UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

Department of Chemistry

Towards the asymmetric synthesis of (+)-maritidine

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Thesis for the degree of Doctor of Philosophy

September 2016

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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Towards the asymmetric synthesis of (+)-maritidine

Two new routes towards the asymmetric synthesis of (+)-maritidine have been proposed and investigated. In both of our routes, the aim was to synthesise the 5,10b-ethanophenanthridone core structure of the target via the tricyclic dihydrodibenzofuran core structure present in galanthamine type compounds. Synthesis of the product in this way would allow formation of the quaternary stereocentre 10b using the efficient and facially selective intramolecular Heck reaction used by multiple groups in the synthesis of galanthamine. Route one attempted the ring opening oxidation of the benzofuran moiety to its respective para-quinone using hypervalent iodine reagents such as (diacetoxyiodo)benzene. From here, reduction of the quinone would be followed by the formation of the final ring structure. Unfortunately, the oxidation only served to form an unwanted tricyclic orthoquinone.

The second route employed was inspired by a bidirectional system from Treu *et al.* for conversion between galanthamine and crinine type alkaloids. Their retro-Michael-Michael reaction however, formed an acyclic intermediate, losing the relevant stereochemistry for the target molecule. We aimed to oxidise the allylc position of the tricyclic scaffold and form a tetracyclic pyrollidine. This intermediate would then be able to undergo a retro-Michael reaction, leaving the stereochemistry of the quaternary centre intact. Progress was made to this end and an advanced intermediate of this route synthesised.

Contents

Declaration

I declare that the work presented in this thesis is of my own composition and has been generated by me as a result of my own original research while in candidature at this university for the degree of Doctor of Philosophy. Where I have consulted the published work of others, this is clearly attributed. Where I have quoted from the work of others, the source is always given and with exception of such quotations this thesis is entirely my own work. No part of this work has been previously published or submitted for a degree of other qualification.

Gareth Sheppard, September 2016

Acknowledgements

I would like to express my sincerest appreciation to my supervisor, Professor Richard Brown, for his continued support, ideas and motivation. Richard has an enthusiasm for all aspects of organic synthesis that encourages me, even now my thesis is finished, to continue to expand my knowledge of the subject in all its forms. Without his patience, reasoning and constant encouragement to improve this thesis would not have been possible. Moreover, I would like to thank him for the faith he has shown in me by allowing me this opportunity.

I would like thank Dr Neil Wells (NMR), Dr John Langley and Julie Herniman (mass spectroscopy) and Dr Mark Light (X-ray diffraction) for their invaluable expertise in their own fields of spectroscopy. Their advice and constant hard work in their respective departments has made not only my work, but the work of every member of the chemistry department infinitly easier.

I owe immense gratitude to Interreg and the AI-Chem project for providing not only the funding that made my PhD possible, but for the numerous meetings and conferences and allowing me to converse with so many like-minded people in similar fields of research.

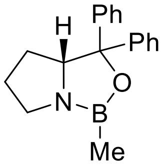
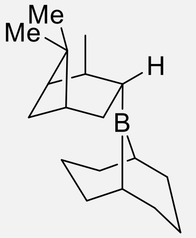
I am completely indebted to every member of the Brown group, past and present, who are too numerous to name individually. Their willingness to exchange ideas, suggest solutions to problems and help wherever possible was only dwarfed by their professionalism, kindness and acceptance of all students and employees who worked with us. They all helped to make our lab, in my opinion, the safest and most well run lab in the department.

I cannot thank my parents enough for supporting me unwaveringly throughout my entire university career. They have been my rock and their love and encouragement will never be forgotten.

Last, but certainly not least, I would like to thank my friends, to whom I cannot find the words to express my gratitude. Without Traher, Kate, Naomi, Dan, Danger, Ollie and Damo supporting me through the darkest times of the past few years I don’t believe I would have made it to the end. Their kindness and loyalty are second to none and I can’t appreciate that enough. I would also like to send a special thankyou to Paola, who gave me the focus and mentaility to get through the last stages of my writing up.

Abbreviations

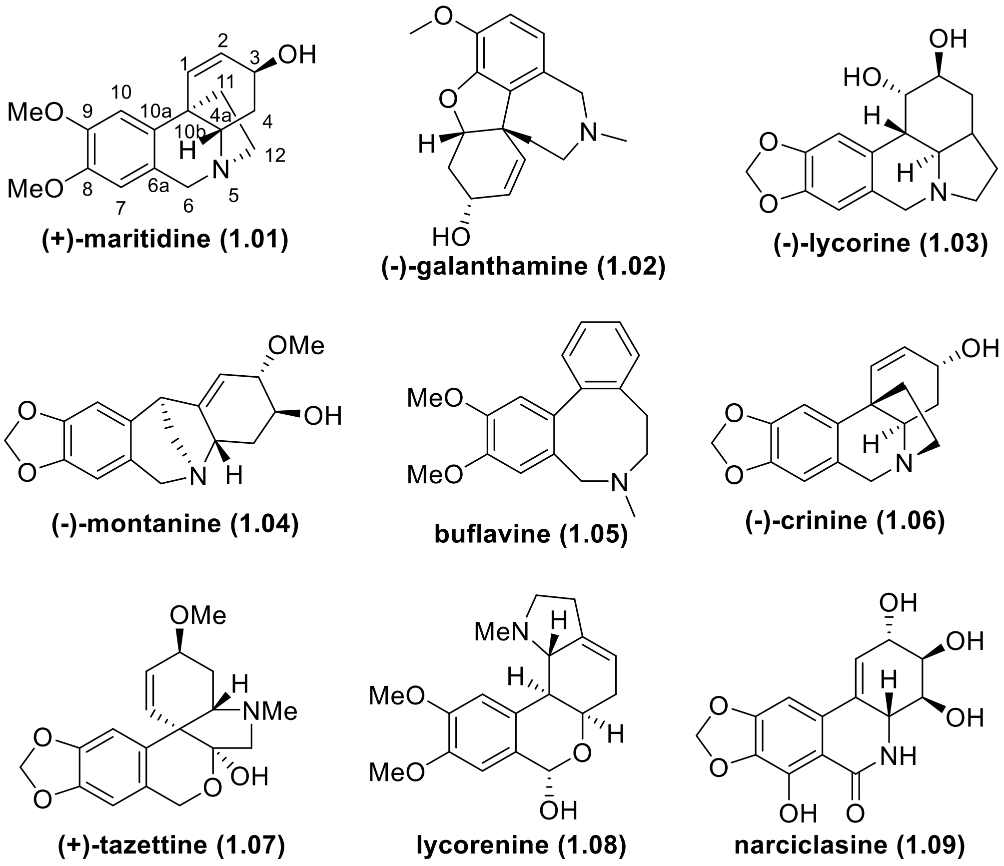
Ac	Acetyl
Aq	Aqueous
Ar	Aryl
BBN	Borobicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BQ	Benzoquinone
BSA	N,O-Bis(trimethylsilyl)acetamide
BTMSA	Bis-(trimethylsilyl)acetylene
Bu	Butyl
CAN	Ceric ammonium nitrate
cap	Caprolactam
Cbz	Benzyloxycarbonyl
CD	Circular Dichroism
dba	Dibenzylideneacetone
DBAD	Di-*tert*-butyl azodicarboxylate
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
Dppp	1,3-Bis(diphenylphosphino)propane
equiv.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
g	gram(s)
h	hour(s)
HMPA	Hexamethylphosphoramide
HQ	Hydroquinone
IR	Infrared
LG	Leaving group
LR	Low Resolution
L-Selectride	Lithium tri-*sec*-butylborohydride
mCPBA	*meta*-chloroperbenzoic acid
Me	Methyl
Min	minute(s)
mL	millilitre(s)
MP	Melting point
MS	Mass spectrometry
Ms	Mesyl
MW	Molecular Weight

n	Normal
NBS	N-bromo-succinimide
NIS	N-iodo-succinimide
NMR	Nuclear Magnetic Resonance
Ns	Nosyl - 2-Nitrobenzenesulfonyl
OCDB	1,2-Dichlorobenzene
ORD	Optical Rotary Dispersion
PCC	Pyridinium chlorochromate
PDC	Pyridinium Dichromate
PG	Protecting group
Ph	Phenyl
PIDA	(diacetoxyiodo)benzene
PIFA	[bis-(trifluoroacetoxy)iodo]benzene
PMA	Phosphomolybdic acid
PDC	Pyridinium dichromate
pTSA	*para*-toluenesulfonic acid
Pyr	Pyridine
Quant	Quantitative
RCM	Ring Closing Metathesis
rt	Room temperature
sat.	Saturated
t* or *tert	Tertiary
TBAI	Tetrabutylammonium iodide
Tbhp	Tert-butyl hydroperoxide
TBS	*tertiary*-butyl dimethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	Tosyl
UV	Ultraviolet
CBS-Cat or CBS catalyst	 (R)-(+)-2-Methyl-CBS-oxazaborolidine
R-Alpine Borane	 B-Isopinocampheyl-9-borabicyclo[3.3.1]nonane

Chapter 1: Introduction

1.1 The Amaryllidaceae Alkaloids

‘Amaryllidaceae’ are a family of roughly 1600 monocotyledonous flowering plant species that are widespread over warmer climates and habitats. Historically, the flowers in this family have been used extensively for both their decorative potential and their chemical makeup. The wide variety of natural products contained within the family as a whole has led them to be used in herbal remedies and, with the rise of modern medicine, pharmaceutical drugs. Among the vast array of natural products found in the Amaryllidaceae family lie a varied collection of alkaloids, which in turn, have been separated into 18 sub-types[1] (**fig. 1**). Within the crinine-type Amaryllidaceae alkaloids we find maritidine. Maritidine can be isolated from the flowers of the Pancratium Maritimum plant of the family Amaryllidaceae and was first isolated in the 1960’s.



(+)-maritidine (1.01) **(-)-galanthamine (1.02)** **(-)-lycorine (1.03)**

(-)-montanine (1.04) **buflavine (1.05)** **(-)-crinine (1.06)**

(+)-tazettine (1.07) **lycorenine (1.08)** **narciclasine (1.09)**

Figure 1 - Maritidine, galanthamine and the title compounds of several Amaryllidaceae sub types

Plants of the Amaryllidaceae family show use in numerous traditional medicines over the globe. These remedies have been used as emetics, diaphoretics and sedatives as well as for the treatment of headache, cystitis, leprosy, sores, wounds, and kidney and bladder infections.[2,3] Pharmacological studies on extracts of several Amaryllidaceae species have also shown them to have anti-inflammatory properties.[4]

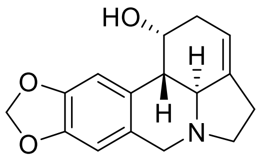
Maritidine has been shown to be a moderate to strong inhibitor of the [^{3}H] citalopram binding to the rat brain serotonin transporter.[5] This transporter is responsible for the reuptake of serotonin into the presynaptic neurones in the brain. Serotonin is thought to be the neurotransmitter responsible for the feeling of wellbeing and happiness. As such, conditions which decrease serotonin levels in the brain have been strongly linked to depression.[6] Reuptake inhibitors function by increasing the time in which serotonin remains in the synaptic cleft between neurones. Maritidine and other similar compounds have also shown cytotoxic activity against HT29 colon adenocarcinoma, lung carcinoma and RXF393 renal cell carcinoma.[7,8] Other members of the Crinine-type alkaloids (crinamine and haemanthamine) have induced strong and selective apoptosis in rat hepatoma cells.[9]

Other alkaloids extracted from the Amaryllidaceae family have been shown to have significant bioactivity for a variety of different purposes, ranging from Acetylcholine esterase (AChE) inhibition to antidepressants and anti-tumour compounds.[10,11] As such, being able to synthesise enantiomerically/diastereomerically pure compounds from this family would be a necessity when it comes to pharmaceutical testing, as racemic mixtures are no longer viable for use as pharmaceutical drugs. Although (±)-maritidine has been synthesised by a number of groups, all previously published syntheses lack the stereocontrol to perform the asymmetric synthesis of (+)-maritidine **1.01**.

Although the main goal of the project is to achieve the total asymmetric synthesis of the target molecule, it is hoped that aspects of the synthesis can be easily extrapolated to not only members of the crinine sub-type, but to other Amaryllidaceae sub-types as well.

1.2 Structural Elucidation

The first elucidation of the structure of maritidine was confirmed by comparison with the structure of crinine **1.06**,[12] the only difference being the presence of two methoxy groups rather than the methylenedioxy moiety. Crinine was found to be isomeric with caranine **1.10** (**fig. 2**).[13] Crinine is stable to selenium dioxide and mercury diacetate. As both of these reagents only oxidise free allylic positions and not allylic alcohols it was deduced that crinine had pre-existing oxidation of the allylic position.

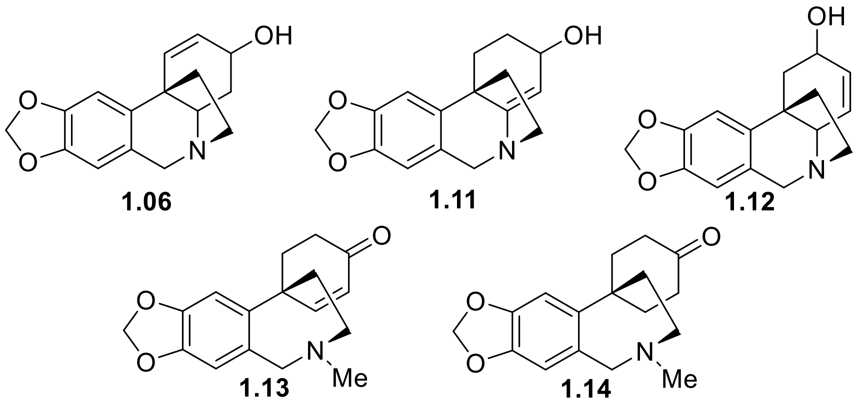


(-)-Caranine (1.10)

Figure 2 - Caranine was shown to be isomeric with crinine, however crinine was shown to resist allylic oxidation conditions

The structure was confirmed further by the very rapid oxidation of the crinine alcohol **1.06** by manganese dioxide to the α,β-unsaturated ketone. Allylic alcohols undergo oxidation with this reagent at much higher rate than their inactivated counterparts.

The failure of crinine to undergo reactions characteristic of caranine suggested the presence of the spiro ring system and the 5,10b-ethanophenanthridine core structure in crinine. This left three remaining possible structures for crinine **1.06**, **1.11**, **1.12** (**fig. 3**).



1.06 **1.11** **1.12** **1.13** **1.14**

Figure 3 - The three decided possible structures of crinine (1.06, 1.11 and 1.12) and the products of the retro-Michael and hydrogenation reactions (1.13 and 1.14 respectively)

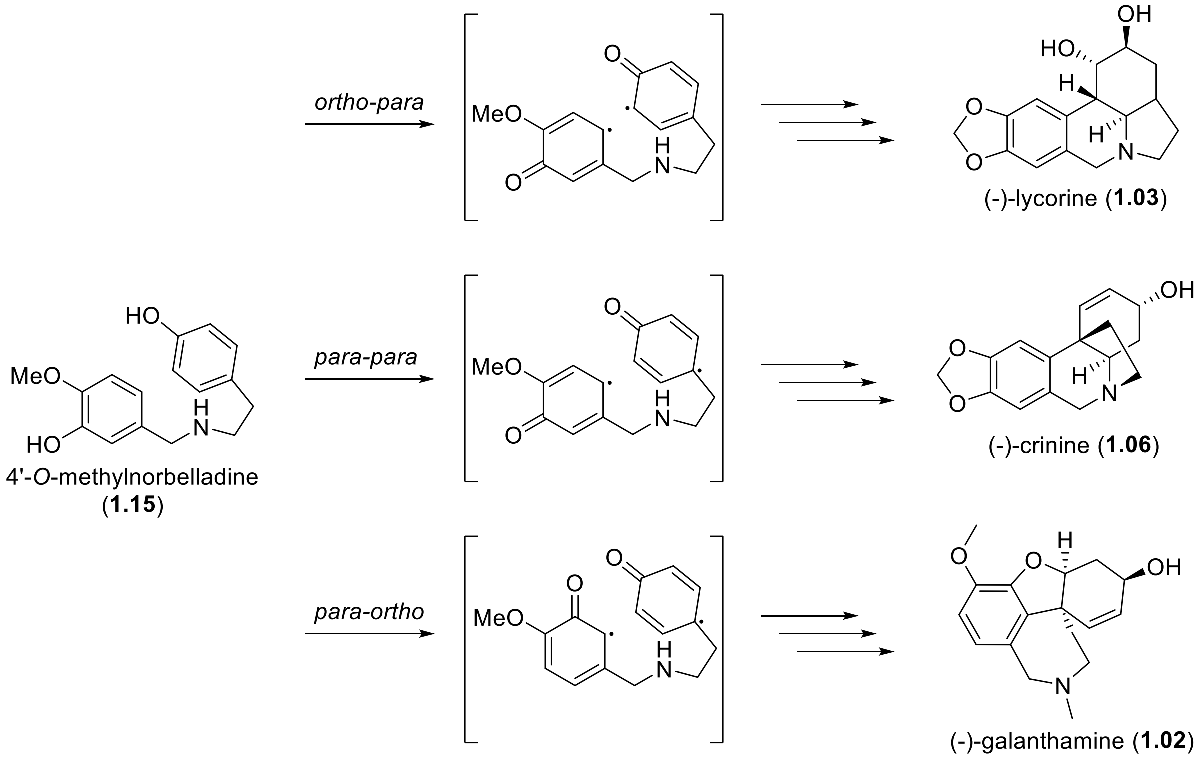
Formation of the *N*-methyl iodide of dihydrooxocrinine and stirring in weak base form gave an optically active methine **1.13** via a retro-Michael elimination. Further catalytic hydrogenation formed an optically inactive achiral dihydro derivative **1.14**. These patterns could only occur from structure **1.06**. The relative stereochemistry was also determined as oxidation of crinine to oxocrinine then reduction with lithium aluminium hydride gave epicrinine, which was shown to be more strongly levorotatory than crinine. The directing effect the bulky ethano- group gives the likely stereochemistry for epicrinine, so the relative stereochemistry for crinine is inferred. The alpha configuration of this hydroxyl group was also suggested by ORD and CD techniques.

More recently two-dimensional NMR methods such as COSY, NOESY, DEPT, HETCOR and HMBC have been used in combination with CD to comprehensively assign the structure and stereochemistry of (+)-maritidine **1.01**.[14]

1.3 Biosynthesis of Amaryllidaceae Alkaloids

Over the last 50 years the biosynthetic pathway of the Amaryllidaceae alkaloids has been thoroughly studied, providing one accepted hypothesis for the basis of the biosynthetic system.[15] This accepted system bases the synthesis of known Amaryllidaceae alkaloids on the intramolecular oxidative phenolic coupling of 4'-*O*-methylnorbelladine **1.15**. The synthesis of this simple intermediate is achieved from the decarboxylation of tyrosine to tyramine, the biosynthesis of 3,4-dihydroxybenzaldehyde from phenylalanine, and the subsequent reductive coupling and *O*-methylation of the two.

This intermediate then goes on to form the multitude of structures present in the Amaryllidaceae family via oxidative phenolic coupling; which is catalysed by cytochrome P-450 dependant enzymes. This oxidative coupling also requires NADPH and diatomic oxygen, although no oxygen is incorporated into the molecule. Abstraction of the labile hydrogen on each phenol in a single electron process followed by resonance of the resulting radical leads to the *ortho* and *para* positions of the ring leads to the diversity in the structure types (**Scheme 1**). The resonance of these phenolic radicals allows the coupling in *para-para*, *para-ortho* and *ortho-para* arrangements, forming crinine-type, galanthamine-type and lycorine-type alkaloids respectively.



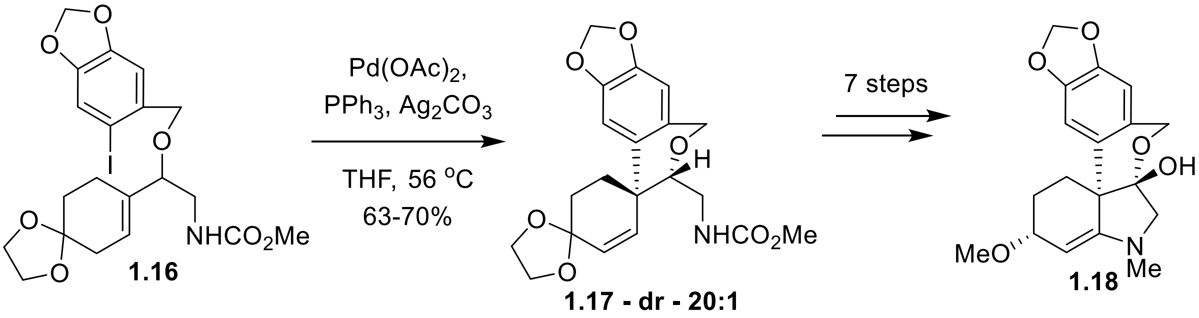
Scheme 1 - The three biosynthetic phenolic oxidative couplings used to generate the structurally diverse Amaryllidaceae family

The ability of nature to synthesise huge families of compounds from a universal starting material like 4'-*O*-methylnorbelladine **1.15** has influenced this project. As such, an objective of this project will be to use an intermediate scaffold system to synthesise not only maritidine but to create a diverging point at which another Amaryllidaceae alkaloid type can be prepared. This will be explained further in later sections.

1.4 Previous Syntheses of Maritidine and Other Amaryllidaceae alkaloids

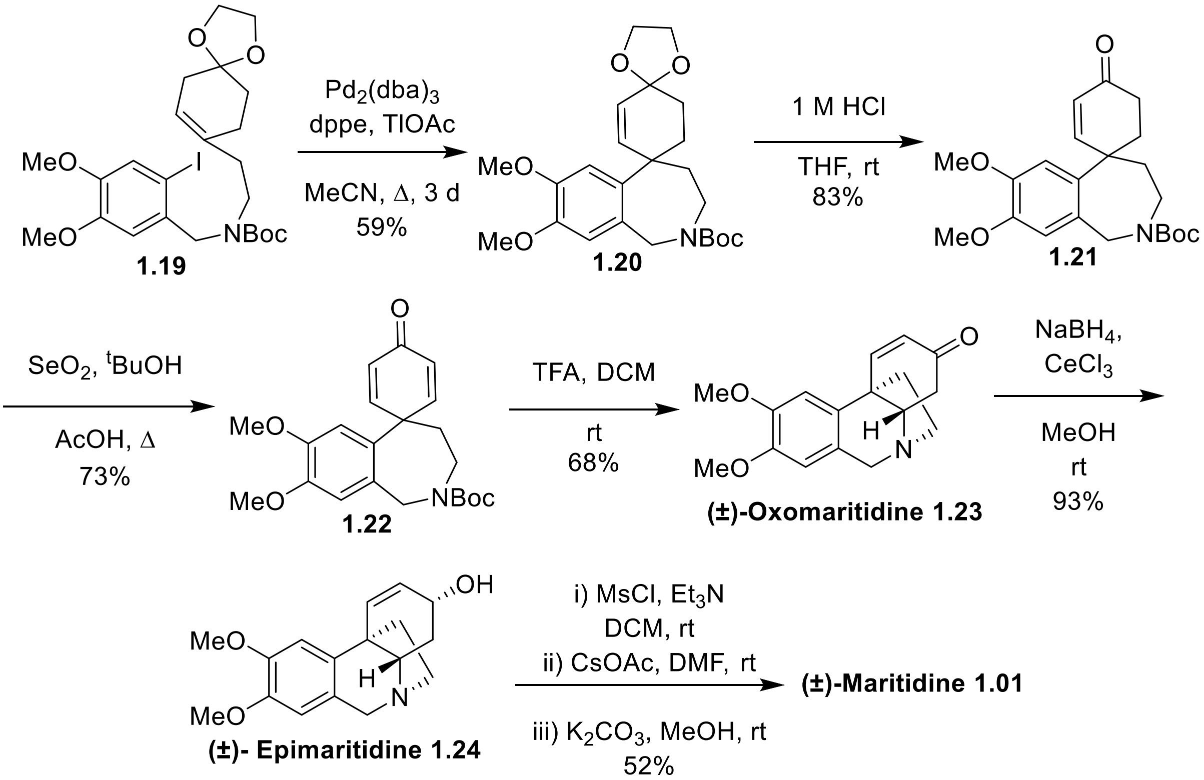
As previously stated, lack of stereocontrol is the main reason for the relatively small number of enantiopure compounds synthesised from this family. This lack of control comes from the presence of the quaternary carbon centre (labelled 10b on **1.01**) from which spans an ethylene bridge to amine, a methylene bridge to amine, an electron rich substituted phenyl ring and a vinyl group. At this time there are no published syntheses of maritidine where control of the stereochemistry at this centre has been achieved.

One of the first and most important advances in creating this quaternary centre in the synthesis of this alkaloid family came from Overman and co-workers over 20 years ago; their innovative synthesis used an intramolecular Heck reaction to form the spiro centre in (±)-tazettine **1.18**.[16] Surprisingly, high stereoinduction was observed here as a result of favourable conformation of the palladium *syn* addition step (**Scheme 2**).



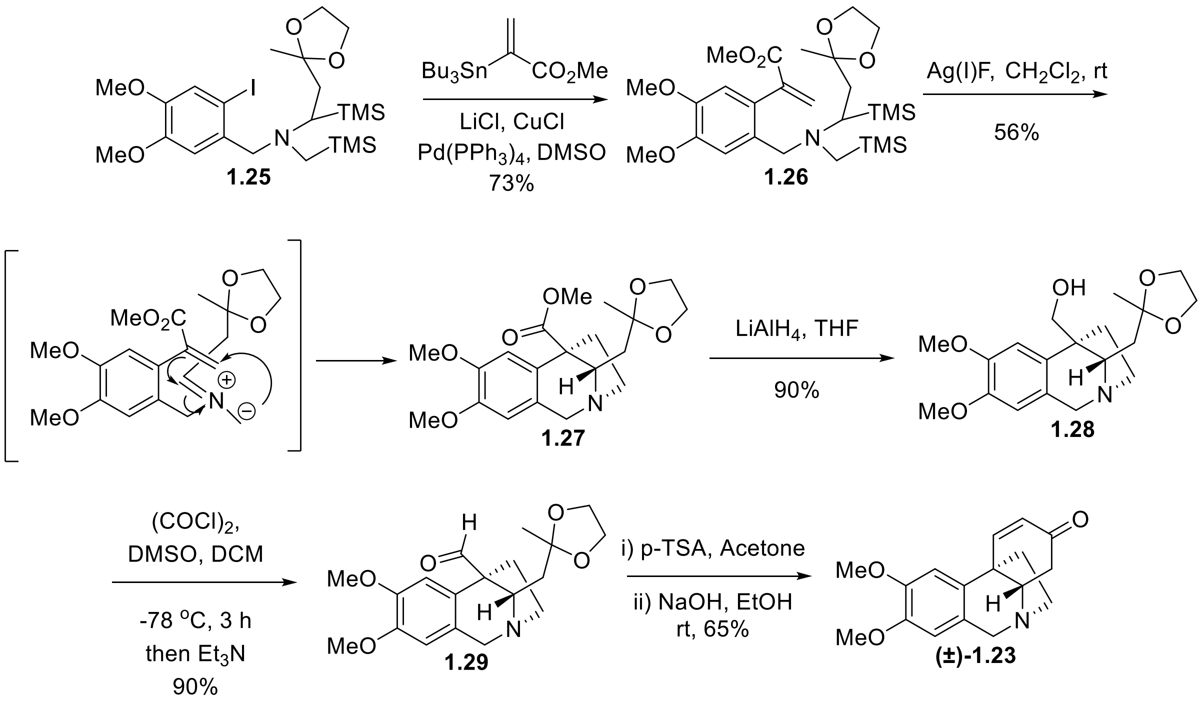
Scheme 2 - Intramolecular Heck coupling in the tazettine synthesis gives the correct relative stereochemistry in the product.

Bru and colleagues have also illustrated an intramolecular Heck reaction of **1.19** to both form the centre and isomerise the double bond to a more suitable position for later steps, by taking advantage of the *β*-hydride elimination step of the reaction (**Scheme 3**).[17] Further oxidation of the cyclohexenone **1.21** to symmetric dienone **1.22** was achieved using selenium dioxide. Formation of Crinine-type structure was completed by initiating Michael addition of the amine to the dienone by cleavage of the Boc protecting group with TFA. As dienone **1.22** has no stereochemical information the amine is free to undergo Michael addition at either of the enone positions, thus providing no stereocontrol. Reduction of the enone **1.23** to form (±)-epimaritidine **1.24** and inversion of stereochemistry about the secondary alcohol completes the synthesis. Aside from the lack of control of absolute stereochemistry this synthesis is very concise and gives a reasonable overall yield. However, unlike the Overman synthesis no stereocontrol of the quaternary centre was observed here.



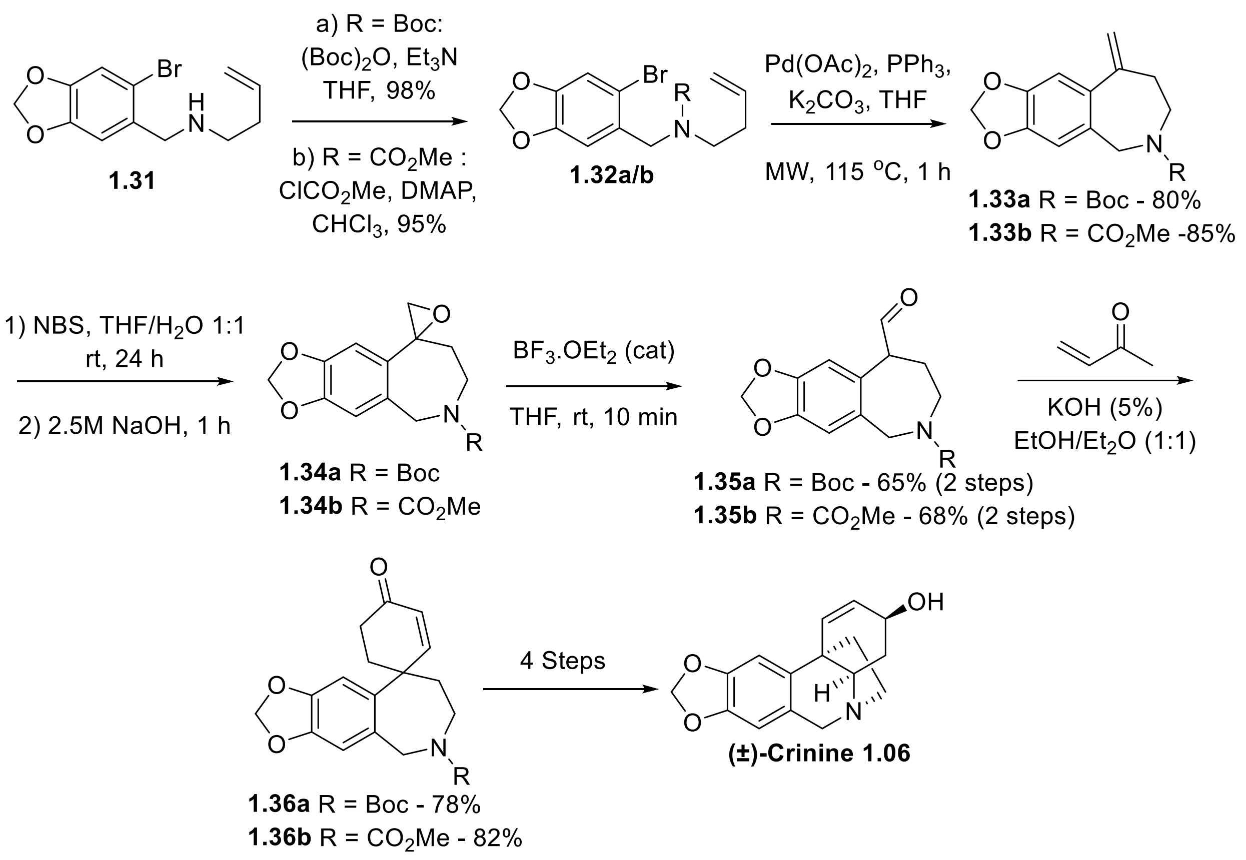
Scheme 3 – The Bru synthesis of (±)-maritidine provides excellent control of the relative stereochemistry, but not the absolute stereochemistry.

Pandey and Gadre have imposed a very different approach in tackling the quaternary centre formation.[18] Their synthesis avoids the intramolecular palladium chemistry. Methyl acrylate is initially coupled using a Stille reaction with its appropriate tributyltin reagent. Lithium chloride and copper chloride addititives were used here to increase the rate of reaction. They then made use of a [3+2] intramolecular cycloaddition between a substituted β-unsaturated ester and an unstabilised azomethine ylide (AMY) to form piperidine **1.27** (**Scheme 4**). In this case the ylide is created *in situ* from the TMS-methyl-alkyl amine **1.26**. A $LiAlH_4$ reduction, a Swern oxidation and an intramolecular aldol reaction then form the final fused cyclohexenone ring, which is finally reduced to (±)-maritidine. However, there are several downfalls to this synthesis, including a 10 step synthesis for starting material (prior to **1.25**) and the relatively low yield of the key cycloaddition step.



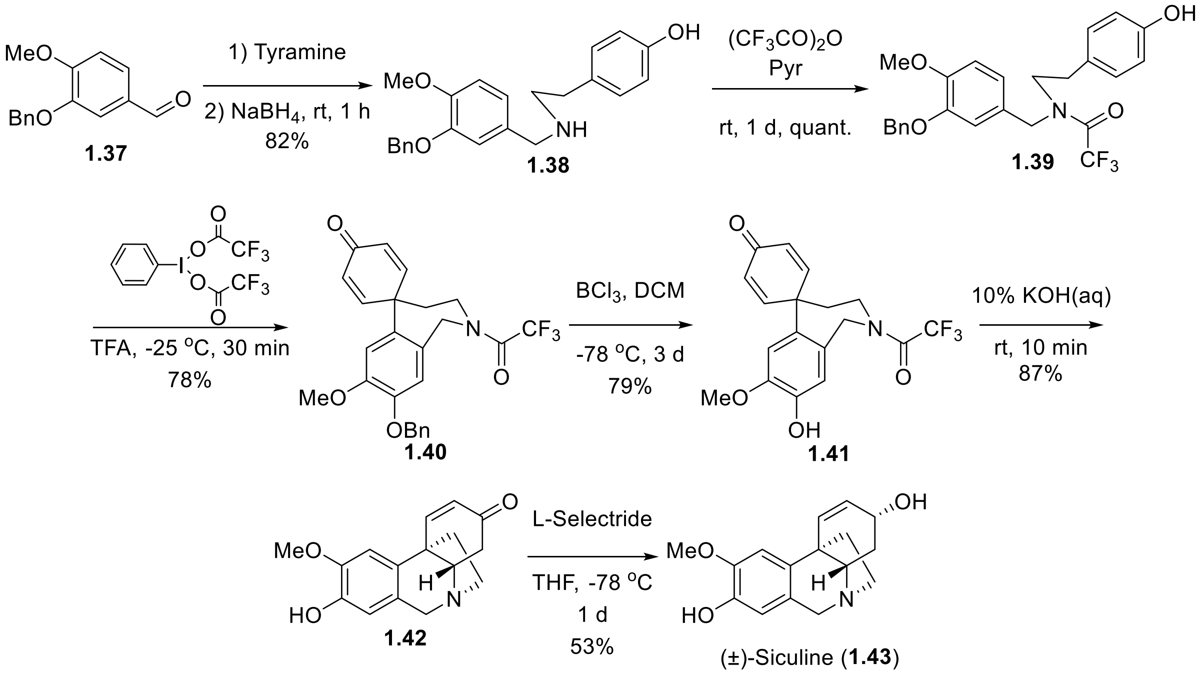
Scheme 4 - Pandey and Gadre's synthesis of (±)-maritidine up to the oxomaritidine stage

Crinine **1.06** is another natural product and a similar analogue to maritidine, but instead replaces the two methoxy substituents with a methylenedioxy ring, which allows some synthetic routes to be effective for both compounds based on the corresponding starting material (see further work by Bru *et al.*). A synthetic route to crinine created by Yang and colleagues may be an example of this (**Scheme 5**).[19] The synthesis they have created gives another example of an intramolecular Heck reaction being effective, performing a 7-*exo*-trig cyclisation favourably over the 8-*endo*-trig transformation. This creates an external double bond; which is subject to epoxidation, ring opening to the aldehyde **1.35a/b** and Robinson annulation to form the cyclohexenone ring of (±)-oxomaritidine **1.23**. The final steps here are somewhat similar to those of the Bru synthesis.



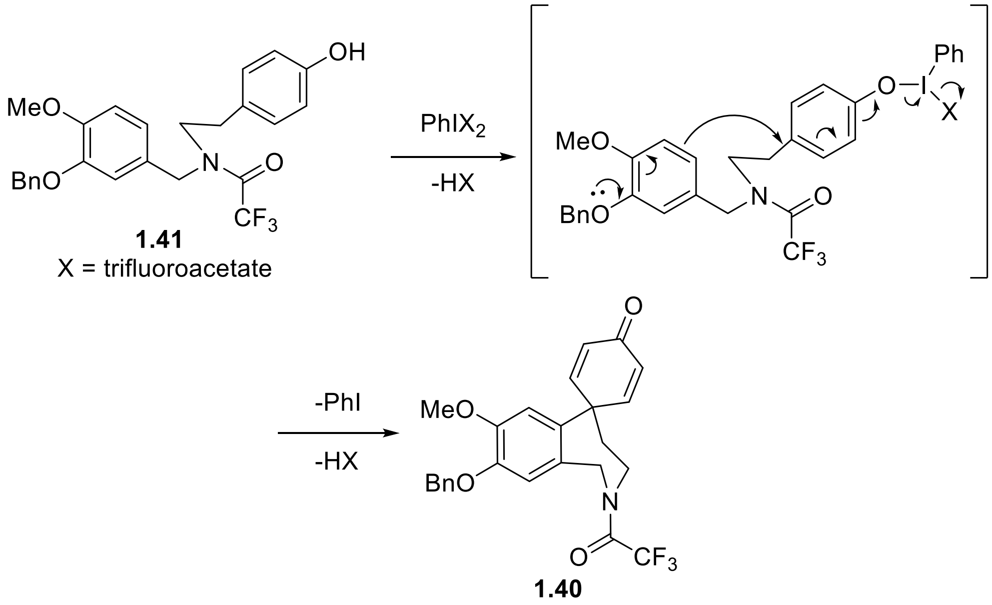
Scheme 5 – Yang's synthesis of (±)-crinine

In other syntheses published, intramolecular palladium catalysed coupling reactions have been replaced with a phenolic oxidative coupling step in order to create the quaternary centre. This synthesis has taken its inspiration from the biosynthetic pathway to crinine-type structures. The most common reagents used for these oxidations are periodinanes, which contain hypervalent iodine. In this case PIFA takes the place of cytochrome P-450 enzymes, NADPH and O_2 utilised in nature. **Scheme 6** shows a synthesis of the crinine type alkaloid (±)-siculine by Kodama *et al.* using PIFA (phenyliodine bis(trifluroacetate)) as the reagent for the oxidative coupling step.[20]



Scheme 6 – Kodama's (±)-siculine synthesis, making use of PIFA mediated oxidative phenolic coupling

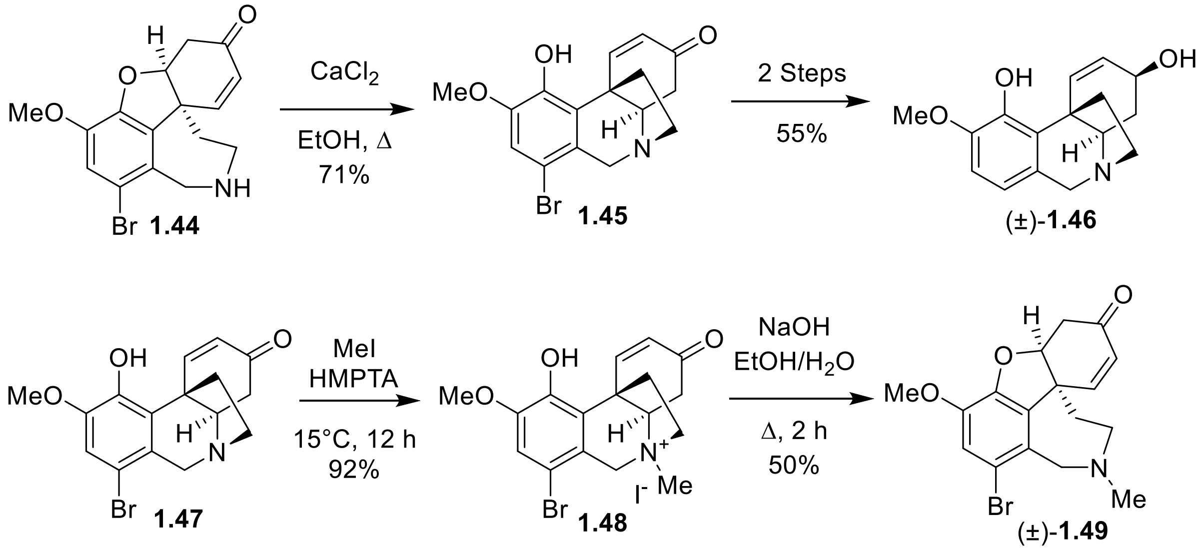
This phenolic oxidation step to **1.40** in this synthesis also highlights the importance of hypervalent iodine reagents in modern alkaloid synthesis. In this mechanistically interesting oxidation the free phenol displaces a trifluoroacetate from the hypervalent iodine. Pushing of electrons during the formation of the benzyl oxonium species allows the nucleophilic attack of the alkoxybenzene onto the phenol ring, eliminating the remaining trifluoroacetate from the hypervalent iodine, whilst simultaneously reducing the iodine from the +3 to +1 oxidation state (**Scheme 7**).



Scheme 7 - PIFA mediated phenolic oxidative coupling step mimics the biosynthesis of crinine-type compounds

Yet again, these syntheses offer no stereoselectivity in terms of the quaternary centre. However, they do offer some advantages over the palladium couplings. Firstly, they remove the need for expensive heavy metal catalysts in the synthesis, helping with both the economic viability and creating simpler work up procedures and less toxic waste. Secondly, in syntheses where further oxidation would be needed to create the dienone for the intramolecular Michael addition step, periodinane reagents already leave the affected ring at the dienone, and possibly increase the overall yield.

The idea of synthesising crinine type alkaloids *via* a galanthamine type scaffold (as described in the project aims) is not an entirely new idea. Treu *et al.* have published syntheses of both of these types *via* bidirectional conversion between the two types (**Scheme 8**).[21]



Scheme 8 - Bidirectional conversion of galanthamine and crinine type structures

This synthesis serves as a novel method of forming these crinine structures from the galanthamine type scaffold, which already has well documented asymmetric syntheses. This should therefore allow for the synthesis of a multitude of crinines with 10-hydroxy substitution. Unfortunately, the study was only performed for the bidirectional conversion between the above bromo-methoxy compounds. As such the scope and limitations of these transformations are currently unknown. In terms of the synthesis of (+)-maritidine this approach is not viable, as the opening of the furan ring goes *via* a retro-Michael-Michael-addition-cascade. This transformation produces an achiral dienone intermediate **1.51**, which forms a racemic mixture of the crinine-type product (**Fig. 4**).

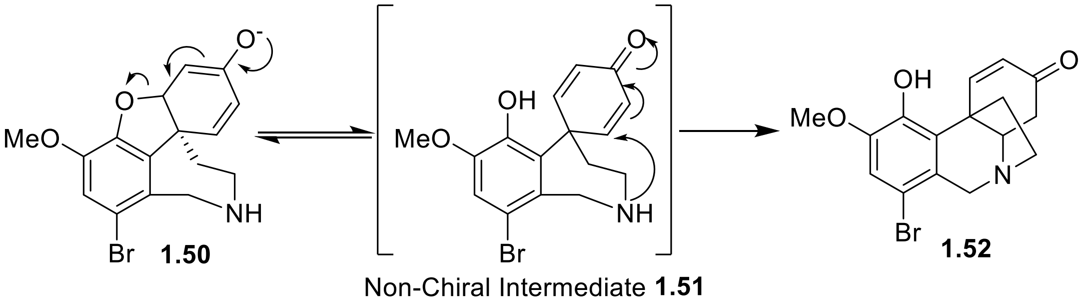
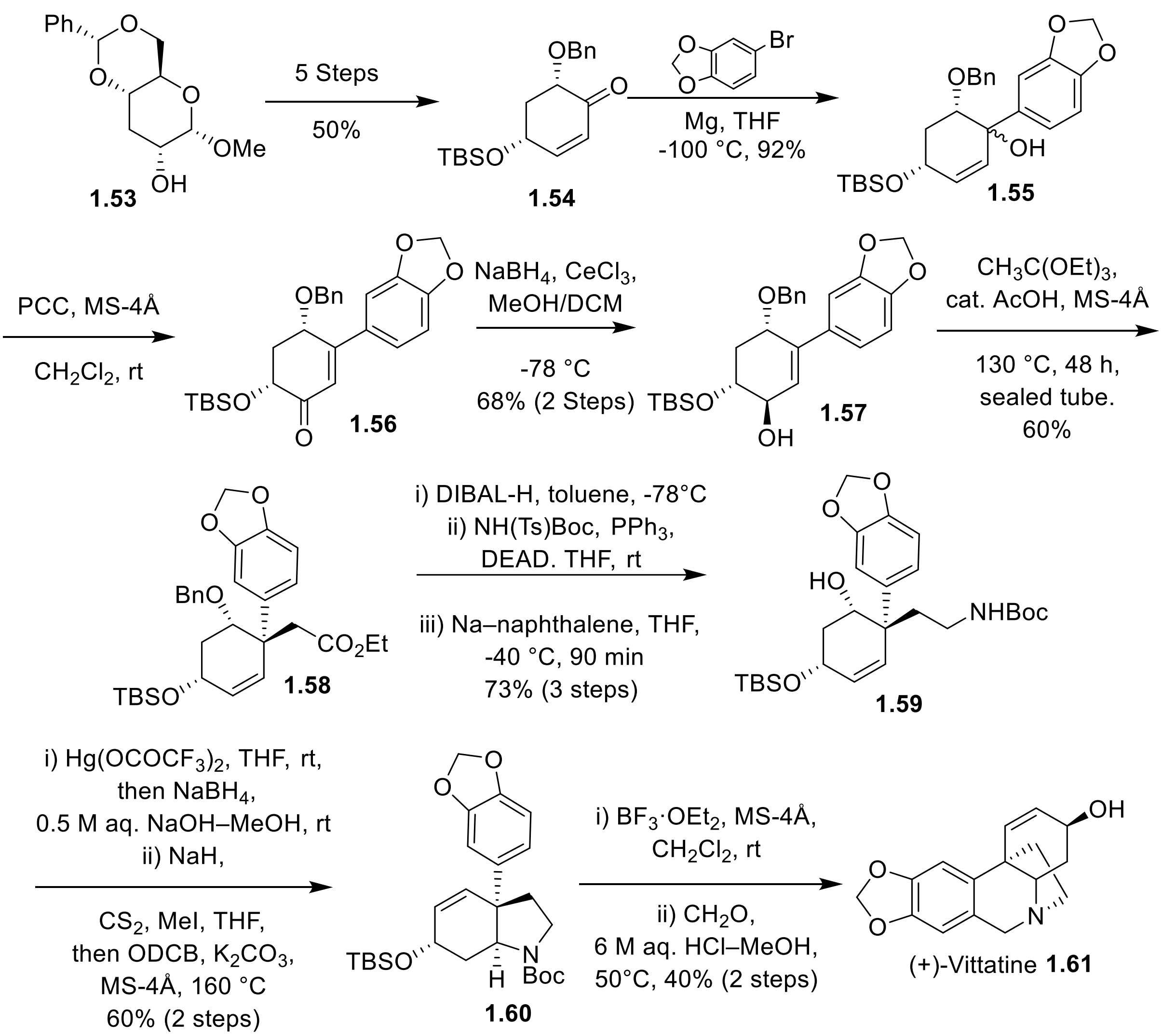


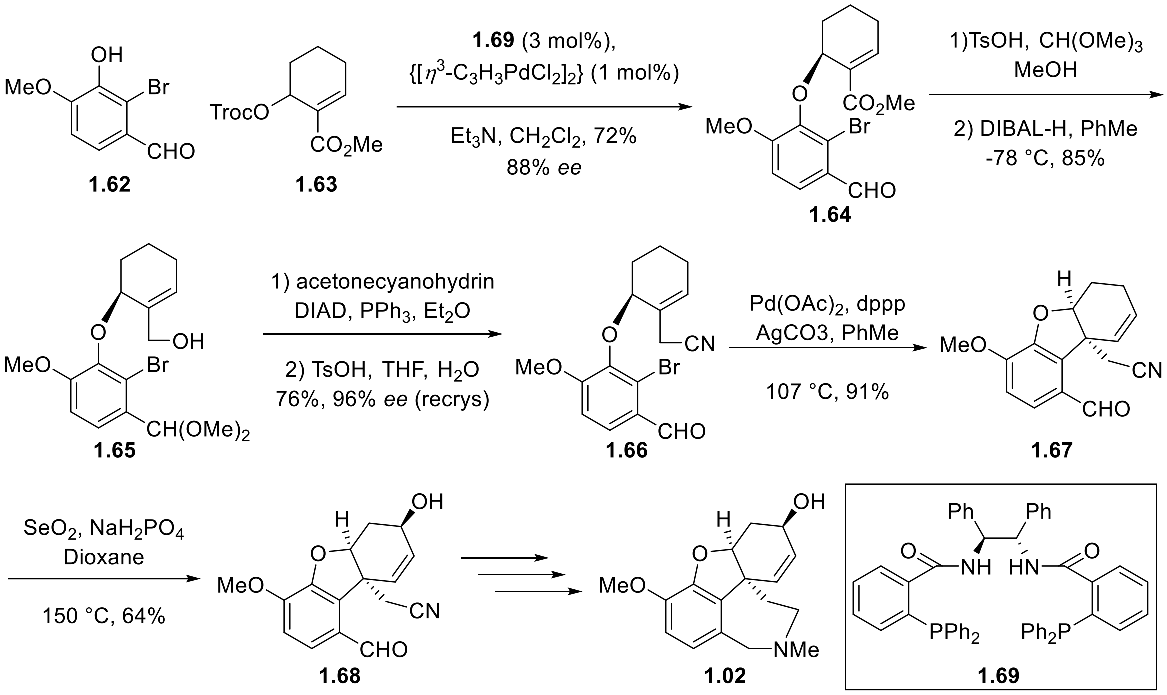
Figure 4 - Retro-Michael-Michael formation of Crinine type structure

Although there are no published syntheses of (+)-maritidine there are syntheses of other members of the crinine type alkaloids. For example, Bohno *et al.* have developed a stereoselective synthesis of (+)-vittatine **1.61** from a cheap and commercially available 3-deoxy-D-glucose derivative **1.53**, making use of the pre-existing stereochemistry in the naturally occurring monosaccharide (**Scheme 9**).[22] In this case the bulky TBS protected 2-hydroxyl group is used to direct a Luche reduction to form a single diastereomer by stereoinduction. The resulting alcohol **1.57** is then used in a Claisen rearrangement, which forms a single diastereomer **1.58** of the key quaternary carbon centre present in all crinine-type alkaloids. The existing stereochemistry on the glucose derived starting material also sets the stereochemistry of the allylic alcohol. This synthesis effectively controls the absolute stereochemistry of the final product; however, it is long at 18 total steps and uses toxic metals in some steps, which would ideally be avoided on a larger scale.



