and 3+ 2 cycloaddition reactions of 2H-chromenes with 2-alkoxy-1, 4-benzoquinones: regioselective synthesis of substituted pterocarpans. *The Journal of Organic Chemistry* **1990,** *55* (4), 1248-1254.
65. Kishali, N.; Polat, M. F.; Altundas, R.; Kara, Y., A Novel One-Pot Conversion of Allyl Alcohols into Primary Allyl Halides Mediated by Acetyl Halide. *Helvetica Chimica Acta* **2008,** *91* (1), 67-72.
66. Huang, C.-W.; Shanmugasundaram, M.; Chang, H.-M.; Cheng, C.-H., Highly chemoselective coupling of allenylstannanes with organic iodides promoted by $Pd(PPh_3)_4$/LiCl: an efficient method for the synthesis of substituted allenes. *Tetrahedron* **2003,** *59* (20), 3635-3641.
67. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S., On the nature of the" copper effect" in the Stille cross-coupling. *The Journal of Organic Chemistry* **1994,** *59* (20), 5905-5911.
68. Mee, S. P.; Lee, V.; Baldwin, J. E., Stille coupling made easier—The synergic effect of copper (I) salts and the fluoride ion. *Angewandte Chemie International Edition* **2004,** *43* (9), 1132-1136.
69. Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C., α, α'-Annulation of 2, 6-Prenyl-Substituted Cyclohexanone Derivatives with Malonyl Chloride: Application to a Short Synthesis of (±)-Clusianone. Formation and Rearrangement of a Biogenetic-Like Intermediate. *Organic Letters* **2007,** *9* (2), 287-289.
70. Horning, E.; Horning, M., Aromatization Studies. IV. Palladium dehydrogenation of arylcyclohexenones to phenols. *Journal of the American Chemical Society* **1947,** *69* (6), 1359-1361.
71. Mphahlele, M. J., Molecular Iodine—An Expedient Reagent for Oxidative Aromatization Reactions of α, β-Unsaturated Cyclic Compounds. *Molecules* **2009,** *14* (12), 5308-5322.
72. Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M., Domino Michael–*O*-alkylation reaction: one-pot synthesis of 2, 4-diacylhydrofuran derivatives and its application to antitumor naphthofuran synthesis. *Journal of the Chemical Society, Perkin Transactions 1* **2001,** (22), 2946-2957.
73. Fatiadi, A. J., Active manganese dioxide oxidation in organic chemistry-part I. *Synthesis* **1976,** *1976,* (2), 65-104.
74. Chen, L.-Y.; Li, S.-R.; Chen, P.-Y.; Chang, H.-C.; Wang, T.-P.; Tsai, I.-L.; Wanga, E.-C., 2, 3-Dichloro-5, 6-dicyanobenzoquinone (DDQ) mediated oxidation-dehydrogenation of 2-aroyl-3, 4-dihydro-2H-benzopyrans: synthesis of 2-aroylbenzopyran-4-ones. *Arkivoc* **2010,** *11*, 64-76.

75. Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M., Cationic η1/η2-Gold (I) Complexes of Simple Arenes. *Angewandte Chemie* **2006,** *118* (33), 5581-5585.
76. Jiang, H.; Sugiyama, T.; Hamajima, A.; Hamada, Y., Asymmetric Synthesis of 2-Substituted Dihydrobenzofurans and 3-Hydroxydihydrobenzopyrans through the Enantioselective Epoxidation of O-Silyl-Protected ortho-Allylphenols. *Advanced Synthesis & Catalysis* **2011,** *353* (1), 155-162.
77. Tu, Y.; Frohn, M.; Wang, Z. X.; Shi, Y., Synthesis of 1, 2: 4, 5-Di-O-Isopropylidene-D-Erythro-2, 3-Hexodiulo-2, 6-Pyranose. A Highly Enantioselective Ketone Catalyst for Epoxidation. *Organic Syntheses* **2003**, 1-8.
78. Ager, D. J.; Anderson, K.; Oblinger, E.; Shi, Y.; VanderRoest, J., An epoxidation approach to a chiral lactone: Application of the Shi epoxidation. *Organic Process Research & Development* **2007,** *11* (1), 44-51.
79. Shu, L.; Shi, Y., An efficient ketone-catalyzed asymmetric epoxidation using hydrogen peroxide (H_2O_2) as primary oxidant. *Tetrahedron* **2001,** *57* (24), 5213-5218.
80. Xiao, X. Y.; Park, S. K.; Prestwich, G. D., Phenyl sulfone-directed diastereoselective cyclization of an epoxy allylsilane system. *The Journal of Organic Chemistry* **1988,** *53* (20), 4869-4872.
81. Chandrasekhar, S.; Chandrashekar, G., The first simple and efficient synthesis of the unusual dipeptide part of Phomopsin A. *Tetrahedron: Asymmetry* **2005,** *16* (13), 2209-2214.
82. Shimizu, H.; Shimizu, K.; Kubodera, N.; Mikami, T.; Tsuzaki, K.; Suwa, H.; Harada, K.; Hiraide, A.; Shimizu, M.; Koyama, K., Industrial synthesis of Maxacalcitol, the antihyperparathyroidism and antipsoriatic vitamin D3 analogue exhibiting low calcemic activity. *Organic Process Research & Development* **2005,** *9* (3), 278-287.
83. Andersen, R. A.; Wilkinson, G.; Lappert, M.; Pearce, R., Bis [(Trimethylsilyl) Methyl] Magnesium. *Inorganic Syntheses, Volume 19* **1979**, 262-265.
84. Matthews, D. P.; Green, J. E.; Shuker, A. J., Parallel synthesis of alkyl tetrazole derivatives using solid support chemistry. *Journal of Combinatorial Chemistry* **2000,** *2* (1), 19-23.
85. VanNieuwenhze, M. S.; Sharpless, K. B., The asymmetric dihydroxylation of *cis*-allylic and homoallylic alcohols. *Tetrahedron Letters* **1994,** *35* (6), 843-846.
86. Gao, Y.; Sharpless, K. B., Vicinal diol cyclic sulfates. Like epoxides only more reactive. *Journal of the American Chemical Society* **1988,** *110* (22), 7538-7539.