Scheme 9- Stereoselective synthesis of (+)-Vittatine from a D-glucose derivative

In combination with the synthesis of the ethanophenanthridine system of maritidine, a secondary objective will be to complete its formation via a tricyclic galanthamine scaffold structure. As such, it is sensible to address the first asymmetric synthesis of galanthamine, completed by the Trost group in 2000[23], with an efficient synthesis published in 2005 (**Scheme 10**).[24] The Trost group were the first to achieve the synthesis of enantioenriched galanthamine without wasteful chiral resolution. The synthesis utilises a Tsuji-Trost reaction to combine phenol **1.62** with Troc cyclohexenol **1.63** using chiral bidentate phosphine ligand **1.69**. This ligand induces asymmetric coupling at the allylic position. Reduction of the vinyl unsaturated ester **1.64** to the alcohol **1.65** was followed by its conversion to the nitrile **1.66** using a Mitsunobu reaction with acetone cyanohydrin. The key reaction in terms of potential application to the synthesis of maritidine is the intramolecular Heck reaction to tricyclic intermediate **1.67**. Due to the set stereochemistry at the allylic position the intramolecular coupling reaction the transformation proceeds with facial selectivity, setting the stereochemistry of the key quaternary centre; which previous syntheses of crinine type have struggled to control. It is hoped that the stereochemistry at this quaternary center can be kept in the conversion from galanthamine to crinine type alkaloids.



Scheme 10 - Trost synthesis of (-)-galanthamine using a facially selective intramolecular Heck reaction

1.5 The Brown Group Retrosynthetic Analysis and Synthetic Approach to (+)-Maritidine

As a secondary aim of the project being to synthesise (+)-maritidine *via* a tricyclic galanthamine type scaffold, the retrosynthetic analysis presents a challenge. The reason for this being that proceeding through to the crinine type structure from a galanthamine scaffold; whilst retaining the stereochemistry at the key quaternary centre, has never been accomplished.

Multiple asymmetric syntheses of (–)-galanthamine **1.02** have been documented that set the stereochemistry at the corresponding key quaternary centre on the tricyclic scaffold. Previous work within the Trost group and later the Brown group, leading to the total synthesis of (–)-galanthamine, stereoselectively formed the quaternary centre by controlling facial selectivity of the intramolecular Heck reaction (**Fig. 5**).[25] This was controlled by asymmetric reduction of the ketone to the allylic alcohol prior to formation of the aryl ether in previous steps.

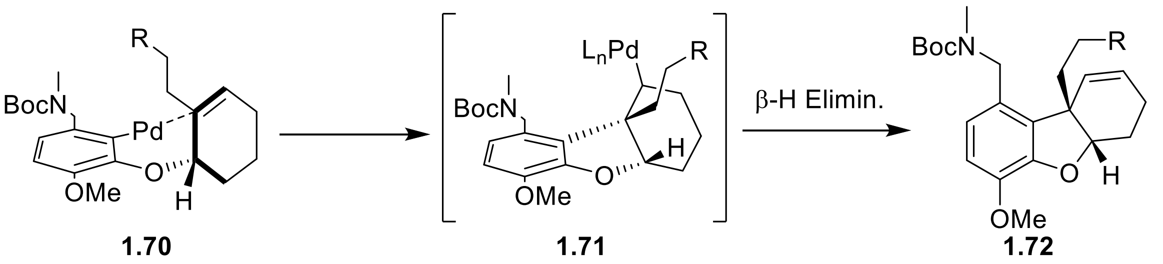


Figure 5 - Brown galanthamine synthesis. Facial selectivity of intramolecular Heck reaction mediated by control of stereochemistry on cyclohexenoyl ring.

The order in which the ABCD ring system of (+)-maritidine is formed is also important (**Fig. 6**). As seen in previous syntheses described in this chapter, formation of the piperidine ring **B** early on, or in conjunction with the **D** ring, leads to formation of multiple diastereomers at the key quaternary centre. This is due to the starting compounds used that allow this dual ring formation being largely achiral. As such, the retrosynthesis was required to form the piperidine **D** ring last, once the stereochemistry at the quaternary centre is set.

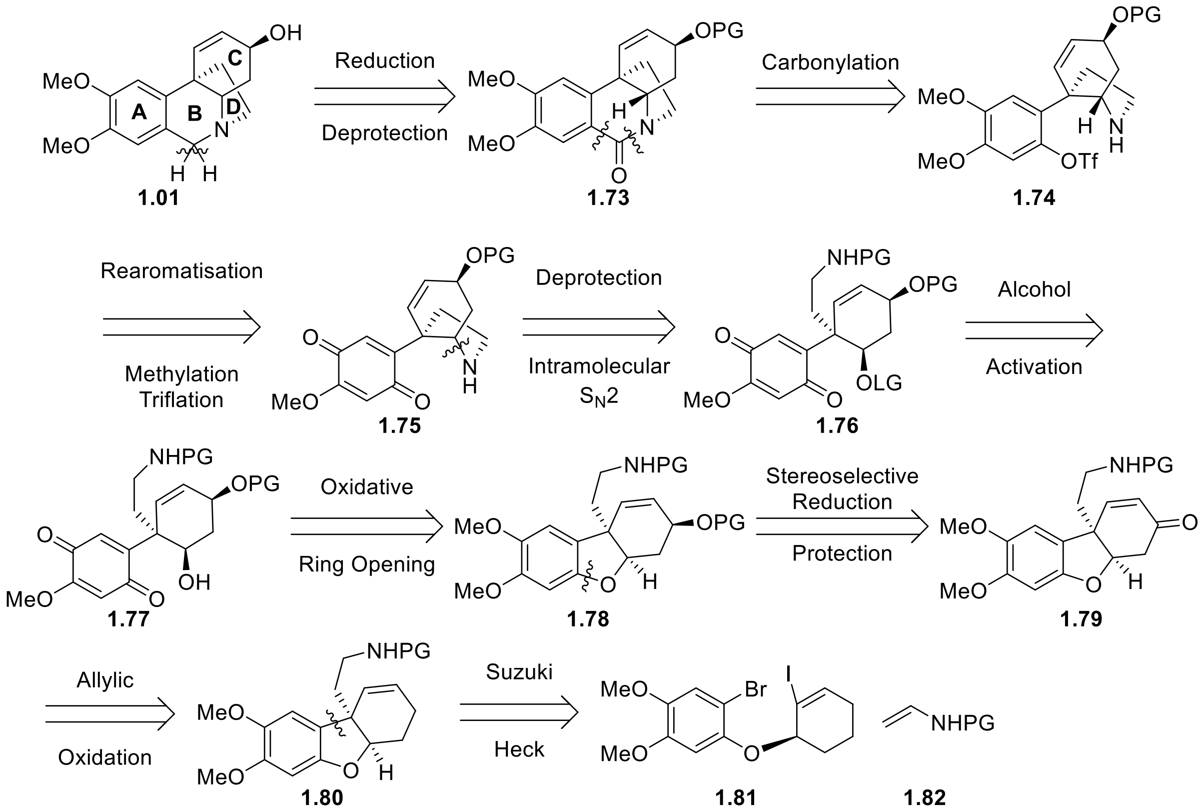


Figure 6 - Retrosynthetic analysis of (+)-maritidine, showing the ABCD ring system of the final product.

Another positive contribution that may occur when going via a galanthamine scaffold is a possible stereoselective reduction of the enone **1.79**. A simple MM2 energy minimising calculations (PerkinElmer Chem 3D Pro) shows the most stable conformation of **1.79** leaves one face of the cyclohexenone more accessible to hydride reduction whereas the most stable configuration of oxomaritidine **1.23** leaves the opposite face more accessible (**Fig. 7**). This is concurrent with previous work performed in the Brown group using similar compounds in the synthesis of (–)-galanthamine.[26] This work used the bulky reducing agent L-Selectride® to ensure the correct stereochemistry was achieved. So, by performing the reduction on the galanthamine scaffold mid synthesis, not the crinine-type structure at the end of the synthesis, no epimerisation will be required at the final step.

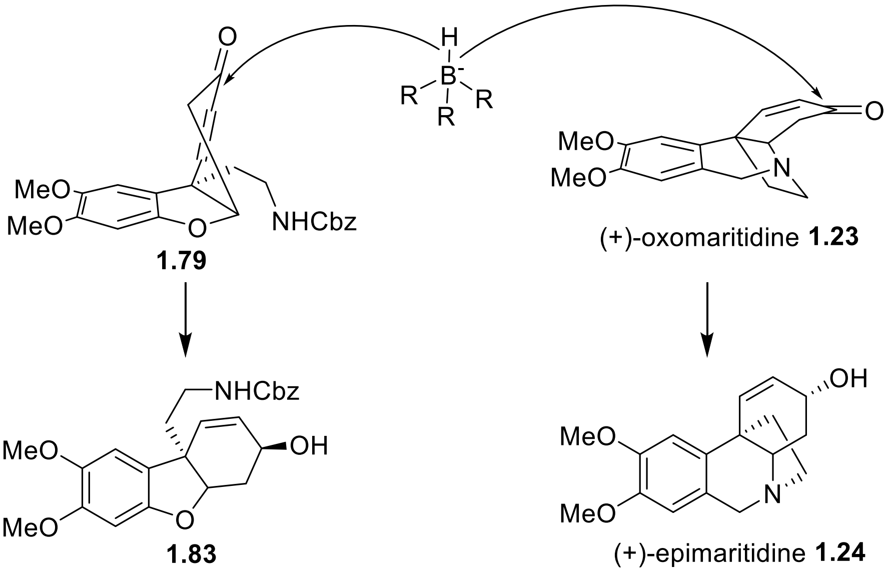
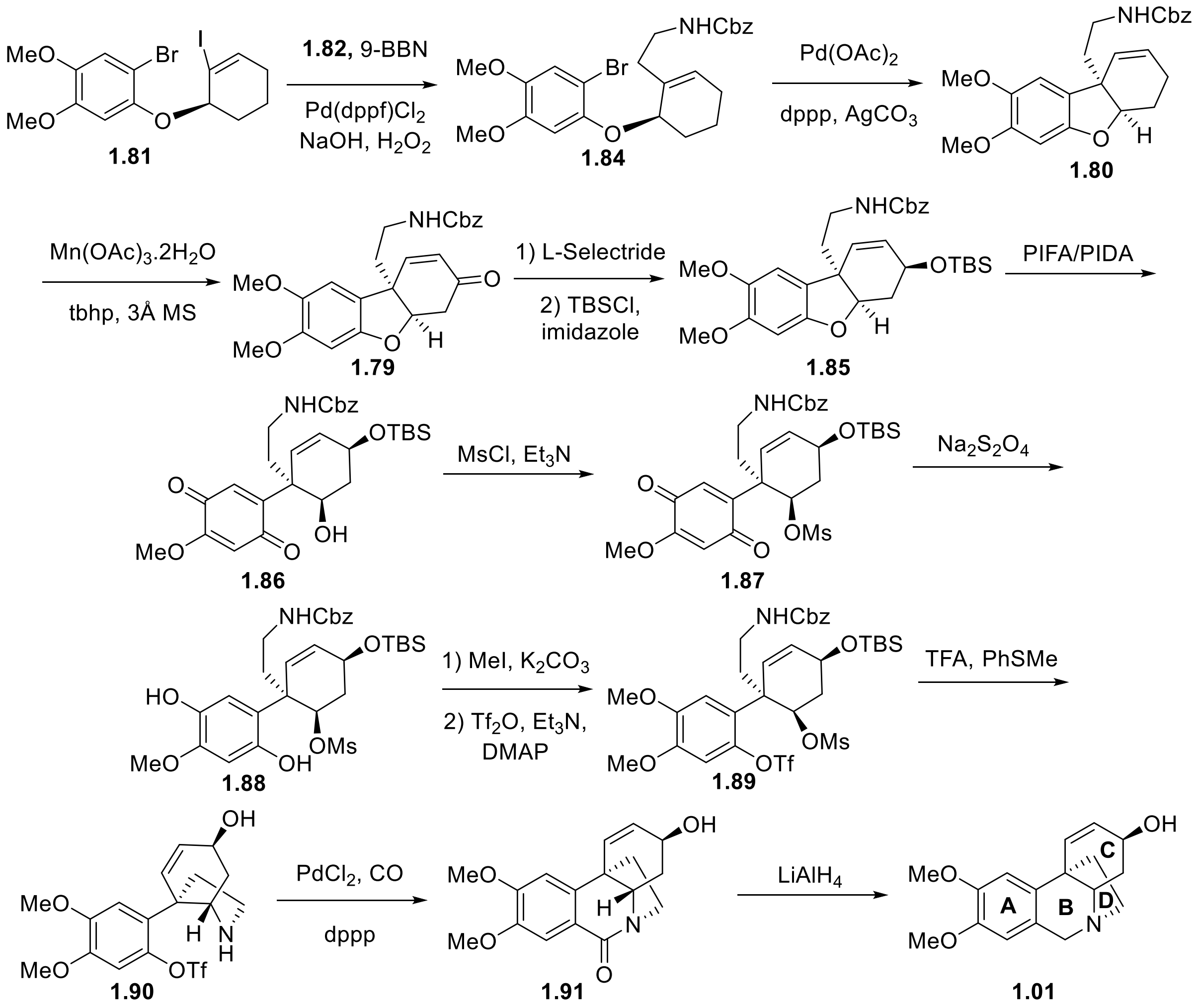


Figure 7 - Facial selectivity of galanthamine scaffolds and crinine type structures under enone reduction conditions

Scheme 11 shows the planned forward synthesis of (+)-maritidine and the general reagents used for the types of tranformations shown. Rationale behind steps performed and their references will be supplied in the relevant section. Later steps in the synthesis such as rearomatisation, alcohol/phenol activation, methylation and intramolecular S_N2 cyclisation were likely to be subject to change in order based on experimental trials.

The overall plan for the synthesis is to install the relevant stereo centres early on using the methods described in this section. The dihydrofuran ring will then be fragmented using a ring opening oxidation step to form quinone **1.87**. A reduction of the quinone to the hydroquinone **1.88** will be attempted using sodium dithionite and the *N*-ethano bridge will then be formed using a simple intramolecular S_N2 to pyrollidine **1.90.** Palladium catalysed carbonylation will be performed to add the final carbon in the 5,10b-ethanophenanthridone structure. The final steps will then be a methylation of the phenol and an amide reduction to form (+)-maritidine **1.01**.



Scheme 11- Planned forward synthesis of (+)-maritidine

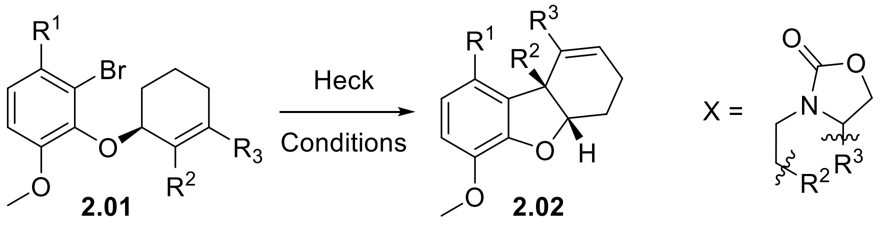
Chapter 2 – First approach to (+)-Maritidine: Ring Opening Oxidation Method

In this chapter the initial approach towards (+)-maritidine will be described. The reader will be guided through the initial precedent, expected scope and limitations of the synthetic method. The results will be reported as to guide the reader through a logical progression of the synthesis and its alterations, rather than its chronological progression in the laboratory setting. As is commonplace in the area of total synthesis, modifications were made to the synthetic plan as the research progressed, in some cases leading to completely different chemical moieties being utilised. This chapter will highlight how seemingly minor changes in chemical structure sometimes have a significant effect on the yield of previously effective reactions, in this case reactions emerging from existing research into the synthesis of galanthamine and maritidine.

2.1 Halogenation of 3,4-dimethoxyphenol

2.1.1 Iodination

The first stage of the synthesis required an investigation into the regioselective halogenation of 3,4-dimethoxyphenol, preparing the functionality for the intramolecular Heck reaction in a later stage of the synthesis. Analysis of previous work into the synthesis of the galanthamine type compounds, which will be used as the scaffold in this synthesis, has led to multiple conclusions. **Scheme 12** shows a compilation of Heck reactions towards the tricyclic galanthamine precursors. By comparison of these different syntheses (each using various Heck reagents), it is apparent that the presence of an electron withdrawing group in the ortho position to the aryl bromine (R^1) leads to more efficient cyclisation. In the cases shown, the more electron withdrawing aldehyde[27,28] and methyl-1,3-dioxolane[29] groups give the highest yields and protected methanol good yields[23], whereas a substrate with no substitution on this position failed to reach 60% yield[30]. Previous work within the Brown group has also shown intramolecular Heck reactions on this system to proceed poorly using aryl bromides[25].

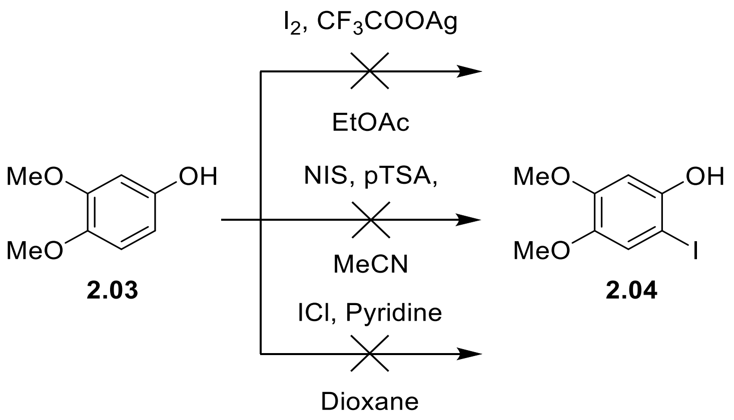


R^1 = H, R^2 and R^3 = X, Yield = 57%[30]
R^1 = CH_2OTBS, R^2 = CH_2OTBS, R^3 = H, Yield = 69%[23]
R^1 = CHO, R^2 = $CH_2CH_2NMeBoc$, R^3 = H, Yield = 82%[28]
R^1 = CH_2-1,3-dioxolane, R^2 = $CH_2CH_2NMeboc$, R^3 = H, Yield = 82%[29]
R^1 = CHO, R^2 = CH_2CN, R^3 = H, Yield = 91%[27]

Scheme 12 - Neighbouring groups have a strong effect on the yield of the intramolecular Heck reaction toward galanthamine type compounds

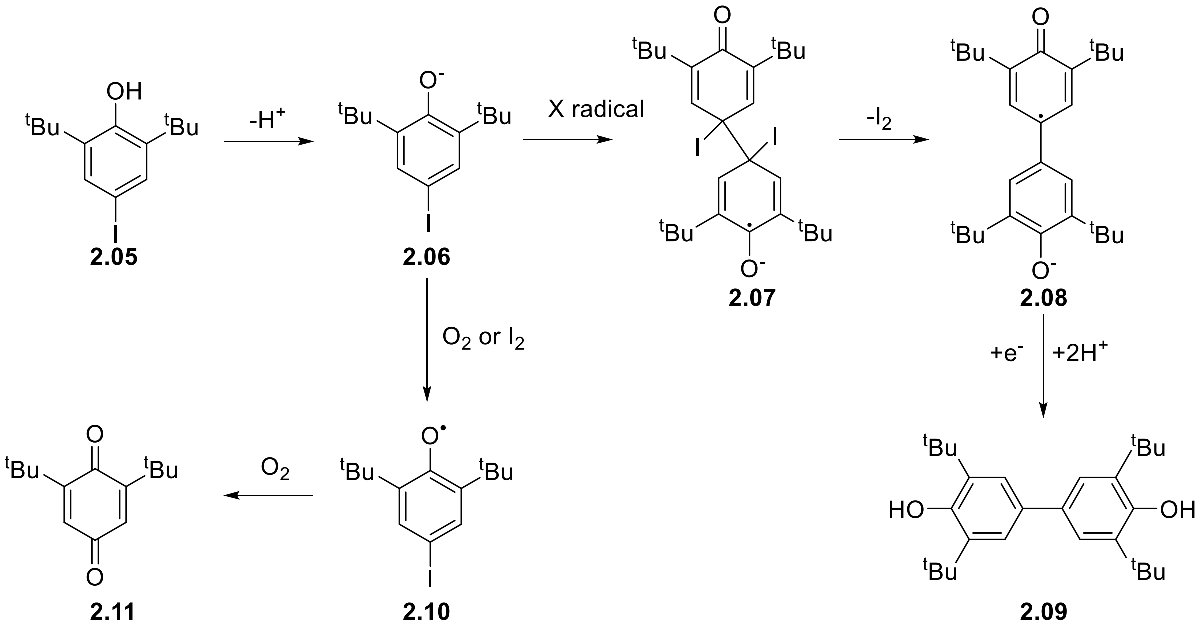
Conversely, aryl iodides contained within these systems have shown to provide Heck yields in excess of 90% with[31] or without the presence of a highly electron withdrawing group ortho to the aryl iodine[32,25], in some examples quantitative yields were achieved with no substitution on this position at all.[33] Also, several methodology papers show varying degrees of yield increase when using aryl iodides over their bromo analogues in multiple variations of the Heck reaction.[34,35] Peshkov *et al.* utilised a 3,4-dimethoxyiodobenzene system (similar to that which the current work has used) in their intramolecular Heck reaction and also showed a marked increase in yield using aryl iodide.[36]

For these reasons, our synthesis initially attempted the formation of the relevant iodophenol **2.04** (**Scheme 13**). However, as its bromo analogue is a known compound, it was feasible that the iodo analogue was synthetically accessible.[37] Three reagent systems were chosen to attempt aromatic iodination as they each provided a different reactive intermediate for the electrophilic aromatic substitution. The iodine/silver trifluoroacetate mixture has been theorised to form *in situ* iodo-trifluoroacetate[38], much like the iodo-acetate formed from the analogous starting material in the Woodward cis-hydroxylation of alkenes[39]. Bovonsombat *et al.* speculated that an NIS/pTSA mixture allowed iodination of the substrate with NIS, while the catalytic pTSA prevents the formation of the phenolate anion.[40] However, Wing-Wah *et al.* claimed their iodine and silver sulfate system formed a reactive iodo-sulfate.[41] So, it would also be feasible to suggest that an *in situ* iodo-toluene-4-sulfonate intermediate could be formed under the Bovonsombat conditions. Finally, ICl is a widely used source of electrophilic iodine.[42]



Scheme 13 - Iodination of the electron rich phenol proved difficult

Unfortunately, the attempted iodination of phenol **2.03** using the 3 different systems all failed to give the target product (**Scheme 13**). The iodine/silver trifluoroacetate and ICl/pyridine systems both gave complex mixtures that could not be purified. The NIS/pTSA method failed to convert any starting material. There are several papers describing dehalogenation methods in halogenophenols that may explain why these reactions have not been successful, assuming that the system allowed the synthesis of the product at all. Reischl *et al.* reported deiodination and dimerisation/trimerisation of 2,6-di-*tert*-butyl-4-iodophenol **2.05** under basic and oxidising conditions, with some conversion to the respective hydroquinone dimer **2.09** (**Scheme 14**). This could account for degradation in the ICl method.[43]



Scheme 14 - Acidic and oxidising conditions are responsiblefor deiodination and dimerisation of aryl iodides

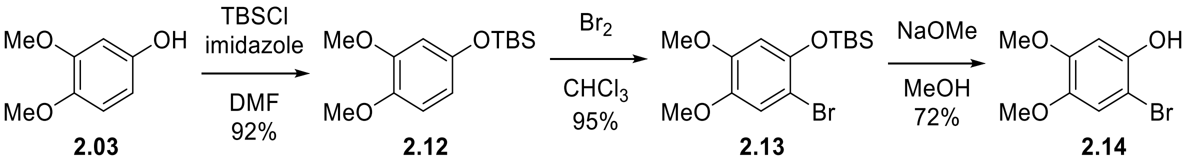
Matasović *et al.* has reported the deiodination of iodophenols, this time by radicals in the presence of ROH.[44] A similar mechanism could be applied, based on the sometimes radical nature of NIS mechanisms combined with the presence of pTSA; which has been used by Kotal *et al.* in combination with DMA as a radical initiator. Other methods of dehalogenation on similar systems will be discussed in the next section.[45]

Providing that the reaction mechanisms themselves are not to blame for the failed iodination attempts (such as those described by Reischl *et al.*), another explanation may be needed. No literature exists for iodination to 2-iodo-4,5-dimethoxyphenol or its 5,6- and 3,6- analogues. 2-Iodo-3,5-dimethoxyphenol has been synthesised by multiple groups, in yields around 50-60% using NIS, ICl and I_2/H_2O_2.[46,47,42] In view of the reported stability all variations of 2-iodo-methoxyphenol and high yielding syntheses, it seems a fair assumption that the added electron density or mesomeric effects of the additional methoxy group have significant adverse effects on the stability of the relevant dimethoxy products or their reaction intermediates.[48,49]

Due to the failure of these three methods it was decided that the bromination of the starting phenol would be attempted instead, accepting that a lower yielding intramolecular Heck reaction later in the synthesis might result. However, unlike the iodo analogue, 2-bromo-4,5-dimethoxyphenol is a known compound.

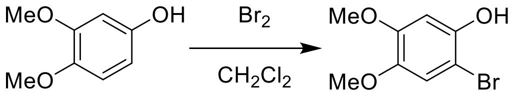
2.1.2 Bromination

Bromination of the starting phenol was most efficiently achieved by Ikawa *et al.* who used TBS protection prior to halogenation (**Scheme 15**).[50]



Scheme 15 – Ikawa's bromination of phenol 2.03 by a protection-bromination-deprotection route

However, as the planned synthetic route already totalled in excess of 13 steps it was decided to attempt a one-step bromination. Initial attempts at the bromination used slow addition of bromine in CH_2Cl_2. The rate of addition proved to be very important to the yield (**Scheme 16**). The optimum addition rate was 0.004 equiv.min^{-1} over 4 h. Decreasing the rate further led to a decrease in overall yield; which may have been down to the stability of the product itself.

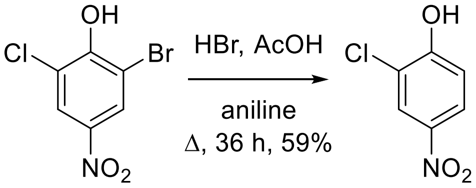


2.03 **2.14**

Total Reaction Time/ min	Rate of Br₂ Addition/ equiv.min^{-1}	Yield/ %
60	0.0183*	19
90	0.0122*	60
240	0.0044**	64
720	0.0015*	44

Scheme 16 - Rate of bromine addition vs yield for bromination from 2.03 to 2.14 (*- 1.1 equiv. total, **-1.05 equiv. total)

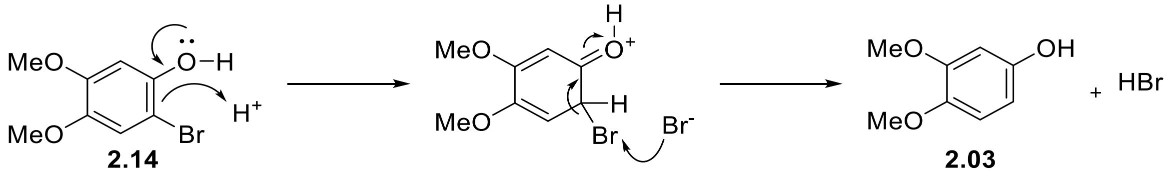
Choi and Chi have reported the use of bromine as a facile protecting group for the synthesis of substituted phenols and anilines, whereby the bromine would block positions ortho- or para- to the mesomerically electron donating -OH or -NH_2 groups.[51] To 'deprotect' the respective 2-bromophenol the mixture was heated under reflux with HBr and an aniline bromine scavenger to force the equilibrium of the reversible bromination/debromination reaction in favour of debromination (**Scheme 17**).



2.15 **2.16**

Scheme 17 - Choi and Chi used bromine a blocking group in phenol substitution, removing it under acidic conditions

With this taken into account, coupled with the apparent instability of electron rich 2-bromophenols, a reasonable hypothesis would be that the point of equilibrium for this reversible process can be more easily pushed in favour of the debromination. The affecting factors here would be the increasing concentration of HBr over the course of the reaction and the increased reaction time given by the slowest rate of bromine addition. The starting phenol **2.03** itself or the brominated phenol **2.14** would theoretically be able to act as bromine scavengers in this case, leading to further by-products and a fairly inefficient reaction (S**cheme 18**). This may be confirmed by the presence of several spots visible in the reaction mixture TLC. This bromine transfer type mechanism has also been described with reactions of 2,6-dibromophenol with quinolines.[52]

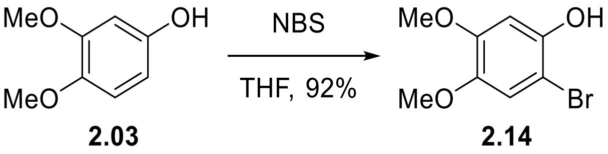


Scheme 18 - Proposed mechanism of acid catalysed debromination of 2.14

A minor source of by-products in the reaction could have been from the in-situ formation of bromochloromethane and dibromomethane from HBr and dichloromethane and the subsequent possible reactions with the starting material or product. However, these reactions are usually performed under basic conditions.[53]

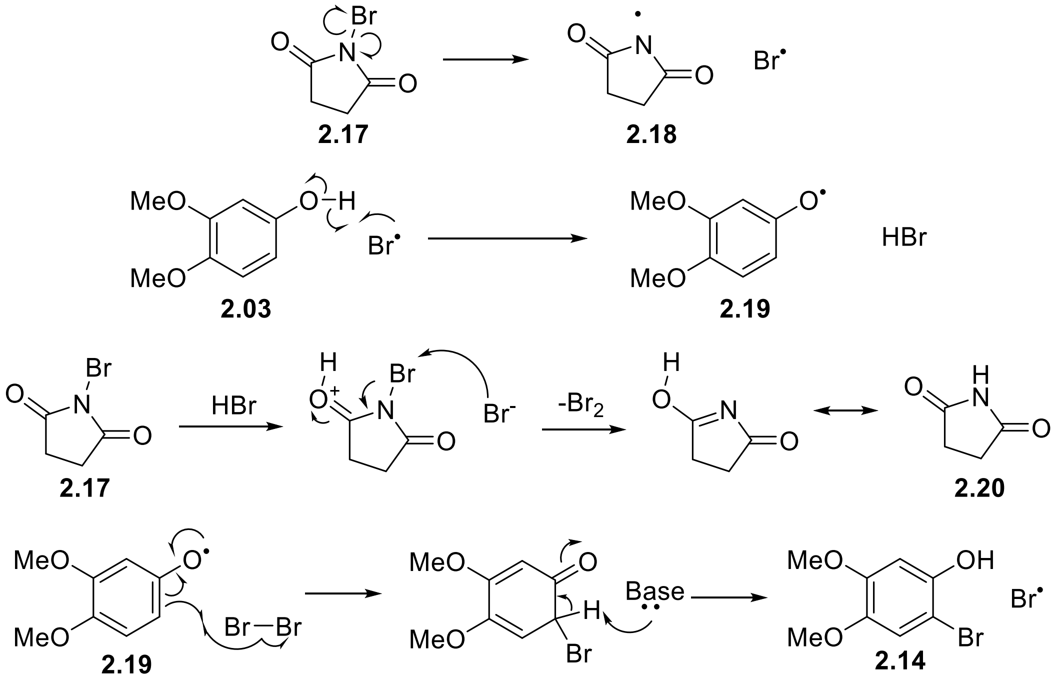
A basic wash of the reaction mixture led to a complete breakdown of the product, likely by the formation of the phenolate anion. Purification of the crude product residue needed to be completed immediately after synthesis or a complete breakdown of the product occurred. The stability of the pure product was also poor, samples had to be stored at -8°C, under nitrogen with minimal exposure to light at all times. Visible degradation of the sample was seen and the slow release of purple and brown residue from the grey solid, indicating the release of diatomic bromine. Jayaramam *et al.* have monitored the UV initiated debromination of 2-bromophenol using multiple spectroscopic techniques.[54] Again, the instability of these highly electron rich dimethoxy-bromophenols could be attributed to severely accelerated degradation in this molecule.

An attempt at the bromination with bromine and acetic acid also proved unsuccessful, also a product was isolated it was confirmed not to be the desired **2.14** by proton NMR.



Scheme 19 - Successful NBS bromination to 2.14

Donohoe *et al.* successfully acheieved the near quantitative bromination of 2,3-dimethoxyphenol with NBS **2.17** during their synthesis of (±)-streptonigrin; which was applied here due to its apparent compatibility with these electron rich phenols.[55] Portion wise addition of NBS to a THF solution of the starting material yielded 92% of the required product with only a 10 minute reaction time (**Scheme 19**). As the only reaction by-product here is succinimide and reaction time is so short, the breakdown mechanisms described above are avoided and the yield is high. Mechanistically, NBS bromination shares some common elements, in that HBr is produced as a by-product however this is quickly converted to Br_2 by reaction with NBS (**Scheme 20**). HBr and Br_2 are kept in low concentrations due to the nature of the mechanism. So, it may be hypothesised that the radical nature of bromination using NBS minimises degradation of the product *in situ* by anionic or cationic pathways. Unfortunately, the stability of the product is still poor, and so does not result from impurities arising from the Br_2 halogenation.

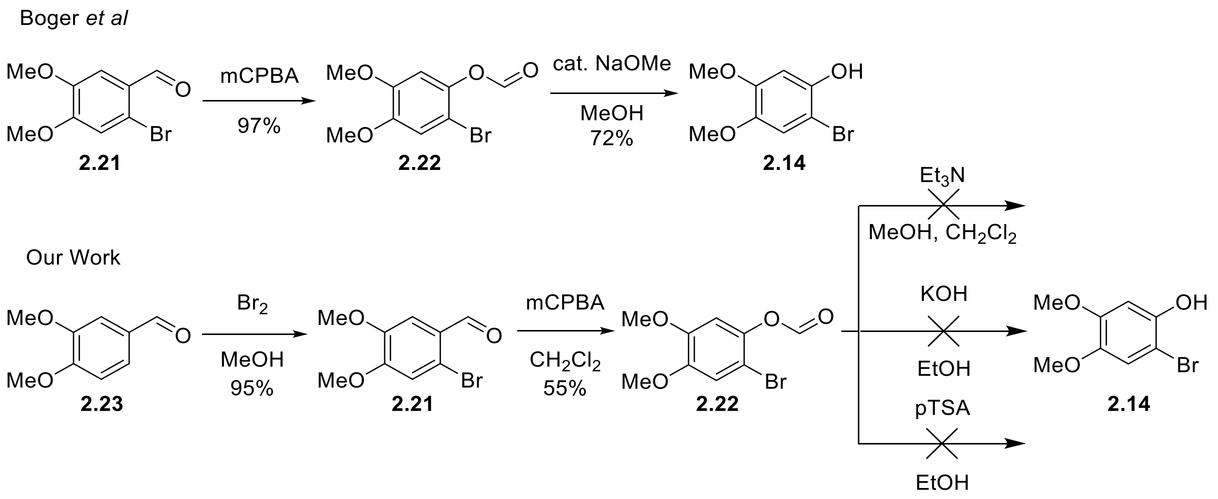


Scheme 20 - Proposed mechanism of NBS bromination to 2.14

2.1.3 Dakin Oxidation Attempts

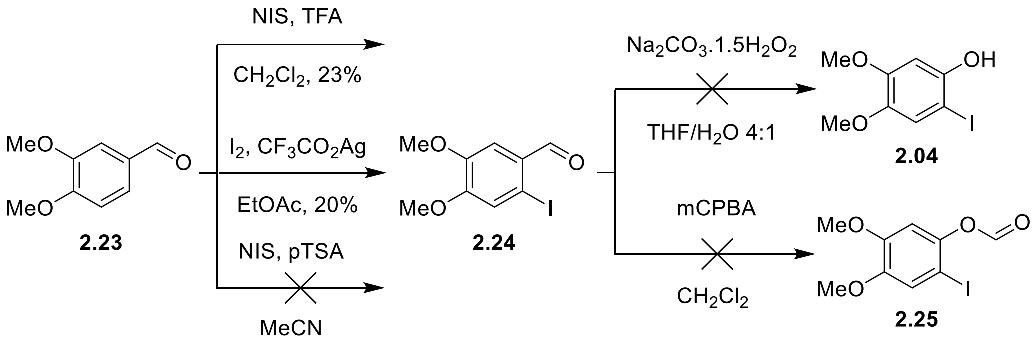
Prior to the implementation of the NBS bromination it was decided to attempt the iodination and bromination to **2.04** and **2.14** respectively by halogenation to their dimethoxybenzaldehyde derivative, followed by oxidation to the formate ester via the Dakin reaction and finally hydrolysis to the target halogenophenol. This was successfully completed for the synthesis of **2.14** by Boger *et al.*, however another intention here was to attempt milder hydrolysis conditions in order to maximise the chances of successful hydrolysis to the iodophenol (**Scheme 21**).[56]

Bromination of 3,4-dimethoxyphenol to **2.21** was achieved in high yield with bromine in methanol, with the subsequent dakin oxidation with mCPBA in dichloromethane yielding 55% of the pure formate, along with a 60% yield of impure product, that was used without further purification (**Scheme 21**).[57] Unfortunately, mild acid and base hydrolysis conditions (cat. pTSA/EtOH and $Et_3N/MeOH/CH_2Cl_2$ respectively) and stronger basic condition (NaOH/EtOH) all failed to successfully give the bromophenol. Both basic conditions failed to convert any starting material and the acidic conditions led to the formation of a complex mixture.



Scheme 21 - Boger Dakin bromination route and our attempted bromination, Dakin and hydrolysis

After these failures it was decided the Boger methoxide hydrolysis would be used if required. Iodination of the 3,4-dimethoxybenzaldehyde to **2.24** was largely unsuccessful, reaching yields of 23% using NIS and TFA and 20% with I_2/AgTFA (**Scheme 22**).[58,59] NIS/pTSA was unsuccessful.[60] However, the Dakin oxidation with mCPBA to **2.25** and a one pot Dakin oxidation/hydrolysis with sodium percarbonate to **2.04** failed.[61] Further evaluation of this route was then halted as it seemed unlikely that a reasonable yield of the iodophenol would be achieved.



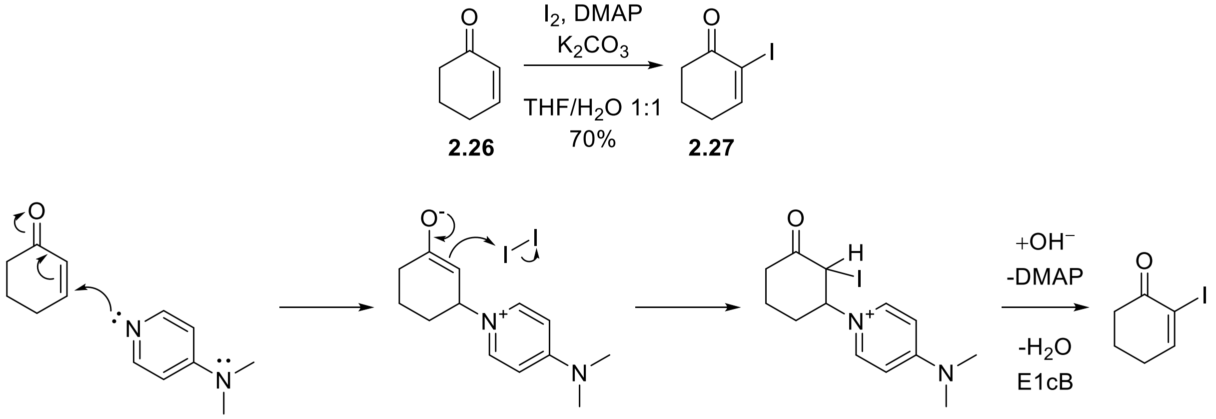
Scheme 22 - Attempted iodination/Dakin oxidation route to 2.04

Over the course of this section we have described the near impossibility of forming the required iodophenol **2.04** using multiple direct iodination conditions, as well as iodination and oxidation of the corresponding benzaldehyde. Although the aryl iodide was preferred, as to pre-empt known problems faced during the intramolecular Heck reaction, a high yielding synthesis of bromophenol **2.14** was developed using NBS.

2.2 Development and Coupling of the Cyclohexenyl Moiety

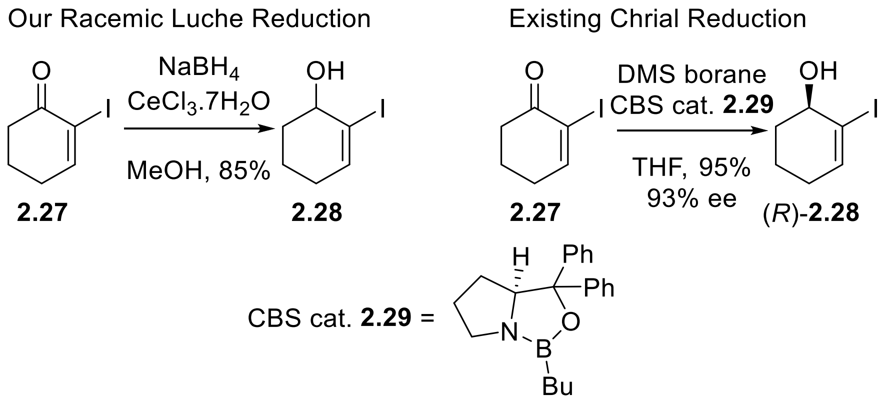
2.2.1 Initial Synthesis of Cyclohexenol 2.28

Although several routes exist for the synthesis of cyclohex-2-enols, the initial chosen route commenced from cyclohex-2-enone due to its low cost. The first step of this branch of the convergent synthesis is the iodination of the 2 position of the cyclohexenone to **2.27** (**Scheme 23**).[62] This transformation was performed using a Baylis-Hillman type reaction; which uses diatomic iodine as the electrophile rather than the traditional aldehyde. DMAP has been used as the nucleophilic base over the more commonly used DABCO and potassium carbonate used for the deprotonation/elimination step. Although the high yields reported were not achieved here, suitable quantities of product were synthesised to continue the synthesis.



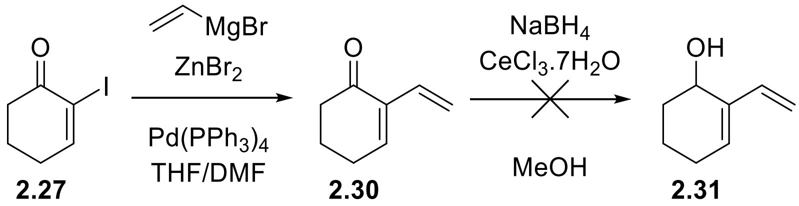
Scheme 23 - Baylis-Hillman iodination of cyclohexenone and mechanism of action

Following activation of the α-position by iodination, two further routes were investigated. The first was the immediate reduction of the ketone to the allylic alcohol in order to continue to the Mitsunobu step. The second was pre-Mitsunobu functionalisation of the α-iodo position to install the β-aminoethyl moiety necessary for the formation of 5-membered D-ring of the maritidine structure. Reduction of ketone **2.27** to allylic alcohol **2.28** was achieved under Luche conditions in an 85% yield (**Scheme 24**).[63] The conditions used for the initial reduction form a racemic mixture of the allylic alcohol. As the stereoselectivity of the intramolecular Heck reaction to the galanthamine scaffold is high and well documented (this will be described in section 2.4.1), it was decided to investigate the synthetic route using racemic material until the oxidative ring opening step was attempted and proved. This also had the advantage of saving the expensive chiral CBS-oxazaborolidine needed for the asymmetric reduction to cyclohexenol (*R*)-**2.24** until necessary.[64]



Scheme 24 - Racemic Luche and asymmetric CBS reduction of 2.27

The pre-Mitsunobu functionalisation route attempted a Negishi cross coupling reaction for the vinylation of iodoketone **2.27**.[65] The vinyl-cyclohexenone **2.30** was successfully synthesised in 85% yield (**Scheme 25**). However, it was found that the product degraded even under storage in the dark at -8°C, forming a complex mixture. Although some of this product was subject to Luche reduction conditions to form **2.31**, this crude mixture degraded within a matter of hours for unknown reasons.



Scheme 25 - Vinylation of ketone 2.30 led to an unexplained breakdown of both the pure ketone.

2.2.2 Mitsunobu Reaction to Aryl Ether 1.81

As the asymmetric synthesis of (+)-maritidine plans to set the stereochemistry of the key quaternary centre by means of a facially selective Heck reaction, it was important the any modification of the chiral hydroxyl carbon of (*R*)-**2.28** or (*S*)-**2.28** proceeds via either complete inversion or retention of stereochemistry. For this reason a Mitsunobu reaction was chosen as this is widely recognised as the best way to form enantiomerically enriched ethers/esters/amines due to complete inversion of stereochemistry on the electrophilic carbon in the vast majority of cases.[66]

Unfortunately, Mitsunobu reactions on cyclohex-2-enol systems are one the few exceptions to rule that the reaction proceeds with complete (or near 100%) inversion. Shull *et al.* carried out an intelligent study on deuterated cyclohexenols that conclusively showed that allylic alcohol systems allow nucleophilic attack on the alkene and concerted elimination of triphenylphosphine oxide, as opposed to the preferred S_N2 type reaction.[67] In the case of diastereomerically enriched 5-monosubstituted cyclohexenols the yield of the required Mitsunobu product ranged between 72-

77%. However, in the case of unsubstituted cyclohexenols the yield of equivalent products totalled 90%, as **2.38** and **2.39** would be identical given the exchange of deuterium with hydrogen (**Fig. 8**, yields adjusted for SM ee). This was considered acceptable to the synthesis given a high enantioselectivity for the asymmetric reduction step.

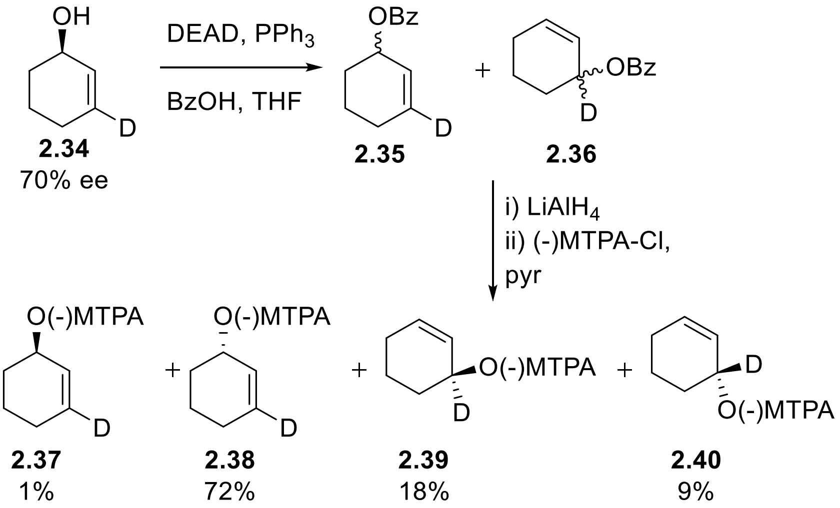
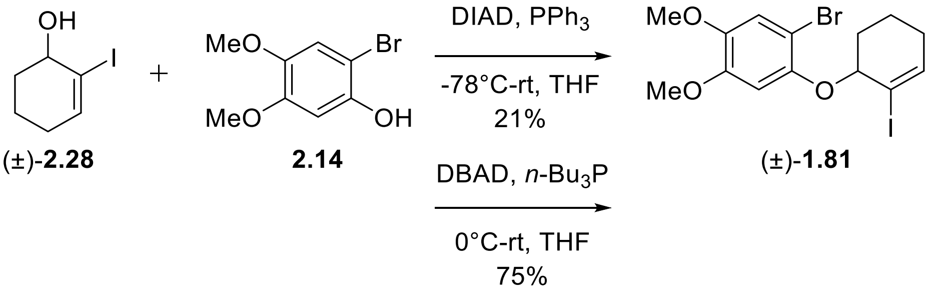


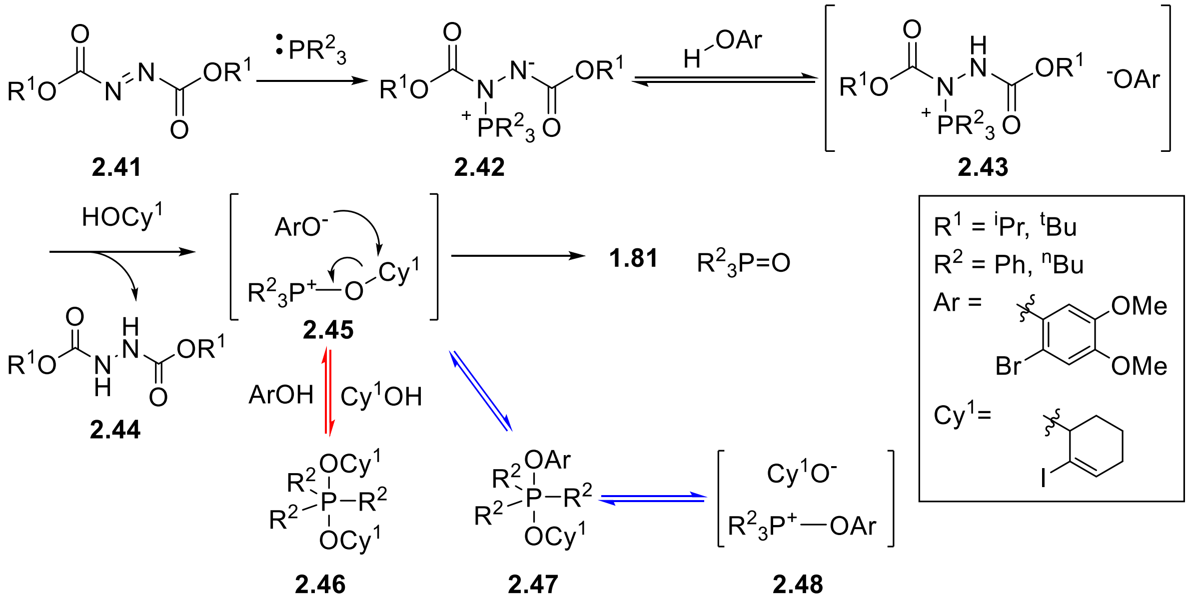
Figure 8 - Shull *et al.* investigated the effect of the possible S_N2 reaction on the yield of Mitsunobu reaction of unbiased cyclohexenols by deuteration of the starting material

The most commonly used Mitsunobu reagents, now that DEAD is largely banned due to its tendency to explode upon heating, are DIAD and triphenylphosphine. These were ineffective as coupling reagents towards ether **1.81** (**Scheme 26**). The reaction was attempted at multiple temperature ranges (-78°C - -20°C, -78°C - -15°C, -78°C – rt, 0°C). The order of addition of the reagents was also altered, as this can have a profound effect on the Mitsunobu reaction depending on the starting materials and reagents. The reactive betaine intermediate **2.42** was prepared *in situ* for some trials (prior to addition of the starting materials), whereas several trials added the azodicarboxylate last to initiate the reaction. Unfortunately, the maximum yield of **1.81** isolated using DIAD/PPh_3 (2 equivalents of each) was 21%, when DIAD was added drop-wise the reaction mixture at -78°C then left to reach room temperature overnight.



Scheme 26 - Switching Mitsunobu reagents greatly increased the yield of aryl ether 1.81

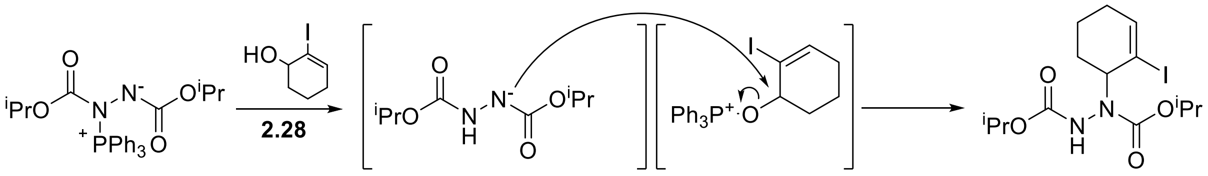
Another coupling reagent pairing, that has gained popularity in recent years, is Di-*tert*-butylazodicarboxylate (DBAD) and tri-*n*-butylphosphine. Experimentally these are useful as DBAD (and its corresponding hydrazine byproduct) breaks down to gaseous by-products upon workup with acid and *n*-Bu$_3$PO (by-product of the reaction) is water soluble.[68] This gives a significant advantage over DIAD and PPh$_3$, both of which produce by-products that can complicate purification. This system was a success, yielding the aryl-cyclohexenyl ether **1.81** in 75% yield. Although the acid workup was not utilised as it was shown to produce a complex mixture, the formation of *n*-Bu$_3$PO proved to greatly simplify separation.



Scheme 27 - The Mitsunobu reaction is a fine balance of reversible and non-reversible reactions. The relative pKa's of the starting materials and intermediates can have a profound effect on the efficency of the reaction, and produce a wide range of unwanted products.

Although an in depth mechanistic study to ascertain why DIAD/PPh$_3$ conditions were ineffective was not practical during this project, previous studies may suggest an explanation (**Scheme 27**). Other than the experimental advantages described above, DBAD and DIAD are almost identical in terms of reactivity, so it is likely that the use of *n*-Bu$_3$P is the contributing factor in the more successful Mitsunobu reaction. Although formation of the zwitterionic betaine intermediate (**2.42**) was originally thought to be a reversible process, work by Crich *et al.* proved this to an irreversible process by adding *n*-Bu$_3$P to a pre-prepared betaine solution of DEAD and PPh$_3$ (and vice versa).[69]

Knowing that the betaine is stable allows us to analyse its reactivity based on the properties of the phosphine used. Without precise rate experiments to compare nucleophilicity of the two phopshines, it is still possible to estimate relative nucleophilicities based on similar measurable properties. Comparison of pKa values of the conjugate acids *n*-Bu$_3$P$^+$H and Ph$_3$P$^+$H in TFA (8.43 and 2.73 respectively) suggests that *n*-Bu$_3$P is superior to PPh$_3$ as a nucleophile, as butyl groups are inductively electron donating and increase electron density on the phosphine.[70,71] Meanwhile, phenyl groups have mesomeric and inductive electron withdrawing effects. Due to the electron donating effect of the *t*-Bu groups, the negative charge on the betaine intermediate **2.42** is localised on the nitrogen; which in turn increases its basicity. Tsonoda *et al.* used the same reasoning in the development of an azodicarbonyl-dipiperidine/tri-*tert*-butylphosphine system for application to coupling of alcohols to nucleophiles with a pKa of more than 11 (this is the pKa at which the product yield starts to lower considerably with conventional Mitsunobu reagents).[72] Although no experimental pKa exists for phenol **2.14**, the pKa values of phenol and *p*-Methoxyphenol (9.95 and 10.20 respectively) can be used to predict that **2.14** will have a pKa between 10 and 11. Due to the lower basicity of the DIAD/PPh_3 betaine and the relatively high pKa of **2.14** the rate of deprotonation to form ion pair **2.49** would be slow. A full mechanistic study performed by Hughes *et al.* found that the overall rate of reaction was based on the basicity of the nucleophilic anion (deprotonates the alcohol in formation of ion pair **2.43**) and its solvation (**Scheme 27**).[73] As the phenolic anion in this case is relatively basic it leaves the previously negligible ion pair **2.48** in the reaction mixture. In cases like this where the alcohol and phenol pKa's are comparable, competition may occur leading to the formation of hydrazine alkylation product **2.50** (**Scheme 28**). This competition and varying rates of reversible reactions are also attributed to the formation of the dialkoxy pentacoordinate phosphoranes shown above.



2.42 **2.49** **2.50**

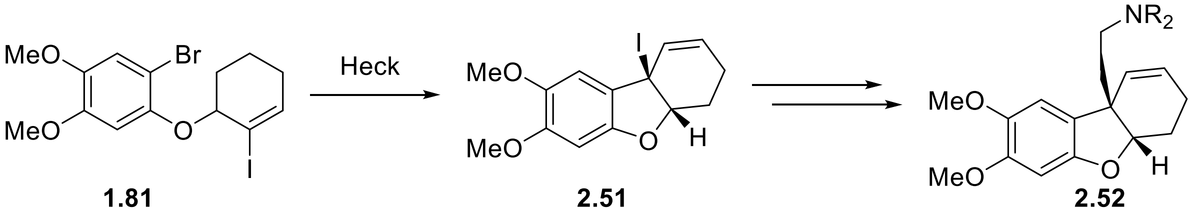
Scheme 28 - Alkylation of the hydrazine anion is a possible side reaction in some Mitsunobu reactions.

A further advantage of using *n*-Bu_3P is that the mild inductive electron releasing effect, coupled with the lack of any mesomeric effects from the butyl groups, localises the positive charge of the betaine onto the phosphorus, facilitating the attack of the alcohol to form the oxophosphonium intermediate **2.45**.

In future work it may be possible to use systems like the azodicarbonyl-dipiperidine/tri-tert-butylphosphine system described earlier to further increase the yield of any Mitsunobu reactions using electron rich phenolic substrates with reduced acidity.

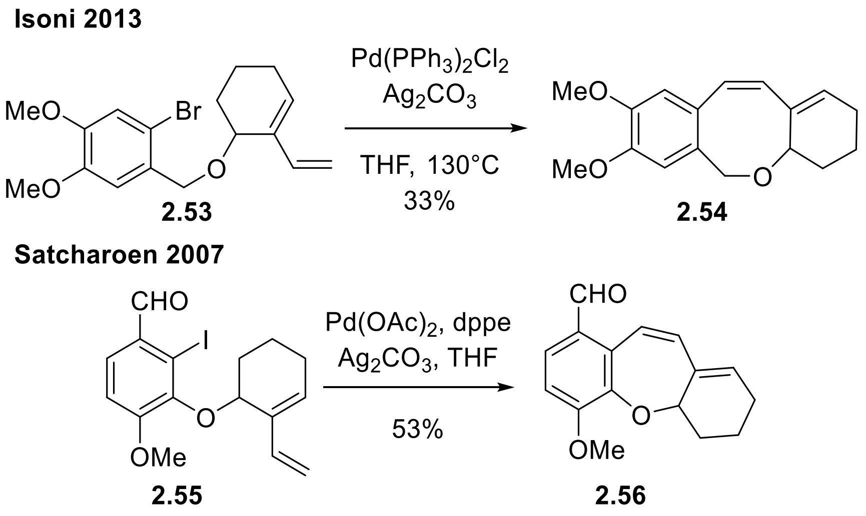
2.3 Introduction of the β-aminoethyl group

As described in section 2.2.1, the presence of the β-aminoethyl group on the cyclohexenyl moiety is required in this synthesis for the formation of the 5-membered D ring of the maritidine. Moreover, it must be installed, in whole or in part, prior to intramolecular Heck reaction to form the tricyclic galanthamine scaffold structure. Leaving the iodocyclohexenyl moiety of **1.81** unmodified may lead to unwanted side reactions spanning from the oxidative insertion of palladium into the vinyl iodide bond. If these reactions do not occur, then it would require palladium coupling to insert the β-aminoethyl group to be performed on an sp^3 hybridised quaternary alkyl iodide **2.51** (**Scheme 29**). Although such sp^3 couplings have been performed, most have been on very electron poor perfluoroalkane systems.[74,75,76] Sterics may be a significant issue here. Also, studies have been completed showing incomplete inversion or retention of stereochemistry at tertiary or quaternary centres.[77] For the sake of an asymmetric synthetic pathway it is sensible to remove or avoid any steps that may reduce diasteromeric purity of a centre at any opportunity.



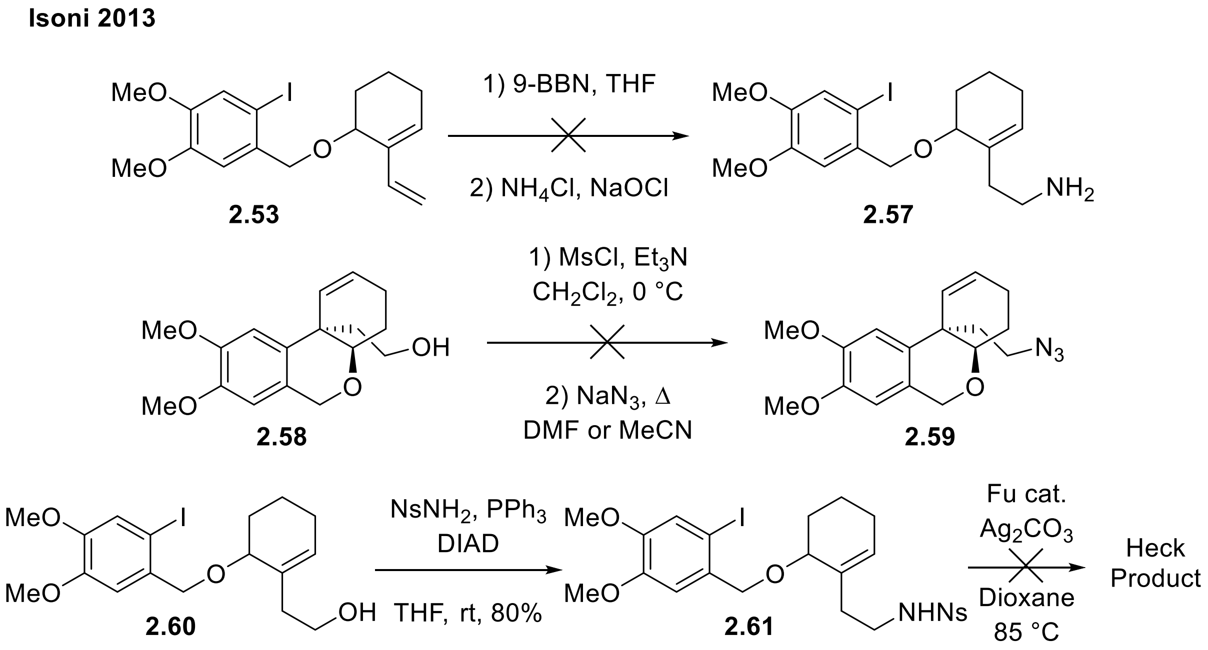
Scheme 29 - Utilisation of the sp^3 hybridised quaternary iodide may lead to severe scrambling of stereochemical information.

Another synthetic consideration is that the substituted group on the cyclohexene cannot be left unmodified. Work within the Brown group by Isoni found that performing the intramolecular Heck reaction with the vinylcyclohexenyl moiety led to endo-cyclisation onto the vinyl group, forming **2.54**, rather than exo-cyclisation onto the cyclohexenyl ring (**Scheme 30**).[26] Earlier work by Satcharoen *et al.* have also showed that the 7-endo cyclisation to **2.56** occurs when attempting to form the tricyclic galanthamine scaffold from phenyl vinylcyclohexenyl ether **2.55**.[25]



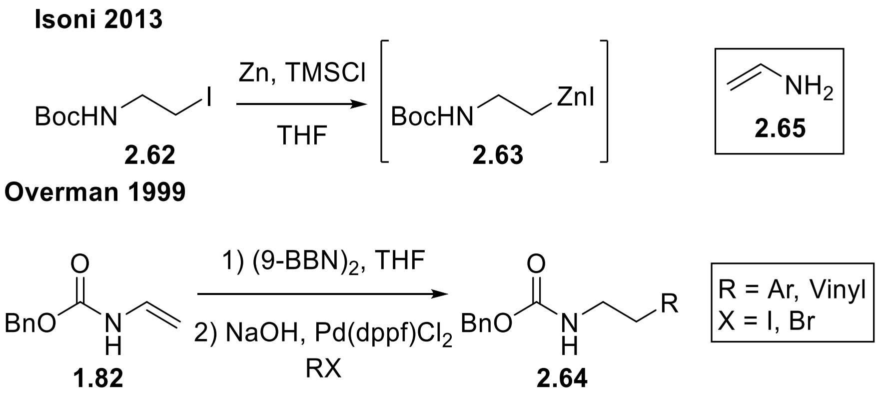
Scheme 30 - Attempting the intramolecular Heck reaction leads to endo-trig cyclisation with the available vinyl group.

Further work by Isoni made attempts at C-N bond formation onto the terminal vinyl position (**Scheme 31**). The initial trial attempted a hydroboration-amination method to **2.57**, using 9-BBN followed by ammonium hydroxide/sodium hypochlorite. A second involved hydroboration/hydroxylation followed by preparation of the mesylate, and then attempted displacement with sodium azide to **2.59**. The final attempt again utilised hydroxylation, followed by Fukuyama-Mitsunobu coupling of the alcohol **2.60** with 2-nitrobenzensulfonamide in the successful formation of the nosyl protected β-aminoethyl group. However, upon treatment of **2.61** with previously optimised Heck conditions, no intramolecular cyclisation occurred. Attempts at the Fukuyama-Mitsunobu on a post-Heck alcohol **2.58** also failed.



Scheme 31 - Instaltion of nitrogen to form a β-aminoethyl group proved difficult for Isoni.

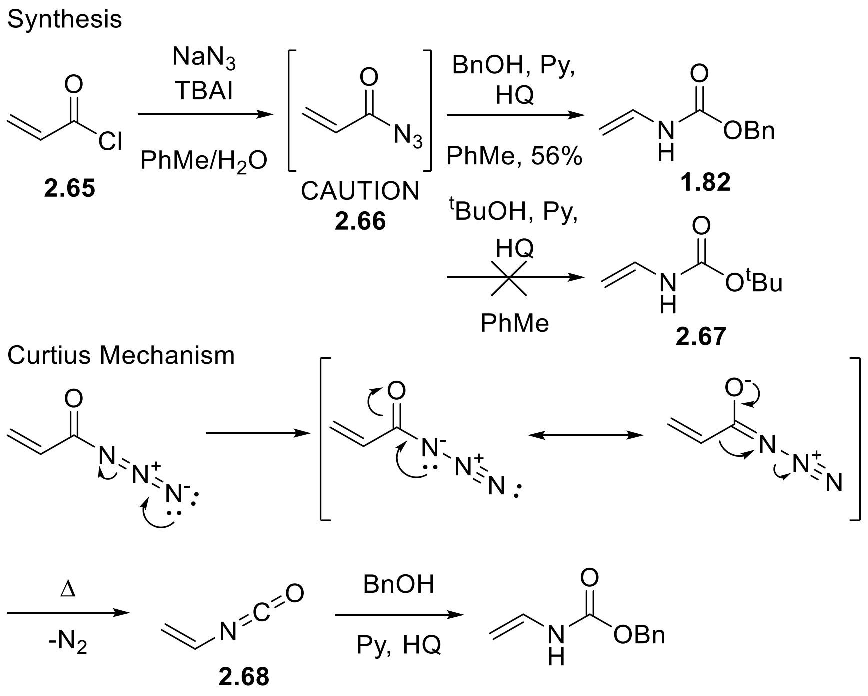
The final attempted syntheses by Isoni to the protected amine aimed to install the entire β-aminoethyl group in one step (**Scheme 32**). One failed trial utilised the Negishi coupling of the *tert*-butyl(2-iodoethyl)carbamate organozinc reagent **2.63**; which was prepared *in situ* using zinc and TMSCl, to the iodocyclohexenyl ether. The second used an innovative a Suzuki coupling of benzyl vinylcarbamate **1.82** developed by Overman *et al.* which also failed.[78] However, due to the method's subsequent use in total synthesis of other alkaloid families, it was decided to pursue this method further.



Scheme 32 - Negishi and Suzuki techniques for installing carbamate protected β-aminoethyl groups.

2.3.1 Classical Benzyl Vinylcarbamate Synthesis

Benzyl vinylcarbamate is not available commercially and so must be synthesised when needed. The synthesis of **1.82** is unusual, as vinylamine **2.65** is unstable and so not available commercially for direct carbamate protection. In a potentially hazardous but innovative synthesis, acryloyl azide **2.66** was synthesised from acryloyl chloride **2.65** and sodium azide (**Scheme 33**).[78] The azide could not be isolated for analysis due to its potentially explosive nature. The azide solution in toluene was then added dropwise to a heated solution of benzyl alcohol, pyridine and hydroquinone, inducing vigorous release of nitrogen and a Curtius rearrangement of the azide to a reactive isocyanate **2.68**. This reactive intermediate was then quenched with the alcohol to form the carbamate. The synthesis of benzyl vinylcarbamate **1.82** proceeded in 56% yield; which was unchanged when using biphasic additive TBAI during the acryloyl azide formation.[79] Although deprotection methods exist for secondary carbamates in the presence of a double bond, it would be preferable to have a Boc group protecting the amine for ease of removal. Unfortunately, attempts to quench the reactive isocyanate with *t*-BuOH to form **2.67** failed, possibly due the increased steric hindrance of the tertiary alcohol.



Due to the potentially hazardous nature of this experiment, it was limited to relatively small scale and repeated numerous times over the course of the project. On some occasions this synthesis, including attempts in flow reactors (see below), failed to reach previous yields and created an unwanted by-product. Upon longer stirring times or slower rate of addition of the acryloyl azide to the benzyl alcohol, the yield of the required product decreased and was replaced by an *N*,*O*-aminal by-product **2.69**. This by-product was found by Ende *et al.* to be an acid catalysed process brought about by impurities from the formation of the azide (**Fig. 9**).[80] Formation of this product was confirmed by proton NMR. To combat this, the group used anhydrous potassium carbonate added to the alcohol mixture to neutralise any present.

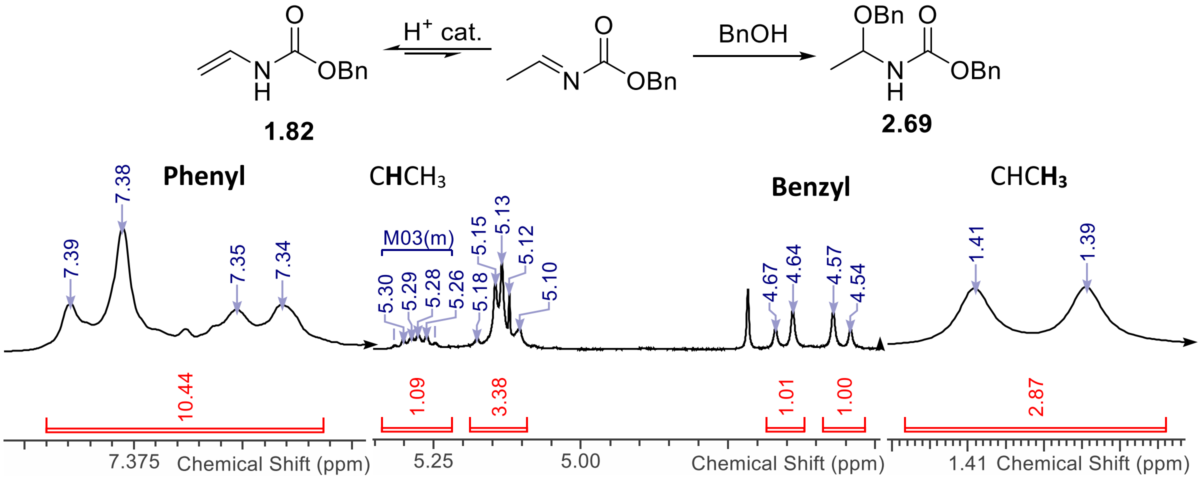


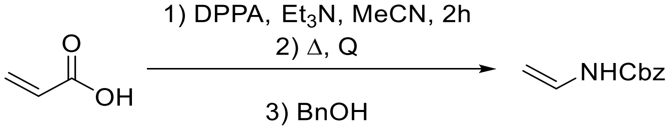
Figure 9 - Significant amounts of unwanted aminal by-product were isolated after long reaction times.

2.3.2 In-Flow Formation of Intermediate Vinyl Isocyanate

Due to potential hazards of the classical batch approach to synthesis of the vinyl carbamate, it was decided that attempts at a flow synthesis would be made. Flow synthesis has many advantages over classical synthesis in situations like this.[81]

- Precise temperature control – This is useful in this case for activation of the Curtius rearrangement, heating plates turning on and off to maintain temperature cause fluctuations in classical synthesis. Temperature gradients within the flask also occur.
- Precise pumping rate control – Unlike using manual syringe or dropping funnel addition in classical synthesis, flow reactors offer precise control of addition rate, allowing the residence time of the mixture in the flow reactor to be set and easily optimised, while also giving uniformity between repeats of the reaction.
- Improved safety – As the reaction is contained within a low diameter and volume coiled tube, the amount of starting material subject to the reaction conditions can be controlled very precisely. Instead of 'scaling up' the reaction to produce more product, the reaction is simply 'scaled out', meaning the total volume of starting solution run through the reactor is increased, keeping the same residence time and concentration(s) optimised for the small scale reaction.
- Other intuitive measures – The flow equipment used in this case was fitted with a back pressure regulator. As the Curtius rearrangement releases nitrogen while being pumped through the system, a back pressure regulator is required to stop the reactive isocyanate being pushed back into the starting material reservoir.

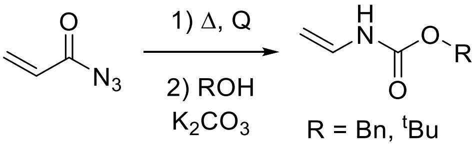
Initial attempts at the flow synthesis of **1.82** made use of pre-existing methods of in-flow Curtius rearrangements devised by Baxendale *et al.* [82,81] His method employed diphenylphosphoryl azide and triethylamine as the azidonation mixture, this time from the carboxylic acid rather than the acyl chloride. As our flow reactor used a heated coil, with no mixing chip, the reaction mixture was made as a pre-stirred solution of all starting materials bar the alcohol (10 mL, 0.1 M starting material). This was then passed through the flow tubing at a small selection of temperatures and retention times/flow rates (Q) (**Fig. 10**). Unfortunately, the first 3 sets of conditions were unsuccessful in producing an acceptable yield of the carbamate. Slower flow rates produced none of the required product and a slight increase in temperature from 120 °C to 130 °C decreased the already poor yield.



Temperature/ °C	Retention Time/ min	Flow Rate/ mLmin^{-1}	Yield/ %
120	20	0.50	8
120	60	0.17	0
130	20	0.50	4

Figure 10 - *In situ* formation of the acyloyl azide in flow proved unsuccessful in synthesising 1.82.

Rather than spend additional time investigating whether the azidonation, Curtius rearrangement or alcohol quenching were to blame for the poor yield, it was decided to use the known method of acryloyl azide synthesis. A stock solution of intermediate **2.66** from acryloyl chloride and sodium azide was prepared as described in the previous section, allowing us to purely alter conditions for the Curtius rearrangement and quenching (**Fig. 11**). Initial efforts with the azide solution proved somewhat successful giving 50% yield of the product **1.82**, compared to 8% for the same retention time and flow rate using the DPPA method. This proved to be the optimal conditions for the Curtius rearrangement, as just under 50% yield of the aminal by-product **2.69** was also isolated from the reaction mixture, indicating the quenching of the isocyanate was still the issue. This required the introduction of potassium carbonate to the stirred alcohol to supress tautomerisation of the benzyl-*N*-vinyl carbamate. Following the reaction, it was found that the solution of azide/isocyanate in the flow reactor had blocked the tubing, requiring the system to be cleaned. For the following attempt the concentration was halved to avoid this happening, however this failed and the reactor became blocked far before completion of the reaction. This problem occurred twice more, even at lower concentrations during attempts at making Boc amine **2.67**.



Concentration/ M	Temperature/ °C	Retention Time/ min	Flow Rate/ mLmin^{-1}	Alcohol	Yield/ %
0.22	120	20	0.5	BnOH	50*
0.11	120	20	0.5	BnOH	0**
0.22	120	20	0.5	^{t}BuOH	0**
0.06	120	20	0.5	^{t}BuOH	0**

Figure 11 - Using the toluene solution of the azide created issues with blockage of the reactor at multiple concentrations. *Near 50% yield aminal **Reactor blocked by azide solution.

Due to this blockage problem, time constraints, and issues with success of the Suzuki step (which will be described in the following section) it was decided to abandon attempts at the flow synthesis of **1.82** and **2.67**. However, the original attempt did give a promising yield, so it is hoped that the work can be revisited at some point and modified to avoid the blockage problem. One way of doing this would be the use of more polar solvents such as DMF, which is suitable for flow synthesis, boils at the appropriate range and is the reported solvent in high yield azidonation of acyl chlorides.[83]

2.3.3 Suzuki-Miyaura Coupling of Vinyl Benzylcarbamate

Following the synthesis of the required carbamate, the next step was a one-pot hydroboration and Suzuki coupling. Overman and co-workers used Pd(dppf)Cl_2 as the catalyst for the reaction, activating the organoborane with aqueous hydroxide.[78] The original investigation into this reaction had a reasonable selection of starting materials, from iodo-cyclohexenols and a cyclohexenyl triflate to bromopyridine and iodo/bromobenzenes. This range was useful for some evaluation prior to the reaction, as both 2-iodocyclohex-2-enyl and a 3,4-dimethoxybromobenzene groups are present in Mitsunobu product **1.81**. Overman and co-workers discovered that the coupling of the aminoethyl group to TIPS-cyclohexenol **2.70** proceeded far more rapidly, using less catalyst and with a higher yield, than 3,4-dimethoxybenzene **2.71** (**Fig.12)**. This significant difference in reactivity should mean that the Suzuki coupling with aryl cyclohexenyl iodide **1.81** is selective for the iodoalkene.

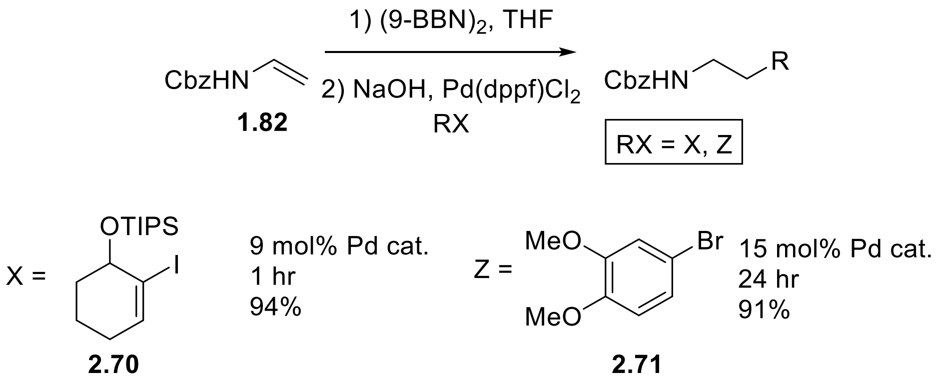
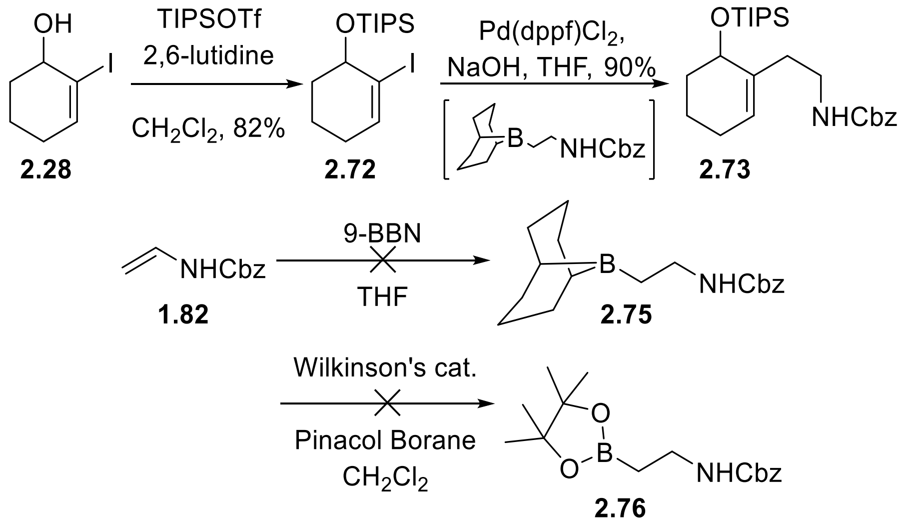


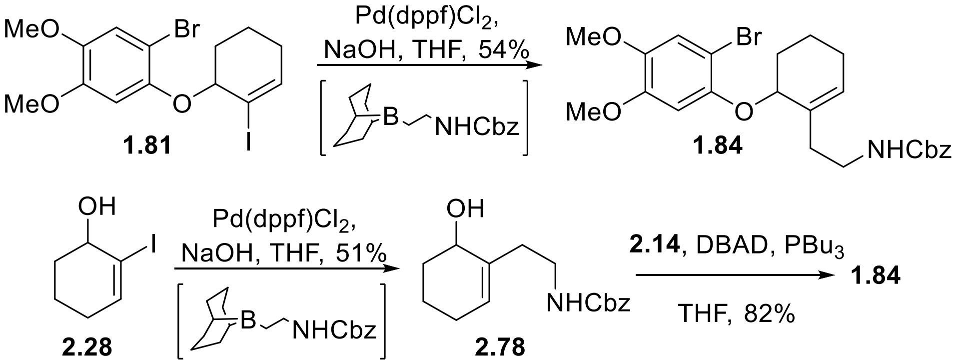
Figure 12 - The Suzuki coupling of carbamate 1.82 is more selective for vinyl iodides than aryl bromides.

For our investigation into the selective cross-coupling TIPS protection of existing cyclohexenol **2.28** was achieved using triisopropylsilyl triflate, with lutidine as the base (**Scheme 33**). Several initial attempts at the Suzuki reaction on both the TIPS protected model compound **2.72** and Mitsunobu compound **1.81** failed for unknown reasons, similar to Isoni's attempts on his pre-maritidine substrates. To investigate we attempted to isolate the hydroboration product of **1.82** and 9-BBN in the hope of identifying which step was causing failure of the overall process (**Scheme 33**). These were also unsuccessful, as were attempts at formation of the pinacol borane **2.75**.[84] This led us to believe that the organoboranes of **1.82** were unstable outside of the reaction mixture or upon contact with silica. The initial coupling trials used a solution of 9-BBN in THF (0.5 M, Sigma). However solid 9-BBN dimer was then used and proved to be effective on the model compound **2.72**, initially in low yield but this was increased to 90%.



Scheme 33 - Suzuki coupling onto the TIPS cyclohexenol was completed using solid 9-BBN dimer. Attempts to isolate any hydroboration of 1.82 were unsuccessful.

Due to initial failures with the Suzuki coupling it was decided change direction and return to the enyne RCM route used in the Brown galanthamine synthesis; this will be described in the next section. Although the enyne route was attempted at this point, further work was completed on the Suzuki reaction due to other literature describing its application to other natural product syntheses.[85] The optimised Suzuki conditions were applied to Mitsunobu product **1.81**, however the yield was considerably lower (54%), possibly due to competition with the aryl bromide or dehalogenation in the presence of palladium and water once the borane had been consumed (**Scheme 34**).

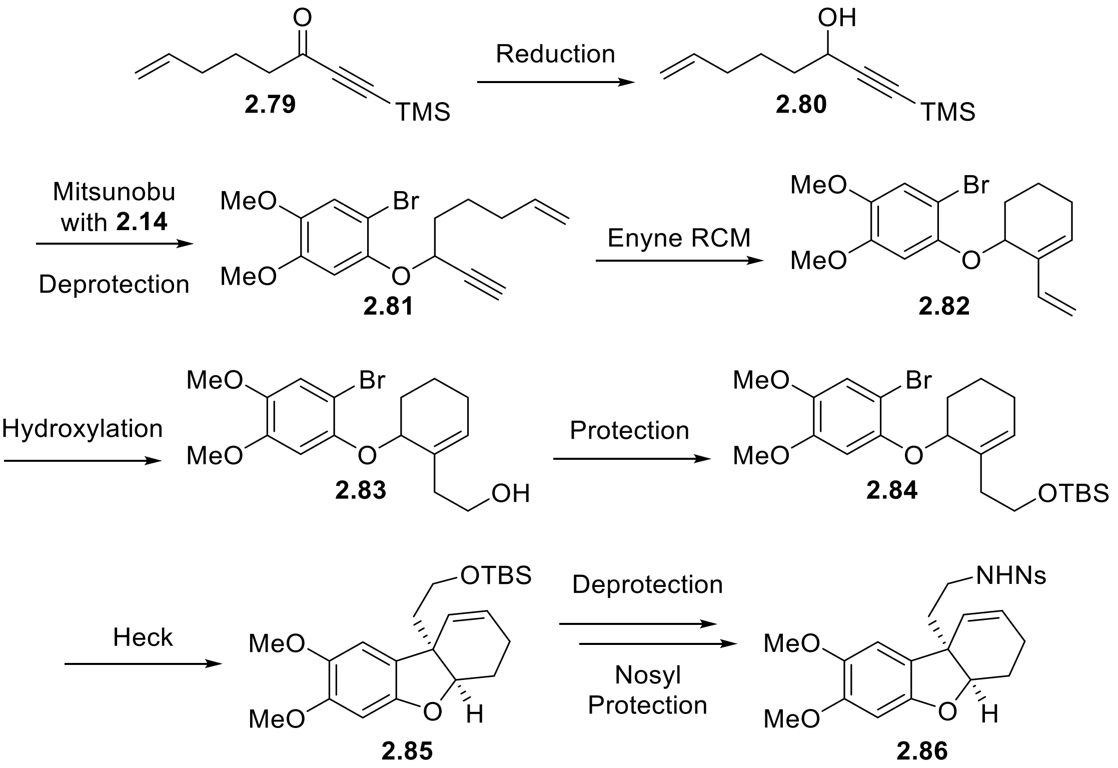


Scheme 34 - Changing the order of the Suzuki and Mitsunobu steps facilitated purification of the products by column chromatography.

It was considered that performing the Suzuki on the cyclohexenol **2.28** would be advantageous for 3 reasons. Firstly, this would create a starting material that could be coupled with other halogenophenols for the synthesis of natural products and possible routes. Secondly, it would eliminate the Suzuki competition between the aryl bromide and vinyl iodide. Finally, it would eliminate the effect of steric issues on the yield, which is a possible reason for the low yield in the formation of **1.84** in comparison to the TIPS protected model compound. Although Suzuki coupling to form **2.78** only proceeded in a 51% yield, the column chromatography purification proved to be easier, leading to cleaner samples being obtained. The subsequent Mitsunobu reaction of **2.78** with bromophenol **2.14** also proceeded more efficiently and cleanly, leading to an improved yield of carbamate protected aryl ether **1.84** of 82%. Although the overall improvement in yield of **1.84** over the two steps was only 1%, this route facilitated the purification by column chromatography. Optimisation of these two steps could also lead to significant improvement.

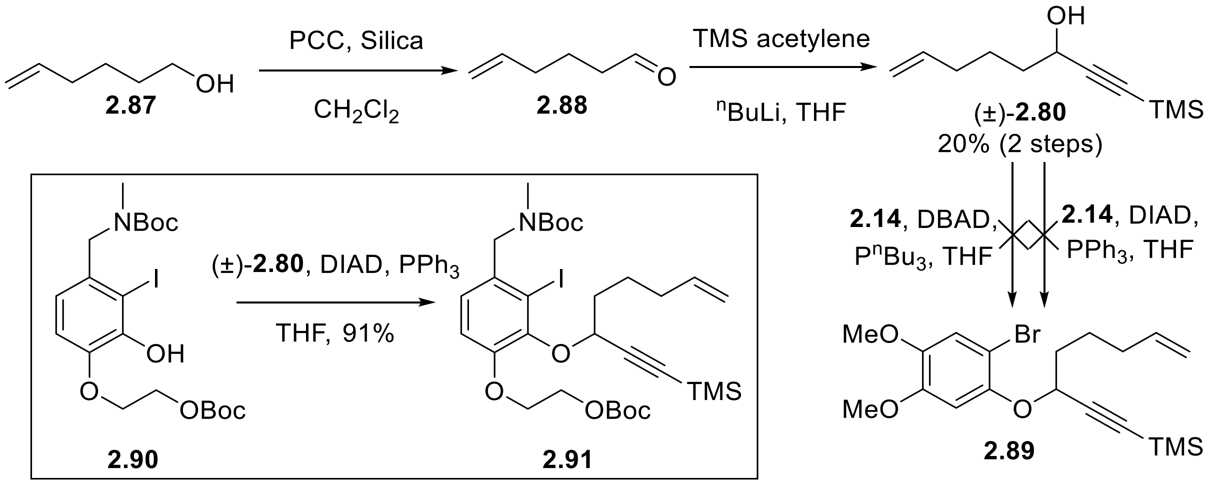
2.3.4 Enyne Ring Closing Metathesis Route

Due to the initial failures of the Suzuki coupling reaction and the tendency of the Negishi coupling product **2.30** to decompose, it was decided to investigate an enyne RCM route to form the cyclohexenyl moiety in parallel (**Scheme 35**). This approach has been used previously within the Brown group.[25] This route has some advantages, in that it does not require coupling of the vinyl group, as this is formed during the metathesis reaction. One disadvantage however, and a reason why this route was not initially used, is that the nitrogen must be inserted at the terminal vinyl position. As shown in section 2.3 Isoni struggled to effectively insert this nitrogen unless via a hydroxylation of the vinyl group and subsequent Mitsunobu coupling of the nosyl sulfonamide. This would seem ideal however he found that presence of the nosyl protection group caused complete failure of the intramolecular Heck reaction. To avoid this, it was decided that protection of the alcohol **2.83** would be performed prior to the Heck reaction, followed by its deprotection and coupling with the protected amine.



Scheme 35 - Planned forward synthesis for the enyne RCM route.

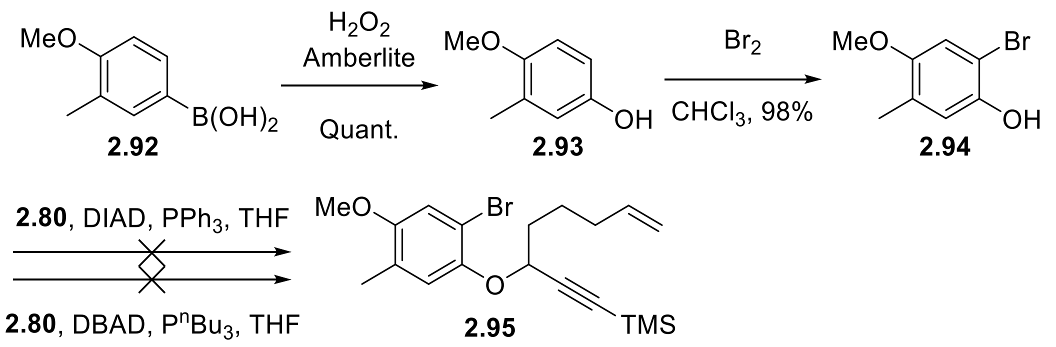
The enyne metathesis approach required synthesis of a propargylic alcohol **2.80** containing both the alkene and alkyne groups for the Grubbs catalysed enyne RCM. This would then be coupled to bromophenol **2.14** under Mitsunobu conditions before deprotection and metathesis to the vinyl cyclohexanone **2.82**. Initial attempts at the synthesis of the alcohol involved oxidation of hex-5-enol **2.87** to its respective aldehyde followed by formation of the propargyl moiety with TMS acetylene and n-butyl lithium (**Scheme 36**).



Scheme 36 - Propargyllic alcohol 2.80 failed to undergo Mitsunobu coupling with the required phenol, but succeeded with an existing galanthamine precursor.

Oxidation to form aldehyde **2.88** using Swern conditions[86] and a PIDA/TEMPO[87] system were unsuccessful due to poor quality reagents and volatility/purification issues respectively. The final oxidation used pyridinium chlorochromate[88], adding silica to improve the ease of workup, giving the product which was used without purification in the propargylation step. This method gave propargyl alcohol **(±)-2.80** in a low yield of 20% over the 2 steps. It was then decided to form the propargyl alcohol via a different route due to the volatility issues with aldehyde **2.88** and to ultimately allow enantiocontrolled synthesis of the propargyllic alcohol **2.80**.[89] Although not important for the 'proof of concept' run of the synthesis, an asymmetric formation of **2.80** would be required for the total synthesis. Another issue at this stage was that Mitsunobu coupling of **2.80** with bromophenol **2.14** failed using both DBAD/P^nBu_3 and DIAD/PPh_3 conditions. A test coupling of propargyl alcohol **2.80** with a sample phenol **2.90** from a previous project within the group showed that bromophenol **2.14** was the problem, as formation of **2.91** proceeded in a high yield of 91%.

At this stage it was decided to alter the phenol to include a less electron donating group instead of the 5-methoxy group; whilst keeping the necessary 4-methoxy group present. It was hoped that the introduction of a less electron donating group would lower the pKa of the phenol and allow the Mitsunobu coupling to proceed. It was decided to use a methyl group at the 5-position instead, this group could then be oxidised at a later stage in the synthesis to access the required substituent.[90]

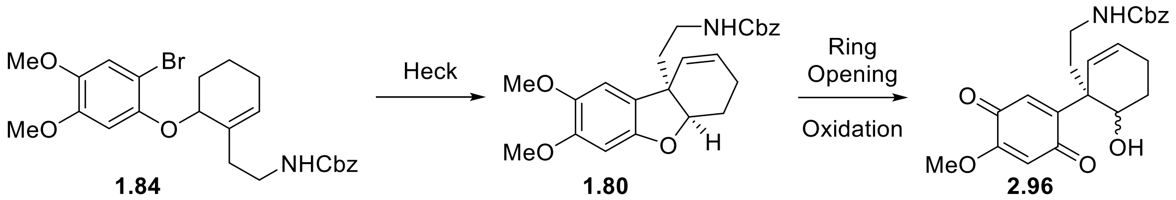


Scheme 37 - Making the phenol ring less electron rich failed to solve the issue of Mitsunobu coupling with the propargylic alcohol.