87. Carroll, A. R.; Addepalli, R.; Fechner, G.; Smith, J.; Guymer, G. P.; Forster, P. I.; Quinn, R. J., Alkaloids from the Australian rainforest tree Ochrosia moorei. *Journal of Natural Products* **2008,** *71* (6), 1063-1065.
88. Husson, H. P., The Strychnos Alkaloids. *Chemistry of Heterocyclic Compounds: Indoles, Part Four, The Monoterpenoid Indole Alkaloids, Volume 25* **1983**, 293-330.
89. Tits, M.; Tavernier, D.; Angenot, L., Strychnozairine, an indole alkaloid from Strychnos variabilis. *Phytochemistry* **1985,** *24* (1), 205-207.
90. Nuzillard, J.-M.; Thépenier, P.; Jacquier, M.-J.; Massiot, G.; Le Men-Olivier, L.; Delaude, C., Alkaloids from root bark of Strychnos panganensis. *Phytochemistry* **1996,** *43* (4), 897-902.
91. Chen, J.; Qu, Y.; Wang, D.; Peng, P.; Cai, H.; Gao, Y.; Chen, Z.; Cai, B., Pharmacological evaluation of total alkaloids from nux vomica: effect of reducing strychnine contents. *Molecules* **2014,** *19* (4), 4395-408.
92. O'Connor, S. E.; Maresh, J. J., Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Natural Product Reports* **2006,** *23* (4), 532-547.
93. Geu-Flores, F.; Sherden, N. H.; Courdavault, V.; Burlat, V.; Glenn, W. S.; Wu, C.; Nims, E.; Cui, Y.; O'Connor, S. E., An alternative route to cyclic terpenes by reductive cyclization in iridoid biosynthesis. *Nature* **2012,** *492* (7427), 138-142.
94. Yamamoto, H.; Katano, N.; Ooi, A.; Inoue, K., Secologanin synthase which catalyzes the oxidative cleavage of loganin into secologanin is a cytochrome P450. *Phytochemistry* **2000,** *53* (1), 7-12.

95. Scott, A. I.; Cherry, P.; Qureshi, A. A., Mechanism of indole alkaloid biosynthesis. The Corynanthe-Strychnos relationship. *Journal of the American Chemical Society* **1969,** *91* (17), 4932-4933.
96. Banwell, M. G.; Lupton, D. W., Exploiting the palladium[0]-catalysed Ullmann cross-coupling reaction in natural products chemistry: application to a total synthesis of the alkaloid (+/-)-aspidospermidine. *Organic & Biomolecular Chemistry* **2005,** *3* (2), 213-5.
97. Wenkert, E.; Hudlicky, T., Synthesis of eburnamonine and dehydroaspidospermidine. *The Journal of Organic Chemistry* **1988,** *53* (9), 1953-1957.
98. Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W., Synthesis of Indoles *via* Palladium [0]-Mediated Ullmann Cross-Coupling of *o*-Halonitroarenes with α-Halo-enones or-enals. *Organic Letters* **2003,** *5* (14), 2497-2500.
99. Palmisano, G.; D'Anniballe, P.; Santagostino, M., Indole alkaloids. A combined chemical and enzymatic route for eburnane ring construction: Formal synthesis of (−)-Eburnamonine. *Tetrahedron* **1994,** *50* (31), 9487-9494.
100. Pearson, A. J.; Chen, Y.-S.; Han, G. R.; Hsu, S.-Y.; Ray, T., A new method for the oxidation of alkenes to enones. An efficient synthesis of Δ 5-7-oxo steroids. *Journal of the Chemical Society, Perkin Transactions 1* **1985**, 267-273.
101. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C.; Wovkulich, P. M.; Uskoković, M. R., Direct α-iodination of cycloalkenones. *Tetrahedron Letters* **1992,** *33* (7), 917-918.
102. Toczko, M. A.; Heathcock, C. H., Total synthesis of (±)-aspidospermidine. *The Journal of Organic Chemistry* **2000,** *65* (9), 2642-2645.
103. Whitlock, H. W.; Smith, G. L., Total synthesis of dl-crinine. *Journal of the American Chemical Society* **1967,** *89* (14), 3600-3606.
104. Kumar, U. S.; Ila, H.; Junjappa, H., A new route to spiropyrrolidinyl-oxindole alkaloids *via* iodide ion induced rearrangement of [(N-aziridinomethylthio)methylene]-2-oxindoles. *Organic Letters* **2001,** *26* (3), 4193-4196.
105. Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A., Dimethyl (methylene) ammonium iodide. *Angewandte Chemie International Edition in English* **1971,** *10* (5), 330-331.
106. Christoffers, J.; Baro, A.; Werner, T., α-Hydroxylation of β-Dicarbonyl Compounds. *Advanced Synthesis & Catalysis* **2004,** *346* (2-3), 143-151.
107. Li, X.; Chen, N.; Xu, J., An Improved and Mild WenkerSynthesis of Aziridines. *Synthesis* **2010,** *2010* (20), 3423-3428.
108. Wystrach, V.; Kaiser, D. W.; Schaefer, F. C., Preparation of ethylenimine and triethylenemelamine. *Journal of the American Chemical Society* **1955,** *77* (22), 5915-5918.
109. Kumar, A.; Ila, H.; Junjappa, H.; Mhatre, S., Reaction of keten dithio-acetals with aziridine. Iodide ion-catalysed rearrangement of thio-aziridino-methylene compounds to novel Δ 1-2-methylthio-3, 3-disubstituted pyrrolines. *Journal of the Chemical Society, Chemical Communications* **1976,** (15), 592-593.
110. Livingston, R.; Halverson, R. R., Solubility of Potassium Iodide in Acetone. *The Journal of Physical Chemistry* **1946,** *50* (1), 1-6.
111. Matsuike, Y., Dielectric Constant of Some Organic Solvents. *Proceedings of the Imperial Academy* **1929,** *5* (1), 29-31.
112. Burgess, J.; Burgess, J., *Metal ions in solution*. Ellis Horwood Chichester: 1978.
113. Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A., Application of a Raney-Cobalt-Mediated Tandem Reductive Cyclization Protocol to Total Syntheses of the Aspidosperma Alkaloids (±)-Limaspermidine and (±)-1-Acetylaspidoalbidine. *Organic Letters* **2012,** *14* (22), 5621-5623.