Synthesis of bromophenol **2.94** was achieved in a near quantitative 2 step synthesis from commercially available 3-methyl-4-methoxyphenyl boronic acid **2.92** (**Scheme 37**).[91] The boronic acid **2.92** was converted to the phenol with peroxide and amberlite proton exchange resin, followed by bromination of **2.93** with Br_2.[92] However, Mitsunobu coupling of **2.94** with propargyl alcohol (±)-**2.80** again failed using both DIAD/PPh_3 (reflux and 45°C) and DBAD/P^nBu_3. Fortunately, at this time the successful Suzuki coupling described in the previous section had been achieved.

2.4 Creation and manipulation of the galanthamine type scaffold

The following section describes construction of a tricyclic galanthamine scaffold, including the formation of the chiral carbon that is present in many types of alkaloid within the amaryllidaceae family, be it a quaternary centre (maritidine **1.01**, galanthamine **1.02** and tazettine **1.07**) or a tertiary one (lycorine **1.03** or montanine **1.04**).



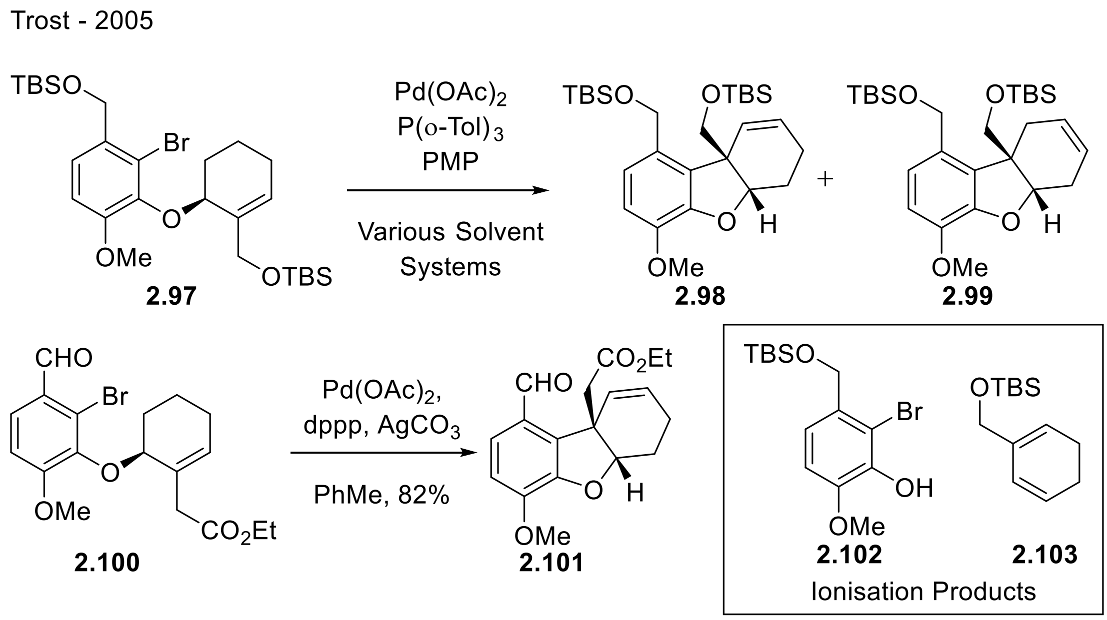
Scheme 38 - Intramolecular Heck attempts will be followed by an investigation into the ring opening oxidation step.

As explained previously, the formation of the quaternary centre in a tested synthetic route, followed by ring opening of the furan ring by breaking of a C-O bond rather a C-C bond is as important a goal as the total synthesis itself. Accomplishing this may allow access to the many types of alkaloids from the amaryllidaceae family. Our attempts at the key ring opening will then be described, along with other modifications to the galanthamine scaffold product **1.80** (**Scheme 38**).

2.4.1 Intramolecular Heck Cyclisation

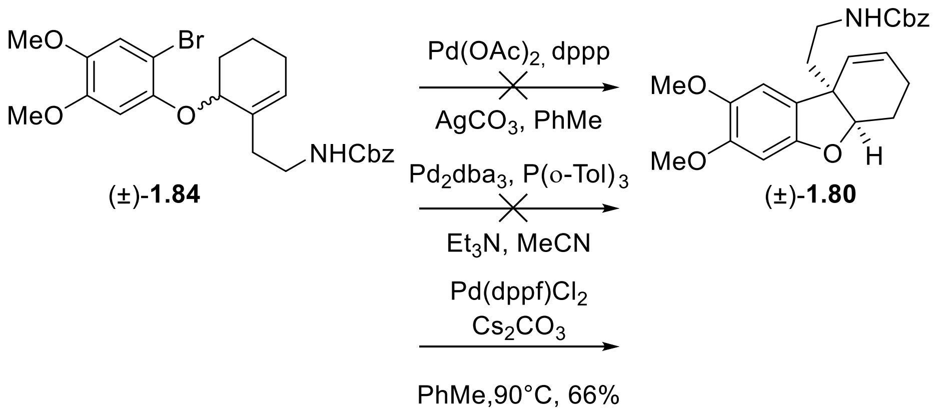
As explained in the rationale in section 2.1, the intramolecular Heck cyclisation to form the galanthamine type tricyclic structure required for this synthesis is temperamental and problematic.

However, these complications do not just stem from differences in reactivity of the aryl halides or the electronic effects of the substituents ortho to the halogen.[93] An in depth study by Trost and co-workers highlighted two main issues with the formation of this system. Firstly, it was shown that certain ligands employed in the reaction caused isomerisation of the cyclohexenyl olefin past the initial β-hydride elimination step (**Scheme 39**).[94]



Scheme 39 - Trost and co-workers found that bidentate ligands gave the highest yield and lowest amount of ionisation and isomerisation during the intramolecular Heck reaction.

They found that monodentate ligands such as P(o-Tol)$_3$ and PPh$_3$ lead to formation of the unwanted isomer **2.99** in increased amounts, whereas the use of any bidentate ligands greatly reduced the proportion of the unwanted isomer. Furthermore, the investigation found that 'classical' Jeffrey type Heck conditions employing no ligands, an inorganic base and tetrabutylammonium salts (phase transfer additive) promoted an 'ionisation' mechanistic pathway which cleaved the aryl-cyclohexenyl ether to from the component phenol **2.102** and the dehydrated cyclohexadiene **2.103**. It was found that use of relatively unhindered organic bases like PMP exacerbated the ionisation. Use of a proton sponge (1,8-bis(dimethylamino)naphthalene) decreased the extent of the ionisation. The final system used by Trost and co-workers used Pd(OAc)$_2$/dppp/AgCO$_3$ in toluene to minimise the unwanted side reactions and achieved a high 82% yield on their required substrate **2.101**.



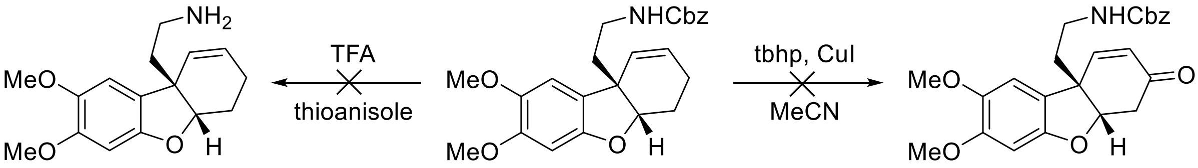
Scheme 40 - The intramolcular Heck reaction was completed using a caesium base and bidentate ferrocenylphosphine ligand (dppf).

Following on from their work, we implimented their optimised conditions to our intramolecular Heck substrate. However, the Trost conditions failed to convert any of the starting ether **1.84** to tricyclic scaffold **1.80**, as did a Pd_2dba_3/P(o-Tol)$_3$/Et_3N in MeCN system (**Scheme 40**). Fortunately, the same palladium catalyst employed in the Suzuki coupling stage was also successful in the Heck cyclisation to **1.80** when combined with caesium carbonate. The required product (±)-**1.80** was isolated as an equal mixture of 2 enantiomers in a 66% yield. The difference in electronic properties of the more electron rich phosphinoferrocene ligand compared to P(o-Tol)$_3$ is a possibility for the success of the reaction over the Trost condtions. The difference in bite angle of the ligand (dppp = 91°, dppf = 96°) could also be a factor.[95]

Although the exact reasons are not clear, numerous studies using Cs_2CO_3 as a base in palladium catalysed cross coupling reactions have shown improved yield compared to the more common potassium or silver salts.[96,97,98] This may be due to increased basicity or polarizability; which leads to increased solubility in organic solvents. Although the isolated yield of 66% was acceptable given the use of the unactivated aryl bromide substrate **1.84**, the reaction was found to be poorly reproducable. Despite extensive drying of the caesium carbonate, extended degassing of the reaction solution with nitrogen and use of higher purity starting material (owing to the change in order of the Suzuki and Mitsunobu reactions described in section 2.3.3) the reaction sometimes failed to reach the 66% yield achieved. In some cases, no conversion of the starting material was observed at all. At this stage however, we have achieved a concise synthetic route to the galanthamine type scaffold, which should be suitable for application to various analogues of the phenolic and cyclohexenyl starting materials to create libraries of galanthamine analogues and hopefully allow access to maritidine and new analogues within the amaryllidaceae family.

2.4.2 Secondary Manipulations of the Tricyclic Scaffold

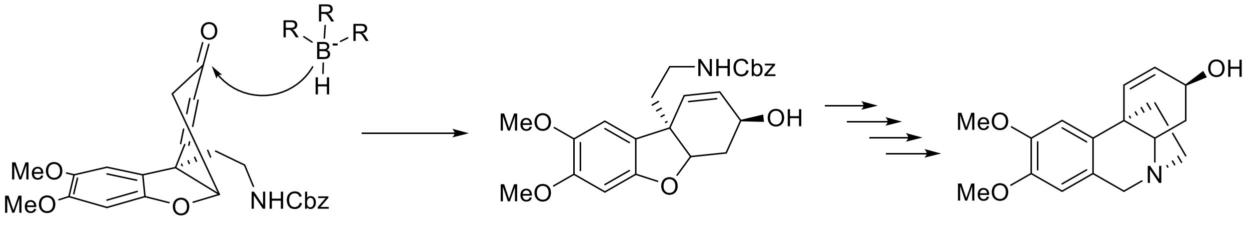
As the tricyclic scaffold **1.80** was free of any obviously chemically labile groups, bar the disubstituted double bond, this opportunity was used to attempt 2 transformations that were required later in the synthesis. Firstly, an attempt to cleave the benzyl carbamate protecting group was made. Typically, hydrogenolysis would be performed to cleave benzyl carbamates, however, these conditions would also reduce the olefin. This would be unacceptable as the double bond is not only integral to the structure but extremely difficult to selectively reintroduce into the cyclohexane ring using current methods. One method that is used in these situations was pioneered by Kiso *et al.* and employs the use of thioanisole as a 'push-pull' catalyst when combined with TFA to greatly increase its deprotecting power.[99] Although these conditions we're successful in consuming the starting material **1.80**, a complex mixture was isolated that showed no signs of the target amine **2.104** (**Scheme 41**). It is possible that the acid/thioether mixture would have opened the furan ring within the molecule leading to unwanted intramolecular reactions with the amine.



2.104 (±)-**1.80** **2.105**

Scheme 41 - Deprotection of the carbamate and allylic oxidation of the cyclohexenyl ring were both unsuccessful.

The second reaction attempted was the allylic oxidation of the cyclohexenyl ring to introduce oxygen functionality present in the final maritidine structure. It is known that reduction of the allylic ketone on the equivalent positions of the galanthamine type structure and crinine type structures have different stereoselectivity (**Scheme 42**)(see section 1.5), with reduction at the galanthamine stage theoretically giving the required epimer at the hydroxyl carbon after conversion to the maritidine structure. For this reason, it seemed advantageous to attempt the allylic oxidation step and reduction to the alcohol prior to the attempted ring opening step, rather than perform the reduction after the ring opening followed by inversion of the centre. One highly tried and tested method of allylic oxidation from the CH_2 to C=O level is using a mixture of copper^{+1} salts and tert-butylhydroperoxide.[100] This proceeds via a single electron transfer mechanism oxidising copper^{+1} to copper^{+2}, forming a tert-butoxy radical that abstracts a hydrogen atom from the allylic position. In our case tbhp was combined with CuI, however, no reaction was observed (**Scheme 41**).

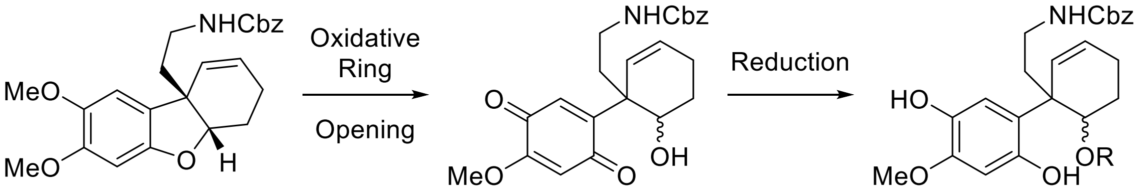


1.80 **1.83** (+)-**1.01**

Scheme 42 - The galanthamine has the opposite selectivity for reduction of the allylic ketone than crinine type structures, so should give the correct hydroxyl epimer for the final (+)-maritidine structure.

2.4.3 Ring Opening Oxidation of the Methoxy-Benzofuran Structure

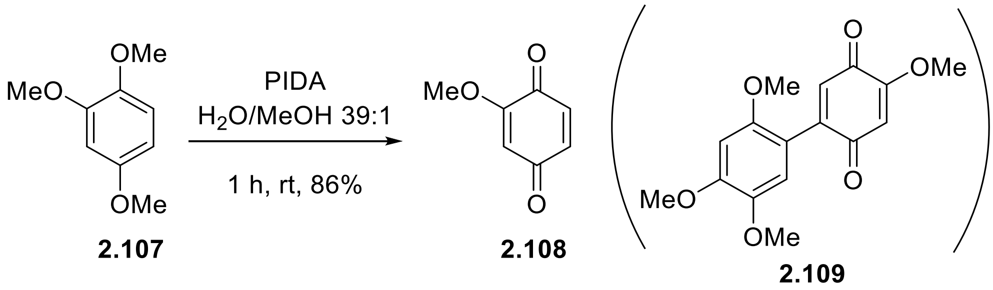
The ring opening oxidation of the tricylic scaffold is the key step along this synthetic route. Achieving this and the following reduction/rearomatisation will give acces to the full tetracyclic ring system of maritidine (**Scheme 43**). Maritidine itself provides the structural requirements necessary for this transformation in the form or the para-di-substitution of the aromatic ring.



1.80 **2.96** **2.106**

Scheme 43 - Overview of planned ring opening oxidation step and subsequent reduction.

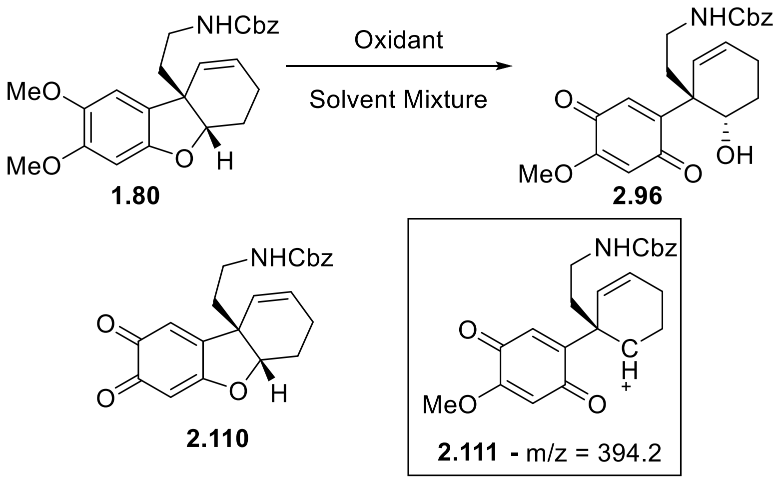
Numerous methods to perform oxidation of *p*-alkoxyphenols exist, for example using CAN[101], HNO_3[102], argentic oxide[103], CoF_3[104] and NBS-H_2SO_4[105]. However, for the purposes of natural product synthesis these methods can be harsh and produce undesirable metal waste. In the case of our starting material the use of strong acid may cause unwanted side reactions with regards to the protected amine and the benzofuran ring as suggested by the failure of the carbamate deprotection step. NBS is also known to react with double bonds and allylic positions. Work by Tohma *et al.* has made use of low toxicity, readily available and easily synthesised hypervalent iodine reagents to perform aromatic oxidations under mild conditions[106]. More recent advances by Dohi *et al.* introduced an oxo-bridged {$[(PhI(OCOCF_3)]_2O$} reagent.[107] It was hoped that the conditions used to oxidise 1,2,4-trimethoxy benzene (**Scheme 44**) will transfer to the analogous trialkoxy moiety of the tricyclic scaffold **1.80**.



Scheme 44 - Tohma oxidation of 1,4-dialkoxybenzenes to their respective para-quinone.

The Tohma group made use of the hypervalent iodine reagents PIDA ((Diacetoxyiodo)benzene) and PIFA ([bis-(trifluoroacetoxy)iodo]benzene) as the oxidant. The reaction proceeds in water with 2.5% methanol as a co-solvent. Hypervalent iodine reagents are generally less reactive than metal-based systems used for aromatic oxidation. The reactivity of iodine reagents can be increased by carrying out the reaction with water as the primary solvent. By doing this the reaction makes use of the 'micellar effect' in which the hydrophobicity of the reagent form reactive pockets in order to increase their effective concentration of the reactive species.

Studies by the Tohma group also used (bis(trifluoroacetoxy)iodo)benzene (PIFA) on a variety of starting substrates. However, when applied to trimethoxybenzene **2.107** a poor yield of 33% was isolated and large amounts of the dimer **2.109** were produced, due to reaction of the starting materials/intermediates *para* to the 2-methoxy position. As the analogous position on tricyclic scaffold **1.80** is blocked with a quaternary carbon centre it was believed that this side reaction would be prevented.

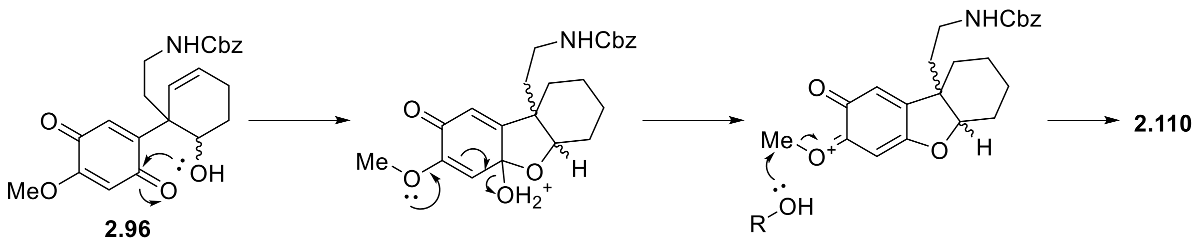


Scheme 45 - Attempts at the oxidation of tricycle 1.80 only led to the synthesis of orthoquinone 2.110.

As the PIDA reagent was the effective reagent for oxidation of trimethoxybenzene, it was investigated for oxidation of tricycle **1.80** (**Scheme 45**). However, no reaction was observed. PIFA was employed next, this consumed all the starting material forming a complex mixture, from which no product was isolated. However, mass spectrometry (ESI+) of the crude mixture did show a peak at m/z = 394.2 that could indicate the presence of the dehydrated cation **2.111** of the target product. Increasing the proportion of methanol to 10% when combined with PIDA led to consumption of the starting material and the synthesis of a benzoquinone product (as shown by its bright orange colour). However, analysis of the product by mass spectrometry tentitavely assigned this as tricyclic orthoquinone **2.110** rather than the ring opened para-quinone **2.96**. Although methods exist for the rearrangement of orthoquinones to paraquinones, less than 20% yield of the orthoquinone was isolated and it proved to be too unstable to purify further, let alone fully characterise.[108] The first use of PIFA and the creation of a complex mixture indicated that PIFA was too reactive. In order to mediate the reactivity of PIFA, acetonitrile was added to the solvent mixture in 20% of the total volume. Although the reaction did not give the messy mixture seen previously, the result was similar to the second PIDA reaction, again producing the tentitavely assigned ortho quinone in very low yield (<20%).

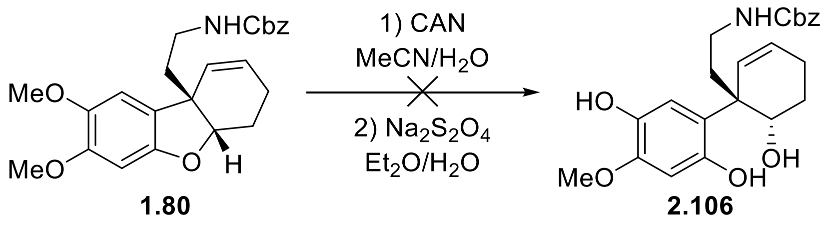
The failure of this method to form the paraquinone may be due to the differences in ability of the methoxy and benzofuran oxygens to form the oxonium cation theorised by the Tohma group to be a necessary intermediate in the oxidation. The C_{Ar}-O-C bond angle of anisole is 120° whereas the corresponding angle in tricyclic benzofuran **1.80** will be different due to ring strain from the 5-membered system.

An alternative mechanistic reason for the formation of the orthoquinone is that the paraquinone is in fact formed, but allows the reformation of the furan ring by attack of the newly formed alcohol on the carbonyl (**Scheme 46**).



Scheme 46 - Alternative mechanism for the formation of orthoquinone 2.110.

Due to the failure of the hypervalent iodine reagents in the oxidation of this scaffold system it was decided to attempt the ring opening using ceric ammonium nitrate as the oxidant. The first attempt at this formed a complex mixture, and it was not possible to isolate any purified products. A second two step method attempted to rearomatise the quinone in situ using sodium dithionate to form the hydoquinone **2.106**, however none of the desired product was isolated (**Scheme 47**).[109] At this point it was decided to abandon the ring opening oxidation route due to the oxidation attempts indicating that numerous side reactions were occurring and the likely product of the reaction would not be the desired paraquinone.



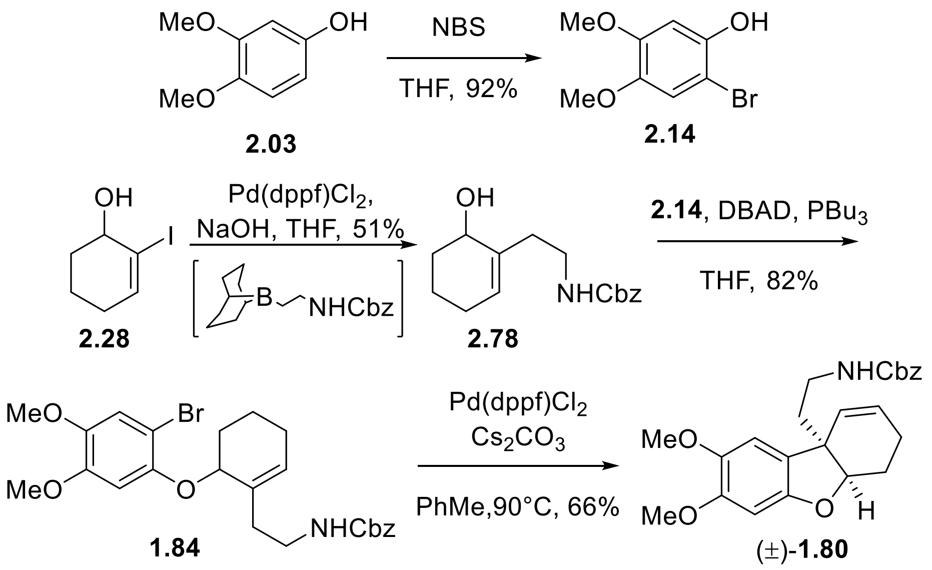
Scheme 47 - Oxidation of the scaffold using CAN was unsuccessful, as was its attempted one-pot oxidation/reduction with CAN/sodium dithionate.

2.4.4. Conclusions

Although the ring opening oxidation step was not achieved on the tricyclic substrate **1.80**, limitations of the oxidation method pioneered by the Tohma group were found, as well as limitations of the tricyclic scaffold structure, such as their instability to highly acidic conditions.

Regardless, a concise and easily adaptable synthesis has been developed to reach the tricyclic galanthamine based scaffold system envisaged to then access other alkaloid types within the amaryllidaceae family and potentially new analogues of the known natural products (**Scheme 48**).

A fast, high yielding bromination of a difficult electron rich phenol **2.03** was achieved using NBS. An investigation of the susbsequent Mitsunobu reaction found that coupling of the bromphenol **2.14** with a propargylic alcohol was problematic, although coupling with cyclohexenols was successful using a DBAD/tributylphosphine reagent system. The Mitsunobu was then optimised by Suzuki coupling of a protected β-aminoethyl group at the α-position of the cyclohexenol prior to the Mitsunobu to **1.84**, removing the labile iodine at that position.



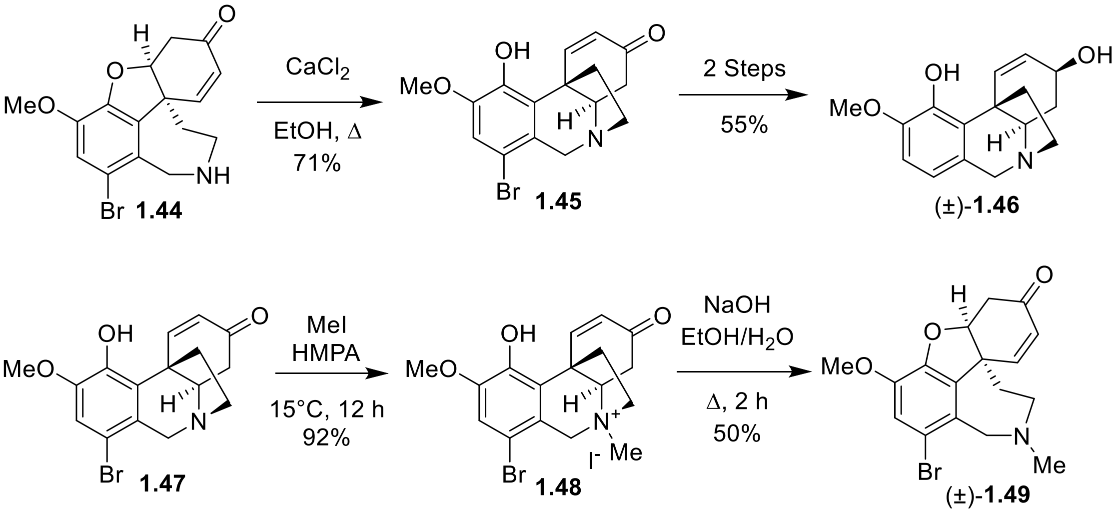
Scheme 48 - We have developed a concise synthesis to tricyclic galanthamine scaffolds.

A reasonable yield was achieved for the intramolecular Heck reaction to **1.80** using a bidentate ferrocenylphosphine ligand. This yield was considered and improvement on previous work considering the problems groups have had with the intramolecular Heck reactions to these tricyclic systems from their arylbromide precursors.

Chapter 3 – Towards (+)-Maritidine; Retro-Michael Rearrangement Approach

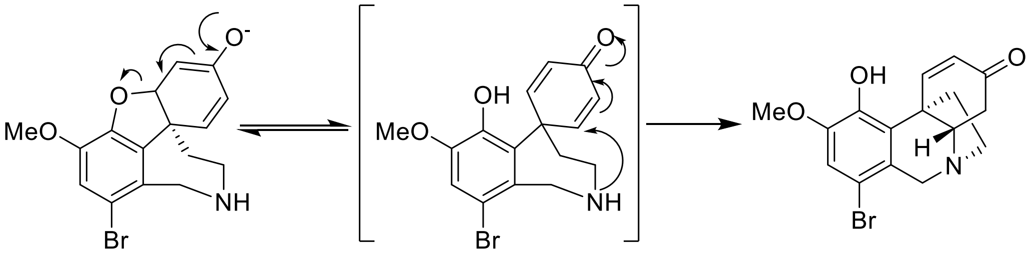
3.1 Introduction

Although the oxidative ring opening route described in chapter 2 was not successful, forming the maritidine structure via the tricyclic galanthamine scaffold was still the main goal of this work. Treu *et al.* have demonstrated a bidirectional conversion procedure to provide a one step route from the galanthamine structure **1.44** to the crinine type **1.45** and two steps for the reverse reaction (**Scheme 49**).[21]



Scheme 49 - Bidirectional conversion of galanthamine and crinine type structures.

This synthesis serves as a novel method to form these crinine structures from a galanthamine type scaffold, which already has well documented asymmetric syntheses. This should therefore allow for the synthesis of multitude of crinines with 10-hydroxy substitution. Unfortunately, the study was only performed for the bidirectional conversion between the bromo-methoxy compounds **1.44** and **1.45**. As such the scope and limitations of these transformations are currently unknown. In terms of the synthesis of (+)-maritidine this approach is not viable, as the opening of the furan ring goes *via* a retro-Michael-Michael-addition-cascade (**Fig. 13**). The retro-Michael transformation produces an achiral dienone intermediate **1.51**, which will lead to a racemic mixture of the crinine-type product.



Enantioenriched Substrate
1.50

Achiral Intermediate
1.51

Racemic Product
1.52

Figure 13 - The retro-Michael reaction of galanthamine type structures leads to an achiral intermediate.

The transformation from the galanthamine structure to the crinine structure is initiated using calcium chloride as a Lewis acid. As such, we believed that a chiral Lewis acid may be used to drive the reaction with some level of enantiopurity. For example, Kumaraswamy *et al.* developed an enantioenriched calcium BINOL catalyst for use with C-C bond forming Michael reactions.[110] Although this would be a reasonable strategy for a simple Michael addition an issue arises when combining it with the preceding retro-Michael reaction. Initial concerns that the chiral Lewis acid would require kinetic control (low temperatures) in order to achieve diastereoselectivity were founded by research into other chiral Michael addition catalysts such as cobalt (II) salen[111] and Silver/ThioClickFerrophos[112] complexes, among others[113,114]. However, retro-Michael reactions using Lewis acids (instead of Bronsted acids and bases) typically require thermodynamic conditions to induce the reaction, effectively negating any chiral control that would be provided by the catalyst.[115,116]As such, it would likely be impossible to employ conditions to satisfy both the kinetic and thermondynamic control required for this one-pot cascade reaction.

Nevertheless, this method was used to devise our second attempt at an asymmetric route via the galanthamine scaffold. When the rearrangement proceeds from the galanthamine to crinine structures via a retro-Michael-Michael cascade the stereochemical information is lost. However, we hoped that if the order of reactions was reversed to a Michael-retro-Michael reaction over two steps, the stereochemical information could be retained.

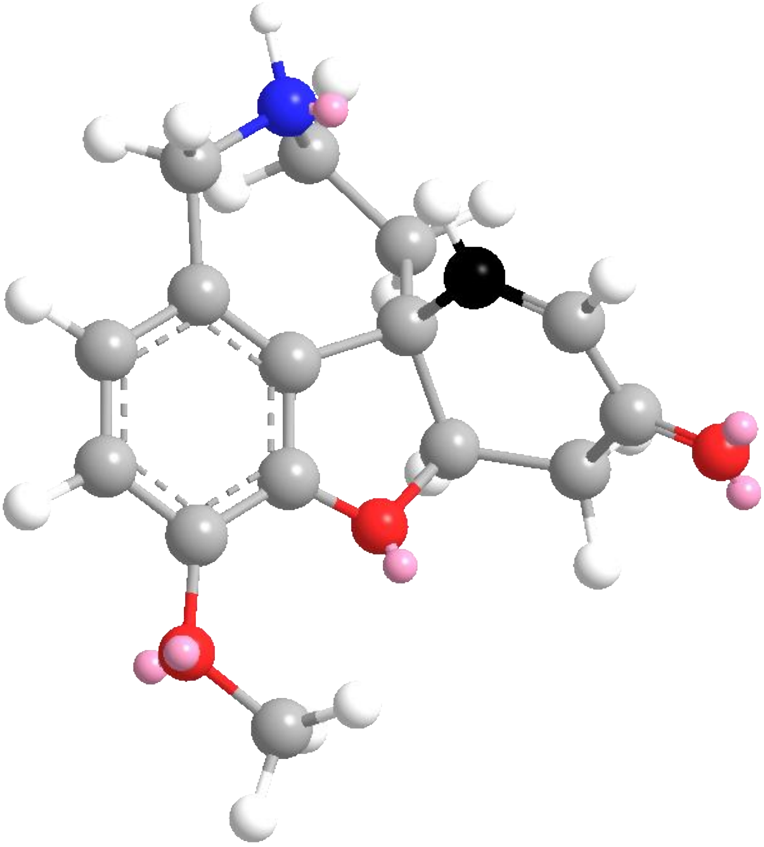
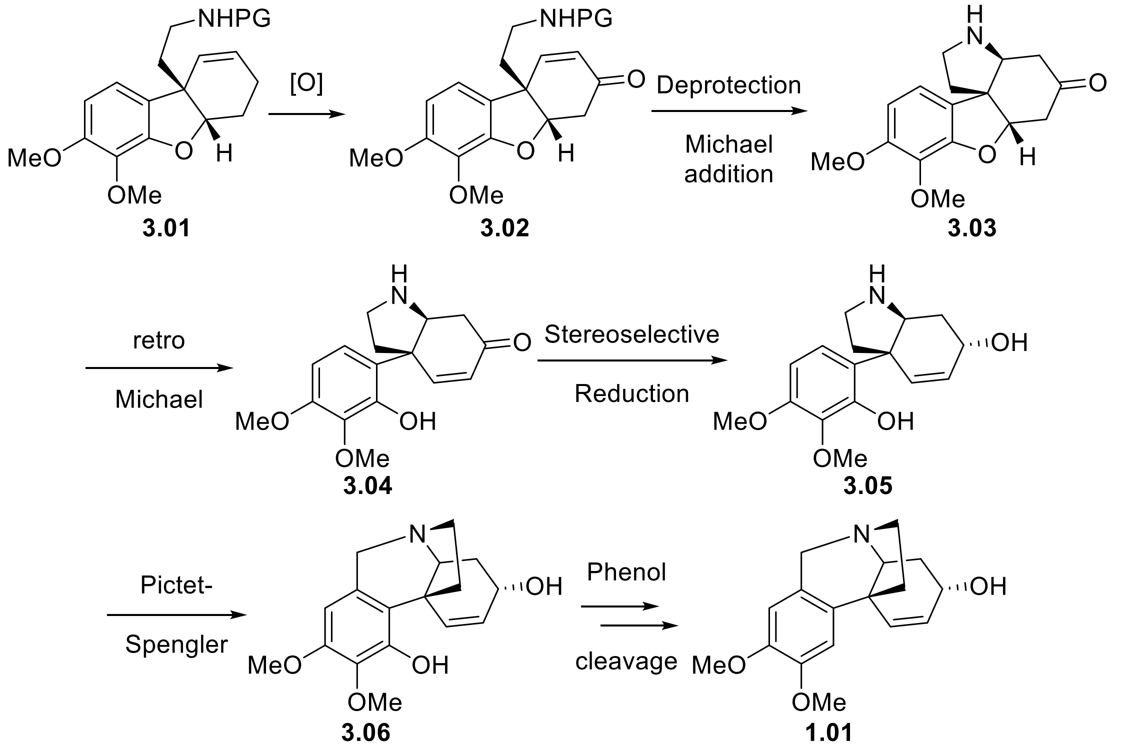


Figure 14 - 3D rendering of the tetracyclic galanthamine type structure shows that the nitrogen (blue) is unlikely to be able to undergo Michael addition to the enone (at black carbon), as it is anchored to the phenyl ring.

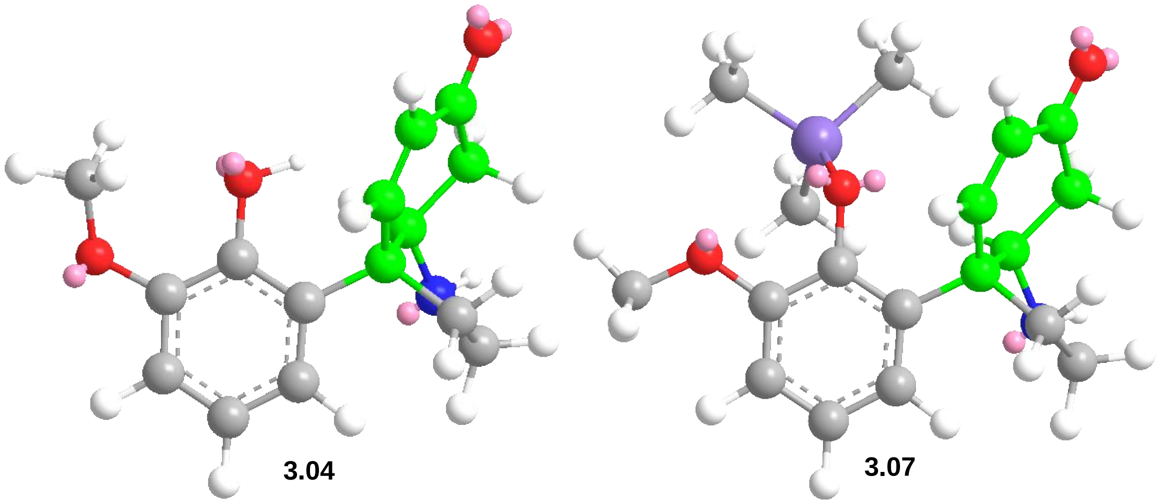
Using basic 3D molecular modelling software, it was decided that the tetracyclic galanthamine core structure and its analogues would be inappropriate starting point for this route (**Fig. 14**). This is because the free amine would be held too far from the unsaturated ketone for 1,4-addition to occur due to conformational restriction from its methylene link to the aromatic ring. As such, a tricyclic core structure similar to those synthesised in our first attempt to maritidine should provide more suitable starting materials.



Scheme 50 - Forward synthesis for Michael-retro-Michael route.

Scheme 50 shows our initial plan for this synthetic route from what was viewed as an easily achievable intermediate based on the previous work over this project. Firstly, the tricylic scaffold requires allylic oxidation to the ketone. The 1,4-addition will then be initiated by the deprotection of the amine; which forms the pyrrolidine ring that will later become the D ring of the maritidine structure. Once the new tetracyclic **3.03** is formed the oxy-retro-Michael reaction can then be induced. In the Treu synthesis, the tertiary amine has to be methylated to form its quaternary ammonium before attempting the aza-retro-Michael reaction as amines have significantly poorer leaving group abilty than phenols. Stronger acids, and therefore weaker conjugate bases makes better leaving groups due to the increased stability of the ion. Primary amines have a pKa of around 36 and phenols around 10. So, assuming a relatively linear first order correlation between pKa and log(k) of the reaction the retro-Michael reaction should almost exclusively eliminate the phenol to form the ring opened tricyclic **3.04**.

From here, it seems logical to reduce the ketone to the allylic alcohol prior to attempting the Pictet-Spengler reaction, eliminating the chance of any unwanted retro-Michael reactions. Moreover, energy minimised molecular models (**Fig. 15**) of the retro-Michael product phenol **3.04** and its trimethylsilyl protected analogue **3.07** would also suggest that reduction at this point, rather than on the final crinine structure, should lead to the required hydroxyl epimer of maritidine. This occurs in the same fashion as with galathamine scaffold model in **figure 7** (section 1.5) and the previous work completed by Valerio Isoni.[26] Although the eliminated phenol moiety acts as a moderate steric blocking group in **3.04**, leaving the desired face open to a bulky borohydride, the TMS protected phenol moiety of **3.07** almost entirely blocks off the undesired face. This should lead to exclusive synthesis of the diastereomer of allylic alcohol **3.05** from **3.04** with the same relative stereochemical configuration shown in **Scheme 50** (if the starting material was enantiopure).

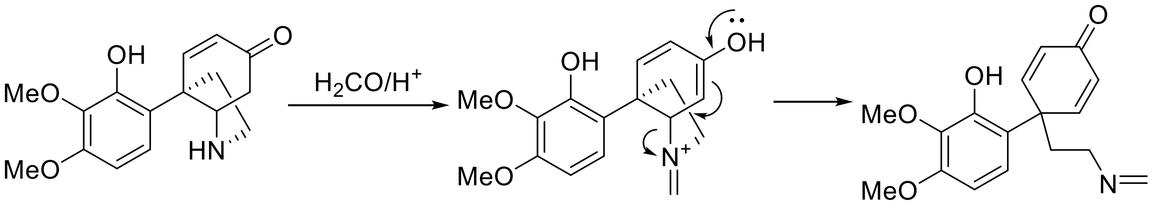


3.04 **3.07**

Figure 15 - The phenol ring should provide significantly more steric hindrance (free or TMS protected phenol) than the fused pyrrolidine ring during the reduction of the cyclohexenone (green) with a bulky borohydride.

One possible issue at this stage could be the unwanted formation of amine-borane complexes, however patent procedures found for their intentional synthesis use more forcing acids/bases/temperatures and longer reaction times, whereas the reduction will be performed below 0 °C for 1-2 hours.[117,118]

The next step is the Pictet-Spengler reaction to form the methylene bridge from the amine to the aromatic ring to from the crinine structure. Regioselectivity will not be an issue for this reaction as one of the possible reactive sites is blocked by the phenol hydroxyl group. The Pictet-Spengler will have to be performed after the reduction of the cyclohexenone **3.04** as formation of the iminium intermediate **3.08** (a good leaving group) would likely lead to an unwanted retro-Michael reaction forming the unwanted imine **3.09** (**Scheme 51**).



3.04 **3.08** **3.09**

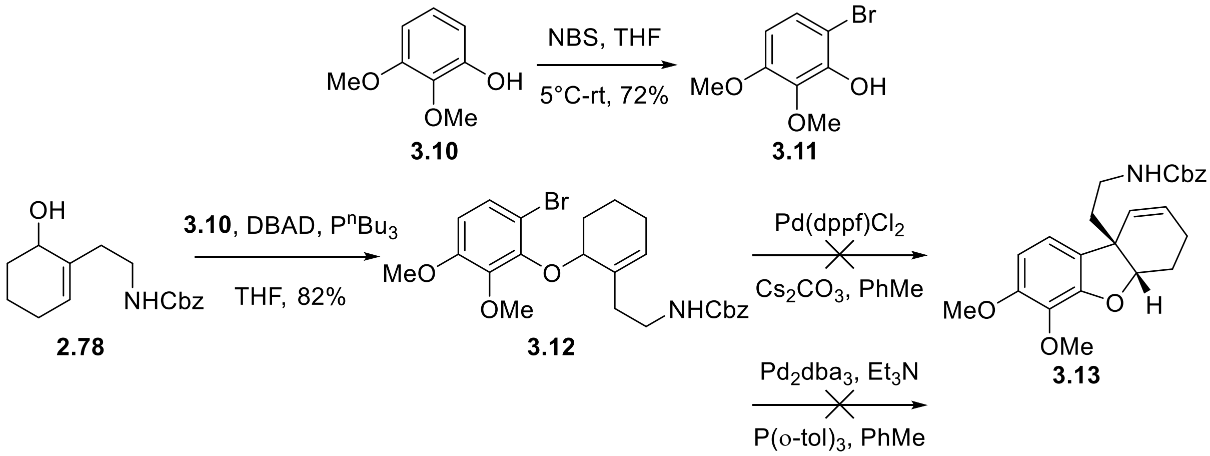
Scheme 51 - Formation of the iminium intermediate beta to the ketone would likely lead to retro-Michael elimination of a good leaving group.

Finally, the phenol will be cleaved to complete the synthesis. Removing the free phenol is not possible, however activation of the phenol by phosphorylation or sulfonylation then cleavage by hydrogenation is a known methodology.

3.2 Synthesis of the Tricyclic Scaffold

Initial experiments were tests on model compounds to determine whether the 2-bromo-5,6-dimethoxyphenyl moiety was suitable for intramolecular Heck cyclisation to the tricyclic scaffold prior to attempting the synthetic pathway with a more suitable amine protecting group (deprotection of the benzyl carbamate would lead to olefin reduction). This was predominantly due to the problems with reproducibility of the analogous reaction during the attempted synthetic route in chapter 2.

Bromophenol **3.11** is a known compound and was synthesised from phenol **3.10** using NBS.[119] As we already had a premade stock of protected aminoethylcyclohexenol **2.78** this was combined with the bromophenol **3.11** under DBAD/P^{n}Bu$_3$ Mitsunobu conditions in 82% yield (**Scheme 52**). The Heck cyclisation to **3.13** was then attempted using both Pd$_2$dba$_3$ and Pd(dppf)Cl$_2$ based conditions, both of which failed to convert any starting material.

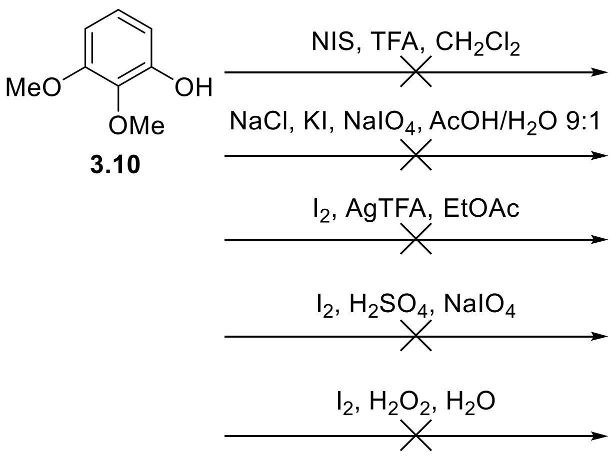


Scheme 52 - Investigation to determine if the new aryl bromide system was suitable for the intramolecular Heck reaction step.

3.2.1 Halogenation of 2,3-Dimethoxyphenol

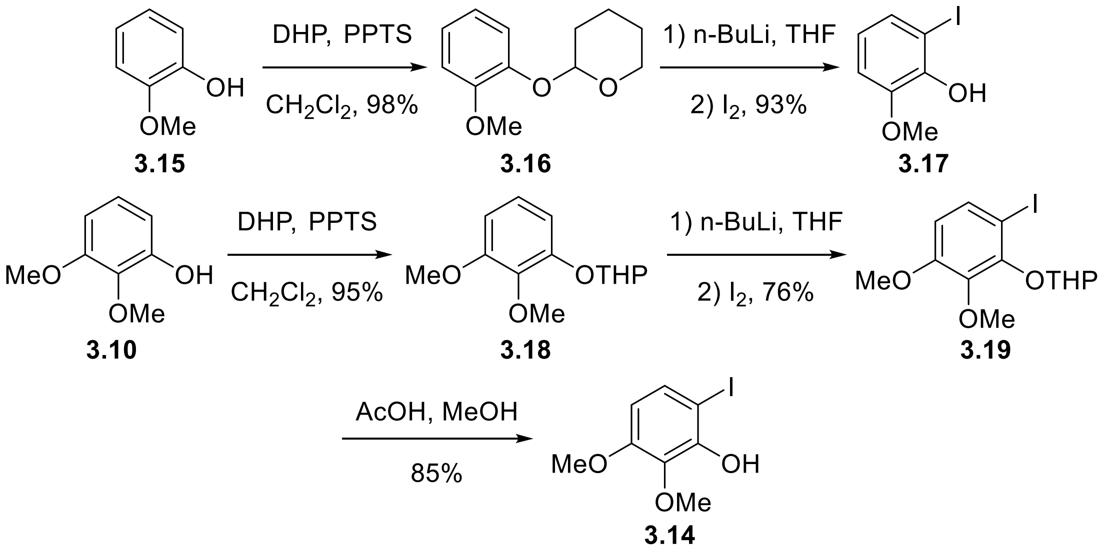
Due to the failure of the bromophenyl Mitsunobu product **3.12** to undergo the intramolecular Heck reaction it was decided that attempts at the analogous iodo-dimethoxyphenol precursor **3.14** were required to allow access to the required tricyclic scaffold, as the aryl iodides have proven to be more efficient at these intramolecular Heck reactions (see section 2.1).

Firstly, two mild iodination conditions were used attempting to make use of the iodo-trifluoroacetate reactive intermediate described in section 2.1.1. Both NIS/TFA[120] and I$_2$/AgTFA[121] failed to convert any starting phenol **3.10** at all (**Scheme 53**). Direct iodination of phenol **3.10** failed under a wide variety of conditions[122]. An indirect route to the known key aryl iodide **3.17** was therefore investigated instead.



Scheme 53 - Direct iodination of the phenol under a variety of conditions proved ineffective.

Iodination of 2-methoxyphenol **3.15** to **3.17** is known and is completed over two steps (**Scheme 54**). Step 1 involved tetrahydropyran protection of the phenol using DHP and PPTS. The group that devised this then cleverly used the protecting group of **3.16** a directing group to force ortho-lithiation of the protected phenol when reacted with n-butyl lithium.[123] The organolithium reagent was prepared *in situ* then added diatomic iodine drop-wise in solution to induce lithium-halogen exchange. The THP protecting group was cleaved in this same step to afford the required aryl iodide **3.17**.



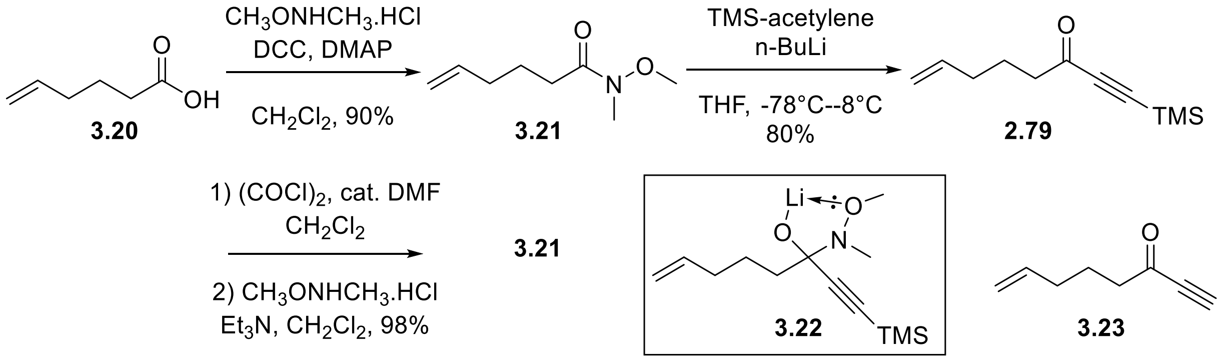
Scheme 54 - Iodination of the two required phenols was completed using an intuitive ortholithiation method.

Iodination of dimethoxyphenol **3.10** was also completed in the same manner. The cleavage of the THP protecting group did not occur under the reaction/workup conditions. As a result, the protected iodophenol **3.19** was isolated and deprotected using 1 equivalent of acetic acid in methanol. Purification of the iodide **3.14** was complicated by the presence of starting material. Due to the small difference in polarity brought about by the introduction of iodine to the highly polar phenol (3 polar methoxy/alcohol groups on one side of the benzene ring) this was not determined by Thin Layer Chromatography. Separation of starting phenol **3.10** and iodophenol **3.14** was not possible after the deprotection step and as such left around 8-10% (by NMR) starting material in the final product. Unfortunately, it was not possible to remedy this issue prior to the end of the project due to time constraints. As such, the monomethoxyphenol **3.17** was used to continue the synthesis.

3.2.2 Preparation of the Propargylic Alcohol 2.79

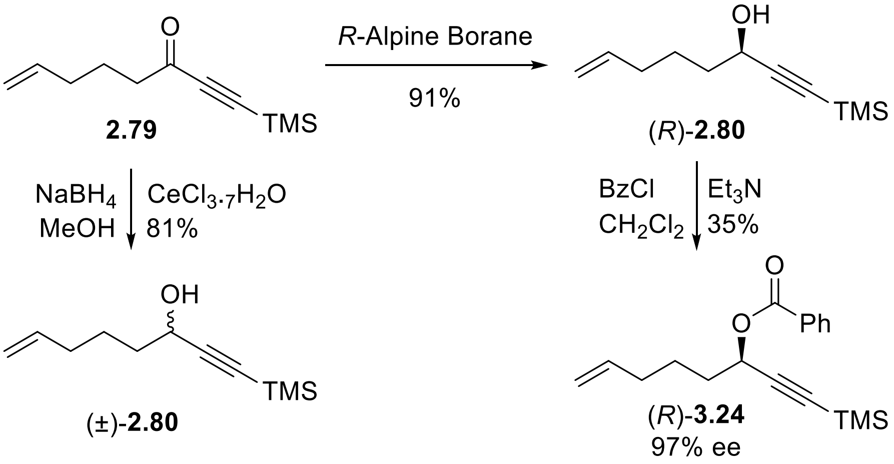
Although we already have the capability to form cyclohexenol ring **2.78** with the benzyl carbamate protecting group, the protecting group is not suitable for the planned synthetic route as any deprotection would initiate an unwanted retro-Michael reaction or hydrogenate the double bond/ketone. For this reason, it was decided to again attempt the enyne RCM route, this time trying to insert another protected amine that could be deprotected under milder or more selective conditions compatible with other functionality present in our desired target.[26,25]

In order to complete this synthesis using an enantiomerically enriched alcohol it was decided to use an asymmetric reduction of the respective propargylic ketone (**Scheme 55**). To synthesise the required ketone **2.79** the simplest method was to synthesis the Weinreb amide to allow mono-alkynation with TMS acetylene. Initial synthesis of the Weinreb amide was achieved using the carbodiimide coupling reagent DCC combined with DMAP. This gave the Weinreb amide **3.21** in 90% yield. When scaled up the DCC method produced large excesses of waste that interferes with the workup and purification. As such, synthesis of the Weinreb amide via the acyl chloride was completed using oxalyl chloride in CH_2Cl_2 with catalytic DMF, followed by addition of the N,O-dimethyl hydroxylamine HCl salt and triethylamine. This method gave the Weinreb **3.21** in a near quantitative yield of 98% whist improving the ease of workup and purification.



Scheme 55 - Synthesis of the required propargyllic ketone from hexenoic acid eliminated the volatility issues experienced in section 2.3.4.

The next step of the synthesis is the formation of the propargyl ketone **2.79** via the nucleophilic attack of the lithiated TMS-acetylene on the amide. The tetrahedral intermediate **3.22** of the nucleophilic attack is stabilised by coordination of the nitrogen and oxygen lone pairs at temperatures as high as -8°C in this case. This prevents double addition of the acetylene group to the ketone. The intermediate undergoes hydrolysis to the propargylic ketone upon workup. Although the propargylation step initially went to completion and provided a high yield with no issues, at one point the reaction completely failed to react correctly, producing complex mixtures with very little required product. Analysis of the crude mixture showed that it contained a 9:1 ratio of the product **2.79** to the deprotected product **3.23**, along with other impurities that proved impossible to completely remove. This led to the alteration of the synthesis of the Weinreb amine to the acid chloride method and its purification improved by distillation as well as column chromatography. 5-Hexenoic acid from Sigma-Aldrich and Alfa-Aesar was trailed as well as TMS acetylene from Sigma-Aldrich, Alfa-Aesar and TCI, without stemming the creation of the unwanted major by-product. Attempts were also made keeping the temperature at -78°C for the entire reaction and raising it to only -20°C after the addition of the amide, both were unsuccessful in fixing the problem. The protected and deprotected products coeluted under column chromatography using several eluent mixtures and were extremely difficult to separate using distillation. Using the mixture of the two products in the subsequent reactions greatly decreased the isolated yields after the racemic reduction, Mitsunobu and deprotection steps, with the amount of deprotected product increasing with each subsequent step. It was also known from previous work within the group that attempting the asymmetric reduction with R-alpine borane was not viable either as the deprotected alkyne deactivates the reagent. It was decided at this stage that it was feasible to explore pre-installation of the alcohol/ketone that would later become the allylic ketone after the intramolecular Heck reaction.

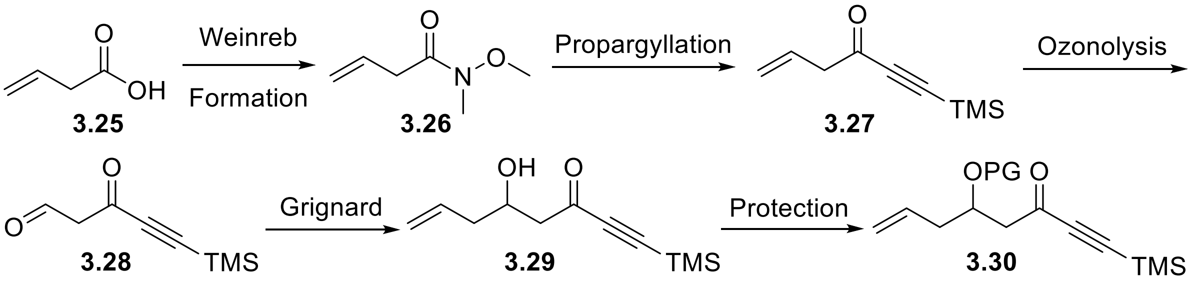


Scheme 56 - The propargyllic alcohol was synthesised in both racemic and enantioenriched forms.

Racemic reduction of the ketone to the alcohol (*R*)-**2.80** under Luche conditions proceeded in 81% yield (**Scheme 56**). The asymmetric reduction using *R*-Alpine Borane proved to be high yielding at 91% and was shown to be highly selective; with a 97% ee measured using chiral-HPLC once the benzoyl ester **3.24** was formed.

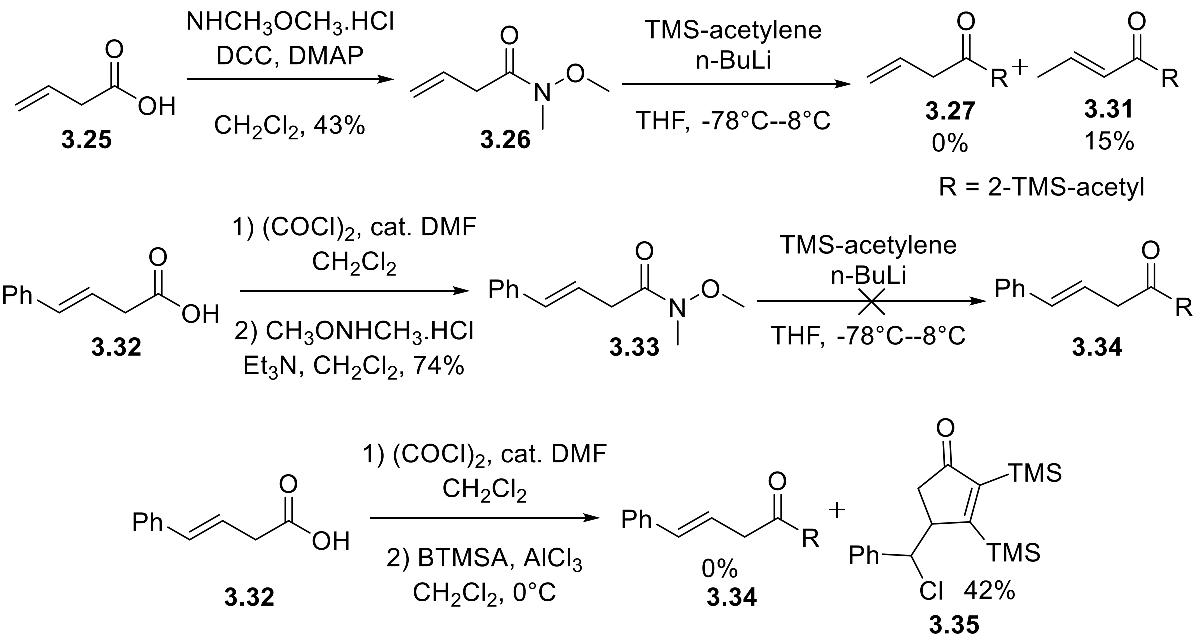
3.2.3 Attempts at the Pre-installation of 5-Hydroxyl Group on the Propargylic Ketone

Due to the issues encountered during the synthesis of ketone **2.79** it was decided to investigate preinstallation of oxygen functionality on the hexenyl moiety. Parsons *et al.* investigated 13 systems for the allylic oxidation of their galanthamine type structure, without yielding any of the desired product.[31] These trials ranged from milder copper, palladium, rhodium and manganese methods to more forceful chromium and lead systems. Also, in their earlier report, Trost *et al.* failed in their attempts at direct allylic oxidation of the teracyclic galanthamine structure with SeO_2 and CuBr/*tert*-butyl peroxybenzoate. Instead, they resorted to a low yielding 4 step process consisting of epoxidation of the double bond, formation of a hydroxyl-selenide intermediate; which was then eliminated and finally isomerised using Osborn's catalyst to the required alcohol in a 15% overall yield across the 4 steps.[23] Due to the extremely low yield of this oxidation it was decided another method was needed to isolate our desired alcohol. During their later attempts at the oxidation in 2002 the selenium dioxide oxidation was improved giving a 57% yield, however it was found to be completely ineffective for the oxidation of our alkene in section 3.4.1.



Scheme 57 - Planned synthesis of the keto-alcohol.

Our plan for the installation of the required hydroxyl group was for 3-butenoic acid **3.25** to be converted to the respective Weinreb amide **3.26** and then propargylic ketone **3.27** as with hexenoic acid (**Scheme 57**). The double bond would then be cleaved to form the keto-aldehyde **3.28**; which would be reacted with allyl magnesium bromide to complete the synthesis of the alcohol **3.29** (or a milder zinc Grignard to reduce competition with the existing ketone). The alcohol would then need protecting until a suitable time in the synthesis. Although ozonolysis, Grignard reaction, protection and deprotection reactions would increase the length of the synthesis by an extra 3 steps, we believed that the failures of other groups to successfully oxidise this position warranted the extra steps.



Scheme 58 - Attempted synthesis of the keto-alcohol was largely unsuccessful, but led to the discovery of an interesting novel reaction.

The formation of Weinreb amide **3.26** from 3-butenoic acid proceeded in a poor 43% yield using DCC (**Scheme 58**). However, the propargylation step produced none of the required product **3.27**, instead giving 15% yield of the ketone **3.31**; in which the β,γ-unsaturated ketone had isomerised to its α,β-unsaturated form. The low yield was attributed to the high volatility of the product ketone **3.31**. To remedy both of these problems it was decided to use styrylacetic acid **3.32** as the starting material instead. It was hoped that the presence of the phenyl group would not only eliminate the volatility issues but also stabilise the skip-conjugated system and avoid isomerisation to the unwanted α,β-unsaturated ketone. This tactic proved to increase the isolated yield of the Weinreb amine **3.33** using the acyl chloride method, however attempts at propargylation to afford ketone **3.34** led to complex mixtures from which no product was isolated.

In a final attempt to form a useful ketone and continue the ozonolysis route an attempt was made to install the propargyl ketone using a Friedel-Crafts reaction between styrylacetyl chloride and bis-TMS-acetylene.[124] However, what we isolated was not only an unexpected product **3.34** but an unexpected reaction type that has not been observed before based on current literature. Instead of synthesising the linear β,γ-unsaturated propargylic ketone **3.34** some form of cyclisation occurred to form the bis-trimethylsilyl cyclopentenone **3.35**. This will be discussed in section 3.3.

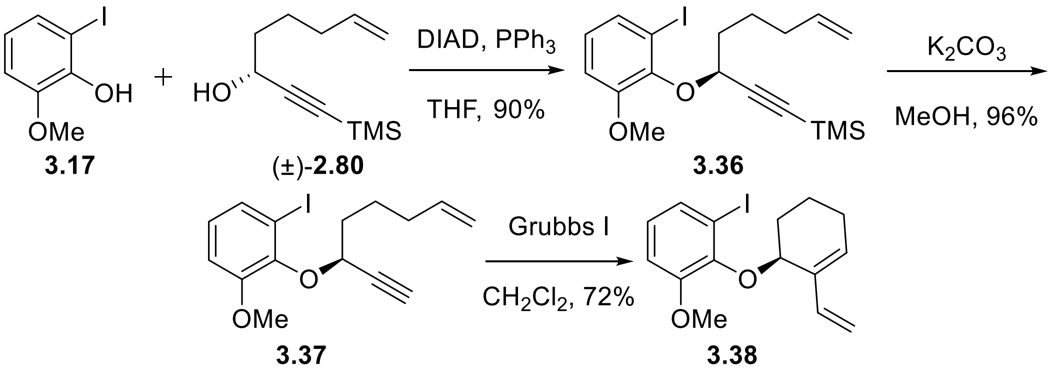
Due to the problems faced in the propargylation step in the synthesis of the 5-hydroxy-propargylic ketone **3.34** it was decided to abandon this avenue of thinking and instead focus on oxidation of the allylic position after the formation of the tricyclic scaffold, hoping to improve on the previous attempts at analogous oxidations on this structure.

3.2.4 Pre-Heck Modification of Vinylcyclohexenyl Moiety.

As with the oxidative ring opening approach to maritidine we attempted, the following inversigations were carried out using racemic material unless otherwise stated. This again was to save on excessive use of the expensive chiral reduction agent (R-alpine borane) until absolutely necessary. As the amount of pure ketone was limited towards the end of the project due to the deprotection issues, it would have been inefficient to use the mixture of protected and deprotected ketones **2.79** and **3.23**, knowing that the deprotected ketone would poison the chiral reagent.

Regardless of the synthetic problems faced in the propargylation to ketone **2.79**, enough was synthesised to allow the continuation of the original plan for the rearrangement route. This section will describe the formation of the tricyclic scaffold attempts at the installation of the β-aminoethyl group prior to the intramolecular Heck reaction.

Mitsunobu coupling of propargylic alcohol **2.80** with iodophenol **3.17** using the DIAD/PPh_3 system proceeded well forming the aryl propargyl ether **3.36** in 90% yield (**Scheme 59**).[25,26]

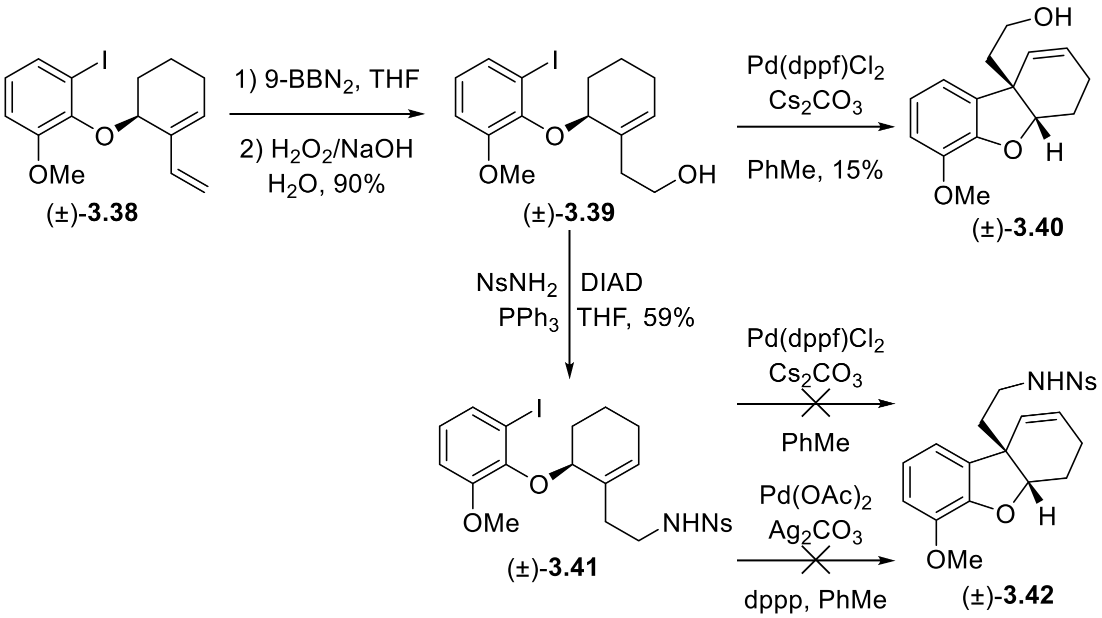


Scheme 59 - Synthesis of the aryl-vinylcyclohexenyl ether by the enyne RCM method proceeded smoothly.

Deprotection of the alkynyl TMS group to **3.37** in preparation for the ring closing metathesis reaction was achieved using potassium carbonate in methanol in 96% yield. The Grubbs I catalysed enyne RCM reaction to **3.38** proceeded in 72% yield. An attempt at the metathesis using Grubbs II catalyst gave a lower yield of 66% and formed a complex mixture of products; which proved more difficult to purify.

As described in chapter 2.3 V. Isoni found it difficult to effectively insert the nitrogen onto the β-vinyl position of his analogous compounds, gaining the most success by the hydroboration/hydroxylation of the vinyl group followed by introduction of the nitrogen by substitution. As many such substitution methods exist, we decided this would likely be the fruitful avenue to explore.

As in chapter 3.2.2 a requirement would be to introduce nitrogen, as a masked or protected amine, in a form that could be deprotected under conditions compatible with the proposed retro-Michael-Michael approach. This would prevent scrambling of the stereochemical information installed in the molecule.



Scheme 60 - The intramoecular Heck step was largely unsuccessful in the presence of the free alcohol or nosyl sulfonamide.

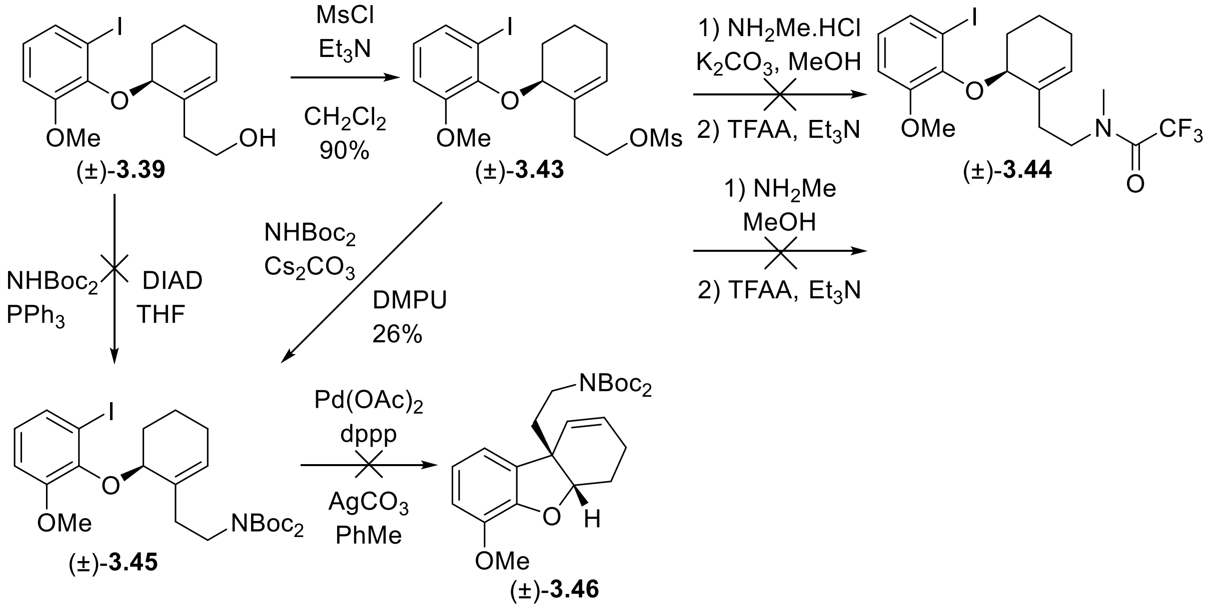
Conversion of the vinyl group the β-hydroxyethyl group was achieved using hydroboration with 9-borobicyclononane then addition of basic peroxide at 0°C, giving the desired product **3.39** in 90% yield (**Scheme 60**).[26] Direct Heck cyclisation from alcohol **3.39** to **3.40** was attempted, although previous work by Trost and Brown reported that Heck reactions to the tricylic structure were largely unsuccessful with the free alcohol. The previously utilised $Pd(OAc)_2$/dppp/$AgCO_3$ system gave no conversion to the desired product, leading us to attempt further functionalisation or protection of the β-ethyl position prior to the Heck reaction. A later attempt at this transformation with Pd(dppf)Cl_2 and Cs_2CO_3 only yielded the desired product in 15% yield.

The nosyl group was chosen as possible amine protection for the synthesis due to its unique and mild form of deprotection using the thiophenolate anion. Addition of the nosyl sulphonamide and deprotection with thiophenolate is known as the Fukuyama amine synthesis. Installation of 2-nitrobenzenesulfonamide at the β-ethyl position of **3.39** was achieved using Mitsunobu conditions in a reasonable yield of 59%. However, it was impossible to isolate enough pure sample for perfect characterisation.[125] Much like with Isoni's analogous compound the intramolecular Heck cyclisation to **3.42** was unsuccessful using both $Pd(OAc)_2$ and Pd(dppf)$_2$ conditions.

tert-Butyl carbamate was also seen as a suitable protecting group. Although the standard deprotection reagent here would be TFA this would likely to initiate the unwanted retro-Michael reaction. However, numerous other methods of Boc deprotection are known, making use of CAN[126], TMSCl[127], TBAF[128], and even boiling water[129] as effective reagents.

Attempted Mitsunobu coupling of di-tert-butyl iminodicarboxylate with alcohol **3.39** failed, however mesylation of the alcohol to **3.43** (90% yield) and conventional substitution of the dicarboxylate in DMPU (26% yield) was successful in producing bis-Boc amine **3.45** (**Scheme 61**). Unfortunately, the subsequent intramolecular Heck reaction to **3.46** with Pd(OAc)$_2$ conditions was ineffective.

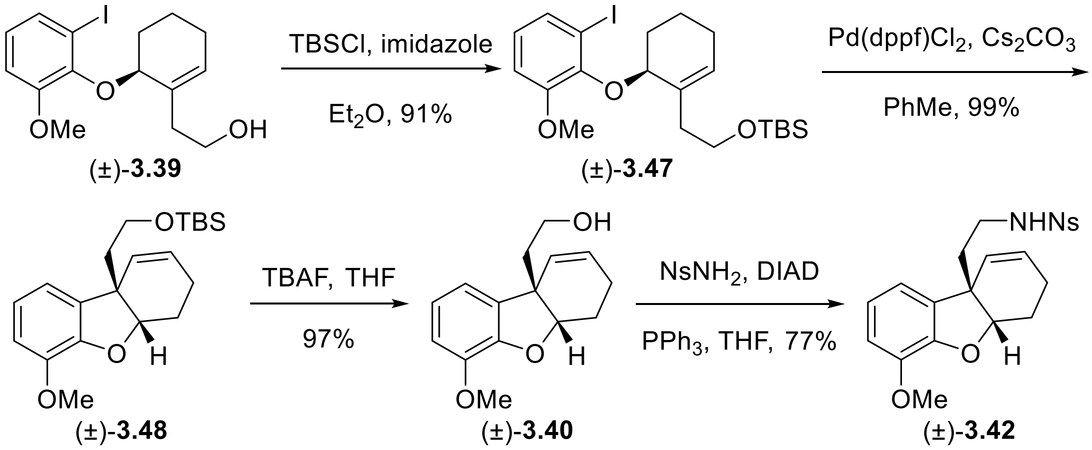
Finally, we attempted to substitute *N*-methyl trifluoroacetamide onto mesylate **3.43**, hoping to use mild basic conditions to deprotect the acetamine then demethylate the amine using a column purification method with sodium percarbonate/4,6-dichloro-2-hydroxy-[1,3,5]triazine sodium salt[130] or chloroethyl chloroformate[131]. However, attempts at forming **3.44** by substitution of methylamine followed by formation of the acetamide with TFAA were unsuccessful.



Scheme 61 - Installing the protected nitrogen in a form that would favour the subsequent Heck reaction proved difficult.

Due to time constraints and the problems in installing the protected amine prior to the Heck reaction it was decided to take on an additional two steps and protect the alcohol prior to the Heck and install the nosyl protecting group afterwards (**Scheme 62**). Protection of the alcohol with a tert-butyldimethylsilyl group using TBSCl and imidazole achieved 91% of the desired product **3.47**. In the absence of strongly coordinating nitrogen or moderately acidic proton on the β-position of the ethyl moiety the intramolecular Heck reaction to **3.48** then proceeded in a high yield of 84% using Pd$_2$dba$_3$, P(o-tol)$_3$ and trimethylamine in toluene, despite the steric bulk of the protecting group. This yield was further improved upon use of our Pd(dppf)Cl$_2$ condition giving a near quantitative yield. Fluoride deprotection of the TBS ether to **3.40** also proceeded in near quantitative yield.

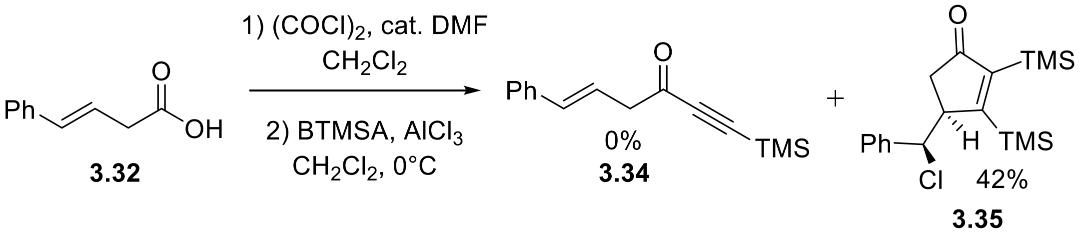
Introduction of the nosyl amine was completed using 2-nitrobenzene sulfonamide, DIAD and PPh_3, giving the protected amine **3.42** in 77% yield.[125] From here it was possible to start trials attempting oxidation at the allylic position prior to the first Michael addition step.



Scheme 62 - Formation of the silyl ether prior to the Heck reaction proved very rewarding.

3.3 A Novel Synthesis of Substituted Cyclohexenones

During the attempted pre -installation of 5-hydroxyl group on the propargylic ketone in section 3.2.3 an unexpected reaction occurred when new propargylation conditions were applied to trans-styreneacetic acid. These conditions formed the acyl chloride of the starting acid then exposed them to a mixture of bis-TMS-acetylene and aluminium chloride.[124] Instead of forming the linear ketone **3.34**, bis-TMS protected cyclopentenone **3.35** was synthesised in 42% yield.



Scheme 63 - Propargylation of the skip conjugated ketone led to an unexpected cyclisation reaction.

1D and 2D NMR of the isolated product suggested a cyclised product from COSY, HSQC and HMBC interactions. The presence of vinyl signals in the ^{13}C NMR with absence of vinyl protons in the ^{1}H NMR, combined with the retention of both TMS groups, suggested the transformation of the alkyne into the alkene contained within the new ring system. This also suggested that the original vinyl protons had been converted to alkyl signals. ESI+ mass spectrometry showed a 3:1 isotopic ratio at the base peak (351.0 + 353.1 $[M+H]^+$); which confirmed that chlorine from the aluminium tetrachloride anion had become incorporated into the product. All these factors and an in depth analysis and interpretation of the combined data led us to suggest the cyclopentenone **3.35** as a likely structure. This was confirmed by acquisition of the crystal structure by X-Ray crystallography (Fig. 16).

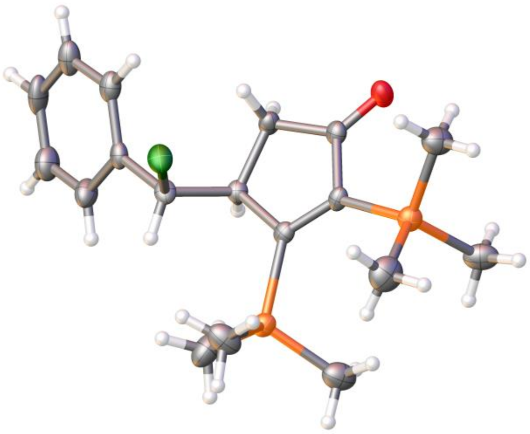
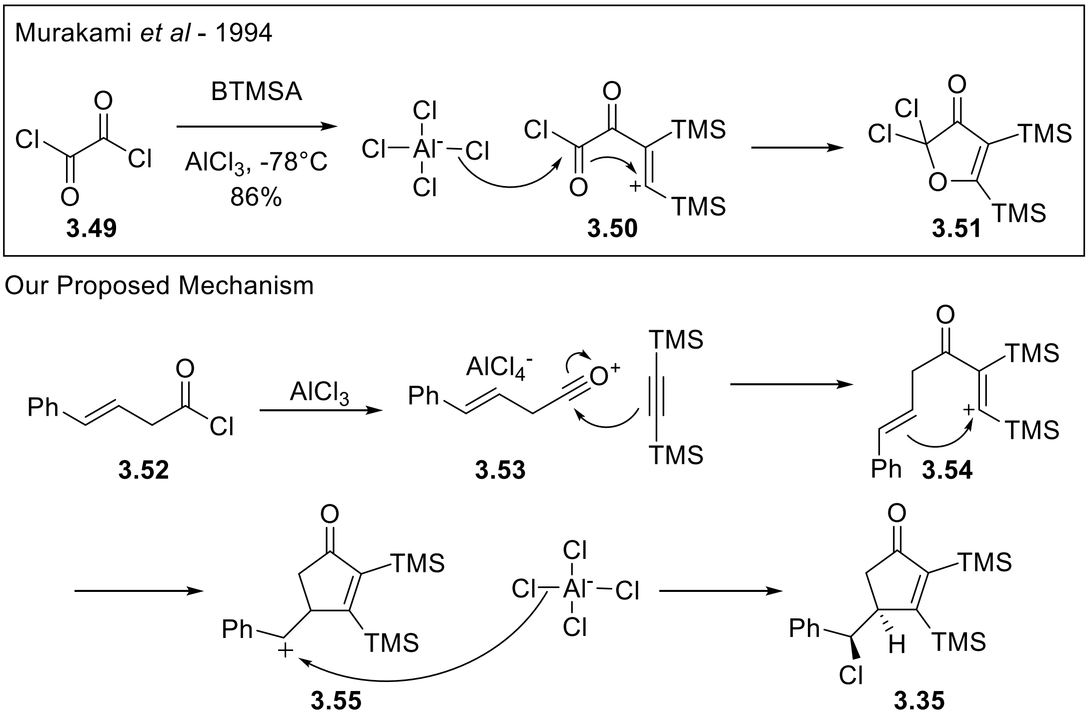


Figure 16 - X-Ray crystallography confirmed the theorised structure.

Determining a reasonable mechanism for this reaction was challenging. The formation of cyclopentenones in the presence of aluminium chloride would initially suggest some form of Nazarov type cyclisation mechanism. However, to achieve the appropriate intermediates a reactive ketene would need to be formed from the acyl chloride then tautomerised; which would only occur under basic conditions. This would not be appropriate for the Lewis acid mediated reaction conditions used here. Any mechanism derived through a pseudo-Nazarov cyclisation here also failed to sensibly account for the incorporation of the chlorine into the structure.

Further research into Friedel-Crafts reactions utilising BTMSA uncovered work leading to more plausible mechanism. Work by Walton in 1972 attempted a similar reaction instead using oxalyl chloride as the second substrate.[132] Instead of forming the predicted 1,6-bis(trimethylsilyl)hexa-1,5-diyne-3,4-dione the reaction instead yielded the furanone **3.51** in 27% yield. This procedure was them improved in 1994 by Murakami *et al.* giving 86% of the product.[133] Both groups suggested the same mechanism shown in **Scheme 64**. Firstly, the acylium ion is formed; which undergoes nucleophilic attack from BTMSA to form the highly stabilised vinyl cationic intermediate **3.50**. The stability of this cation is derived from the β-silyl effect; which is a specific type of hyperconjugation.[134] On bis-trimethylsilylvinyl cations McGibbon *et al.* measures the vinyl cation stabilisation energy to be as much as 29.5 kcalmol^{-1} for the α-TMS group and 43.5 kcalmol^{-1} for the β-TMS group.[135,136] These calculations were made using a combination of known thermochemical data and their own mass spectrometric techniques. The extremely high stabilisation energy given by this effect is likely the reason the reaction takes another pathway, rather than eliminating the trimethylsilyl group and reforming the alkyne, as would occur if no other options were available. In the case of Murakami and co-workers, their proposed favoured reaction is the nucleophilic attack of the aluminium tetrachloride anion on the carbonyl followed by the nucleophilic attack of the oxygen anion on the vinyl cation to form the 5-membered ring (**Scheme 64**). Whether this is a tandem or concerted process is not addressed.

However, as the aluminium tetrachloride anion is only a weak nucleophile, it seems more feasible that it is the electron rich olefin of cation **3.54** that is the nucleophile that attacks the vinyl cation (**Scheme 64**). The subsequent benzylic cation **3.55** is then able to react with the aluminium tetrachloride anion to complete the synthesis. The Friedel-Crafts reaction is strong evidence for this proposal, as the *in situ* acylium ion intermediate will react with an unactivated benzene ring (similar to an olefin) over the aluminium tetrachloride anion. NMR analysis of the product revealed that only one diastereomer (or more likely 2 enantiomeric diastereomers) were formed from this reaction. This is unexpected as there are no chiral components present in the starting materials. Although a precise reason for this is not known, it can be assumed that a combination of steric and electronic effects govern the nucleophilic attack of chloride on the benzylic cation **3.55**.

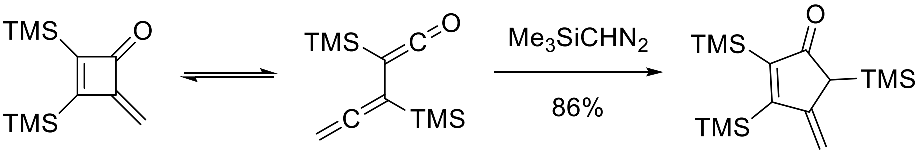


Scheme 64- Our mechanism differs slightly from the Murakami proposition, instead using the unactivated alkene as intramolecular nucleophile instead of the chloride activated acyl chloride.

Styryl acetic acid was exposed to the same reaction conditions as before, instead using mono-TMS-acetylene as the nucleophile. Unfortunately, this reaction only led to the formation of a complex mixture. This shows that the reaction is not suitable for use with terminal alkynes; which is not a serious issue as the TMS groups of **3.35** can be cleaved using fluoride. Due to time constraints it was not possible to dedicate time to researching this reaction in depth to identify its advantages and limitations.

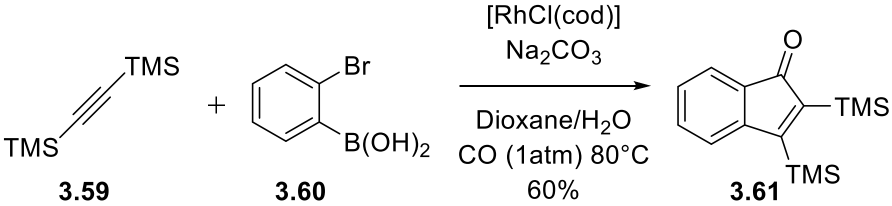
Only 3 other methods of synthesising these 2,3-bis(trimethylsilyl)-furanones have been investigated in literature (**Scheme 65**), each with their distinct advantages and disadvantages.[137–139] From first glance however, it appears that if successful in methodological studies, ours would be the first to allow installation chloroalkanes on the 4-position and would also allow varied and possibly stereoselective substitution on the 5-position by substitution onto the carboxylic acid precursor. The use of easily available and easily customisable starting materials is also a distinct advantage here.

Huang - 2000 - [4+1] Cycloaddition of Allenylketenes[137]



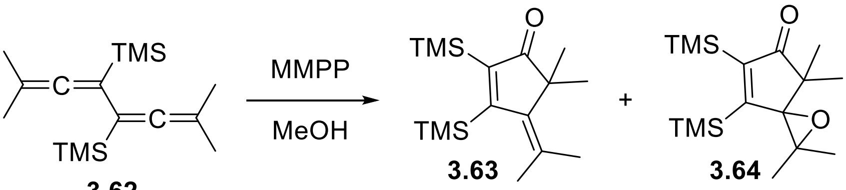
3.56 **3.57** **3.58**

Harada *et al* - 2007 - Rh(I)-Catalyzed Carbonylative Cyclization[138]



3.59 **3.60** **3.61**

Stamm - 2013 - Oxidative Cyclisation of Acyclic Conjugated Bisallenes[139]



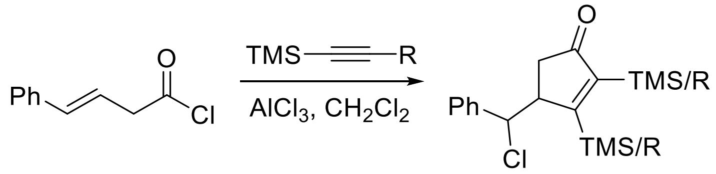
3.62 **3.63** 54% **3.64** 24%

Scheme 65 - Previous syntheses of bis-TMS-cyclopentenones either have severe limitations or use reagents that are expensive or difficult to synthesise.

In terms of future work for this project there are 3 main avenues that should be explored. Optimisation of the reaction with BTMSA should first be attempted, in order to maximise any yields from other alkynyl subtrates. Temperature, reaction time, concentration and method/rate of substrate addition can all be altered. Murakami and co-workers initially ran their similar reaction at -78 °C but found improved yields with BTMSA at -30 °C.

Secondly, variation of the alkyne substrate I the reaction should be investigated. As shown in our work, although BTMSA proceeded in the reaction, use of the mono-protected TMS-acetylene with a terminal hydrogen led to a complex mixture. As such, it would be wise to investigate how a variety of substituted TMS-acetylenes behave under the reaction conditions. This would allow us to assess the effect of alkanes, phenyl rings, alkyene and electron withdrawing/donating groups on both the yield and regioselectivity of the reaction (**Scheme 66**). As it is a major assumption of ours (and the

Murakami group) that the presence of the TMS group is essential for the reaction, attempts should also be made at utilising other unprotected alkynes under the optimised conditions.

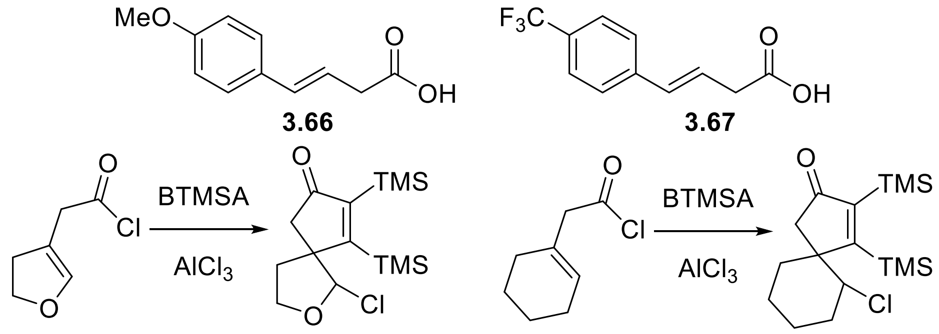


3.52 **3.65**

R = Ph, ^{t}Bu, ^{n}Bu, CO_2Me, ρ-$PhCF_3$, ρ-PhOMe

Scheme 66 - Planned methodological study with various TMS-acetylenes.

Lastly, experimentation with other skip conjugated substrates would allow assessment of the effect of olefin substitution on the reaction (**Fig. 17**). For example, do groups that stabilise the skip conjugated β,γ-unsaturated system have a positive or negative effect of the yield? This reaction may also allow access to novel spiro systems using substrates such as 2-(4,5-dihydro-3-furanyl)-acetic acid **3.68**.



3.66 **3.67**

3.68 **3.69** **3.70** **3.71**

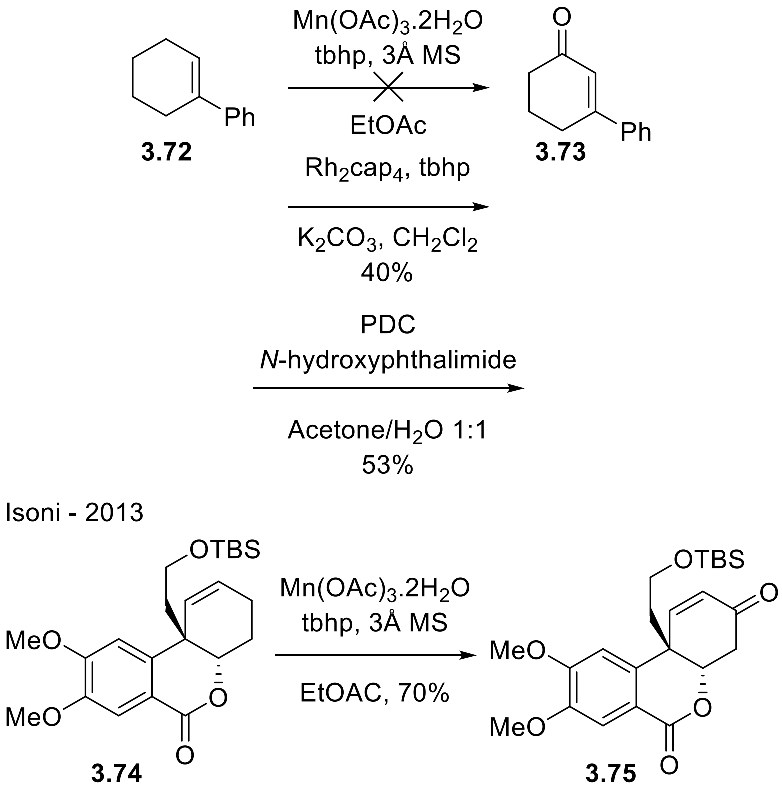
Figure 17 - Altering the unsaturated ketone may lead to increased yields or interesting novel spiro structures.

3.4 Allylic Oxidation Trials of the Tricyclic Scaffold

As illustrated by work by the groups of Trost and Parsons allylic oxidation of these systems is very challenging. However, as both of these groups made their attempts on the full tetracyclic galanthamine structure, it was hoped that attempts on the tricyclic structure would be more successful. Moreover, these groups attempted the oxidation with the presence of a free amine or amide, so it was hoped the absence of a somewhat labile nitrogen would aid in the transformation.

3.4.1 Direct Allylic Oxidation

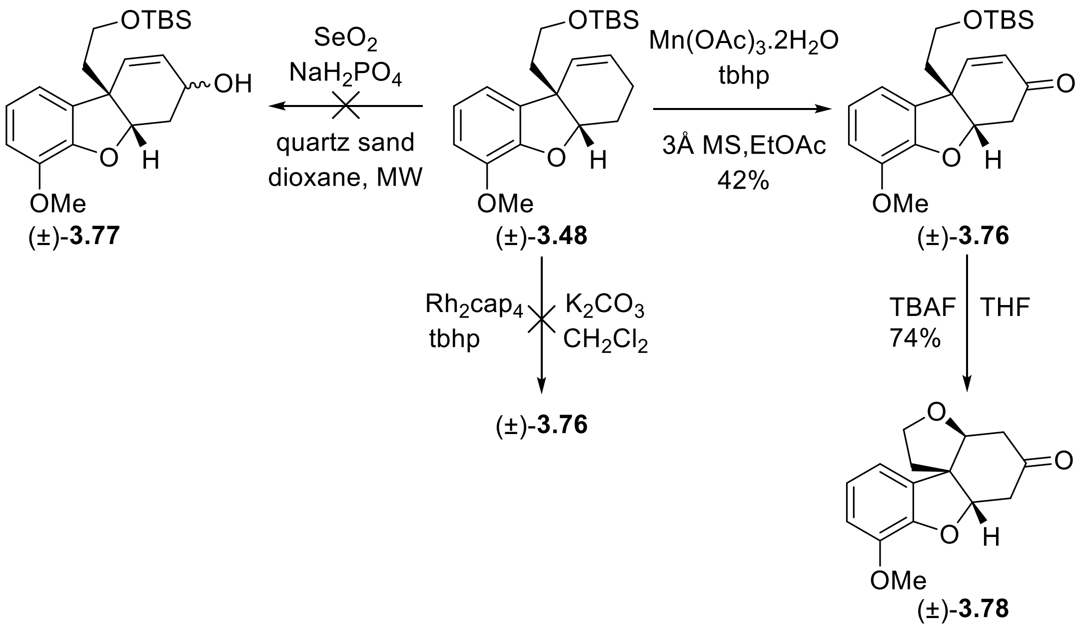
Oxidation trials were performed on 1-phenylcyclohexene **3.72** in order to justify the use of these reagents with the desired substrate. Three reagent mixtures were chosen based on their different mechanistic pathways and previous use with similar substrates to our own (**Scheme 67**).[140–142]



Scheme 67 - Isoni had some success at allylic oxidation on a similar substrate to our own. Our trials on a model cyclohexene proved less effective.