114. Burnett, J. F.; Zahler, R. E., Aromatic Nucleophilic Substitution Reactions. *Chemical Reviews* **1951,** *49* (2), 273-412.
115. Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry: Part A: Structure and Mechanisms*. Springer Science & Business Media: 2007.

116. Scott, T. L.; Söderberg, B. C., Palladium-catalyzed synthesis of 1, 2-dihydro-4 (3H)-carbazolones. Formal total synthesis of murrayaquinone A. *Tetrahedron* **2003,** *59* (33), 6323-6332.
117. Solé, D.; Bosch, J.; Bonjoch, J., 3a-(*o*-Nitrophenyl) octahydroindol-4-ones: Synthesis and spectroscopic analysis. *Tetrahedron* **1996,** *52* (11), 4013-4028.
118. Zhang, X.; Yang, D.; Liu, Y., Effects of electron acceptors and radical scavengers on nonchain radical nucleophilic substitution reactions. *The Journal of Organic Chemistry* **1993,** *58* (1), 224-227.
119. Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B., Nucleophilic substitution reactions by electron transfer. *Chemical Reviews* **2003,** *103* (1), 71-168.
120. Gaudry, R., Glycolonitrile. *Organic Syntheses*, 41-41.
121. Garegg, P. J.; Regberg, T.; Stawiński, J.; Strömberg, R., A phosphorus nuclear magnetic resonance spectroscopic study of the conversion of hydroxy groups into iodo groups in carbohydrates using the iodine–triphenylphosphine–imidazole reagent. *Journal of the Chemical Society, Perkin Transactions 2* **1987,** (3), 271-274.
122. Pinhey, J. T., Organolead (iv) triacetates in organic synthesis. *Pure and Applied Chemistry* **1996,** *68* (4), 819-824.
123. Morgan, J.; Pinhey, J. T., Reaction of arylboronic acids and their derivatives with lead tetra-acetate. The generation of aryl–lead triacetates, and meta-and para-phenylenebis (lead triacetate), *in situ* for electrophilic arylation. *J. Chem. Soc., Perkin Trans. 1* **1990,** (3), 715-720.
124. Ackland, D. J.; Pinhey, J. T., Use of the electrophilic c-arylation by aryllead triacetates in the construction of synthons for aizoaceae and amaryllidaceae alkaloid synthesis. *Tetrahedron Letters* **1985,** *26* (43), 5331-5334.
125. Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z., Total synthesis of (±) maoecrystal V. *Journal of the American Chemical Society* **2010,** *132* (47), 16745-16746.
126. Dong, C.-Z.; Ahamada-Himidi, A.; Plocki, S.; Aoun, D.; Touaibia, M.; Habich, N. M.-B.; Huet, J.; Redeuilh, C.; Ombetta, J.-E.; Godfroid, J.-J., Inhibition of secretory phospholipase A 2. 2-Synthesis and structure–activity relationship studies of 4, 5-dihydro-3-(4-tetradecyloxybenzyl)-1, 2, 4-4H-oxadiazol-5-one (PMS1062) derivatives specific for group II enzyme. *Bioorganic & Medicinal Chemistry* **2005,** *13* (6), 1989-2007.
127. Kosugi, M.; Ohya, T.; Migita, T., Preparation of aryltributyltin having electron-withdrawing group by palladium catalyzed reaction of hexabutylditin with aryl iodide. *Bulletin of the Chemical Society of Japan* **1983,** *56* (12), 3855-3856.
128. Kozyrod, R.; Pinhey, J., Arylation with Aryllead Triacetates Produced *in situ* by Mercury-Lead Exchange. *Australian Journal of Chemistry* **1985,** *38* (8), 1155-1161.
129. Raju, M.; Mäeorg, S.; Tšubrik, O.; Mäeorg, U., Efficient solventless technique for Boc-protection of hydrazines and amines. *Arkivoc* **2009,** *6*, 291-297.
130. Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G.; Siddiqui, M.; Snieckus, V., Combined metalation-palladium-catalyzed cross coupling strategies. A formal synthesis of the marine alkaloid amphimedine. *The Journal of Organic Chemistry* **1995,** *60* (2), 292-296.
131. Davidson, D.; Bogert, M. T., The preparation of aromatic alcohols by the crossed Cannizzaro reaction with formaldehyde. *Journal of the American Chemical Society* **1935,** *57* (5), 905-905.
132. Schwartz, M. A.; Zoda, M.; Vishnuvajjala, B.; Mami, I., A convenient synthesis of *o*-and p-hydroxy substituted phenylacetonitriles and phenethylamines. *The Journal of Organic Chemistry* **1976,** *41* (14), 2502-2503.
133. Pinhey, J. T., Organolead (IV) tricarboxylates, new reagents for organic synthesis. *Australian Journal of Chemistry* **1991,** *44* (10), 1353-1382.
134. Kurti, L.; Czakó, B., *Strategic applications of named reactions in organic synthesis*. Elsevier: 2005.

135. James, M. J.; O'Brien, P.; Taylor, R. J.; Unsworth, W. P., Synthesis of Spirocyclic Indolenines. *Chemistry–A European Journal* **2015**.
136. Sharp, L. A.; Zard, S. Z., A short total synthesis of (±)-Aspidospermidine. *Organic Letters* **2006,** *8* (5), 831-834.
137. Wang, T. S., Fisher indole synthesis the synthesis of 1-acetyl-6: 7-dihydro-2: 3-benzindolo (2': 3'-4: 5) azepine. *Tetrahedron Letters* **1975,** *16* (19-20), 1637-1638.
138. Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K., Fischer Indolizations as a Strategic Platform for the Total Synthesis of Picrinine. *The Journal of Organic Chemistry* **2015,** *80* (18), 8954-8967.
139. Rodriguez, J.-G.; Temprano, F.; Esteban-Calderon, C.; Martinez-Ripoll, M., Synthesis of 4-(N, *N*-dimethylaminoethyl)-1, 2, 3, 4-tetrahydrocarbazole: molecular structure and reactivity of the 1, 2-dihydrocarbazol-4 (3H)-one and derivatives. *Journal of the Chemical Society, Perkin Transactions 1* **1989,** (11), 2117-2122.
140. Schammel, A. W.; Chiou, G.; Garg, N. K., Interrupted Fischer Indolization Approach toward the Communesin Alkaloids and Perophoramidine. *Organic Letters* **2012,** *14* (17), 4556-4559.
141. Kong, X.; He, Z.; Zhang, Y.; Mu, L.; Liang, C.; Chen, B.; Jing, X.; Cammidge, A. N., A mesogenic triphenylene− perylene− triphenylene triad. *Organic Letters* **2011,** *13* (4), 764-767.
142. Banwell, M. G.; Lupton, D. W.; Willis, A. C., Application of the Palladium (0)-Catalyzed Ullmann Cross-Coupling Reaction in a Total Synthesis of (±)-Aspidospermidine and thus Representing an Approach to the Lower Hemisphere of the Binary Indole–Indoline Alkaloid Vinblastine. *Australian Journal of Chemistry* **2005,** *58* (10), 722-737.
143. Love, B. E.; Boston, T. S.; Nguyen, B. T.; Rorer, J. R., A comparison of imine forming methodologies. *Organic Preparations and Procedures International* **1999,** *31* (4), 399-405.
144. Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X., Total Synthesis of (±)-Kopsihainanine A. *Chemistry–A European Journal* **2012,** *18* (22), 6729-6732.
145. Martin, D. B.; Vanderwal, C. D., A synthesis of strychnine by a longest linear sequence of six steps. *Chemical Science* **2011,** *2* (4), 649-651.
146. Kondo, H.; Satomi, M.; Odera, T., Alkaloids of Stephania Japonica. XIV. On Hasubanonine. I (Alkaloids of Menisperrnaceae. LXXXIV.). *Annu. Rep. ITSUU Lab* **1951,** *2*, 35-43.
147. Bentley, K., The biogenesis of the morphine alkaloids and related topics. *Experientia* **1956,** *12* (7), 251-253.
148. Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M., Structure of hasubanonine. *Tetrahedron Letters* **1964,** *5* (40), 2937-2944.
149. King, S. M.; Herzon, S. B.; Knölker, H., *The Hasubanan and Acutumine Alkaloids*. Academic Press: Burlington: 2014; Vol. 73.
150. Semwal, D. K.; Badoni, R.; Semwal, R.; Kothiyal, S. K.; Singh, G. J. P.; Rawat, U., The genus Stephania (Menispermaceae): Chemical and pharmacological perspectives. *Journal of Ethnopharmacology* **2010,** *132* (2), 369-383.
151. Choi, H.-S.; Kim, H.-S.; Min, K. R.; Kim, Y.; Lim, H. K.; Chang, Y. K.; Chung, M. W., Anti-inflammatory effects of fangchinoline and tetrandrine. *Journal of Ethnopharmacology* **2000,** *69* (2), 173-179.
152. Carroll, A. R.; Arumugan, T.; Redburn, J.; Ngo, A.; Guymer, G. P.; Forster, P. I.; Quinn, R. J., Hasubanan Alkaloids with δ-Opioid Binding Affinity from the Aerial Parts of Stephania japonica. *Journal of Natural Products* **2010,** *73* (5), 988-991.
153. Williams, M.; Kowaluk, E. A.; Arneric, S. P., Emerging molecular approaches to pain therapy. *Journal of Medicinal Chemistry* **1999,** *42* (9), 1481-1500.
154. Schultz, A. G.; Wang, A., First asymmetric synthesis of a hasubanan alkaloid. Total synthesis of (+)-cepharamine. *Journal of the American Chemical Society* **1998,** *120* (32), 8259-8260.
155. Battersby, A. R.; Jones, R. C.; Kazlauskas, R.; Poupat, C.; Thornber, C. W.; Ruchirawat, S.; Staunton, J., The biosynthesis of hasubanonine and protostephanine. *Journal of the Chemical Society, Chemical Communications* **1974,** (19), 773-775.

156. Novak, B. H.; Hudlicky, T.; Reed, J. W.; Mulzer, J.; Trauner, D., Morphine synthesis and biosynthesis-an update. *Current Organic Chemistry* **2000,** *4* (3), 343-362.
157. Battersby, A. R.; Jones, R. C.; Minta, A.; Ottridge, A. P.; Staunton, J., Biosynthesis. Part 25. Proof that hasubanonine and protostephanine are biosynthesised from the 1-benzylisoquinoline system. *Journal of the Chemical Society, Perkin Transactions 1* **1981**, 2030-2039.
158. Battersby, A. R.; Jones, R. C.; Kazlauskas, R.; Thornber, C. W.; Ruchirawat, S.; Staunton, J., Biosynthesis. Part 24. Speculative incorporation experiments with 1-benzylisoquinolines and a logical approach *via* C 6–C 2 and C 6–C 3 precursors to the biosynthesis of hasubanonine and protostephanine. *Journal of the Chemical Society, Perkin Transactions 1* **1981**, 2016-2029.
159. Allen, R.; Kirby, G., A common aziridinium ion intermediate in the solvolysis of halogeno-codeinone and-neopinone acetals. *Journal of the Chemical Society D: Chemical Communications* **1971,** (18), 1121-1122.
160. Saucier, M.; Monković, I., Synthetic Morphinans and Hasubanans. II. On the Mechanism of Acid-catalyzed Transformations of 17-(N-Phenylthioamido)-3-methoxy-Δ8, 14-morphinan. *Canadian Journal of Chemistry* **1974,** *52* (15), 2736-2743.
161. Petit, L.; Banwell, M. G.; Willis, A. C., The total synthesis of the crinine alkaloid hamayne *via* a Pd[0]-catalyzed intramolecular alder-ene reaction. *Organic Letters* **2011,** *13* (21), 5800-5803.
162. Austin, K. A.; Banwell, M. G.; Willis, A. C., A formal total synthesis of platencin. *Organic Letters* **2008,** *10* (20), 4465-4468.
163. Trost, B. M.; Pedregal, C., Palladium-catalyzed cycloisomerization of alkynyl *N*-acyl enamines. *Journal of the American Chemical Society* **1992,** *114* (18), 7292-7294.
164. Trost, B. M.; Lautens, M., Cyclization *via* isomerization: a palladium (2+)-catalyzed carbocyclization of 1, 6-enynes to 1, 3-and 1, 4-dienes. *Journal of the American Chemical Society* **1985,** *107* (6), 1781-1783.