Strangely, oxidation with manganese triacetate dihydrate and *tert*-butyl hydroperoxide failed. However, work by Isoni within the Brown group shows the oxidation to be successful when applied to an analogue **3.74**, achieving a yield of 70%.[26] This analogue is very similar to our target substrate **3.48**, replacing the 5 membered furan ring with a 6 membered lactone. As such these conditions were still applied to our model substrate. The next oxidation also made use of tbhp, but instead used dirhodium tetracaprolactamate, a very low loading catalyst, achieving a 40% yield of the model product **3.73**.[141] A harsher chromium based oxidation using PDC and *N*-hydroxyphthalimide proceeded in 54% yield.[142]

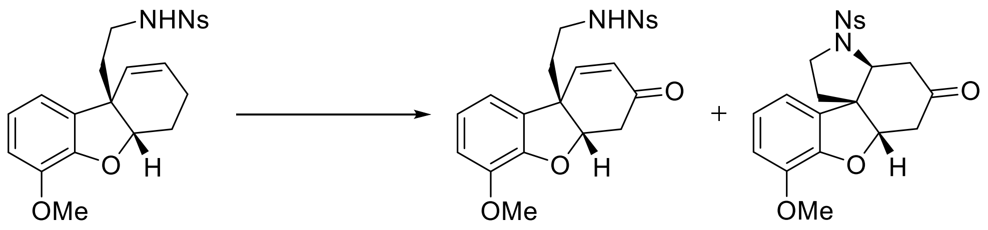
Oxidation trials were then started on the TBS protected galanthamine scaffold **3.48** (**Scheme 68**). Firstly, attempts were made at oxidation of **3.48** to the allylic alcohol using the proven selenium dioxide conditions that were used in the Brown galanthamine synthesis.[27,143] However, a complex mixture was formed and no product **3.77** was isolated.



Scheme 68 – Oxidation of the galanthamine scaffold to the ketone or alcohol proved difficult, especially as deprotection of the alcohol led to the unwanted bis-furan 3.78.

The dirhodium tetracaprolactamate conditions yielded no product and in fact converted no starting material, regardless of the promising yields achieved in its testing by Catino *et al.* (60-94%) in synthesising cyclic allylic ketones from simple cyclohexenes and cyclopentenes.[141] They also achieved higher yields when the starting material contained steric protection of the alternate allylic position. As the second allylic position of tricyclic scaffold **3.48** is blocked entirely a good yield was expected for the oxidation.

However, as expected based on the work of Isoni, the oxidation using manganese triacetate dehydrate to **3.76** was successful, albeit with a moderate isolated 42% yield as opposed to the 70% Isoni isolated of ketone **3.75**. In an attempt to continue the synthesis from this point ketone **3.76** was treated with TBAF to deprotect the alcohol in preparation for Mitsunobu coupling of the 2-nitrobenzenesulfonamide (**Scheme 68**). However, once deprotected the alkoxy anion somewhat predictably acted as a nucleophile, undergoing Michael addition onto the unsaturated ketone to form the tetracyclic tetrahydrofuran **3.78** in 74% yield. As such, the oxidation would have to be performed on the nosyl protected tricylic **3.42**.



(±)-**3.42** (±)-**3.79** (±)-**3.80**

Conditions	Yield **3.79** /%	Yield **3.80** /%
$Mn(OAc)_3.2H_2O$, tbhp, K_2CO_3, EtOAc, 50°C	0	28
AlPO (Va:Ti 9%:1%), tbhp, ^{t}BuOH or Decane, 100°C or 50°C	0*	0
$Pd(OH)_2/C$, tbhp, K_2CO_3, CH_2Cl_2, rt	0*	0
$Co(OAc)_2.4H_2O$, tbhp, MeCN, rt	0*	0
CrO_3, 2,5-dimethylpyrazole, CH_2Cl_2, -20°C-rt	0**	0
PCC, MS 3Å, PhMe, reflux	0**	0

Scheme 69 - Allylic oxidation on the nosyl protected scaffold gave unexpected results. *Recovered SM **Decomposition of SM

Oxidation attempts to synthesise **3.79** were similarly ineffective in completing the allylic oxidation on our nosyl protected tricyclic scaffold system (**Scheme 69**). Radical oxidation methods using managanese triacetate, palladium hydroxide on carbon[144] and cobalt acetate[145] were all investigated (utilising tbhp as the oxidant) to little avail. Porous AlPO catalyst doped with 9% vanadium and 1% titanium was also explored due to its reasonable success in a colleague's project, but without success. Harsher conditions using chromium reagents such as chromium trioxide[146] and pyridinium chlorochromate[147] only served to from a complex mixture, without identifiable product.

Although these methods failed in the synthesis of allylic ketone **3.79**, the manganese triacetate/tbhp conditions were somewhat successful in the oxidation of the allylic position. However, upon formation of the allylic ketone it seems that the nosyl protected amine was still reactive enough to act as the nucleophile in the Michael addition to form tetracyclic nosyl pyrrolidine **3.80** in 28% yield. Further attempts at this reaction to increase the yield were unsuccessful. Increasing the quantities of reagents to push the reaction to completion did not lead to an increased yield, whilst increased reaction time led to less isolated product. Working with the crude and pure pyrrolidine **3.80** showed that it was quite unstable to heat, acid, base, solvation and temperature increase. This is likely due to steric strain combined with reasonable leaving group ability of the nosyl amide increasing the likelihood of spontaneous retro-Michael elimination.

Although it would be hard to justify specifically why allylic oxidations are so ineffective on these tricyclic galanthamine scaffolds and their full tetracyclic structures without an in depth study on numerous analogues, we can start to analyse possibilities from known reactions.

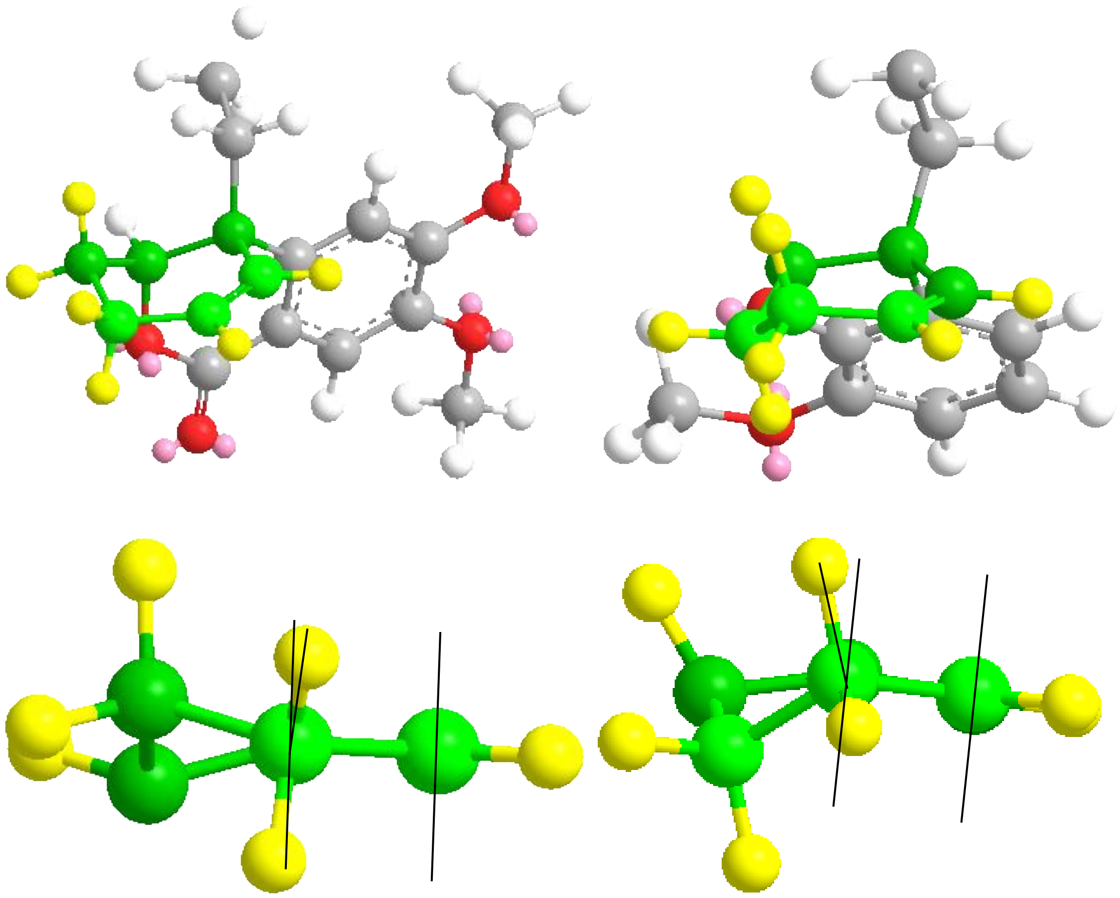
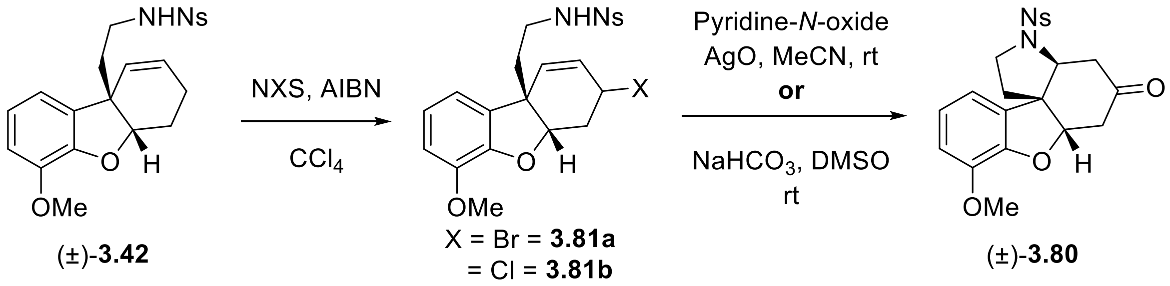


Figure 18 - 3D models comparing Isoni's tricyclic substrate (left) and our tricyclic substrate (right) show poorer orbital overlap between the vinyl p orbital and and allylic sp^3 orbital. Note the parallel lines show the ideal orbital overlap, with intersecting line showing the deviation from this angle.

As seen in the **figure 18** the conformation of the cyclohexenyl rings on Isoni's tricyclic valerolactone **3.74** and our tricyclic furan **3.48** (β substituent on ethylene arm removed from these models) differ in some respects. Firstly, the allylic position has been flipped, with the equatorial and axial hydrogens taking up the opposite positions. Both cyclohexenyl rings are forced to take up a half chair conformation. However, as seen in the 3D representations of the cyclohexenyl rings of the valerolactone **3.74** (left) and the furan **3.48** (right) above, our tricyclic furan is folded to a larger extent. This had led to an increased angle between the C-H bonding orbital of the allylic position and the remaining p-orbital of the α-vinyl carbon. With this increased angle, poorer orbital overlap is achieved, leading to decreased activation of the allylic position, activation which usually attributed to interaction between these orbitals (and the subsequent allylic radical/anion/cation produced as an intermediate).

3.4.2 Allylic Position Activation and Aza-Wacker Cyclisation

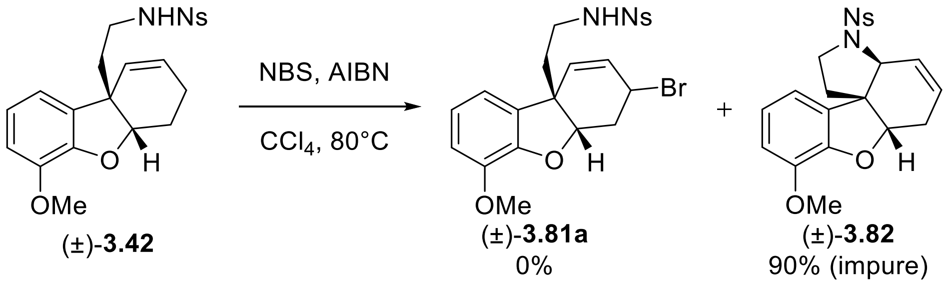
One possible solution to the allylic oxidation problem other than brute force oxidation conditions was to activate the allylic position with introduction of another atom/group prior to the oxidation. One such method found that achieves this activates the allylic positions by radical halogenation using the respective *N*-halogeno-succinimide and AIBN, followed by oxidation of the allylic halide with an appropriate source.[148,149]



Scheme 70 - Planned allylic activation by halogenation and subsequent oxidation.

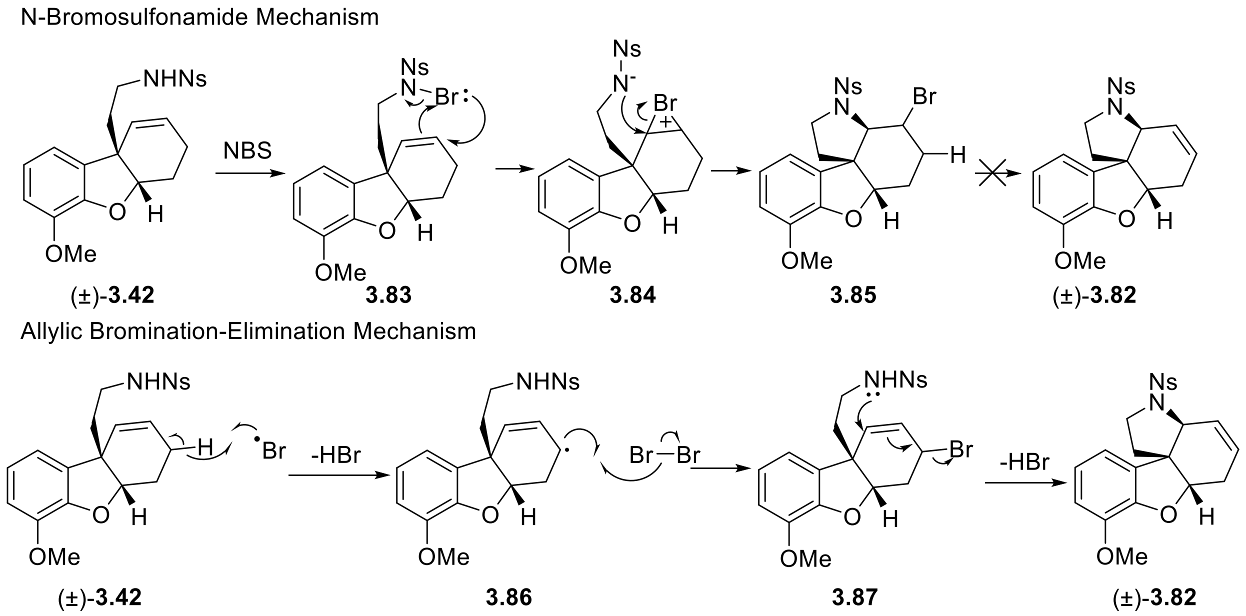
Oxidation of the allylic bromide or chloride employs pyridine-*N*-oxide as the oxygen source and silver (II) oxide[150] (as a Lewis acid to help cleave the halogen) or DMSO as the oxygen source in the presence of hydrogen carbonate[151], respectively. **Scheme 70** shows the planned activation and oxidation of tricyclic scaffold **3.42**, assuming the same spontaneous Michael addition that occurred during the direct allylic oxidation.

In practise, however, an unexpected reaction occurred upon the allylic bromination reaction (**Scheme 71**). When exposed to NBS and AIBN the tetracyclic compound **3.82** is isolated in 90% yield (not allowing for some impurities that could not be separated or identified).



Scheme 71 - Allylic bromination led to the immediate elimination of the bromine by nuceophillic attack by the nitrogen through the olefin.

Mechanistically there are two proposals for this transformation (**Scheme 72**). When exposed to NBS, sulfonamides are known to react to form *N*-bromosulfonamides **3.83**; which are highly electrophilic brominating reagents.[152] This would then form the bromonium cation **3.84** from the alkene; which would in turn be opened by nucleophilic attack from sulfonamide anion. However, from here, there is no feasible explanation for the formation of the double bond from **3.85** as radical or spontaneous HBr eliminations seem unlikely.

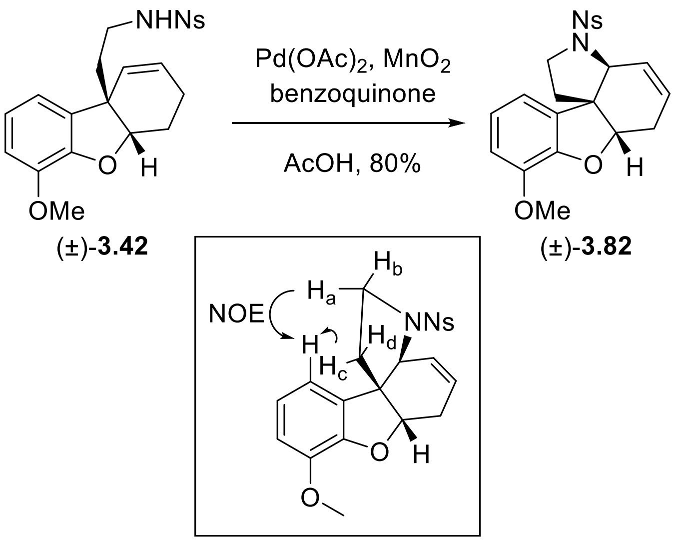


Scheme 72 - Proposed mechanisms of the bromination/elimination reaction.

Therefore, it is proposed that the reaction would proceed via radical bromination of the allylic position; which would proceed through the accepted pathway of the Wohl-Ziegler bromination.[153] Diatomic bromine is present in small quantities in NBS then undergoes homolytic cleavage using the radical initiator. The hydrogen bromide formed upon the hydrogen abstraction then regenerates Br_2 from NBS.[154] As seen in the formation of **3.82**, the sulphonamide nitrogen is still somewhat reactive, so acts as the nucleophile in the attack of the alkene and eliminates HBr.

Upon multiple attempts at this reaction, although the yield was high, there were still inseparable impurities. It also seemed unlikely that it would be possible to stop the elimination of the bromine without a significant change to the synthesis to install a more deactivating nitrogen protecting group. As such it was decided that we would explore other methods for the synthesis of tetracyclic alkene **3.82**, with a view to bypassing the allylic oxidation completely in favour of a Wacker oxidation of the double bond to form tetracyclic ketone **3.80**.

Nakanishi *et al.* performed a similar transformation via an aza-Wacker cyclisation in their synthesis of (-)-strychnine, forming a pyrrolidine ring onto a cyclohexene ring.[155] The difference with their synthesis was the presence of a Boc protecting group on the nitrogen instead of a sulfonamide. However, studies into these cyclisations using oxygen as the reoxidant confirmed that the reaction proceeds well using sulfonamide protecting groups.[156] Nosyl protected scaffold **3.42** was heated to 50 °C in the presence of palladium acetate, benzoquinone and manganese (IV) oxide to form the tetracylic alkene **3.82** in high 80% yield, with no impurity issues (**Scheme 73**).



Scheme 73 - Aza-Wacker cyclisation to the tetracyclic alkene.

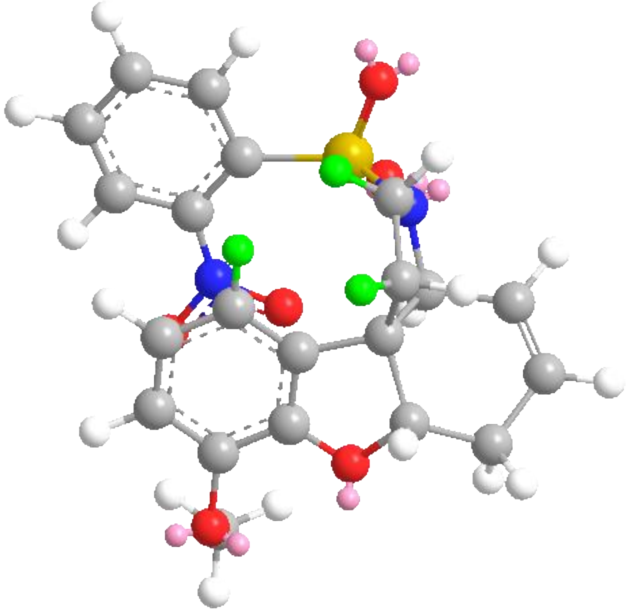


Figure 19 - 3D modelling of alkene 3.82 shows a very conformationally restricted molecule.

NOESY NMR studies of alkene **3.82** also show the predicted conformation of the pyrrolidine ring within the entire molecule (given by a ChemDraw 3D energy minimization calculation). These studies show NOE interactions between protons H_c, H_a (**Scheme 73**) and the para-methoxy aromatic proton. These protons are highlighted in green in the three-dimensional model of **3.82** (**Fig. 19**). The lack of NOE interactions of the aromatic protons with H_b and H_d suggests the tetracyclic structure is very conformationally restricted.

It was hoped that the new tetracyclic structure of alkene **3.82** would alleviate the possible conformational issues preventing oxidation of the β-allylic position and allow the direct oxidation of the α-vinyl position to form ketone **3.80**.

3.4.3 Wacker and Hydroboration Oxidation of Tetracyclic Alkene 3.82

One possible issue when attempting Wacker oxidations is the regioselectivity of the reaction. When dealing with oxidation of terminal alkenes methods exist for the selective oxidation of the terminal position[157,158] and the internal position[159–161]. However, when faced with 2 internal vinyl positions the regioselectivity is harder to control. The 3-dimensional model below (**Fig. 20**) shows the Wacker substrate **3.82** (with the cyclohexenyl moiety highlighted in green). Both vinyl positions are relatively accessible in this molecule due to the extreme folding of the cyclohexenyl ring from the plane of the aromatic ring.

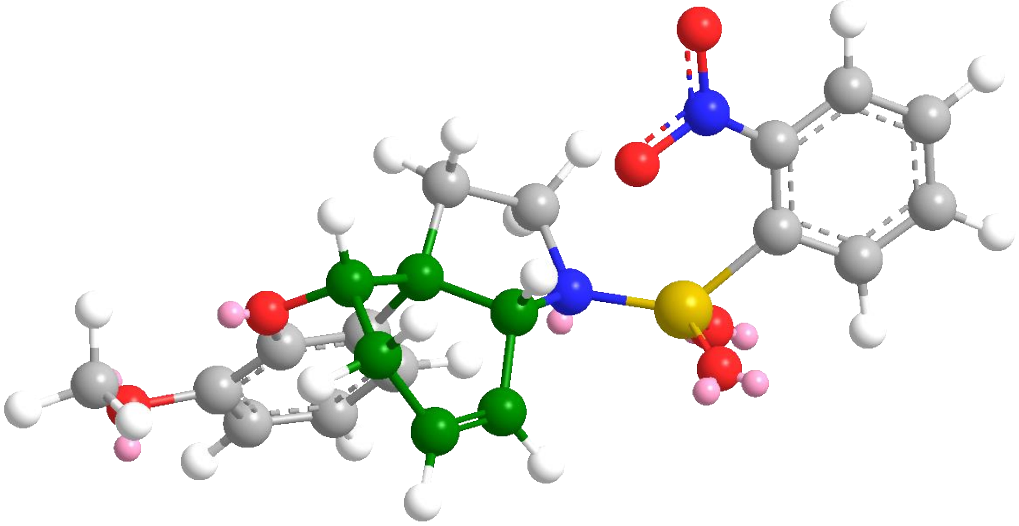
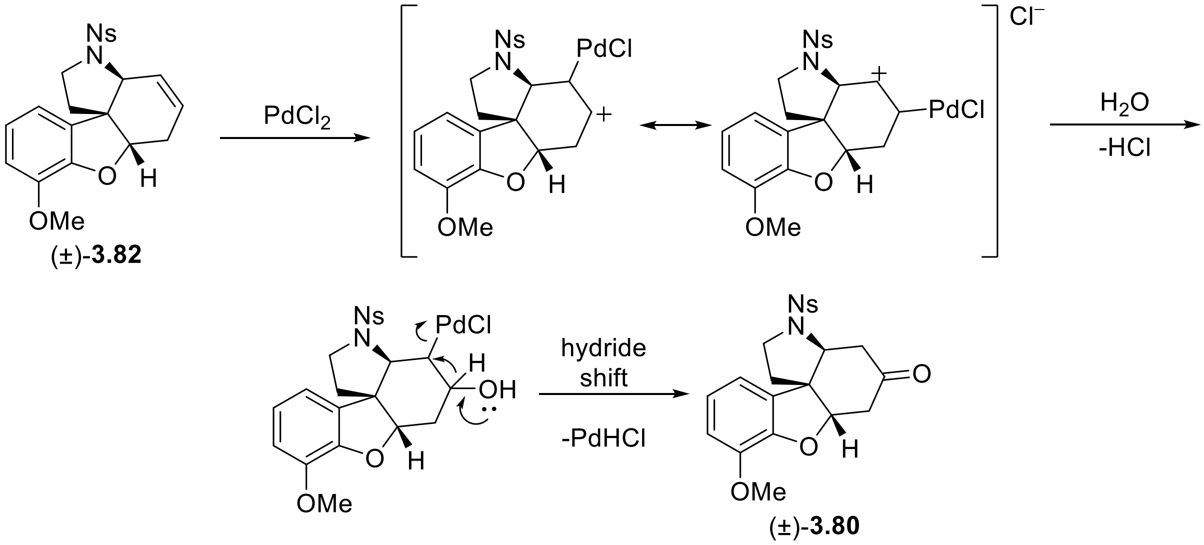


Figure 20 - Both positions of the alkene are suceptible to Wacker oxidation.

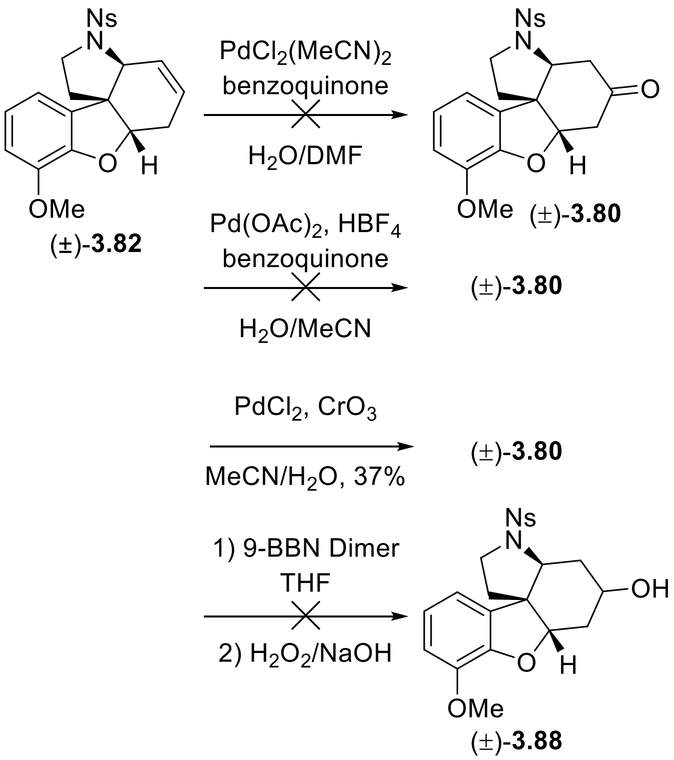
Moreover, there are no mesomeric resonance structures that can occur within the intermediates of the reaction of **3.82** (**Scheme 74**).[162]



Scheme 74 - Mechanism of the Wacker oxidation shows there are no available resonance structures that can effect the regioselectivity.

One factor that may affect the selectivity of the oxidation of **3.82** is the presence of the nosyl protecting group. This group has positions that may chelate with the palladium catalyst by the sulfonyl oxygens,[163] the nitro group[164] or the aromatic ring itself. This chelation may be enough to force carbopalladation onto the vinyl position closest to the protecting group, allowing water (or other oxidant) to undergo nucleophilic attack onto the required position. Examples of coordination of sulfonyl/sulfonamide groups in both intermediate states and stable complexes with palladium and other transition metals are shown in available literature.

The first Wacker oxidation made use of benzoquinone to oxidise palladium (0) back to palladium (II) to complete the catalytic cycle (**Scheme 75**). The classical Wacker reaction uses $CuCl_2$ to perform this oxidation, however literature showed multiple high yielding reactions using the organic reoxidant, especially when used to oxidise internal olefins.[165,166] Under these conditions there was no conversion of starting material. The second attempt utilised a method used by Morandi *et al.*, which changes the solvent to acetonitrile and adds hydrofluoroboric acid to increase the rate of reaction.[160,159] Unfortunately, this method also failed to generate any product **3.80**. Following the failure of these two methods it was decided to attempt the hydroboration hydroxylation of the double bond to **3.88**; which would likely occur at the required position due to the steric bulk of the reagent, 9-borobicyclononane. The alcohol could then be easily oxidised to the required ketone **3.80**. Yet again no oxidation product **3.88** was isolated.



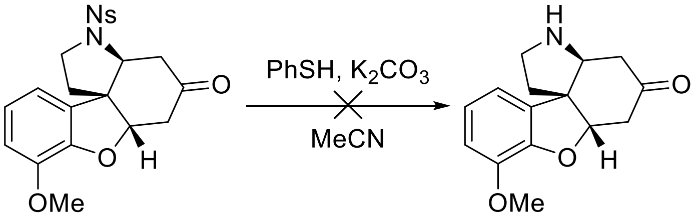
Scheme 75 - Wacker oxidation of the tetracyclic alkene had some success.

Some success was achieved using a more forceful Wacker procedure that uses chromium (iv) oxide as both the sole oxidant in the reaction.[167] Oxidation of the tetracyclic alkene **3.82** under the palladium chloride and chromium (iv) oxide conditions formed the tetracyclic ketone **3.80** in 37% yield. This yield was considered to be sufficient to progress the synthesis. Use of higher quality chromium (iv) oxide and catalyst did not increase the yield further.

Feasible reasons for the yield limitations met during the both the direct allylic oxidation and Wacker oxidation to ketone **3.80** include the production of acidic species *in situ*. The mild manganese acetate conditions create acetic acid as a result of the catalytic cycle, whilst the more forcing Wacker conditions produce chromic acid upon the dissolution of chromium trioxide in water. These acidic species can initiate the unwanted retro-Michael reaction described in chapter 3.2.2.

Although the nosyl protecting group provided a labile enough nitrogen to enable the Michael addition to **3.80** and aza-Wacker cyclisation to **3.82**, the 2-nitrobenzylsulfonyl group has the ability to strongly stabilise the sulfonamide anion leaving group from any unwanted retro-Michael elimination. As such, any acidic or basic conditions given as a result of reactions to form ketone **3.80**, have the ability to catalyse the undesirable transformation.

As a direct result of this sucesptability to the retro-Michael elimination, perhaps heightened by the conformational and steric strains of the tricyclic core based around the quaternary stereogenic centre, ketone **3.80** is inherently unstable. Being stored at room temperature, excessive heating upon removal of solvent and dissolution of the product into chloroform or dichloromethane (which can be mildly acidic unless dried fully) all led to some degradation of the sample. Moreover, the attempted deprotection of the amine using thiophenol/potassium carbonate, in order form a secondary amine as a poorer leaving group, led to the formation of a complex mixture (**Scheme 76**).[125] Although the deprotected amine **3.89** was detected in the crude reaction mixture by reverse phase LCMS I was unable to isolate any by colomn chromatography for analysis.



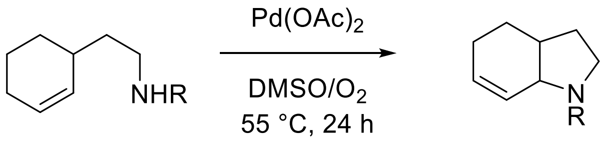
(±)-**3.80** (±)-**3.89**

Scheme 76- Attempted nosyl deprotection led to the formation of a complex mixture.

In retrospect the ‘early’ Michael addition brought on by the labile sulfonamide may have been detrimental due to the leaving group ability. However, a new synthetic route was devised from this realisation, using aspects from each of the 2 major synthetic routes developed over the project.

3.4.4 Aza-Wacker Cyclisation Route Utilising Benzyl Carbamate Protection

Based upon research reported by Rönn *et al.* detailing aza-Wacker cyclisations towards the synthesis of these cyclohexenyl pyrrolidine systems we know that the reaction does not need a labile sulfonamide to complete a high yielding transformation (**Scheme 77**).[156] Instead, benzyl carbamate can be used as a viable protecting group.



R = Ts **3.90a** R = Ts 93% **3.91a**
R = COOBn **3.90b** R = COOBn 95% **3.91b**

Scheme 77 - Rnn *et al.* completed aza-Wacker cyclisations with sulfonamides and carbamates.

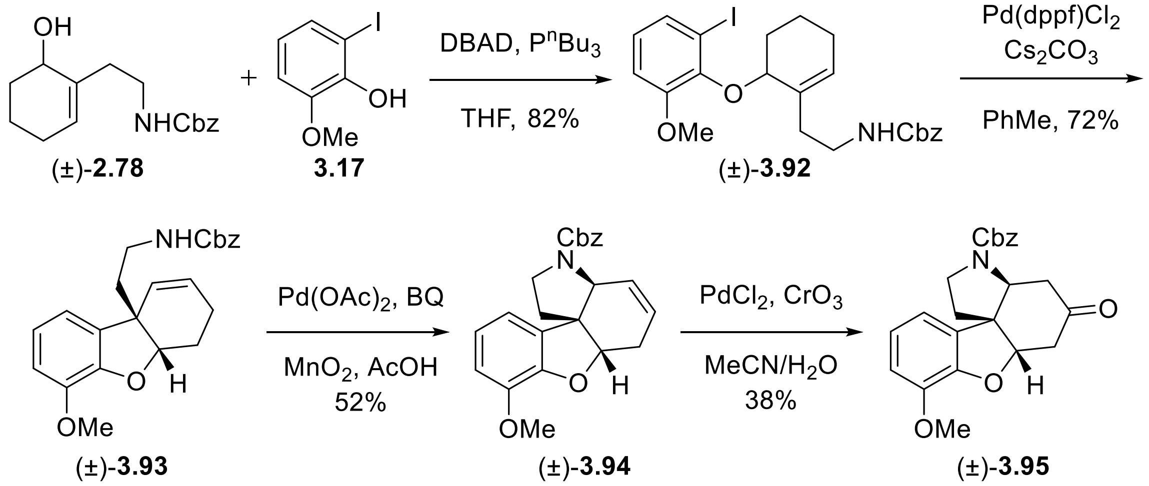
In terms of a synthesis via the aza-Wacker cyclisation/Wacker oxidation route, the advantages of installing the carbamate protecting group over the sulfonamide are two-fold. Firstly, once oxidised to the ketone, the presence of the much less electron withdrawing carbamate will reduce the leaving group ability of the nitrogen. In turn this should reduce the prevalence of the unwanted retro-Michael reaction prior to the removal of the group.

Secondly, the inclusion of the benzyl carbamate protecting group should allow for an easier, more functional group tolerant deprotection of the nitrogen. The main issue with the inclusion of the benzyl carbamate protecting group in the first synthetic route (described in chapter 2) was that deprotection by hydrogenolysis was not considered viable due to the presence of a double bond. Under the aza-Wacker-Wacker route the tetracyclic structure is formed and the double bond is absent, partially alleviating the problem. However, after the Wacker oxidation a similar issue presents itself as the carbamate protecting group needs to be cleaved in the presence of ketone, whilst also being performed under neutral conditions so not to initiate the unwanted retro-Michael reaction.

During hydrogenolysis of benzyl carbamate protecting groups, diatomic H_2 is predominantly used as the hydrogen source. This poses a problem as hydrogenation conditions with palladium on carbon and gaseous hydrogen will reduce not only the carbamate but the ketone as well. The use of other sources of hydrogen can be used to solve this issue. Numerous procedures are documented using cyclohexene or cyclohexa-1,4-diene as the hydrogen source for carbamate hydrogenolysis.[168–170] However, the reactivity is seemingly altered by this adjustment. Based on extensive literature searching it became apparent that hydrogenation in the presence of these two hydrogen sources does not reduce the ketone. This was shown most simply by Carde *et al.*, who used a Pd/C and cyclohexene hydrogenation procedure to selectively reduce the nitro group of a nitrobenzophenone.[171] This left the ketone untouched, which was then reduced using hydroboration conditions.

As well as hydrogenolysis, benzyl carbamates have also been cleaved using TBAF refluxing in THF[172] or boron trifluoride;[173] producing high yields of the free amine. Flouride is only weakly basic so should only have a minimal effect on the ketone.

The modified synthetic route (**Scheme 78**) synthesised benzyl carbamate protected 2-(β-aminoethyl)-cyclohexenol **2.78** using Suzuki coupling of benzyl vinylcarbamate. This was coupled with iodophenol **3.17** under DBAD/tri-*n*-butylphosphine Mitsunobu conditions forming ether **3.92** in 82% yield. The facially selective intramolecular Heck reaction was again completed using Pd(dppf)Cl_2 to form the tricyclic galanthamine scaffold **3.93** in 72% yield. The manganese dioxide/benzoquinone aza-Wacker cyclisation and subsequent chromium trioxide Wacker oxidation were completed to synthesis tetracyclic alkene **3.94** and tetracyclic ketone **3.95** in 52% then 38% yield respectively.



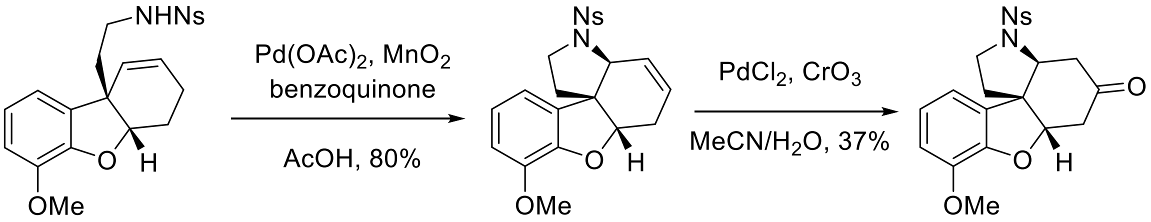
Scheme 78 - Use of the carbamate protecting group over the nosyl group led to a shorter, more efficient synthesis prior to any optimisation, producing a more stable carbamate protected ketone 3.95.

It is worth noting at this point that due to time constraints at this stage of the project we were only able to complete each of the reactions shown in **scheme 78** once. As such, no reaction optimisation was achieved. However, with no reaction optimisation and on a small scale, the Wacker oxidation to **3.95** still surpassed the yield achieved from the same reaction on the nosyl protected **3.80**. Moreover, the ketone **3.95** was treated to harsher temperatures with no noticeable breakdown of the product observed during isolated. There were minor impurities that could not be removed. However, it is anticipated that performing the reactions on a larger scale will facilitate purification in the future.

3.4.5 Conclusions

In this chapter we have attempted the synthesis of the tetracyclic ethanophenanthridine core of maritidine via a modification of a bidirectional conversion procedure originally developed for conversion between a full tetracyclic oxo-galanthamine structure and a full oxo-maritidine structure.

A reasonable synthesis of the retro-Michael precursor **3.80** was completed using both racemic and enantioenriched starting propargyllic alcohol (**Scheme 79**). This made use of a clever two step aza-Wacker cyclisation and Wacker oxidation to synthesise the tetracyclic structure required for the retro-Michael step.



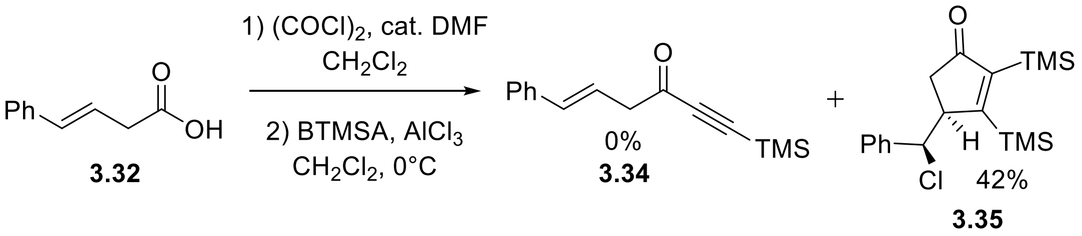
(-)-**3.42** (-)-**3.82** (-)-**3.80**

Scheme 79 - An asymmetric synthesis of ketone 3.80 was completed.

However, in our attempts to bypass the symmetrical intermediate present in their synthesis by formation of the enantioenriched tetracyclic structures present in ketones **3.89** and **3.95**, two major difficulties were encountered.

Firstly, unforeseen problems were encountered in the propargylation step to ketone **2.79** that could not be rectified by use of higher purity starting materials, reagents from multiple sources or condition optimisation. This hindered progress of the project greatly.

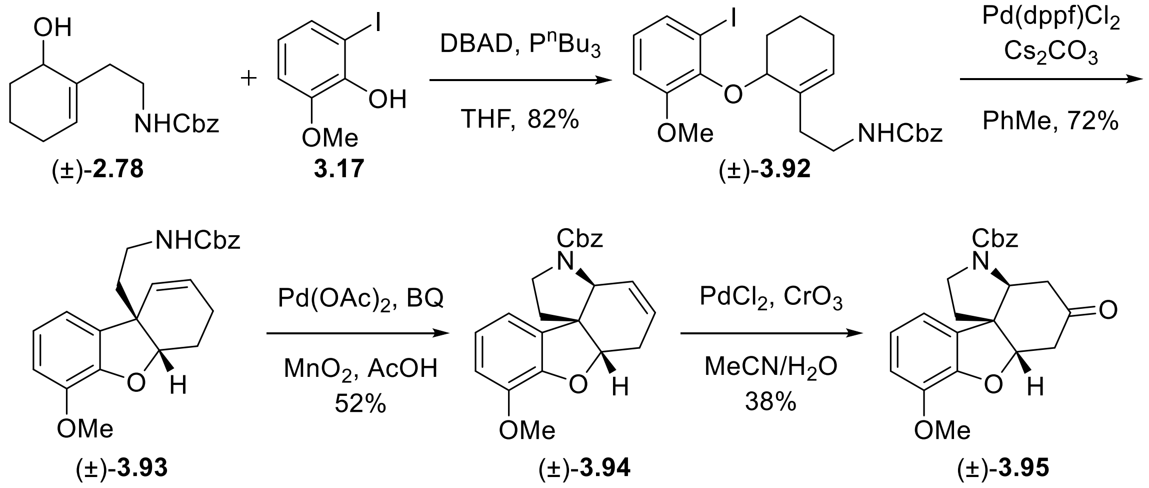
Secondly, direct allylic oxidation of tricyclic galanthamine scaffolds **3.48** and **3.42** was found to be nearly impossible to achieve with either high conversion or acceptable isolated yields. It is proposed that this is most likely due to stereoelectronic requirements of the oxidation reaction that are not satisfied by the rigid cyclohexenyl structure present in the tricyclic scaffolds. This is somewhat substantiated by the high yield achieved in the allylic oxidation on tricyclic benzo-cyclohexenyl-δ-valerolactone **3.74** by Valerio Isoni in previous work. Attempted pre-installation of the oxidised (future) allylic position during the propargylation stages prior to the Mitsunobu coupling with the phenol proved unsuccessful. However, these attempts accidentally revealed a simple new synthetic route from substituted cyclopentenones (**Scheme 80**).



Scheme 80 - A new synthetic route to substituted bis-TMS-cyclopentenones was discovered.

Lastly, upon achieving the unexpected synthesis of the tetracyclic ketone **3.80** by the poor allylic oxidations then by the aza-Wacker-Wacker route, it was discovered the leaving group ability of the nosyl sulfonamide group not only made the ketone inherently unstable but also hindered its own deprotection.

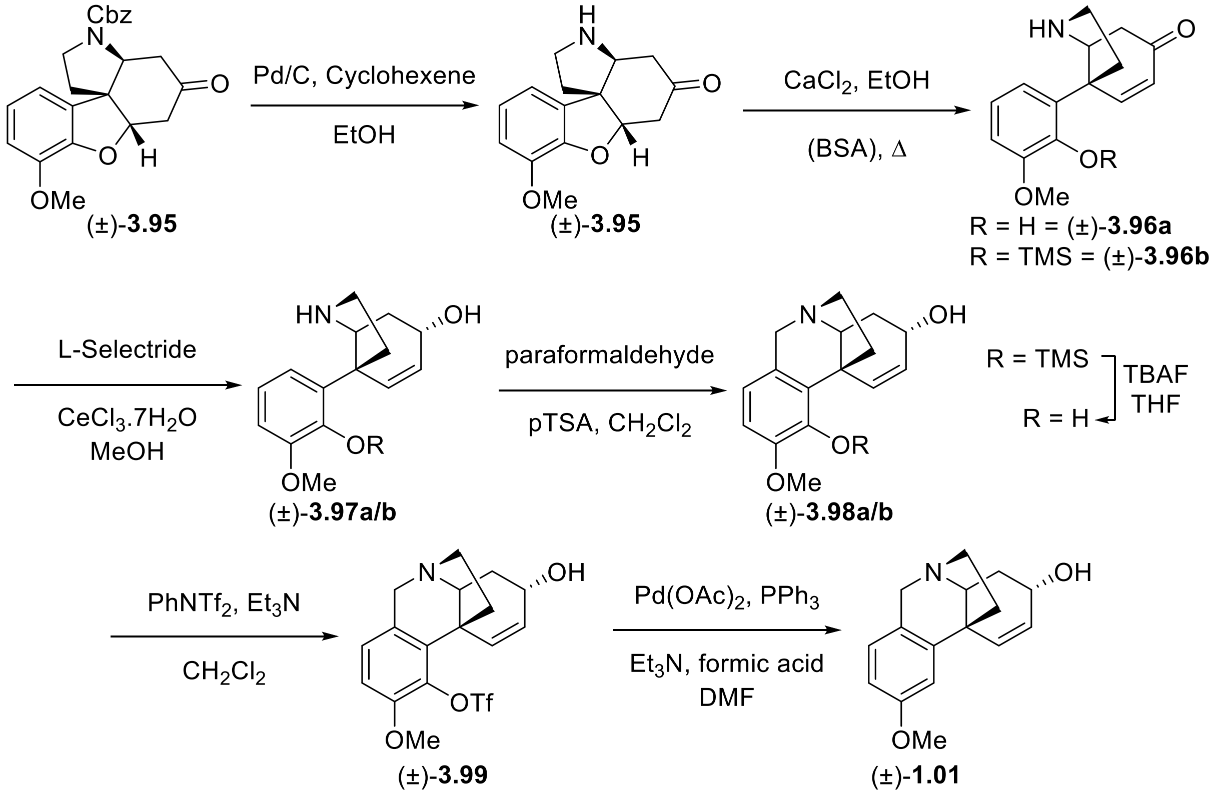
To combat these issues a new synthesis was envisaged and initiated, taking elements of the synthetic routes from chapters 1 and 2 and compiling them into a short 7-step linear synthesis of the benzyl carbamate protected tetracyclic ketone **3.95** (**Scheme 81**). Although time constraints only allowed for a single attempt at each reaction in this synthesis and no further optimisation, the stability of the product was observed to be higher than that of its nosyl analogue. Moreover, the designed future synthesis uses methods much less likely to initiate the unwanted retro-Michael reaction then the basic deprotection of the nosyl sulfonamide.



Scheme 81 - Changing to the benzyl carbamate protecting group allowed a much shorter, more efficient synthesis, that resolved problems with the stability of the tetracyclic ketone.

3.4.6 Future Work

Now that we have successfully reached a stage where the amine protecting group can potentially be cleaved using neutral means, I believe it is possible to reach the end of the synthesis provided the success of the retro-Michael elimination of the phenol. The planned final stages of the synthesis are shown below (**Scheme 82**). Once this route has been proven the full synthesis can be attempted using the dimethoxy phenol starting material **3.14**.



Scheme 82 - Planned synthesis towards the final martidine structure.