165. Trost, B. M.; Tanoury, G. J., Intramolecular carbametalations. A [2+ 2+ 2] cycloaddition as evidence for a palladacyclopentene intermediate. *Journal of the American Chemical Society* **1987,** *109* (15), 4753-4755.
166. Alder, K.; Pascher, F.; Schmitz, A., Substituting additions. I. Addition of maleic anhydride and azodicarboxylic esters to singly unsaturated hydrocarbons. Substitution processes in the allyl position. *Berichte Der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen B* **1943,** *76*, 27-53.
167. Huntsman, W. D.; Lang, P. C.; Madison, N. L.; Uhrick, D. A., A Study of the Thermal Cyclization of 1, 7-Alkadienes and Monocyclic Dienes. *The Journal of Organic Chemistry* **1962,** *27* (6), 1983-1988.
168. Oppolzer, W., Asymmetric Diels-Alder and Ene Reactions in Organic Synthesis. New Synthetic Methods. *Angewandte Chemie International Edition in English* **1984,** *23* (11), 876-889.
169. Nugent, J. Towards the Framework of the Hasubanan Alkaloids. Honours Thesis, The Australian National University, Canberra, Australia, 2012.
170. Grossman, R. B., *The Art of Writing Reasonable Organic Reaction Mechanisms*. Springer Science & Business Media: 2007.
171. Overman, L. E., Thermal and mercuric ion catalyzed [3, 3]-sigmatropic rearrangement of allylic trichloroacetimidates. 1, 3 Transposition of alcohol and amine functions. *Journal of the American Chemical Society* **1974,** *96* (2), 597-599.
172. Luche, J. L., Lanthanides in organic chemistry. 1. Selective 1, 2 reductions of conjugated ketones. *Journal of the American Chemical Society* **1978,** *100* (7), 2226-2227.
173. Shepherd, R. G.; White, A. C., 2-Bromo-3-methoxycyclohex-2-enone, a new reagent for the α-arylation of lactams. *Journal of the Chemical Society, Perkin Transactions 1* **1987**, 2153-2155.

174. Song, Y. S.; Kim, B. T.; Heo, J.-N., An efficient synthesis of 2-aryl-3-methoxy-2-cycloalkenones *via* Suzuki–Miyaura reaction under microwave irradiation. *Tetrahedron letters* **2005,** *46* (36), 5987-5990.
175. Overman, L. E., A general method for the synthesis of amines by the rearrangement of allylic trichloroacetimidates. 1, 3 Transposition of alcohol and amine functions. *Journal of the American Chemical Society* **1976,** *98* (10), 2901-2910.
176. (a) Lee, S. I.; Moon, S. Y.; Hwang, G.-S.; Ryu, D. H., Facile Approach to Optically Active α-Alkylidene-β-amino Esters by Thermal Overman Rearrangement. *Organic Letters* **2010,** *12* (14), 3234-3237; (b) Matveenko, M.; Willis, A. C.; Banwell, M. G., The regio-and stereo-selective formation of allylic chlorides during the Overman rearrangement of trichloroacetimidates derived from certain brominated conduritols. *Australian Journal of Chemistry* **2009,** *62* (1), 64-68.
177. Alder, R. W., Strain effects on amine basicities. *Chemical Reviews* **1989,** *89* (5), 1215-1223.
178. Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y., Use of conjugated dienones in cyclialkylations: total syntheses of arucadiol, 1, 2-didehydromiltirone,(±)-hinokione,(±)-nimbidiol, sageone, and miltirone. *The Journal of Organic Chemistry* **1997,** *62* (20), 6928-6951.
179. Padwa, A.; Murphree, S. S., Epoxides and aziridines-A mini review. *Arkivoc* **2006,** *3*, 6-33.
180. (a) Jiang, H.; Holub, N.; Jørgensen, K. A., Simple strategy for synthesis of optically active allylic alcohols and amines by using enantioselective organocatalysis. *Proceedings of the National Academy of Sciences* **2010,** *107* (48), 20630-20635; (b) Chen, G.; Sasaki, M.; Yudin, A. K., Facile preparation of allyl amines and pyrazoles by hydrazinolysis of 2-ketoaziridines. *Tetrahedron Letters* **2006,** *47* (3), 255-259; (c) Silva, S.; Rodrigues, P.; Bento, I.; Maycock, C. D., The Aza-Wharton Reaction: Syntheses of Cyclic Allylic Amines and Vicinal Hydroxyamines from the Respective Acylaziridines. *The Journal of Organic Chemistry* **2015,** *80* (6), 3067-3074.
181. (a) Hennessy, J., Aziridine synthesis: Protection not included. *Nature Chemistry* **2014,** *6* (3), 168-168; (b) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R., Direct Stereospecific Synthesis of Unprotected NH and *N*-Me Aziridines from Olefins. *Science* **2014,** *343* (6166), 61-65; (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T., Copper-catalyzed aziridination of olefins by (N-(p-toluenesulfonyl) imino) phenyliodinane. *The Journal of Organic Chemistry* **1991,** *56* (24), 6744-6746; (d) Evans, D. A.; Bilodeau, M. T.; Faul, M. M., Development of the copper-catalyzed olefin aziridination reaction. *Journal of the American Chemical Society* **1994,** *116* (7), 2742-2753; (e) Antunes, A. M.; Bonifácio, V. D.; Nascimento, S. C.; Lobo, A. M.; Branco, P. S.; Prabhakar, S., Palladium (II) mediated aziridination of olefins with bromamine-T as the nitrogen source: scope and mechanism. *Tetrahedron* **2007,** *63* (30), 7009-7017; (f) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K., Phenyliodine (III) diacetate as a mild oxidant for aziridination of olefins and imination of sulfoxides with *N*-aminophthalimide. *Arkivoc* **2005,** *4*, 26-38.
182. Mahoney, J. M.; Smith, C. R.; Johnston, J. N., Brønsted Acid-Promoted Olefin Aziridination and Formal a nti-Aminohydroxylation. *Journal of the American Chemical Society* **2005,** *127* (5), 1354-1355.
183. Lwowski, W.; Maricich, T. J., Carbethoxynitrene by α-Elimination. Reactions with Hydrocarbons1, 2. *Journal of the American Chemical Society* **1965,** *87* (16), 3630-3637.
184. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; Jesús, M., The aza-Wittig reaction: an efficient tool for the construction of carbon–nitrogen double bonds. *Tetrahedron* **2007,** *63* (3), 523-575.
185. El-Sheikh, M. I.; Cook, J. M., New perspectives on the Semmler-Wolff aromatization reaction. *The Journal of Organic Chemistry* **1980,** *45* (13), 2585-2587.
186. Kokko, B. J.; Edmondson, S. D., *O*-Methylhydroxylamine. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd: 2001.

187. Merino, P., New developments in nucleophilic additions to nitrones. *Comptes Rendus Chimie* **2005,** *8* (5), 775-788.
188. Cogan, D. A.; Ellman, J. A., Asymmetric synthesis of α, α-dibranched amines by the trimethylaluminum-mediated 1, 2-addition of organolithiums to tert-butanesulfinyl ketimines. *Journal of the American Chemical Society* **1999,** *121* (1), 268-269.
189. Padwa, A.; Pearson, W. H., *Synthetic applications of 1, 3-dipolar cycloaddition chemistry toward heterocycles and natural products*. John Wiley & Sons: 2003; Vol. 59.
190. Sims, J.; Houk, K., Reversal of nitrone cycloaddition regioselectivity with electron-deficient dipolarophiles. *Journal of the American Chemical Society* **1973,** *95* (17), 5798-5800.
191. (a) Padwa, A.; Koehler, K.; Rodriguez, A., Nitrone cycloaddition. New approach to. beta.-lactams. *Journal of the American Chemical Society* **1981,** *103* (16), 4974-4975; (b) Tanaka, J.; Kanemasa, S., Ab initio study of Lewis acid catalyzed nitrone cycloaddition to electron deficient alkenes. Does a Lewis acid catalyst change the reaction mechanism? *Tetrahedron* **2001,** *57* (5), 899-905.
192. Sibi, M. P.; Ma, Z.; Jasperse, C. P., Exo selective enantioselective nitrone cycloadditions. *Journal of the American Chemical Society* **2004,** *126* (3), 718-719.
193. van Staden, L. F.; Gravestock, D.; Ager, D. J., New developments in the Peterson olefination reaction. *Chemical Society Reviews* **2002,** *31* (3), 195-200.
194. Nicolaou, K.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K., Total synthesis of echinopines A and B. *Journal of the American Chemical Society* **2010,** *132* (11), 3815-3818.
195. Gillies, M. B.; Tønder, J. E.; Tanner, D.; Norrby, P.-O., Quantum chemical calculations on the Peterson olefination with α-silyl ester enolates. *The Journal of Organic Chemistry* **2002,** *67* (21), 7378-7388.
196. Manske, R. H., The Alkaloids of Fumaraceous Plants: II. Dicentra Cucullaria. *Canadian Journal of Research* **1932,** *7* (3), 265-269.
197. Wang, X.; Geng, Y.; Li, F.; Shi, X.; Liu, J., Large-scale separation of alkaloids from Corydalis decumbens by pH-zone-refining counter-current chromatography. *Journal of Chromatography A* **2006,** *1115* (1), 267-270.
198. Welch, A. D.; Henderson, V., A comparative study of hydrastine, bicuculline and adlumine. *Journal of Pharmacology and Experimental Therapeutics* **1934,** *51* (4), 482-491.
199. Curtis, D.; Duggan, A.; Felix, D.; Johnston, G., GABA, bicuculline and central inhibition. *Nature* **1970**, *226*, 1222
200. Johnston, G. A., Advantages of an antagonist: bicuculline and other GABA antagonists. *British Journal of Pharmacology* **2013,** *169* (2), 328-336.
201. (a) Muβhoff, U.; Madeja, M.; Bloms-Funke, P.; Speckmann, E.-J., Effects of the epileptogenic agent bicuculline methiodide on membrane currents induced byN-methyl-d-aspartate and kainate (oocyte; Xenopus laevis). *Brain Research* **1994,** *639* (1), 135-138; (b) Piggott, S. M.; Kerkut, G.; Walker, R., The actions of picrotoxin, strychnine, bicuculline and other convulsants and antagonists on the responses to acetylcholine glutamic acid and gamma-aminobutyric acid on Helix neurones. *Comparative Biochemistry and Physiology Part C: Comparative Pharmacology* **1977,** *57* (2), 107-116; (c) Mayer, M.; Straughan, D., Effects of 5-hydroxytryptamine on central neurones antagonized by bicuculline and picrotoxin. *Neuropharmacology* **1981,** *20* (4), 347-350.
202. (a) Zhang, Z. W.; Feltz, P., Bicuculline blocks nicotinic acetylcholine response in isolated intermediate lobe cells of the pig. *British Journal of Pharmacology* **1991,** *102* (1), 19-22; (b) Liu, Q.-Y.; Dunlap, V.; Barker, J. L., gamma-Aminobutyric acid type A receptor antagonists picrotoxin and bicuculline alter acetylcholine channel kinetics in cultured embryonic rat skeletal muscle. *Molecular Pharmacology* **1994,** *46* (6), 1197-1203.
203. Demuro, A.; Palma, E.; Eusebi, F.; Miledi, R., Inhibition of nicotinic acetylcholine receptors by bicuculline. *Neuropharmacology* **2001,** *41* (7), 854-861.

204. Beaudoin, G. A.; Facchini, P. J., Benzylisoquinoline alkaloid biosynthesis in opium poppy. *Planta* **2014,** *240* (1), 19-32.
205. (a) Bauer, W.; Zenk, M. H., Two methylenedioxy bridge forming cytochrome P-450 dependent enzymes are involved in (S)-stylopine biosynthesis. *Phytochemistry* **1991,** *30* (9), 2953-2961; (b) Sariyar, G.; Shamma, M., Six alkaloids from Papaver species. *Phytochemistry* **1986,** *25* (10), 2403-2406.
206. Gözler, B.; Gözler, T.; Shamma, M., Egenine: a possible intermediate in phthalideisoquinoline biogenesis. *Tetrahedron* **1983,** *39* (4), 577-580.
207. Battersby, A.; Hirst, M.; McCaldin, D.; Southgate, R.; Staunton, J., Alkaloid biosynthesis. Part XII. The biosynthesis of narcotine. *Journal of the Chemical Society C: Organic* **1968**, 2163-2172.