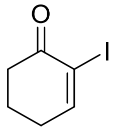
As described in section 3.4.4, the benzyl carbamate protecting group should be selectively cleaved, using palladium on carbon with cyclohexene as the hydrogen source, to amine **3.95**. After this, the retro-Michael elimination of the phenol can be induced using the conditions employed by Treu *et al.*[21] Failing this, other Lewis acids can be employed to induce the transformation. One possible issue here is the spontaneous reversal of the reaction from **3.96a** to **3.95**. This could be managed by a change of solvent from the alcohol and the inclusion of a silylating reagent, trimethylsilyl chloride or N,O-Bis(trimethylsilyl)acetamide, to cap the free alcohol and form **3.96b**. Reduction of the ketone to **3.97b** can then be achieved using a bulky reducing agent like L-Selectride combined with cerium trichloride to minimise 1,4-addition of the hydride. The presence of a trimethylsilyl protecting group on the phenol would help here, not only to help drive the selectivity of the reaction (see section 3.1) but to lower the amount of reducing agent needed. One equivalent of the borohydride would deprotonate the phenol and likely induce the Michael addition and reverse the previous reaction. From here, the Pictet-Spengler reaction using paraformaldehyde and para-toluenesulfonic acid will form the methylene bridge to the phenyl ring. The removal of the silyl protection group can then be achieved with TBAF in THF or potassium carbonate in methanol. Selective triflation of the phenol to **3.99** with *N*-phenylbis(trifluoromethanesulfonimide) and palladium catalysed reduction of the triflate under standard conditions with formic acid will complete the synthesis.[174]

Chapter 4 –Experimental Details

4.1 General Methods

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Fluorochem or Alfa Aesar. All air/moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame-dried glassware. The solvents THF (from Na/benzophenone), CH_3CN and CH_2Cl_2 (from CaH_2) and MeOH (from $Mg(OMe)_2$) were distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques.[175] TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} indicator; visualised under UV light (254 nm) and/or by staining with anisaldehyde, ceric ammonium molybdate, iodine, phosphomolybdic acid, potassium permanganate or vanillin. Flash column chromatography was performed using; high purity silica gel, pore size 60 Å, 230-400 mesh particle size, purchased from Merck. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3CN, acetone-*d6* or DMSO-*d6* solutions (purchased from Cambridge Isotope Laboratories) at 298 K using Bruker DPX400 (400 and 101 MHz respectively) spectrometers. Chemical shifts are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra; CD_3CN: 1.94 ppm for ^1H NMR spectra and 1.4 and 118.7 ppm for ^{13}C NMR spectra; acetone-*d6*: 2.09 ppm for ^1H NMR spectra and 29.9 and 206.7 ppm for ^{13}C NMR spectra; DMSO-*d6*: 2.50 ppm for ^1H NMR spectra and 39.52 ppm for ^{13}C NMR spectra). All spectra were reprocessed using ACD/Labs software version: 2015 or ACD/Spectrus. Coupling constants (*J*) were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), spt (septet), br (broad), and m (multiplet). Electrospray (ES) low resolution mass spectra were recorded on a Waters TQD quadrupole spectrometer. Electron impact (EI) low resolution mass spectra were recorded on a Trace 2000 Series GC-MS. High resolution mass spectra were recorded on a Bruker APEX III FT-ICR mass spectrometer. Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 fitted with a Smart Orbit Goldengate attachment using OMNIC software package. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra. Melting points were obtained using a Gallenkamp Electrothermal apparatus.

2-Iodocyclohex-2-enone (2.27)



C_6H_7IO

MW: 222.03 $gmol^{-1}$

Following a modified procedure by Krafft *et al.*,[176] to a solution of cyclohex-2-enone (9.29 mL, 95.9 mmol, 1.0 equiv.) in THF/water (250 mL 1:1) was sequentially added DMAP (2.34 g, 19.2 mmol, 0.2

equiv.), K_2CO_3 (15.97 g, 115 mmol, 1.2 equiv.) and iodine (36.5 g, 144 mmol, 1.5 equiv.) portion-wise. The reaction mixture was then stirred at rt for 2.5 h. Upon completion (TLC) the reaction mixture was diluted with EtOAc (250 mL), saturated $Na_2S_2O_3$ (aq)(250 mL) was added and the mixture was stirred for 5 min. The layers were separated and the aqueous layer extracted with EtOAc (200 mL). The combined organic layers were washed with 0.1 M HCl (200 mL). The HCl layer was then extracted with EtOAc (200 mL). The combined organic layers were then dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was dissolved in 30% EtOAc in hexane and filtered through a silica plug. The solvent was removed under reduced pressure, yielding the title compound **73** as a yellow crystalline solid (15.00 g, 67.2 mmol, 70%). Spectroscopic data are consistent with those reported.[177]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 7.77 (t, *J*=4.2 Hz, 1 H,C=C**H**), 2.70-2.65 (m, 2 H, C**H₂**C=O), 2.40 - 2.49 (m, 2 H, =CHC**H₂**), 2.09 (quin, *J*=6.3 Hz, 2 H, C**H₂**CH₂C=O) ppm

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ = 192.2 (**C**=O), 159.4 (=**C**H), 103.8 (=**C**-I), 37.2 (**C**H₂C=O), 29.9 (=CH**C**H₂), 22.8 (CH₂**C**H₂CH₂) ppm

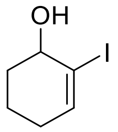
MP: 48-50 °C [lit. Mp: 49-51 °C][178]

FT-IR (neat) ν_{max} (cm^{-1}): 2937 (m), 1672 (s), 1582 (s), 1420 (m), 1311 (s), 1119 (s), 966 (s), 913 (s), 800 (s).

LR MS (ESI$^+$) (m/z): 223.1 [M+H]$^+$, 244.8 [M+Na]$^+$

HRMS (ES$^+$): Calculated for C_6H_8IO 222.9614, found 222.9614 Da

(±)-2-Iodocyclohex-2-enol (2.28)



C_6H_9IO

MW: 224.04 gmol^{-1}

Follwing a procedure by Larock *et al.*,[179] to a stirred solution of enone **2.27** (10.00 g, 45.0 mmol, 1.00 equiv.) in MeOH (100 mL) was added $CeCl_3.7H_2O$ (17.33 g, 45.9 mmol, 1.02 equiv.). The mixture was then cooled to –5 °C and stirred until homogenous. To the solution was then added $NaBH_4$ (1.87 g, 49.5 mmol, 1.10 equiv.) portionwise, maintaining the temperature at ≤–5 °C. The reaction mixture was then left to reach rt and then stirred for 2 h. Upon completion (TLC) the reaction was quenched with saturated NH_4Cl (aq)(50 mL) and stirred briefly. The solvent was then removed under reduced pressure and the gummy residue partitioned between EtOAc (100 mL) and saturated NH_4Cl (aq)(100 mL) and stirred. EtOAc/NH_4Cl (aq) mixture was decanted off and kept. The remaining gummy residue was triturated in EtOAc (100 mL) and the organic solution decanted into the EtOAc/NH_4Cl mixture. The layers were then separated and the aqueous extracted with EtOAc (2 x 50 mL). The combined organic layers were then dried (Na_2SO_4) and the solvent removed under reduced pressure, yielding the product as pale yellow oil (8.61 g, 38.4 mmol, 85%). Spectroscopic data were consistent with those reported.[26]

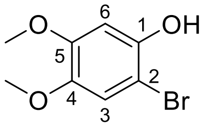
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 6.50 (t, *J*=4.1 Hz, 1 H, =C**H**), 4.19 (t, *J*=4.8 Hz, 1 H, C(OH)**H**), 2.22 – 1.52 (m, 6 H, C**H$_2$**C**H$_2$**C**H$_2$**) ppm

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ = 141.0 (=**C**H), 103.7 (=**C**-I), 72.1 (**C**OH), 31.9 (**C**H$_2$COH), 29.4 (=CH**C**H$_2$), 17.7 (CH$_2$**C**H$_2$CH$_2$) ppm

FT-IR (neat) *v*$_{max}$ (cm^{-1}): 3111 (br. m), 2939 (m), 2865 (w), 1625 (w), 1423 (w), 1053 (m), 968 (s)

LR MS (ESI$^+$) (m/z): 207.0 [M–OH]$^+$, 246.6 [M+Na]$^+$

2-Bromo-4,5-dimethoxyphenol (2.14)



$C_8H_9BrO_3$

MW: 233.06 gmol^{-1}

To a solution of 3,4-dimethoxyphenol (2.48 g, 16.1, mmol, 1.00 equiv.) in THF (30 mL) was added NBS (2.92 g, 16.4 mmol, 1.02 equiv.) portionwise. The resulting solution was stirred for 10 min. Upon completion the reaction mixture was diluted with EtOAc and washed with saturated $Na_2S_2O_3$ (aq), water and brine. The solvent was removed under reduced pressure and the crude residue purified by column chromatography (3:7 EtOAc/hexane), isolating the product as a dark grey solid that decomposed upon heating (3.45 g, 14.8 mmol, 92%). Spectroscopic data were consistent with those reported.[180]

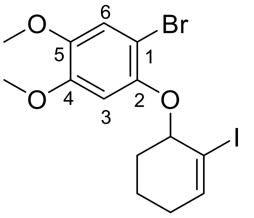
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 6.91 (s, 1 H, Ar$_3$**-H**), 6.62 (s, 1 H, Ar$_6$**-H**), 5.15 (s, 1 H, O**H**), 3.84 (s, 1 H, OC**H$_3$**), 3.82 (s, 1 H, OC**H$_3$**) ppm

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ = 149.9 (**C$_{Ar}$**OMe), 146.7 (**C$_{Ar}$**OMe), 143.7 (**C$_{Ar}$**OH), 114.5 (**C$_{Ar}$3**H), 100.4 (**C$_{Ar}$6**H), 98.5 (**C$_{Ar}$**Br), 56.7 (O**C**H$_3$), 56.1 (O**C**H$_3$) ppm

LR ESI$^-$ MS (m/z): 216.0 and 218.1 (^{79}Br and ^{81}Br)[M-Me]$^-$, 231.1 and 233.1(^{79}Br and ^{81}Br)[M-H]$^-$

LR MS (ESI$^+$) (m/z): 233.1 and 235.1 (^{79}Br and ^{81}Br)[M+H]$^+$

(±)-1-Bromo-2-((2-iodocyclohex-2-en-1-yl)oxy)-4,5-dimethoxybenzene (1.81)



$C_{14}H_{16}BrIO_3$

MW: 439.09 gmol^{-1}

A solution of phenol **2.14** (1.09 g, 4.7 mmol, 1.05 equiv.) in THF (20 mL) was added n-Bu_3P (2.25 mL, 9.0 mmol, 2.00 equiv.), causing the brown/purple solution to turn a pale yellow. To the solution was then added both cyclohexenol **2.28** (1.00 g, 4.5 mmol, 1.00 equiv.) in THF (20 mL) then DBAD (2.07 g, 9.0 mmol, 2.00 equiv.) in THF (20 mL) slowly, dropwise, via cannula. The reaction mixture was stirred at rt for 1 h then quenched with water (60 mL). The layers were then separated and extracted with Et_2O (3 x 60 mL). The combined organic layers were then dried (Na_2SO_4) and solvent removed under reduced pressure. Purification by column chromatography (1:4 EtOAc/hexane) yielded the product as a pale yellow/clear oil (1.50 g, 3.57 mmol, 76%).

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 7.00 (s, 1 H, Ar_6-**H**), 6.83 (s, 1 H, Ar_3-**H**), 6.70 (dd, *J*=4.8, 2.9 Hz, 1 H. =C**H**), 4.61 (m, 1 H, ArOC**H**), 3.87 (s, 3 H, OC**H₃**), 3.84 (s, 3 H, OC**H₃**), 1.37 - 2.38 (m, 6 H=CHC**H₂**C**H₂**C**H₂**) ppm

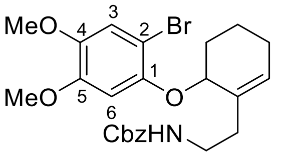
^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ = 149.0 (**C**$_{Ar}$OMe), 148.9 (**C**$_{Ar}$OMe), 145.1 (**C**$_{Ar}$OCH), 143.6 (=**C**H-CH(O)-), 115.5 (**C**$_{Ar}$**6**H), 104.5 (=**C**-I), 104.3 (**C**$_{Ar}$**3**H), 96.2 (**C**$_{Ar}$Br), 83.1 (**C**OAr), 56.4 (O**C**H_3), 56.2 (O**C**H_3), 29.5 (**C**H_2COAr), 28.1 (=CH**C**H_2), 16.7 (CH_2**C**H_2CH_2) ppm

FT-IR (neat) *ν*$_{max}$ (cm^{-1}): 2935 (m), 3837 (w), 1500 (s), 1196 (s), 992 (s)

LR MS (ESI$^+$) (m/z): 438.1 and 440.1 (^{79}Br and ^{81}Br) [M+H]$^+$

HRMS (ES$^+$): Calculated for $C_{14}H_{16}BrIO_3Na$ 460.9220, found 460.9232 Da

(±)- Benzyl (2-(6-(2-bromo-4,5-dimethoxyphenoxy)cyclohex-1-en-1-yl)ethyl)carbamate (1.84)



$C_{24}H_{28}BrNO_5$

MW: 490.39 gmol^{-1}

Suzuki Method

To a solution of benzyl-*N*-vinyl carbamate **1.82** (0.212 g, 1.20 mmol, 1.10 equiv.) in THF (1 mL) was added a solution of 9-BBN dimer (0.146 g, 0.60 mmol, 0.55 equiv.) in THF (4 mL) dropwise at -15 °C. The suspension was then allowed to reach rt, during which time it became homogenous. It was then stirred at rt for 4 h. To the reaction mixture was then added 3 M NaOH (1 mL, 3.00 mmol), and it was stirred for 10 min. This mixture was then added, dropwise, via cannula to an orange suspension of aryl cyclohexenyl ether **1.81** (0.439 g, 1.00 mmol, 1.00 equiv.) and Pd(dppf)Cl_2 (0.066 g, 0.09 mmol, 0.09 equiv.) in THF (3 mL), turning the mixture dark brown. The reaction mixture was then stirred at rt for 20 h. Upon completion the reaction mixture was diluted with hexane (10 mL), cooled to 0 °C and a solution of 2:1 phosphate buffer (pH 7): 30 wt% H_2O_2 (aq)(20 mL) added dropwise. The palladium precipitates were then removed by filtration through a celite plug, washing with Et_2O. The layers were separated and the aqueous layer extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:4-2:3 EtOAc/hexane), affording the product as a colourless oil (0.265 g, 0.54 mmol, 54%).

Mitsunobu Method

To a solution of bromophenol **2.14** (0.187 g, 0.80 mmol, 1.1 equiv.) in THF (5 mL) was added n-Bu_3P (0.28 mL, 1.10 mmol, 1.5 equiv.) then a solution of benzyl (2-(6-hydroxycyclohex-1-en-1-yl)ethyl)carbamate **2.78** (0.200 g, 0.73 mmol, 1.0 equiv.) in THF (15 mL). The reaction mixture was cooled to 0 °C, then added DBAD (0.252 g, 1.10 mmol, 1.5 equiv.) was slowly added, dropwise, during which time the solution turned green. The reaction mixture was allowed to reach rt and stirred for 14 h. Upon completion the solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:4 EtOAc/Hexane w/ 0.1 % Et_3N), yielding the product as a colourless oil (0.292 g, 0.60 mmol, 82%).

^{1}H NMR (400 MHz, ACETONITRILE-d$_3$) δ = 7.27-7.39 (m, 5H, Ar$_{Cbz}$-**H**), 7.07 (s, 1H, Ar$_3$-**H**), 6.79 (s, 1H, Ar$_6$-**H**), 5.77 (br s, 1H, C=C**H**), 5.59 (br s, 1H, N**H**), 5.05 (d, *J*=13.1 Hz, 1H, C**H$_2$**Ph), 5.01 (d, *J*=13.1 Hz, 1H, C**H$_2$**Ph), 4.75 (br s, 1H, ArOC**H**), 3.81 (s, 3H, OC**H$_3$**), 3.74 (s, 3H, OC**H$_3$**), 3.15-3.34 (m, 2H, C**H$_2$**NHCbz), 2.30 (m, 1H, C**H$_2$**CH$_2$NHCbz), 2.25 (m, 1H, C**H$_2$**CH$_2$NHCbz), 2.10 (m, 1H, C=CH-C**H$_2$**), 1.99 (m, 1H, C=CH-C**H$_2$**), 1.85 (m, 1H, ArOCHC**H$_2$**), 1.75 (m, 1H, CH$_2$C**H$_2$**CH$_2$), 1.65 (m, 1H, ArOCHC**H$_2$**), 1.54 (m, 1H, CH$_2$C**H$_2$**CH$_2$) ppm

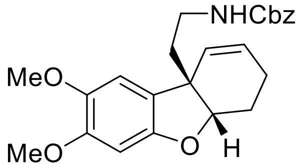
^{13}C NMR (101 MHz, ACETONITRILE-d$_3$) δ = 156.9 (**C**=O), 150.2 (**C$_{Ar}$**-O), 149.2 (**C$_{Ar}$**-O), 145.0 (**C$_{Ar}$**-O), 138.2 (**C$_{ArCbz}$**), 134.2 (**C**=CH), 130.0 (C=**C**H), 129.0 (**C$_{ArCbz}$**-H), 128.4 (**C$_{ArCbz}$**-H), 128.2 (**C$_{ArCbz}$**-H), 116.9

(**C$_{Ar}$3**-H), 103.2 (**C$_{Ar}$6**-H), 103.0 (**C$_{Ar}$**-Br), 75.7 (ArO**C**H), 66.2 (**C**H$_2$Ph), 56.7 (O**C**H$_3$), 56.4 (O**C**H$_3$), 40.0 (**C**H$_2$NHCbz), 35.3 (**C**H$_2$CH$_2$NHCbz), 28.0 (ArOCH**C**H$_2$), 25.7 (C=CH-**C**H$_2$), 18.3 (CH$_2$**C**H$_2$CH$_2$) ppm

LR MS (ESI$^+$) m/z: 512.1 + 514.1 (^{79}Br and ^{81}Br) [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{24}H_{28}{}^{79}BrNO_5Na$]$^+$ 512.1043, found 512.1044 Da

(±)-benzyl (2-((5aS,9aS)-2,3-dimethoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)ethyl)carbamate (1.80)



$C_{24}H_{27}NO_5$

MW: 409.48 gmol^{-1}

A solution of aryl bromide **1.84** (0.488 g, 0.99 mol, 1.00 equiv.) in toluene (15 mL) was degassed (N_2, 30 min) them added Pd(dppf)Cl_2, (0.110 g, 0.15 mmol, 0.15 equiv.) and Cs_2CO_3 (0.970 g, 2.98 mmol, 3.00 equiv.) were added and the resulting mixture stirred at 90-95 °C for 15 h. Upon completion the reaction mixture was left to cool to rt, diluted with hexane (10 mL), cooled to –15 °C and a solution of phosphate buffer (pH 7)/30% H_2O_2 2:1 (20 mL) was added dropwise. The palladium salts were removed by filtering through a pad of celite, washing with Et_2O. The layers were then separated and the aqueous extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (2:3 EtOAc/Hexane), yielding the product as colourless oil (0.270 g, 0.32 mmol, 66%).

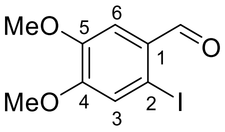
^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 7.35 (m, 5H, Ar$_{Cbz}$-**H**), 6.64 (s, 1H, Ar-**H**), 6.44 (s, 1H, Ar-**H**), 5.84 (m, 1H, CH=C**H**-CH$_2$), 5.60 (d, *J*=9.9 Hz, 1H, C**H**=CH-CH$_2$), 5.09 (s, 2H, C**H$_2$**Ph), 4.85 - 4.71 (m, 2H, ArOC**H** and N**H**), 3.82 (s, 6H, OC**H$_3$**), 3.33 - 3.13 (m, 2H, C**H$_2$**NHCbz), 2.23 - 2.05 (m, 2H, CH=CH-C**H$_2$**), 1.97 - 1.87 (m, 2H, CH=CHCH$_2$C**H$_2$**), 1.86 - 1.61 (m, 2H, C**H$_2$**CH$_2$NH) ppm

^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 156.2 (**C**=O), 152.6 (**C$_{Ar}$**-O), 149.6 (**C$_{Ar}$**-O), 143.6 (**C$_{Ar}$**-O), 136.5 (**C$_{ArCbz}$**), 130.4 (**C**=CH-CH$_2$), 128.5 (C=**C**H-CH$_2$), 128.1 (**C$_{ArCbz}$**-H), 127.2 (**C$_{ArCbz}$**-H), 125.8 (**C$_{ArCbz}$**-H), 123.8 (**C**$_{Ar}$-C$_{quart}$), 107.3 (**C$_{Ar}$**H), 95.5 (**C$_{Ar}$**H), 85.9 (ArO**C**H), 66.7 (**C**H$_2$Ph), 57.0 (O**C**H$_3$), 56.0 (O**C**H$_3$), 47.2 (C$_{quart}$), 39.1 (**C**H$_2$NHCbz), 37.5 (**C**H$_2$CH$_2$NHCbz), 25.0 (ArOCH**C**H$_2$), 19.5 (C=C-**C**H$_2$) ppm

LR MS (ESI$^+$) m/z: 432.2 [M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{24}H_{27}NO_5Na]^+$ 432.1781, found 432.1781 Da

2-Iodo-4,5-dimethoxybenzaldehyde (2.24)



$C_9H_9IO_3$

MW: 292.07 gmol^{-1}

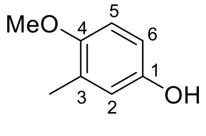
To a solution of 3,4-dimethoxybenzaldehyde (0.80 g, 4.80 mmol, 1.0 equiv.) and silver trifluoroacetate (1.06 g, 4.80 mmol, 1.0 equiv.) In EtOAc (10 mL) was added a solution of iodine (1.22 g, 4.80 mmol, 1.0 equiv.) in EtOAc (15 mL,) dropwise, over 30 min, during which time a cream ppt formed (AgI). Further amounts of silver trifluroacetate and iodine were added (up to a total 2 equiv.) over time. However the reaction did not proceed to completion. The reaction mixture was filtered, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was purified by column chromatography (1:1 Et_2O/hexane, product rf = 0.3) affording a pale yellow powder (194 mg, 0.624 mmol, 13%). Spectroscopic data were consistent with those reported.[181]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 9.88 (s, 1 H, C**H**O), 7.42 (s, 1 H, Ar_6-**H**), 7.32 (s, 1 H, Ar_3-**H**), 3.96 (s, 3 H, OC**H₃**), 3.93 (s, 3 H, OC**H₃**) ppm

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ = 194.9 (**C**HO), 154.5 (**C_{Ar}4**), 149.8 (**C_{Ar}5**), 128.4 (**C_{Ar}1**), 121.8 (**C_{Ar}6**), 111.1 (**C_{Ar}3**), 92.7 (**C_{Ar}**I), 56.5 (O**C**H_3), 56.1 (O**C**H_3) ppm

Mp: 140-142 °C [lit. 137-139 °C][182]

4-Methoxy-3-methylphenol (2.93)



$C_8H_{10}O_2$

MW: 138.17 gmol^{-1}

Following a procedure by Mulakayala *et al.*, [91] to a solution of (4-methoxy-3-methylphenyl)boronic acid (0.914 g, 5.50 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added 30 wt % H_2O_2 (aq)(20 mL) and Amberlite Resin (0.100 g). The reaction mixture was then stirred for 1 h at rt. Upon completion the Amberlite Resin was removed by filtration, washing with CH_2Cl_2. The layers were separated the and aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 5% $NaHCO_3$ (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure, yielding the product as a tan powdery solid (0.760 g, 5.50 mmol, quant.). Spectroscopic and physical data were consistent with those reported.[183]

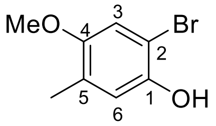
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 6.69 (d, *J* = 8.3 Hz, 1 H, Ar_5-**H**) 6.64 (dd, *J* = 7.9, 3.0 Hz, 1 H, Ar_6-**H**) 6.60 (d, *J* = 3.0 Hz, 1 H, Ar_2-**H**) 4.71 (s, 1 H, -O**H**) 3.77 (s, 3 H, -OC**H$_3$**) 2.18 (s, 3 H, ArC**H$_3$**) ppm

^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 152.0 (**C$_{Ar}$**OMe), 149.0 (**C$_{Ar}$**OH), 128.1 (**C$_{Ar}$**Me), 118.0 (**C$_{Ar}$**H), 112.5 (**C$_{Ar}$**H), 111.3 (**C$_{Ar}$6**H), 56.0 (O**C**H$_3$), 16.2 (Ar**C**H$_3$) ppm

FT-IR (neat) *ν*$_{max}$ (cm^{-1}): 3161 (br), 2939 (s), 2866 (s), 2820 (s)

Mp: 44-46 °C (lit. 46-46.5 °C)[184]

2-Bromo-4-methoxy-5-methylphenol (2.94)



$C_8H_9BrO_2$

MW: 217.06 gmol^{-1}

A solution of 4-methoxy-3-methylphenol **2.93** (0.740 g, 5.50 mmol, 1.00 equiv.) in $CHCl_3$ (20 mL) was cooled to –15 °C, then a solution of bromine (0.880 g, 5.51 mmol, 1.02 equiv.) in $CHCl_3$ (50 mL) was added, dropwise, over 3 h, maintaining the reaction temperature at < –10 °C. The reaction mixture was stirred for a further 15 min after addition, then quenched with saturated $Na_2S_2O_3$ (aq)(40 mL) and stirred for 5 min. The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with water, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The phenol was isolated as a tan solid (1.15 g, 5.30 mmol, 98%). Spectroscopic and physical data were consistent with those reported.[92]

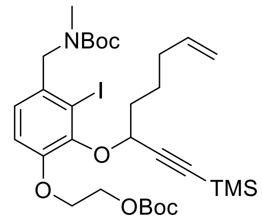
^{1}H NMR (300MHz, CHLOROFORM-d) δ = 6.87 (s, 1H, Ar**H**), 6.83 (s, 1H, Ar**H**), 5.04 (s, 1H, -O**H**), 3.76 (s, 3H, -OC**H$_3$**), 2.15 (s, 3H, ArC**H$_3$**) ppm

^{13}C NMR (75MHz, CHLOROFORM-d) δ = 152.1 (**C$_{Ar}$**OMe), 145.9 (**C$_{Ar}$**OH), 128.2 (**C$_{Ar}$**Me), 117.9 (C$_{Ar}$H), 113.4 (**C$_{Ar}$**H), 105.9 (**C**Br), 56.0 (O**C**H$_3$), 16.0 (Ar**C**H$_3$) ppm

FT-IR (neat) *ν*$_{max}$ (cm^{-1}): 3224 (br), 3004 (s), 2958 (s), 2830 (s), 1506 (s), 1411 (s), 1194 (s).

M.p. 74-76 °C [lit. 76-78 °C][92]

(±)-tert-Butyl (4-(2-((tert-butoxycarbonyl)oxy)ethoxy)-2-iodo-3-((1-(trimethylsilyl)oct-7-en-1-yn-3-yl)oxy)benzyl)(methyl)-λ^4-azanecarboxylate (2.91)



$C_{31}H_{48}INO_7Si$

MW: 701.71 gmol^{-1}

To a solution of *t*-butyl (4-(2-((tert-butoxycarbonyl)oxy)ethoxy)-3-hydroxy-2-iodobenzyl)(methyl)-λ^4-azanecarboxylate **2.90** (0.100 g, 0.19 mmol, 1.1 equiv.) and PPh_3 (0.091 g, 0.35 mmol, 2.0 equiv.) in THF (3 mL) was added (±)-1-(trimethylsilyl)oct-7-en-1-yn-3-ol (**86**, 0.034 g, 0.17 mmol, 1.0 equiv.) in THF (4 mL) then DIAD (0.069 mL, 0.35 mmol, 2.0 equiv.) drop wise. The reaction mixture stirred at 47 °C for 20 h. The reaction mixture was quenched with water and diluted with Et_2O. The layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was then purified by column chromatography (1:4 EtOAc/hexane), yielding the product as an off white solid (0.111 g, 0.16 mmol, 91 %).

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 6.91 - 6.74 (m, 2H, Ar$_5$-**H**, Ar$_6$-**H**), 5.87 (ddt, *J*=17.0, 10.3, 6.7 Hz, 1H, H_2C=C**H**-), 5.25 (br s, 1H, ArOC**H**), 5.06 (br dd, J=17.0, 1.5 Hz, 1H, **H$_{trans}$**HC=CH-), 4.99 (br d, J=10.2 Hz, 1H, **H$_{cis}$**HC=CH-), 4.54 - 4.35 (m, 4H, C**H$_2$**OBoc , C**H$_2$**NMeBoc), 4.20 (t, *J*=4.5 Hz, 2H, ArOC**H$_2$**), 2.90 - 2.74 (br. s, 3H, NC**H$_3$**), 2.18 (q, *J*=7.0 Hz, 2H, H_2C=CHC**H$_2$**-), 2.06 - 1.91 (m, 2H, OCHC**H$_2$**-), 1.85 - 1.66 (m, 2H, CH_2C**H$_2$**CH_2), 1.53 - 1.42 (m, 18H, C(C**H$_3$**)$_3$), 0.03 (s, 9H, -TMS) ppm

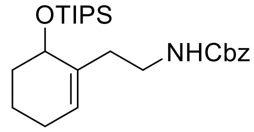
^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 153.7 (**C$_{Ar}$**O), 150.4 (**C$_{Ar}$**O), 138.9 (**C**=CH_2), 122.3 (**C$_{Ar}$**-H), 115.0 (C=**C**H$_2$), 114.1 (**C$_{Ar}$**-H), 104.0 (**C**≡C-TMS), 92.6 (**C$_{Ar}$**-I), 82.8 (C≡**C**-TMS), 80.1 (**C$_{Ar}$**-CH_2), 72.4 (ArO**C**H), 67.4 (O**C**H$_2$), 65.2 (O**C**H$_2$), 58.0 (**C**H$_2$NMeBoc), 35.7 (ArOCH**C**H$_2$), 34.4 (N**C**H$_3$), 33.8 (C=C-CH_2), 28.7 ((**C**CH$_3$)$_3$), 28.1 (**C**(CH$_3$)$_3$), 24.8 (**C**H$_2$), 0.0 (Si(**C**H$_3$)$_3$) ppm

LR MS (ESI$^+$) m/z: 724.4 [M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{31}H_{48}INO_7SiNa]^+$ 724.2137, found 724.2144 Da

FT-IR (neat) ν_{max} (cm^{-1}): 2976 (w), 2359 (w), 1742 (s), 1692 (s), 1250 (s), 1153 (s), 843 (m), 731 (m).

(±)- Benzyl (2-(6-((triisopropylsilyl)oxy)cyclohex-1-en-1-yl)ethyl)carbamate (2.73)



$C_{25}H_{41}NO_3Si$

MW: 431.69 gmol^{-1}

Follwing a procedure by Overman *et al.*,[78] to a solution of benzyl-*N*-vinyl carbamate **1.82** (0.195 g, 1.10 mmol, 1.10 equiv.) in THF (1mL) was added a solution of 9-BBN dimer (0.134 g, 0.55 mmol, 0.55 equiv.) in THF (5 mL), dropwise, at –15 °C. The suspension was then allowed to reach rt, during which time it became homogenous, stirring was continued at rt for 4 h. 2M NaOH (2.0 mL, 4.00 mmol, 4.00 equiv.) was then added and the mixture was stirred for 10 min. This mixture was then added, dropwise, via cannula to an orange suspension of ((2-iodocyclohex-2-en-1-yl)oxy)triisopropylsilane **2.72** (0.380 g, 1.00 mmol, 1.00 equiv.) and Pd(dppf)Cl_2 (0.066 g, 0.09 mmol, 0.09 equiv.) in THF (3 mL), turning the mixture dark brown. The reaction mixture was then stirred at rt for 20 h. Upon completion the reaction mixture was diluted with hexane, cooled to 0 °C and added, dropwise, a solution of 2:1 phosphate buffer (pH 7): 30 wt % H_2O_2 (aq). The palladium precipitates were removed by filtration through a celite plug, washing with Et_2O. The layers were then separated and the aqueous layer extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/hexane), affording the product as a clear oil (0.388 g, 0.90 mmol, 90%). Spectroscopic and physical data were consistent with those reported.[78]

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 7.45 - 7.28 (m, 5H, Ar**H**), 5.54 (m, 1H, =C**H**), 5.11 (s, 2H, PhC**H₂**), 4.90 (m, 1H, N**H**), 4.30 (m, 1H, C**H**OSi), 3.46 - 3.25 (m, 2H, C**H₂**N), 2.43 (m, 1H, NCH$_2$C**H₂**), 2.24 (m, 1H, NCH$_2$C**H₂**), 2.12 - 1.89 (m, 2H, C**H₂**CH=), 1.85 - 1.70 (m, 3H, C**H₂**C**H₂**CHOSi), 1.55 (m, 1H, C**H₂**C**H₂**CHOSi), 1.10 (br s, 21H, -OTIPS) ppm

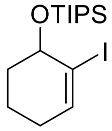
13C NMR (75 MHz, CHLOROFORM-d) δ = 156.3 (**C**=O), 137.13 (**C**$_{\mathbf{Cbz}}$), 136.7 (CH=**C**-CH$_2$), 128.5 (**C**H=C-CH$_2$), 128.1 (**C**$_{\mathbf{Cbz}}$-H), 128.0 (**C**$_{\mathbf{Cbz}}$-H), 126.1 (**C**$_{\mathbf{Cbz}}$-H), 68.4 (**C**HOSi), 66.5 (**C**H$_2$Ph), 39.6 (**C**H$_2$NHCbz), 33.5 (**C**H$_2$CHOSi), 32.2 (**C**H$_2$CH$_2$NHCbz), 25.4 (**C**H$_2$CH=C), 18.3 (CH$_2$**C**H$_2$CH$_2$), 18.2 (Si**C**H), 12.9 (SiCH(**C**H$_3$)$_2$) ppm

LR (ESI+) MS m/z: 454.3 [M+Na]$^+$, 886.5 [2M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{25}H_{41}NO_3SiNa$]$^+$ 454.2748, found 454.2749 Da

FT-IR (neat) ν_{max} (cm^{-1}): 3337 (br. w), 2939 (m), 2864 (m), 1701 (s), 1515 (s), 1457 (s), 1244 (s), 1063 (s), 1012 (s), 882 (m).

(±)((2-iodocyclohex-2-en-1-yl)oxy)triisopropylsilane (2.72)



$C_{15}H_{29}IOSi$

MW: 380.39 gmol^{-1}

Follwing a procedure by Overman *et al.*,[78] to a solution of 2-iodocyclohex-2-enol **2.28** (0.10 g, 0.45 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was added TIPS-OTf (0.14 mL, 0.54 mmol, 1.2 equiv.) then 2,6-Lutidine (0.10 mL, 0.90 mmol, 2.0 equiv.) and the mixture was stirred at rt for 72 h. Upon completion (TLC) the reaction mixture was diluted with CH_2Cl_2 and washed with 2M HCl, water and brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure, yielding the crude as anoff white oil. The crude residue was purified by column chromatography (1:9 EtOAc/Hexane) to afford the product as clear oil (0.14 g, 0.36 mmol, 82 %) yield. Spectroscopic and physical data were consistent with those reported.[78]

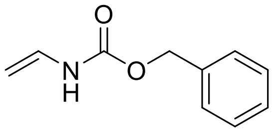
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 6.47 (t, *J*=4.0 Hz, 1 H, =C**H**), 4.37 (s, 1 H, C**H**OTIPS), 1.56 - 2.20 (m, 6 H, C**H$_2$**C**H$_2$**C**H$_2$**CH-O-TIPS), 1.07 - 1.16 (m, 21 H, OTIPS) ppm

^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 140.32 (C=**C**H), 103.5 (**C**=CH), 73.0 (**C**HOTIPS), 33.7 (**C**H$_2$CHOSi), 29.5 (**C**H$_2$CH=C), 18.4 (Si**C**H), 17.5 (CH$_2$**C**H$_2$CH$_2$), 12.9 (SiCH(**C**H$_3$)$_2$) ppm

LR (ESI+) MS m/z: 381.0 [M+H]$^+$

FT-IR (neat) ν_{max} (cm^{-1}): 2940 (s), 2863 (s), 1462 (m), 1094 (s), 1060 (s)

Benzyl-*N*-Vinylcarbamate (1.82)



$C_{10}H_{11}NO_2$

MW: 177.20 gmol^{-1}

Follwing a procedure by Overman *et al.*,[78] A solution of sodium azide (2.00 g, 30.0 mmol, 1.50 equiv.) in H_2O (20 mL) was cooled to –8 - 0 °C and a solution of acryloyl chloride (1.63 mL, 20.0 mmol, 1.00 equiv.) in toluene (15 mL) was added slowly, dropwise, followed by TBAI (0.37 g, 1.00 mmol, 0.05 equiv.). The mixture was stirred at <0 °C for 6 h. The reaction mixture was then left to reach rt, the layers were separated and the aqueous layer extracted with toluene. The combined organic layers were washed with saturated Na_2CO_3 (aq) and dried over Na_2SO_4, storing the solution over Na_2SO_4 at <0 °C overnight.

A solution of anhydrous benzyl alcohol (5.00 mL, 29.0 mmol, 1.45 equiv.), hydroquinone (0.12 g, 1.10 mmol, 0.06 equiv.) and anhydrous pyridine (0.810 mL, 10.0 mmol, 0.50 equiv.) was then heated to 100 °C and the solution of acryloyl azide was added, dropwise, over 40 min. The solution was then stirred at 110 °C for 1 h, allowed to cool to rt and washed with saturated Na_2CO_3 (aq). The organic layer was then dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/hexane w/ 0.5% Et_3N) to afford the product as a low melting white solid (2.00 g, 11.2 mmol, 56 %). Spectroscopic and physical data were consistent with those reported.[78]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 7.45 - 7.28 (m, 5 H, Ph), 6.72 (m, 1 H, =C**H**), 6.57 (br s, 1 H, N**H**), 5.14 (s, 2 H, OC**H₂**Ph), 4.48 (d, *J*=15.5 Hz, 1 H, $\mathbf{H_{trans}}$C=CH), 4.29 (d, *J*=8.7 Hz, 1 H, $\mathbf{H_{cis}}$C=CH) ppm

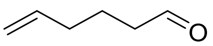
^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 153.4 (**C**=O), 135.8 ($\mathbf{C_{Ar}}$CH₂), 129.8 ($\mathbf{C_{Ar}}$H), 128.6 (C=**C**HNH), 128.3 ($\mathbf{C_{Ar}}$H), 128.2 ($\mathbf{C_{Ar}}$H), 93.3 (**C**H₂=CH), 67.2 (**C**H₂Ph) ppm

FT-IR (neat) ν_{max} (cm^{-1}): 3275 (s), 1693 (s), 1643 (s), 1528 (s), 1249 (s), 1080 (s)

Mp: 40.2 – 42.6 °C [lit. 43-44 °C][78]

LR MS (ESI$^+$) m/z: 218.2 $[M + MeCN + H]^+$, 554.1 $[3M + Na]^+$

5-Hexenal (2.85)

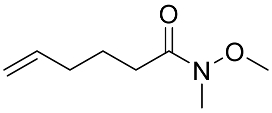


$C_6H_{10}O$

MW: 98.14 gmol^{-1}

To a mixture of silica Gel 60 (16 g) in CH_2Cl_2 (100 mL) was added PCC (16.2 g, 75.0 mmol, 1.5 equiv.). The mixture was stirred for 10 min then cooled to 0 °C, upon which time 5-hexen-1-ol (5.00 g, 50.0 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added, dropwise, via cannula. The reaction mixture was stirred at rt for 3 h then Et_2O (100 mL) was added, stirred for a further 5 min then filtered through a plug of silica, washing with Et_2O. The solvent was removed under reduced pressure to give the crude mixture (3.14 g); which was used in the next step without further purification.

N-methoxy-*N*-methylhex-5-enamide (3.21)



$C_8H_{15}NO_2$

MW: 157.21 gmol^{-1}

DCC Method

To a solution of 5-hexanoic acid (2.10 mL, 17.5 mmol, 1.00 equiv.) in CH_2Cl_2 (100 mL) was added DCC (5.43 g, 26.3 mmol, 1.50 equiv.), DMAP (3.74 g, 30.6 mmol, 1.75 equiv.) and *N*,*O*-dimethylhydroxylamine. HCl (2.56 g, 26.3 mmol, 1.50 equiv.). The resulting mixture was stirred at rt for 4.5 h. Upon completion (TLC) the reaction mixture was quenched with brine (100 mL), filtered (washing with CH_2Cl_2) the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with 2 M HCl (100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was then triturated with Et_2O, collecting the supernatant (3 x 100 mL). The solvent was then removed under reduced pressure and the crude oil purified by column chromatography (2:3 EtOAc/hexane), yielding the product as a colourless oil (2.48 g, 15.8 mmol, 90 %). Spectroscopic and physical data were consistent with those reported.[185]

Acyl Chloride Method

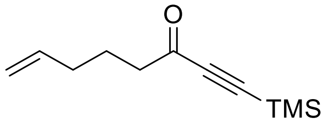
Follwing a procedure by Satcharoen *et al.*,[143] A solution of hexenoic acid (4.53 g, 39.7 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) containing 5 drops of anhydrous DMF was cooled to 0 °C, then oxalyl chloride (4.0 mL, 47.6 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was the stirred at rt for 1.5 h, until excess gas evolution had ceased. Solvent and excess oxalyl chloride was removed under reduced pressure, and the residue redissolved in CH_2Cl_2 (100 mL). The solution was then cooled to 0 °C and *N*,*O*-dimethylhydroxylamine.HCl (4.26 g, 44.0 mmol, 1.1 equiv.) was added followed by dropwise addition of Et_3N (13.8 mL, 99.3 mmol, 2.5 equiv.). The mixture was allowed to reach rt and stirred for 18 h. Upon completion the reaction mixture was quenched with saturated NH_4Cl (aq) and the layers separated. The organic layer was washed with saturated Na_2CO_3(aq) then 2 M HCl (aq). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/Hexane), yielding the product as a colourless oil (6.01 g, 38.2 mmol, 98 %). Spectroscopic and physical data were consistent with those reported.[185]

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 5.80 (ddt, *J*=17.0, 10.2, 6.7 Hz, 1H, =C**H**-), 5.09 - 4.92 (m, 2H, C**H₂**=), 3.67 (s, 3H, NOC**H₃**), 3.17 (s, 3H, NCH_3), 2.42 (t, *J*=7.5 Hz, 2H, -C**H₂**C(O)N-), 2.11 (q, *J*=7.4 Hz, 2H, =CHC**H₂**-), 1.74 (quin, *J*=7.5 Hz, 2H, =CHCH₂C**H₂**) ppm

^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 174.4 (**C**=O), 138.1 (CH₂=CH), 115.0 (CH₂=**C**H), 61.1 (O**C**H₃), 33.2 (C=C-**C**H₂), 32.2 (N**C**H₃), 31.0 (**C**H₂C=O), 23.6 (CH₂**C**H₂CH₂) ppm

FT-IR (neat) ν_{max} (cm^{-1}): 2938 (w), 1660 (s), 1383 (m), 944 (m), 911 (m)

1-(Trimethylsilyl)oct-7-en-1-yn-3-one (2.79)



$C_{11}H_{18}OSi$

MW: 194.35 gmol^{-1}

Follwing a procedure by Satcharoen *et al.*,[143] to a solution of TMS acetylene (0.54 mL, 3.82 mmol, 1.5 equiv.) in THF (20 mL) at –78 °C was added n-BuLi (1.78 M in THF, 2.16 mL, 3.82 mmol, 1.5 equiv.) dropwise over 10 min. The solution was stirred at –78 °C for 2.5 h, after which time a solution of Weinreb amide **93** (0.400 g, 2.54 mmol, 1 equiv.) in THF (5 mL) was added drop wise via cannula. The reaction mixture was stirred at –78 to –60 °C for 3.5 h then left sealed in the freezer at –8 °C for 18 h. Upon completion (TLC) the reaction was quenched with saturated NH_4Cl (aq)(10 mL), stirred for 5 min, the diluted with water (10 mL). The layers were separated and the aqueous extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (CH_2Cl_2), yielding the product as a clear oil (0.399 g, 0.31 mmol, 80 %). Spectroscopic and physical data were consistent with those reported.[143]

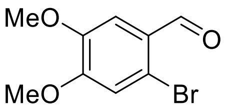
^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 5.78 (ddt, *J*= 17.1, 10.3, 6.7 Hz, 1H, =C**H**-), 5.09 - 4.96 (m, 2H, C**H₂**=), 2.57 (t, *J*=7.3 Hz, 2H, -C**H₂**C(O)-), 2.10 (d, *J*=6.7 Hz, 2H, =CHC**H₂**-), 1.78 (quin, *J*=7.3 Hz, 2H, =CHCH₂C**H₂**), 0.25 (s, 9H, Si(C**H₃**)₃) ppm

^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 187.6 (**C**=O), 137.6 (CH₂=**C**H), 115.4 (**C**H₂=CH), 102.0 (**C**ΞC-TMS), 97.7 (CΞ**C**-TMS), 44.5 (**C**H₂C=O), 32.8 (C=C-**C**H₂), 23.0 (CH₂**C**H₂CH₂), -0.8 (Si(**C**H₃)₃) ppm

LR MS (ESI$^+$) m/z: 195.1 [M+H]$^+$

FT-IR (neat) *ν*$_{max}$ (cm^{-1}): 2961 (w), 1676 (s), 1251 (m), 841 (s)

2-Bromoveratraldehyde (2.21)



$C_9H_9BrO_3$

MW: 245.07 gmol^{-1}

To a rapidly stirred solution of 3,4-dimethoxybenzaldehyde (4.00 g, 24.0 mmol, 1.0 equiv.) in MeOH (40 mL) at 0 °C was slowly added a solution of bromine (1.35 mL, 26.4 mmol, 1.1 equiv.) in MeOH (10 mL) over 30 min, with cooling to maintain the temperature below 20 °C. The reaction mixture was then allowed to reach rt and was stirred for 18 h. Upon completion the solvent was removed under reduced pressure. Cold water was added to the residue with stirring and the suspension was filtered and dried under reduced pressure, yielding the product as an off white solid (5.56 g, 22.8 mmol, 95 %). Spectroscopic and physical data were consistent with those reported, although lower mp indicates some impurity or incomplete drying.[186]

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ = 10.19 (s, 1 H, C**H**O), 7.42 (s, 1 H, C_{Ar}6-**H**), 7.06 (s, 1 H, C_{Ar}3-**H**), 3.96 (s, 3 H, OC**H₃**), 3.92 (s, 3 H, OC**H₃**) ppm

^{13}C NMR (75MHz, CHLOROFORM-d) δ = 190.8 (**C**=O), 154.5 (**C$_{Ar}$**-OMe), 148.9 (**C$_{Ar}$**-OMe), 126.6 (**C$_{Ar}$**C=O), 120.4 (**C$_{Ar}$**-Br), 115.5 (**C$_{Ar}$3**H), 110.5 (**C$_{Ar}$6**H), 56.5 (O**C**H$_3$), 56.2 (O**C**H$_3$) ppm

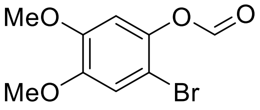
LR MS (ESI$^+$) m/z: 245.0 and 247.0 (^{79}Br and ^{81}Br) [M+H]$^+$

HRMS (ES$^+$): Calculated for $[C_9H_{10}{}^{79}BrO_3]^+$ 244.9808, found 244.9801 Da

FT-IR (neat) *v*$_{max}$ (cm^{-1}): 3008 (w), 2359 (w), 1006 (s), 1503 (s), 1268 (s)

Mp: 142.5-144.5 °C [lit. 150.5-150.6 °C][186]

2-Bromo-4,5-dimethoxyphenyl formate (2.22)



$C_9H_9BrO_4$

MW: 261.07 gmol^{-1}

To a solution of 2-bromoveratraldehyde **2.21** (1.00 g, 4.08 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at 0 °C was added mCPBA (1.37 g, 6.12 mmol, 1.5 equiv.) portionwise, maintaining the temperature below 3 °C. The reaction mixture was left to reach rt and stirred for 18 h. Upon completion the reaction mixture was treated with saturated $NaHCO_3$ (aq), the layers separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was triturated to give an orange solid and the product isolated by recrystalisation from boiling Et_2O, yielding the product as a pale yellow solid (0.59 g, 2.24 mmol, 55 %). Spectroscopic and physical data were consistent with those reported.[187]

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 8.30 (s, 1H, OC**H**=O), 7.06 (s, 1H, Ar_6-**H**), 6.71 (s, 1H, Ar_3-**H**), 3.88 (s, 3H, OC**H₃**), 3.86 (s, 3H, OC**H₃**) ppm

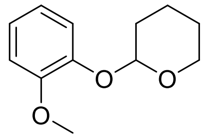
^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 158.5 (OCH=O), 149.0 (**C**$_{Ar}$-OMe), 147.9 (**C**$_{Ar}$-OMe), 140.6 (**C**$_{Ar}$-OCHO), 115.1 (**C**$_{Ar}$**3**H), 106.7 (**C**$_{Ar}$**6**H), 105.0 (**C**$_{Ar}$-Br), 56.4 (O**C**H$_3$), 56.2 (O**C**H$_3$) ppm

LR MS (ESI$^+$) m/z: 261.1 and 263.1 (^{79}Br and ^{81}Br) [M+H]$^+$, 283.2 and 284.7 (^{79}Br and ^{81}Br)[M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_9H_9{}^{79}BrO_4Na$]$^+$ 282.9576, found 282.9573 Da

FT-IR (neat) *ν*$_{max}$ (cm^{-1}): 2979 (w), 1736 (s), 1502 (s), 1097 (m)

2-Methoxyphenoxy)tetrahydro-2H-pyran (3.16)



$C_{12}H_{16}O_3$

MW: 208.26 gmol^{-1}

Follwing a procedure by Weinstabl *et al.*, [123] A solution of guaiacol (3.00 g, 24.17 mmol, 1.0 equiv.), DHP (20.50 mL, 241.80 mmol, 10.0 equiv.) and PPTS (1.21 g, 4.83 mmol, 0.2 equiv.) in CH_2Cl_2 (20 mL) was stirred at rt for 4 h. Upon completion of the reaction the reaction mixture was added saturated NaOH (aq)(6 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude oil was then purified by column chromatography (1:9 EtOAc/Hexane), yielding the product as a colourless solid (4.91 g, 23.60 mmol, 98 %). Spectroscopic data are consistent with those reported.[123]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.15 (dd, *J*= 7.8, 1.5 Hz, 1H, Ar-**H**), 7.01 - 6.96 (m, 1H, Ar-**H**), 6.94 - 6.87 (m, 2H, Ar-**H**), 5.40 (t, *J*=3.3 Hz, 1H, OC**H**O), 4.04 (m, 1H, OC**H$_2$**), 3.87 (s, 3H, OC**H$_3$**), 3.61 (dtd, *J*=11.3, 4.0, 1.5 Hz, 1H, OC**H$_2$**), 2.02 - 1.84 (m, 3H, C**H$_2$**C**H$_2$**C**H$_2$**), 1.78 - 1.53 (m, 3H, C**H$_2$**C**H$_2$**C**H$_2$**) ppm

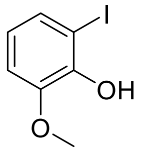
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 150.4 (**C**$_{Ar}$-O), 146.4 (**C**$_{Ar}$-OMe), 122.6 (**C**$_{Ar}$-H), 120.9 (**C**$_{Ar}$-H), 118.1 (**C**$_{Ar}$-H), 112.5 (**C**$_{Ar}$-H), 97.6 (O**C**HO), 62.2 (O**C**H$_2$), 56.1 (O**C**H$_3$), 30.4 (**C**H$_2$), 25.3 (**C**H$_2$), 18.9 (**C**H$_2$) ppm

LR MS (ESI$^+$) m/z: 231.0 [M+Na]$^+$, 439.1 [2M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{12}H_{16}O_3Na$]$^+$ 231.0992, found 231.0991 Da.