208. Groenewoud, P., G,. and Robinson, R., 1936, Synthesis of bicuculline. Part I. *J. Chem. Soc* **1936,** *199*.
209. (a) Slemon, C. E.; Hellwig, L. C.; Ruder, J.-P.; Hoskins, E. W.; MacLean, D. B., Synthesis of phthalideisoquinolines from 3-halophthamdes and 3, 4-dihydroisoquinolinium salts. *Canadian Journal of Chemistry* **1981,** *59* (21), 3055-3060; (b) Shono, T.; Usui, Y.; Hamaguchi, H., New electroreductive synthesis of phthalide alkaloids1). *Tetrahedron Letters* **1980,** *21* (14), 1351-1354; (c) Maria Del Pilar, C. S.; Shankaraiah, N.; Santos, L. S., Short synthesis of noscapine, bicuculline, egenine, capnoidine, and corytensine alkaloids through the addition of 1-siloxy-isobenzofurans to imines. *Tetrahedron Letters* **2010,** *51* (13), 1770-1773.
210. Kardos, J.; Blandl, T.; Luyen, N.; Dörnyei, G.; Gács-Baitz, E.; Simonyi, M.; Cash, D.; Blaskó, G.; Szántay, C., Synthesis, anti-GABA activity and preferred conformation of bicuculline and norbicuculline enantiomers. *European Journal of Medicinal Chemistry* **1996,** *31* (10), 761-765.
211. Rein, K. S.; Gawley, R. E., Synthesis of the phthalide isoquinoline alkaloids (-)-egenine,(-)-corytensine, and (-)-bicuculline by asymmetric carbonyl addition of chiral dipole-stabilized organometallics. *The Journal of Organic Chemistry* **1991,** *56* (4), 1564-1569.
212. Gawley, R. E.; Zhang, P., 1-Magnesiotetrahydroisoquinolyloxazolines as Chiral Nucleophiles in Stereoselective Additions to Aldehydes: Auxiliary Optimization, Asymmetric Synthesis of (+)-Corlumine,(+)-Bicuculline,(+)-Egenine, and (+)-Corytensine, and Preliminary 13C NMR Studies of 1-Lithio-and 1-Magnesiotetrahydroisoquinolyloxazolines. *The Journal of Organic Chemistry* **1996,** *61* (23), 8103-8112.
213. McPherson, L. M. Towards the Asymmetric Synthesis of (+)-Bicuculline. Honours Thesis, The Australian National University, Canberra. Australia, 2013.
214. Mattson, R. J.; Sloan, C. P.; Lockhart, C. C.; Catt, J. D.; Gao, Q.; Huang, S., Ortho-directed lithiation of 3, 4-(alkylenedioxy) halobenzenes with LDA and LiTMP. The first ortho lithiation of an iodobenzene. *The Journal of Organic Chemistry* **1999,** *64* (21), 8004-8007.
215. Struble, J. R.; Lee, S. J.; Burke, M. D., Ethynyl MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis. *Tetrahedron* **2010,** *66* (26), 4710-4718.
216. Pasfield, L. A., Unpublished Works. The Australian National University: 2013.
217. Donohoe, T. J.; Callens, C. K.; Flores, A.; Lacy, A. R.; Rathi, A. H., Recent developments in methodology for the direct oxyamination of olefins. *Chemistry–A European Journal* **2011,** *17* (1), 58-76.
218. Donohoe, T. J.; Callens, C. K.; Thompson, A. L., Tethered aminohydroxylation (TA) reaction of amides. *Organic Letters* **2009,** *11* (11), 2305-2307.
219. Harris, L.; Mee, S. P.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A., Alkyl 4-chlorobenzoyloxycarbamates as highly effective nitrogen source reagents for the base-free, intermolecular aminohydroxylation reaction. *The Journal of Organic Chemistry* **2010,** *76* (2), 358-372.

220. Chouhan, G.; Alper, H., Palladium-catalyzed carboxamidation reaction and aldol condensation reaction cascade: A facile approach to ring-fused isoquinolinones. *Organic Letters* **2008,** *10* (21), 4987-4990.
221. (a) Mohan, K. K.; Narender, N.; Kulkarni, S., Simple and regioselective oxyiodination of aromatic compounds with ammonium iodide and Oxone®. *Tetrahedron letters* **2004,** *45* (43), 8015-8018; (b) Tietze, L. F.; Vock, C. A.; Krimmelbein, I. K.; Wiegand, J. M.; Nacke, L.; Ramachandar, T.; Islam, K.; Gatz, C., Synthesis of novel structurally simplified estrogen analogues. *Chemistry–A European Journal* **2008,** *14* (12), 3670-3679; (c) Castanet, A.-S.; Colobert, F.; Broutin, P.-E., Mild and regioselective iodination of electron-rich aromatics with *N*-iodosuccinimide and catalytic trifluoroacetic acid. *Tetrahedron Letters* **2002,** *43* (29), 5047-5048; (d) Vankar, Y. D.; Kumaravel, G., *N*-chlorosuccinimide/sodium iodide: a convenient source of *N*-iodosuccinimide. Synthesis of α-iodo carbonyl compounds and *trans*-1, 2-iodoacetates. *Tetrahedron Letters* **1984,** *25* (2), 233-236.
222. Brook, M. A.; Chan, T., A simple procedure for the esterification of carboxylic acids. *Synthesis* **1983,** *1983* (3), 201-203.
223. Carpita, A.; Mannocci, L.; Rossi, R., Silver (I)-Catalysed Protiodesilylation of 1-(Trimethylsilyl)-1-alkynes. *European Journal of Organic Chemistry* **2005,** *2005* (9), 1859-1864.
224. Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L., Efficient and general protocol for the copper-free Sonogashira coupling of aryl bromides at room temperature. *Organic Letters* **2003,** *5* (22), 4191-4194.
225. Hay, A. S., Oxidative coupling of acetylenes. II1. *The Journal of Organic Chemistry* **1962,** *27* (9), 3320-3321.
226. (a) Koseki, Y.; Omino, K.; Anzai, S.; Nagasaka, T., Silver salt-promoted direct cross-coupling reactions of alkynylsilanes with aryl iodides: synthesis of aryl-substituted alkynylamides. *Tetrahedron Letters* **2000,** *41* (14), 2377-2380; (b) Nishihara, Y.; Inoue, E.; Ogawa, D.; Okada, Y.; Noyori, S.; Takagi, K., Palladium/copper-catalyzed sila-Sonogashira reactions of aryl iodides with alkynylsilanes *via* a direct C–Si bond activation. *Tetrahedron Letters* **2009,** *50* (32), 4643-4646.
227. Schilz, M.; Plenio, H., A guide to Sonogashira cross-coupling reactions: the influence of substituents in aryl bromides, acetylenes, and phosphines. *The Journal of Organic Chemistry* **2012,** *77* (6), 2798-2807.
228. Petrov, O. I.; Gerova, M. S.; Chanev, C. D.; Petrova, K. V., New Efficient Synthesis of CombretastatinA-4 *via* Colvin Rearrangement. *Synthesis* **2011,** *2011* (22), 3711-3715.
229. Odlo, K.; Klaveness, J.; Rongved, P.; Hansen, T. V., Synthesis of combretastatins A-1 and B-1. *Tetrahedron Letters* **2006,** *47* (7), 1101-1103.
230. Giraud, A.; Provot, O.; Hamzé, A.; Brion, J.-D.; Alami, M., One-pot hydrosilylation–protodesilylation of functionalized diarylalkynes: a highly selective access to *Z*-stilbenes. Application to the synthesis of combretastatin A-4. *Tetrahedron Letters* **2008,** *49* (7), 1107-1110.
231. Lattanzi, A., Handbook of Heterogenous Catalytic Hydrogenation for Organic Synthesis. *Synthesis* **2002,** *2002* (09), 1310-1310.
232. Marciniec, B., *Hydrosilylation: a comprehensive review on recent advances*. Springer Science & Business Media: 2008; Vol. 1.
233. Colvin, E. W., *Silicon in organic synthesis*. Krieger Publishing Company: 1981.
234. Rotta, R.; Neto, Á. C.; De Lima, D. P.; Beatriz, A.; Da Silva, G. V. J., Configuration of stilbene derivatives by 1 H NMR and theoretical calculation of chemical shifts. *Journal of Molecular Structure* **2010,** *975* (1), 59-62.
235. Usachova, N.; Leitis, G.; Jirgensons, A.; Kalvinsh, I., Synthesis of hydroxamic acids by activation of carboxylic acids with N, N'-carbonyldiimidazole: exploring the efficiency of the method. *Synthetic Communications®* **2010,** *40* (6), 927-935.

236. Dubé, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M., Carbonyldiimidazole-Mediated Lossen Rearrangement. *Organic Letters* **2009,** *11* (24), 5622-5625.
237. Donohoe, T. J.; Bataille, C. J.; Gattrell, W.; Kloesges, J.; Rossignol, E., Tethered aminohydroxylation: dramatic improvements to the process. *Organic Letters* **2007,** *9* (9), 1725-1728.
238. (a) Brown, H. C.; Heim, P., Selective reductions. XVIII. Fast reaction of primary, secondary, and tertiary amides with diborane. Simple, convenient procedure for the conversion of amides to the corresponding amines. *The Journal of Organic Chemistry* **1973,** *38* (5), 912-916; (b) Das, S.; Zhou, S.; Addis, D.; Enthaler, S.; Junge, K.; Beller, M., Selective catalytic reductions of amides and nitriles to amines. *Topics in Catalysis* **2010,** *53* (15-18), 979-984.
239. Pace, V.; Holzer, W.; Olofsson, B., Increasing the Reactivity of Amides towards Organometallic Reagents: An Overview. *Advanced Synthesis & Catalysis* **2014,** *356* (18), 3697-3736.
240. (a) Jesberger, M.; Davis, T. P.; Barner, L., Applications of Lawesson's reagent in organic and organometallic syntheses. *Synthesis* **2003,** (13), 1929-1958; (b) Ozturk, T.; Ertas, E.; Mert, O., Use of Lawesson's reagent in organic syntheses. *Chemical Reviews* **2007,** *107* (11), 5210-5278.
241. Kalaus, G.; Greiner, I.; Kajtar-Peredy, M.; Brlik, J.; Szabo, L.; Szantay, C., Synthesis of vinca alkaloids and related compounds. 64. Total syntheses of (.+-.)-pseudovincadifformine and (+)-20-epipseudovincadifformine. *The Journal of Organic Chemistry* **1993,** *58* (22), 6076-6082.
242. Pelletier, G.; Bechara, W. S.; Charette, A. B., Controlled and chemoselective reduction of secondary amides. *Journal of the American Chemical Society* **2010,** *132* (37), 12817-12819.
243. Wang, Z., Meerwein's Salt. In *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc.: 2010.
244. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A., NMR chemical shifts of common laboratory solvents as trace impurities. *The Journal of Organic Chemistry* **1997,** *62* (21), 7512-7515.
245. Pirrung, M. C., *The synthetic organic chemist's companion*. John Wiley & Sons: 2007.
246. Still, W. C.; Kahn, M.; Mitra, A., Rapid chromatographic technique for preparative separations with moderate resolution. *The Journal of Organic Chemistry* **1978,** *43* (14), 2923-2925.
247. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., Safe and convenient procedure for solvent purification. *Organometallics* **1996,** *15* (5), 1518-1520.
248. Kiehlmann, E.; Lauener, R., Bromophloroglucinols and their methyl ethers. *Canadian Journal of Chemistry* **1989,** *67* (2), 335-344.
249. Naruta, Y.; Nishigaichi, Y.; Maruyama, K., Tributyl (3-Methyl-2-Butenyl) Tin. *Organic Syntheses* **1992**, 118-118.
250. Liu, C.; Xie, J. H.; Li, Y. L.; Chen, J. Q.; Zhou, Q. L., Asymmetric Hydrogenation of α, α'-Disubstituted Cycloketones through Dynamic Kinetic Resolution: An Efficient Construction of Chiral Diols with Three Contiguous Stereocenters. *Angewandte Chemie International Edition* **2013,** *52* (2), 593-596.
251. Ikeda, M.; El Bialy, S. A.; HIROSE, K.-i.; Kotake, M.; Sato, T.; Bayomi, S. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T., A formal total synthesis of (-)-cephalotaxine. *Chemical and Pharmaceutical Bulletin* **1999,** *47* (7), 983-987.