FT-IR (neat) *v*max (cm^{-1}): 2944 (w), 2916 (w), 1588 (w), 1499 (s), 1452 (m), 1249 (s), 752 (s)

2-Iodo-6-methoxyphenol (3.17)



$C_7H_7IO_2$

MW: 250.04 gmol^{-1}

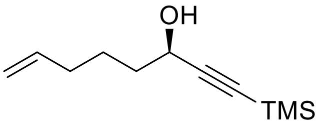
Follwing a procedure by Weinstabl *et al.*, [123] A solution of 2-(2-methoxyphenoxy)tetrahydro-2H-pyran **3.16** (2.00 g, 9.61 mmol, 1.0 equiv.) in THF (40 mL) at 0 °C was added n-BuLi (2.27 M in THF, 6.35 mL, 14.42 mmol, 1.5 equiv.) slowly, dropwise, over 20 min. The reaction mixture was allowed to reach rt and stirred for 2.5 h, then cooled to –50 °C and added a solution of iodine (4.88 g, 19.22 mmol, 2 equiv.) in THF (40 mL) over 30 min. The reaction mixture was allowed to reach rt and stirred over 18 h, then concentrated under reduced pressure. The crude residue was the partitioned between CH_2Cl_2 and water. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with saturated Na_2SO_3 (aq) and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude was purified by column chromatography (3:7 CH_2Cl_2/Hexane) yielding the product as colourless crystals (2.24 g, 8.95 mmol, 93 %). Spectroscopic data are consistent with those reported.[123]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.30 (d, *J*=8.1 Hz, 1H, Ar-**H**), 6.84 (d, *J*=8.3 Hz, 1H, Ar-**H**), 6.64 (t, *J*=8.1 Hz, 1H, Ar_4-**H**), 6.10 (s, 1H, O**H**), 3.90 (s, 3H, OC**H₃**) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 146.2 (**C**$_{Ar}$-OH), 145.7 (**C**$_{Ar}$-OMe), 130.6 (**C**$_{Ar}$-H), 121.6 (**C**$_{Ar}$-H), 110.7 (**C**$_{Ar}$-H), 81.4 (**C**$_{Ar}$-I), 56.2 (O**C**H_3) ppm

FT-IR (neat) *v*max (cm^{-1}): 3396 (b,s), 1589 (m), 1479 (s), 1434 (s), 1014 (s), 752 (s)

(*R*)-1-(Trimethylsilyl)oct-7-en-1-yn-3-ol (2.80)



$C_{11}H_{20}OSi$

MW: 196.36 gmol^{-1}

Asymmetric Reduction

Follwing a procedure by Satcharoen *et al.*,[143] propargyl ketone **2.79** (0.96 g, 4.93 mmol, 1 equiv.) was cooled to 0 °C and added R-Alpine Borane (0.5 M in THF, 24.6 mL, 12.3 mmol, 2.5 equiv.), then concentrated under reduced pressure. The yellow oil was then stirred at rt for 18 h, then quenched with acetaldehyde (1.5 mL). The mixture was cooled to 0 °C and added Et_2O then ethanolamine (0.77 mL, 12.82 mmol, 1.3 equiv.). The mixture was stirred for 1.5 h, during which time a colourless precipitate formed, then filtered through a pad of celite, washing with Et_2O. The filtrate was washed with water, then brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (1:9 EtOAc/Hexane then CH_2Cl_2) yielding the product as a colourless oil (0.88 g, 4.47 mmol, 91 %). Spectroscopic data are consistent with those reported.[143]

Racemic Reduction

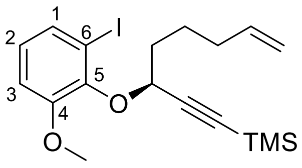
To a solution of propargyl ketone **2.79** (0.350 g, 1.80 mmol, 1 equiv.) in MeOH (7 mL) was added $CeCl_3.7H_2O$ (0.693 g, 1.84 mmol, 1.02 equiv.) The solution was stirred for 30 min then cooled to –5 °C and added $NaBH_4$ (0.0750 g, 1.98 mmol, 1.1 equiv.) portionwise. The reaction mixture was allowed to reach rt and stirred for 2 h. The reaction was quenched with saturated NH_4Cl (aq)(7 mL). The MeOH was removed under reduced pressure and the residue partitioned between water (6 mL) and EtOAc (6 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (aq)(10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was the purified by column chromatography (CH_2Cl_2), yielding the product as a colourless oil (0.287 g, 1.46 mmol, 81 %). Spectroscopic and physical data were consistent with those reported.[143]

^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 5.82 (ddt, *J*=16.9, 10.2, 6.7 Hz, 1H, $CH_2=C\mathbf{H}$), 4.94-5.08 (m, 2H, $C\mathbf{H_2}=CH$), 4.37 (q, *J*=6.3 Hz, 1H, $C\mathbf{H}OH$), 2.11 (q, *J*=7.1 Hz, 2H, $C=CHC\mathbf{H_2}$), 1.81 (d, *J*=5.5 Hz, 1H, $O\mathbf{H}$), 1.66-1.78 (m, 2H, $C\mathbf{H_2}COH$), 1.50-1.64 (m, 2H, $CH_2C\mathbf{H_2}CH_2$), 0.18 (s, 9H, $Si(C\mathbf{H_3})_3$) ppm

^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 138.4 ($CH_2=\mathbf{C}H$), 114.8 ($\mathbf{C}H_2=CH$), 106.7 ($\mathbf{C}\equiv C$-TMS), 89.4 ($C\equiv\mathbf{C}$-TMS), 62.7 ($\mathbf{C}HOH$), 37.1 ($C=CH\mathbf{C}H_2$), 33.2 ($\mathbf{C}H_2COH$), 24.3 ($CH_2\mathbf{C}H_2CH_2$), -0.2 ($Si(\mathbf{C}H_3)_3$) ppm

FT-IR (neat) ν_{max} (cm^{-1}): 3314 (br. w), 2956 (w), 1249 (m), 838 (s)

(*S*)-(3-(2-Iodo-6-methoxyphenoxy)oct-7-en-1-yn-1-yl)trimethylsilane (3.36)



$C_{18}H_{25}IO_2Si$

MW: 428.39 gmol^{-1}

To a solution of 2-iodo-6- methoxyphenol **3.17** (0.60 g, 2.4 mmol. 1.1 equiv.) and PPh_3 (0.87 g, 3.3 mmol, 2.0 equiv.) in THF (10 mL) were added (*R*)-1-(trimethylsilyl)oct-7-en-1-yn-3-ol **2.80** (0.43 g, 2.2 mmol, 1.0 equiv.) then DIAD (0.65 mL, 3.3 mmol, 2.0 equiv.) dropwise. The reaction was stirred at 45 °C for 1.5 h. Upon completion the reaction was quenched with water, diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were then dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/Hexane) affording the product as a colourless oil (0.85 g, 2.0 mmol, 90 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.36 (dd, *J*=7.9, 1.5 Hz, 1H, Ar$_1$-**H**), 6.87 (dd, *J*=8.2, 1.5 Hz, 1H, Ar$_3$-**H**), 6.79 (t, 7.8 Hz, 1H, Ar$_2$-**H**), 5.87 (ddt, *J*=17.1, 10.3, 6.6 Hz, 1H, CH$_2$=C**H**), 5.16 (t, 6.4 Hz, 1H, ArOC**H**), 5.07 (ddd, *J*=17.2, 3.6, 1.7 Hz, 1H, C**H**$_{\mathbf{trans}}$H$_{cis}$=CH), 4.99 (ddt, *J*=10.2, 2.1, 1.1 Hz, 1H, CH$_{trans}$**H**$_{\mathbf{cis}}$=CH), 3.77-3.90 (s, 3H, OC**H$_3$**), 2.11-2.25 (m, 2H, C=CHC**H$_2$**), 1.93-2.07 (m, 2H, C**H$_2$**CHOAr), 1.65-1.86 (m, 2H, CH$_2$C**H$_2$**CH$_2$), 0.02-0.12 (m, 9H, Si(C**H$_3$**)$_3$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 153.1 (**C$_{Ar}$**-OMe), 146.7 (**C$_{Ar}$**-OCH), 139.0 (CH$_2$=**C**H), 131.0 (**C$_{Ar}$1**-H), 126.0 (**C$_{Ar}$2**-H), 115.0 (**C**H$_2$=CH), 112.7 (**C$_{Ar}$3**-H), 103.9 (**C**ΞC-TMS), 94.8 (CΞ**C**-TMS), 92.6 (**C$_{Ar}$**-I), 72.2 (ArO**C**H), 56.2 (O**C**H$_3$), 35.6 (**C**H$_2$CHOAr), 33.7 (C=CH**C**H$_2$), 24.8 (CH$_2$**C**H$_2$CH$_2$), 0.0 (Si(**C**H$_3$)$_3$) ppm

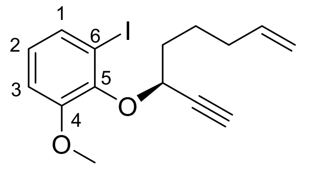
LR MS (ESI$^+$) m/z: 429.2 [M+H]$^+$, 451.2 [M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{18}H_{25}IO_2SiNa]^+$ 451.0561, found 451.0564 Da.

FT-IR (neat) *v*max (cm^{-1}): 2957 (w), 1578 (w), 1465 (m), 1259 (m), 1032 (m), 904 (s), 842 (m), 727 (s)

[α]$_D$: +4.33 (c 1.05, MeCN, 22 °C)

(*S*)-1-Iodo-3-methoxy-2-(oct-7-en-1-yn-3-yloxy)benzene (3.37)



$C_{15}H_{17}IO_2$

MW: 356.20 gmol^{-1}

To a solution of (*S*)-TMS-propargyl aryl ether **3.36** (0.113 g, 0.26 mmol, 1.0 equiv.) in MeOH (5 mL) was added K_2CO_3 (0.039 g, 0.29 mmol, 1.1 equiv.). The reaction mixture was stirred for 1.5 h. Upon completion the reaction was quenched with saturated NH_4Cl (aq), concentrated under reduced pressure and the residue was partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was isolated as an oil without the need for further purification (0.089 g, 0.25 mmol, 96 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.38 (dd, *J*=1.4, 7.9 Hz, 1H, Ar$_1$-**H**), 6.89 (dd, *J*=1.2, 8.1 Hz, 1H, Ar$_3$-**H**), 6.85 - 6.76 (m, 1H, Ar$_2$-**H**), 5.87 (ddt, *J*=17.0, 10.3, 6.6 Hz, 1H, CH$_2$=C**H**), 5.20 (dt, *J*=2.1, 6.4 Hz, 1H, ArOC**H**), 5.07 (dd, *J*=17.1, 1.7 Hz, 1H, C**H**$_{\mathbf{trans}}$H$_{cis}$=CH), 5.00 (dd, *J*=10.1, 0.9 Hz, 1H, CH$_{trans}$**H**$_{\mathbf{cis}}$=CH), 3.85 (s, 3H, OC**H$_3$**), 2.39 (d, *J*=2.2 Hz, 1H, CΞC-**H**), 2.24 - 2.12 (m, 2H, C=CHC**H$_2$**), 2.08 - 1.95 (m, 2H, C**H$_2$**CHOAr), 1.87 - 1.65 (m, 2H, CH$_2$C**H$_2$**CH$_2$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.7 (**C$_{Ar}$**-OMe), 146.2 (**C$_{Ar}$**-OCH), 138.5 (CH$_2$=**C**H), 130.9 (**C$_{Ar}$1**-H), 125.8 (**C$_{Ar}$2**-H), 114.8 (**C**H$_2$=CH), 112.7 (**C$_{Ar}$3**-H), 93.9 (**C$_{Ar}$**-I), 81.9 (**C**ΞC-H), 75.2 (ArO**C**H), 71.3 (CΞ**C**-H), 55.9 (O**C**H$_3$), 35.3 (**C**H$_2$CHOAr), 33.4 (C=CH**C**H$_2$), 24.4 (CH$_2$**C**H$_2$CH$_2$) ppm

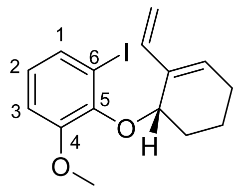
LR MS (ESI$^+$) m/z: 356.9 [M+H]$^+$, 378.9 [M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{15}H_{18}IO_2]^+$ 357.0346, found 357.0344 Da.

FT-IR (neat) *v*max (cm^{-1}): 3291 (w), 2939 (w), 1578 (m), 1464 (s), 1258 (s), 1029 (s)

[α]$_D$: -1.80 (c 1.03, MeCN, 22 °C)

(*S*)-1-Iodo-3-methoxy-2-((2-vinylcyclohex-2-en-1-yl)oxy)benzene (3.38)



$C_{15}H_{17}IO_2$

MW: 356.20 gmol^{-1}

To a solution of (*S*)-propargyl aryl ether **3.37** (0.089 g, 0.25 mmol, 1.0 equiv.) in CH_2Cl_2 (8 mL) was added Grubbs catalyst – 1st Generation (6.2 mg, 7.5µmol, 0.03 equiv.). The reaction mixture was stirred at rt for 18 h. Upon completion the solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:19 EtOAc/Hexane) affording the product as a colourless oil (0.065 g, 0.18 mmol, 72 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.36 (dd, *J*=7.9, 1.5 Hz, 1H, Ar$_1$-**H**), 6.87 (dd, *J*=8.2, 1.3 Hz, 1H, Ar$_3$-**H**), 6.73 (t, *J*=7.9 Hz, 1H, Ar$_2$-**H**), 6.36 (dd, *J*=17.6, 11.1 Hz, 1H, CH$_2$=C**H**), 6.05 (dd, *J*=5.4, 4.2 Hz, 1H, C=C**H**-CH$_2$), 5.43 (t, *J*=3.4 Hz, 1H, ArOC**H**), 5.35 (d, *J*=17.5 Hz, 1H, C**H$_{trans}$**H$_{cis}$=CH), 4.90 (d, *J*=11.0 Hz, 1H, CH$_{trans}$**H$_{cis}$**=CH), 3.87 (s, 3H, OC**H$_3$**), 2.00-2.39 (m, 4H, ArOCHC**H$_2$**, C=CH-C**H$_2$**, CH$_2$C**H$_2$**CH$_2$), 1.45-1.63 (m, 2H, CH$_2$C**H$_2$**CH$_2$, ArOCHC**H$_2$**) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.4 (**C$_{Ar}$**-OMe), 147.0 (**C$_{Ar}$**-OCH), 138.2 (CH$_2$=**CH**), 136.0 (**C**-CH=CH$_2$), 132.6 (C=**C**H-CH$_2$), 131.3 (**C$_{Ar}$1**-H), 124.6 (**C$_{Ar}$2**-H), 112.6 (**C$_{Ar}$3**-H), 111.7 (**C**H$_2$=CH), 93.9 (**C$_{Ar}$**-I), 72.6 (ArO**C**H), 55.7 (O**C**H$_3$), 28.1 (ArOCH**C**H$_2$), 25.9 (C=CH**C**H$_2$), 17.7 (CH$_2$**C**H$_2$CH$_2$) ppm

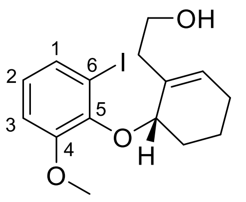
LR MS (ESI$^+$) m/z: 378.9 [M+Na]$^+$, 734.8 [2M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{15}H_{17}IO_2Na]^+$ 379.0165, 379.0174 Da.

FT-IR (neat) *v*max (cm^{-1}): 2937 (m), 2833 (w), 1578 (m), 1463 (s), 1256 (s), 1028 (s)

[α]$_D$: -211.32 (c 1.95, MeCN, 22 °C)

(*S*)-2-(6-(2-iodo-6-methoxyphenoxy)cyclohex-1-en-1-yl)ethan-1-ol (3.39)



$C_{15}H_{19}IO_3$

MW: 374.22 gmol^{-1}

To a solution of enyne metathesis product **3.38** (1.09 g, 3.1 mmol, 1.0 equiv.) in THF (10 mL) was added 9-BBN (0.5 M in THF, 9.18 mL, 4.6 mmol, 1.5 equiv.) slowly, dropwise. The reaction mixture was stirred for 18 h then added NaOH (aq)(3 M, 2.5 mL), cooled to 0 °C and added hydrogen peroxide (aq)(30 %w/v, 2.5 mL) slowly, dropwise. The reaction mixture was stirred at 0 °C for 30 min. Upon completion the mixture was diluted with H_2O and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:19-1:9 EtOAc/Hexane), affording the product as a colourless oil (1.03 g, 2.8 mmol, 90 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.38 (dd, *J*=7.9, 1.3 Hz, 1H, Ar$_1$-**H**), 6.89 (dd, *J*=8.2, 1.2 Hz, 1H, Ar$_3$-**H**), 6.77 (t, *J*=8.0 Hz, 1H, Ar$_2$-**H**), 5.85 (br s, 1H, C=C**H**), 4.99 (br s, 1H, ArOC**H**), 3.74-3.91 (m, 5H, OC**H$_3$**, C**H$_2$**OH), 2.68 (dt, *J*=14.1, 7.7 Hz, 1H, C**H$_2$**CH$_2$OH), 2.46 (dt, *J*=13.8, 6.7 Hz, 1H, C**H$_2$**CH$_2$OH), 2.22 (m, 1H, C=CH-C**H$_2$**), 1.98-2.14 (m, 2H, C=CH-C**H$_2$**, CH$_2$C**H$_2$**CH$_2$), 1.84-1.97 (m, 2H, ArOCHC**H$_2$**, O**H**), 1.44-1.60 (m, 2H, ArOCHC**H$_2$**, CH$_2$C**H$_2$**CH$_2$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.5 (**C$_{Ar}$**-OMe), 146.5 (**C$_{Ar}$**-OCH), 134.1 (**C**=CH), 131.3 (**C$_{Ar}$1**-H), 130.3 (C=**C**H), 125.1 (**C$_{Ar}$2**-H), 112.7 (**C$_{Ar}$3**-H), 93.8 (**C$_{Ar}$**-I), 61.8 (**C**H$_2$OH), 55.6 (O**C**H$_3$), 38.0 (**C**H$_2$CH$_2$OH), 28.2 (ArOCH**C**H$_2$), 25.6 (C=CH-**C**H$_2$), 18.6 (CH$_2$**C**H$_2$CH$_2$) ppm

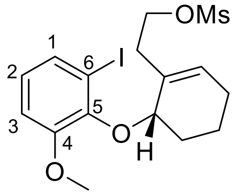
LR MS (ESI$^+$) m/z: 396.9 $[M+Na]^+$, 771.9 $[2M+Na]^+$

HRMS (ES$^+$): Calculated for $[C_{15}H_{19}IO_3Na]^+$ 397.0271, found 397.0277 Da.

FT-IR (neat) *v*max (cm^{-1}): 3346 (b, w), 2934 (m), 2834 (m), 1578 (m), 1463 (s), 1255 (s), 1027 (s)

$[\alpha]_D$: -76.13 (c 0.905, MeCN, 22 °C)

(*S*)-2-(6-(2-Iodo-6-methoxyphenoxy)cyclohex-1-en-1-yl)ethyl methanesulfonate (3.43)



$C_{16}H_{21}IO_5S$

MW: 452.30 gmol^{-1}

To a solution of alcohol **3.39** (0.30 g, 0.80 mmol, 1.0 equiv.) and Et$_3$N (0.15 mL, 1.04 mmol, 1.3 equiv.) in CH$_2$Cl$_2$ (10mL) at 0 °C was added MsCl (0.07 mL, 0.96 mmol, 1.2 equiv.) and the solution stirred for 1 h. Upon completion the reaction mixture was washed with H$_2$O and brine, dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude oil was purified by column chromatography (1:4 EtOAc/Hexane) affording the product as a colourless oil (0.33 g, 0.72 mmol, 90 %).

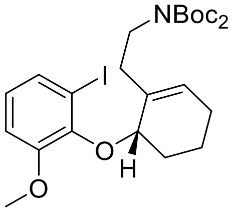
^{1}H NMR (400 MHz, CHLOROFORM-d) δ =7.38 (dd, *J*=7.9, 1.5 Hz, 1H, Ar$_1$-**H**), 6.90 (dd, *J*=8.3, 1.4 Hz, 1H, Ar$_3$-**H**), 6.79 (t, *J*=8.1 Hz, 1H, Ar$_2$-**H**), 5.87 (br t, *J*=3.3 Hz, 1H, C=C**H**), 4.90 (t, *J*=3.9 Hz, 1H, ArOC**H**), 4.41-4.54 (m, 2H, C**H$_2$**OMs), 3.86 (s, 3H, OC**H$_3$**), 3.01 (s, 3H, SO$_2$C**H$_3$**), 2.74 (m, 1H, C**H$_2$**CH$_2$OMs), 2.67 (dt, *J*=14.1, 7.0 Hz, 1H, C**H$_2$**CH$_2$OMs), 2.19 (m, 1H, C=CH-C**H$_2$**), 1.98-2.13 (m, 2H, C=CH-C**H$_2$**, CH$_2$C**H$_2$**CH$_2$), 1.95 (m, 1H, ArOCHC**H$_2$**), 1.43-1.58 (m, 2H, ArOCHC**H$_2$**, CH$_2$C**H$_2$**CH$_2$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.5 (**C**$_{Ar}$-OMe), 146.7 (**C**$_{Ar}$-OCH), 132.0 (**C**=CH), 131.4 (C=**C**H), 131.2 (**C**$_{Ar}$**1**-H), 125.4 (**C**$_{Ar}$**2**-H), 112.6 (**C**$_{Ar}$**3**-H), 93.9 (**C**$_{Ar}$-I), 77.0 (ArO**C**H), 69.9 (**C**H$_2$OMs), 55.6 (O**C**H$_3$), 37.4 (SO$_2$**C**H$_3$), 34.6 (**C**H$_2$CH$_2$OMs), 28.3 (ArOCH**C**H$_2$), 25.6 (C=CH-**C**H$_2$**)**, 18.7 (CH$_2$**C**H$_2$CH$_2$) ppm

LR MS (ESI$^+$) m/z: 475.1 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{16}H_{21}IO_5SNa$]$^+$ 475.0047, found 475.0049 Da.

(*S*)-2-(6-(2-Iodo-6-methoxyphenoxy)cyclohex-1-en-1-yl)ethyl di-tert-butyl iminodicarboxylate (3.45)



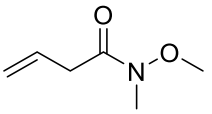
$C_{25}H_{36}INO_6$

MW: 573.47 gmol^{-1}

Mesylate **3.43** (0.064 g, 0.14 mmol, 1.0 equiv.), Cs_2CO_3 (0.111 g, 0.34 mmol, 2.4 equiv.) and di-tert-butyl iminodicarboxylate (0.034 g, 0.16 mmol, 1.1 equiv.) in DMPU (5 mL) was stirred at 75 °C for 18 h. Upon completion the reaction mixture was added to NaCl (aq)(5 %w/v, 50 mL) and EtOAc (150 mL) and the layers separated. The organic layer was washed with further NaCl (aq), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:19 EtOAc/Hexane) yielding the product as a clear oil (0.021 g, 0.037 mmol, 26 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.37 (d, *J*=7.8 Hz, 1H, Ar-**H**), 6.87 (d, *J*=7.6 Hz, 1H, Ar-**H**), 6.75 (m, 1H, Ar-**H**), 5.72 (m, 1H, C=C**H**), 4.98 (br s, 1H, ArOC**H**), 3.95 (m, 1H, C**H$_2$**Nboc$_2$), 3.84 (s, 3H, OC**H$_3$**), 3.66 (ddd, *J*=13.6, 7.5, 4.0 Hz, 1H, C**H$_2$**Nboc$_2$), 2.70 (m, 1H, C**H$_2$**CH$_2$Nboc$_2$), 2.42 (m, 1H, C**H$_2$**CH$_2$Nboc$_2$), 2.07-2.22 (m, 2H, C=CH-C**H$_2$**), 1.87-2.01 (m, 2H, ArOCHC**H$_2$**), 1.52 - 1.46 (m, 18H, boc, CH$_2$C**H$_2$**CH$_2$) ppm

N-Methoxy-*N*-methylbut-3-enamide (3.26)



$C_6H_{11}NO_2$

MW: 129.16 gmol^{-1}

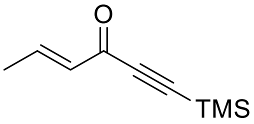
A solution of DCC (7.19 g, 34.85 mmol, 1.50 equiv.), DMAP (4.97 g, 40.65 mmol, 1.75 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (3.40 g, 34.85 mmol, 1.50 equiv.) in CH_2Cl_2 (50 mL) was added 3-butenoic acid (1.97 mL, 23.23 mmol, 1.00 equiv.) and the suspension stirred at rt for 3 h. Upon completion the reaction mixture was filtered through a pad of celite, washing with CH_2Cl_2. The filtrate was washed with H_2O and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (2:3 EtOAc/Hexane) then distillation (80 °C, 8mbar), affording the product as a clear oil (1.30g, 10.07 mmol, 43 %). Spectroscopic and physical data were consistent with those reported.[188]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 6.06 - 5.88 (m, 1H, CH_2=C**H**), 5.21 - 5.17 (m, 1H, C**H₂**=CH), 5.15 (m, 1H, C**H₂**=CH), 3.70 (s, 3H, OC**H₃**), 3.23 (br d, *J*=6.7 Hz, 2H, C**H₂**), 3.21 - 3.16 (m, 3H, NC**H₃**) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 172.37 (**C**=O), 131.15 (CH_2=**C**H), 118.09 (**C**H_2=CH), 61.28 (O**C**H_3), 37.12 (**C**H_2), 32.16 (N**C**H_3) ppm

LR MS (ESI$^+$) m/z: 152.1 $[M+Na]^+$, 192.9 $[M+Na+MeCN]^+$, 281.1 $[2M+Na]^+$

(*E*)-1-(Trimethylsilyl)hex-4-en-1-yn-3-one (3.31)



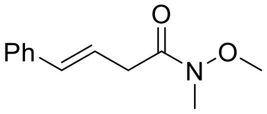
$C_9H_{14}OSi$

MW: 166.30 gmol^{-1}

A solution of TMS acetylene (0.62 mL, 4.64 mmol, 1.5 equiv.) in THF (15 mL) at –78 °C was added ^{n}BuLi (2.3 M, 2.02 mL, 4.64 mmol, 1.5 equiv.), dropwise, over 10 min, maintaining the temperature at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 2.5 h, then cooled to –20 °C and added *N*-methoxy-*N*-methylbut-3-enamide **3.26** (0.400 g, 3.10 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred at –20 °C for 2 h. Upon completion the reaction was quenched with saturated NH_4Cl (aq), the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified using column chromatography (0:1-1:9 EtOAc/Hexane) yielding the product as a colourless oil (0.074 g, 0.44 mmol, 14 %). Product lost due to volatility. Spectroscopic and physical data were consistent with those reported.[189]

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.19 (m, 1H, CH=C**H**-CH_3), 6.17 (dd, *J*=15.7, 1.5 Hz, 1H, C**H**=CH-CH_3), 1.99 (dd, *J*=6.8, 1.5 Hz, 3H, C**H₃**), 0.22-0.31 (m, 9H, Si(C**H₃**)₃) ppm

_N_-Methoxy-_N_-methyl-4-phenylbut-3-enamide (3.33)



$C_{12}H_{15}NO_2$

MW: 205.26 gmol^{-1}

To a solution of Styrylacetic acid (1.50 g, 9.25 mmol, 1.00 equiv.) and DMF (catalytic) in CH_2Cl_2 (40 mL) at 0 °C was added oxalyl chloride (1.37 mL, 16.19 mmol, 1.75 equiv.) drop-wise, over 5 min. The reaction mixture was stirred at 0 °C for 5 min then allowed to reach rt and stirred for 45 min. Excess solvent and oxalyl chloride was then removed under reduced pressure and the acyl chloride dissolved in CH_2Cl_2 (40 mL) and added _N_,_O_-dimethylhydroxylamine hydrochloride (1.08 g, 11.10 mmol, 1.20 equiv.). The reaction mxiture was cooled to 0 °C and added pyridine (1.65 mL, 20.35 mmol, 2.20 equiv.) drop-wise, over 5 min. The mixture was stirred at 0 °C for 5 min then allowed to reach rt and stirred for 1.5 h. Upon completion the reaction mixture was washed with 2M HCl (aq), H_2O and saturated $NaHCO_3$(aq). The organic layer was then dried ($MgSO_4$) and the solvent removed under reduced pressure. Crude purified by column chromatography (3:17 EtOAc/Hexane) yielding the product as colourless solid upon cooling (1.40 g, 6.82 mmol, 74 %).

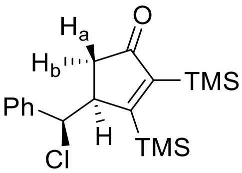
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.31-7.38 (m, 2H, Ph-**H**), 7.16-7.31 (m, 3H, Ph-**H**), 6.48 (d, _J_=16.0 Hz, 1H, Ph-C**H**=CH), 6.35 (dt, _J_=15.7, 6.8 Hz, 1H, Ph-CH=C**H**), 3.70 (s, 3H, OC**H₃**), 3.36 (br d, _J_=6.6 Hz, 2H, C**H₂**), 3.18 (s, 3H, NC**H₃**) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 172.3 (**C**=O), 137.0 (**C$_{Ph}$**-CH), 133.1 (C$_{Ph}$-**C**H), 128.4 (**C$_{Ph}$**), 127.3 (**C$_{Ph}$**), 126.2 (**C$_{Ph}$**), 122.8 (Ph-CH=**C**H), 61.4 (O**C**H$_3$), 36.5 (**C**H$_2$), 32.2 (N**C**H$_3$) ppm

LR MS (ESI$^+$) m/z: 206.0 [M+H]$^+$, 228.0 [M+Na]$^+$

FT-IR (neat) _v_max (cm^{-1}): 3025 (w), 2937 (w), 2360 (w), 1660 (s), 1382 (m), 1174 (m), 1108 (m), 733 (s)

4-(Chloro(phenyl)methyl)-2,3-bis(trimethylsilyl)cyclopent-2-en-1-one (3.35)



$C_{18}H_{27}ClOSi_2$

MW: 351.03 gmol^{-1}

A solution of Styrylacetic acid (0.50 g, 3.08 mmol, 1.00 equiv.) and DMF (catalytic) in CH_2Cl_2 (20 mL) at 0 °C was added oxalyl chloride (0.46 mL, 5.40 mmol, 1.75 equiv.) drop-wise over 5 min. The reaction mixture was stirred at 0 °C for 5 min then left to warm to rt and stirred for 1 h. The solvent/excess oxalyl chloride was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), added bis-TMS-acetylene (0.74 mL, 3.39 mmol, 1.10 equiv.), cooled to 0 °C, then added $AlCl_3$ (0.49 g, 3.70 mmol, 1.20 equiv.) portion-wise over 5 min, turning the solution dark brown. The reaction mixture was stirred at 0 °C for 5 min then left to reach rt and stirred for 1 h. Upon completion the reaction was quenched by pouring into 2M HCl (aq) at 0 °C. The layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:99 EtOAc/Hexane), affording the product as yellow crystals (0.45 g, 1.28 mmol, 42 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.30-7.48 (m, 5H, Ph-**H**), 5.41 (d, *J*=1.6 Hz, 1H, PhC**H**Cl), 3.69 (dt, *J*=6.9, 1.8 Hz, 1H, CHClC**H**CH$_2$), 2.40 (dd, *J*=18.5, 2.0 Hz, 1H, CH$_a$**H$_b$**C=O), 2.00 (dd, *J*=18.5, 7.0 Hz, 1H, C**H$_a$**H$_b$C=O), 0.43 (s, 9H, CHCSi(C**H$_3$**)$_3$), 0.30 (s, 9H, O=CCSi(C**H$_3$**)$_3$) ppm

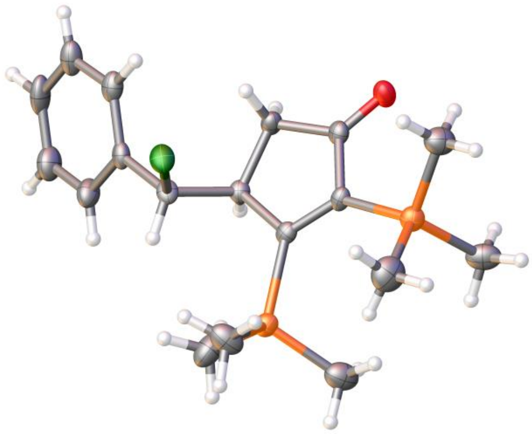
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 212.7 (C=O), 187.3 (**C**=C-C=O), 158.8 (C=**C**-C=O), 140.2 (**C$_{Ph}$**CHCl), 128.7 (**C$_{Ph}$**-H), 128.1 (**C$_{Ph}$**-H), 126.6 (**C$_{Ph}$**-H), 64.1 (Ph**C**HCl), 54.5 (CHCl**H**CH$_2$), 35.6 (**C**H$_2$), 0.8 (CHCSi(**C**H$_3$)$_3$), 0.4 (O=CCSi(**C**H$_3$)$_3$) ppm

LR MS (ESI$^+$) m/z: 351.0 + 353.1 [M+H]$^+$

HRMS (ES$^+$): Calculated for $[C_{18}H_{27}{}^{35}ClOSi_2Na]^+$ 373.1181, found 373.1178 Da.

FT-IR (neat) *v*max (cm^{-1}): 2952 (w), 2898 (w), 1689 (s), 1540 (m), 1249 (s), 1209 (s), 889 (m)

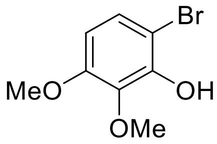
Crystal Structure:



Single clear colourless block-shaped crystals of (**3.35**) were recrystallised from DCM by slow evaporation. A suitable crystal (0.25 × 0.05 × 0.02 mm^3) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at *T* = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the ShelXT (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with version of **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

$C_{18}H_{27}ClOSi_2$, M_r = 351.02, monoclinic, Pc (No. 7), a = 12.7841(5) Å, b = 42.4732(11) Å, c = 12.7357(4) Å, ⍰ = 119.505(5)°, ⍰ = ⍰ = 90°, V = 6018.4(4) Å^3, T = 100(2) K, Z = 12, Z' = 6, μ(MoK$_⍰$) = 0.310, 40993 reflections measured, 20422 unique (R_{int} = 0.0394) which were used in all calculations. The final wR_2 was 0.2329 (all data) and R_1 was 0.1007 (I > 2(I)).

6-Bromo-2,3-dimethoxyphenol (3.11)



$C_8H_9BrO_3$

MW: 233.06 gmol^{-1}

To a solution of 2,3-dimethoxyphenol (2.00 g, 12.97 mmol, 1.00 equiv.) in THF (50 mL) was added NBS (2.36 g, 13.23 mmol, 1.02 equiv.) portion-wise over 15 min, maintaining the temperature below 5 °C. The reaction mixture was stirred at rt for 30 min. Upon completion the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (50 mL). The solution was washed with saturated $Na_2S_2O_3$ (aq) and the layers separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were filtered through celite, washing with CH_2Cl_2 to remove succinimide. The solvent was removed under reduced pressure, leaving a yellow oil which was triturated with hexane and filtered to afford the product as white crystals (2.18 g, 9.34 mmol, 72 %). Spectroscopic and physical data were consistent with those reported.[119]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.16 (d, *J*=9.0 Hz, 1H, Ar-**H**), 6.42 (d, *J*=8.9 Hz, 1H, Ar-**H**), 6.02 (s, 1H, O**H**), 3.92 (s, 3H, OC**H₃**), 3.86 (s, 3H, OC**H₃**) ppm

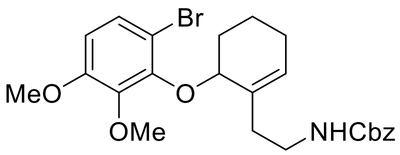
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.01 (**C**$_{Ar}$-OH), 146.79 (**C**$_{Ar}$-OH), 136.42 (**C**$_{Ar}$-OH), 126.75 (**C**$_{Ar}$-H), 105.14 (**C**$_{Ar}$-H), 100.30 (**C**$_{Ar}$-Br), 61.05 (O**C**H$_3$), 56.03 (O**C**H$_3$) ppm

LR MS (ESI$^+$) m/z: 232.9 + 234.8 [M+H]$^+$

HRMS (ES$^+$): Calculated for $[C_8H_9{}^{79}BrO_3Na]^+$ 254.9627, found 254.9624 Da.

FT-IR (neat) *v*max (cm^{-1}): 3472 (b, s), 2949 (m), 2837 (w), 1589 (m), 1454 (s), 1426 (s), 1086 (s), 990 (s)

(±)-Benzyl (2-(6-(6-bromo-2,3-dimethoxyphenoxy)cyclohex-1-en-1-yl)ethyl)carbamate (3.12)



$C_{24}H_{28}BrNO_5$

MW: 490.39 gmol^{-1}

To a solution of bromophenol **3.11** (0.092 g, 0.40 mmol, 1.1 equiv.), cyclohexenol **2.78** (0.099 g, 0.36 mmol, 1.0 equiv.) and PPh$_3$ (0.189 g, 0.72 mmol, 2.0 equiv.) in THF (10 mL) was added DBAD (0.166 g, 0.72 mmol, 2.0 equiv.) portionwise. The reaction mixture was then stirred at rt for 90 min. Upon completion the reaction was quenched with H$_2$O and diluted with EtOAc. The layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9:0.05 to 3:20 EtOAc/Hexane w/ 0.1 % Et$_3$N) yielding the product as an oil (0.140 g, 0.29 mmol, 80 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.28-7.40 (m, 5H, Ar$_{Cbz}$-**H**), 7.23 (d, *J*=8.9 Hz, 1H, Ar$_4$-**H**), 6.58 (d, *J*=9.0 Hz, 1H, Ar$_5$-**H**), 5.79 (br s, 1H, C=C**H**), 5.09 (d, *J*=1.2 Hz, 2H, C**H$_2$**Ph), 5.01 (m, 1H, N**H**), 4.88 (br s, 1H, ArOC**H**), 3.86 (s, 3H, OC**H$_3$**), 3.81 (s, 3H, OC**H$_3$**), 3.39-3.52 (m, 2H, C**H$_2$**NHCbz), 2.61 (m, 1H, C**H$_2$**CH$_2$NHCbz), 2.41 (m, 1H, C**H$_2$**CH$_2$NHCbz), 2.15 (br d, *J*=12.0 Hz, 1H, C=CH-C**H$_2$**), 1.92-2.04 (m, 2H, C=CH-C**H$_2$**, CH$_2$C**H$_2$**CH$_2$), 1.87 (m, 1H, ArOCHC**H$_2$**), 1.54 (m, 1H, CH$_2$C**H$_2$**CH$_2$), 1.40 (m, 1H, ArOCHC**H$_2$**) ppm

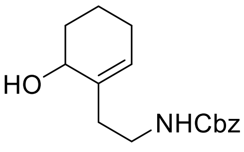
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 156.4 (**C**=O), 153.4 (**C$_{\mathbf{Ar}}$**-OMe), 148.6 (**C$_{\mathbf{Ar}}$**-OMe), 143.7 (**C$_{\mathbf{Ar}}$**-O), 136.8 (**C$_{\mathbf{ArCbz}}$**-CH$_2$), 133.7 (**C**=CH), 130.3 (C=**C**H), 128.5 (**C$_{\mathbf{ArCbz}}$**-H), 128.1 (**C$_{\mathbf{ArCbz}}$**-H), 128.0 (**C$_{\mathbf{ArCbz}}$**-H), 127.2 (**C$_{\mathbf{Ar}}$4**-H), 109.5 (**C$_{\mathbf{Ar}}$**-Br), 108.3 (**C$_{\mathbf{Ar}}$5**-H), 77.6 (ArO**C**H), 66.5 (**C**H$_2$Ph), 61.1 (O**C**H$_3$), 56.1 (O**C**H$_3$), 39.9 (**C**H$_2$NHCbz), 34.6 (**C**H$_2$CH$_2$NHCbz), 27.8 (ArOCH**C**H$_2$), 25.6 (C=CH-**C**H$_2$), 18.0 (CH$_2$**C**H$_2$CH$_2$ ppm

LR MS (ESI$^+$) m/z: 512.0 + 513.9 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{24}H_{28}{}^{79}BrNO_5Na$]$^+$ 512.1043, found 512.1046 Da.

FT-IR (neat) *v*max (cm^{-1}): 3330 (b, w), 2937 (w), 2837 (w), 1703 (s), 1089 (s), 730 (s)

(±)-Benzyl (2-(6-hydroxycyclohex-1-en-1-yl)ethyl)carbamate (2.78)



$C_{16}H_{21}NO_3$

MW: 275.15 gmol^{-1}

To a solution of benzyl vinylcarbamate **1.82** (0.60 g, 3.39 mmol, 1.2 equiv.) in THF (2 mL) was added 9-BBN (0.5M in THF, 8.5 mL, 4.24 mmol, 1.5 equiv.) drop-wise at –5 °C then left to reach rt and stirred for 4 h. The solution was added NaOH (aq)(4M, 2.1 mL, 8.47 mmol, 3 equiv.) and stirred for 30 min. The mixture was then added via cannula to a solution of 2-iodocyclohex-2-en-1-ol **2.28** (0.66 g, 2.82 mmol, 1 equiv.) and Pd(dppf)Cl_2 (0.19g, 0.25 mmol, 9 mol%) in THF (3 mL) then stirred for 18 h. Upon completion the reaction mixture was diluted with hexane and filtered through a celite plug, washing with EtOAc. The solvent was removed under reduced pressure and the residue partitioned between EtOAc and H_2O. The layers were separated and the organic layer dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude residue purified by column chromatography (3:7 EtOAc/Hexane w/ 0.05 % Et_3N) affording the product as a colourless oil (0.50 g, 1.82 mmol, 51 %).

^{1}H NMR (CHLOROFORM-d, 400 MHz) δ = 7.32-7.37 (m, 5H, Ar-**H**), 5.56 (br s, 1H, C=C**H**), 5.04-5.13 (m, 3H, C**H₂**Ph, N**H**), 4.06 (br s, 1H, C**H**OH), 3.50 (dq, *J*=13.4, 6.6 Hz, 1H, C**H₂**NHCbz), 3.24 (m, 1H, C**H₂**NHCbz), 2.36 (m, 1H, C**H₂**CH_2NHCbz), 2.24 (m, 1H, C**H₂**CH_2NHCbz), 1.94 (br s, 2H, C=CH-C**H₂**), 1.69-1.75 (m, 2H, HOCHC**H₂**), 1.64 (m, 1H, CH_2C**H₂**CH_2), 1.54 (m, 1H, CH_2C**H₂**CH_2) ppm

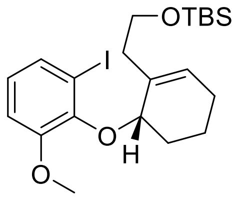
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 156.9 (**C**=O), 136.7 (**C**$_{Ph}$-CH_2), 135.9 (**C**=CH), 128.5 (**C**$_{Ar}$-H), 128.2 (**C**$_{Ar}$-H), 128.1 (C=**C**H, **C**$_{Ar}$-H), 67.3 (HO**C**H), 66.6 (Ph**C**H_2), 40.0 (**C**H_2NHCbz), 35.9 (**C**H_2CH_2NHCbz), 32.5 (C=CH-**C**H_2), 25.5 (HOCH**C**H_2), 17.9 (CH_2**C**H_2CH_2) ppm

LR MS (ESI$^+$) m/z: 258.0 $[M-H_2O]^+$, 298.1 $[M+Na]^+$, 573.1 $[2M+Na]^+$

HRMS (ES$^+$): Calculated for $[C_{16}H_{21}NO_3Na]^+$ 298.1414, found 298.1415 Da.

FT-IR (neat) *v*max (cm^{-1}): 3334 (b,w), 2933 (w), 1695 (s), 1519 (m), 1250 (m), 908 (m), 728 (s)

(*S*)-tert-Butyl(2-(6-(2-iodo-6-methoxyphenoxy)cyclohex-1-en-1-yl)ethoxy)dimethylsilane (3.47)



$C_{21}H_{33}IO_3Si$

MW: 488.48 gmol^{-1}

To a solution of alcohol **3.39** (0.47 g, 1.26 mmol, 1.0 equiv.) in Et_2O (50 mL) was added imidazole (0.13 g, 1.89 mmol, 1.5 equiv.) then TBSCl (0.29 g, 1.89 mmol, 1.5 equiv.), and the solution was stirred for 18 h. Upon completion the reaction was quenched with saturated NH_4Cl (aq). The layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude was purified by column chromatography (1:39 EtOAc/Hexane) affording the product as a colourless oil (0.56 g, 1.15 mmol, 91 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.38 (dd, *J*=7.9, 1.5 Hz, 1H, Ar$_3$-**H**), 6.88 (dd, *J*=8.2, 1.5 Hz, 1H, Ar$_5$-**H**), 6.76 (t, *J*=8.0 Hz, 1H, Ar$_4$-**H**), 5.77 (m, 1H, C=C**H**), 4.88 (t, *J*=4.0 Hz, 1H, ArOC**H**), 3.84 (s, 3H, OC**H$_3$**), 3.72-3.82 (m, 2H, C**H$_2$**OTBS), 2.62 (m, 1H, C**H$_2$**CH$_2$OTBS), 2.40 (m, 1H, C**H$_2$**CH$_2$OTBS), 2.05-2.21 (m, 2H, C=CH-C**H$_2$**, CH$_2$C**H$_2$**CH$_2$), 1.90-2.05 (m, 2H, C=CH-C**H$_2$**, ArOCHC**H$_2$**), 1.41-1.57 (m, 2H, ArOCHC**H$_2$,** CH$_2$C**H$_2$**CH$_2$), 0.86-0.91 (m, 9H, C(C**H$_3$**)$_3$), 0.00-0.07 (m, 6H, Si(C**H$_3$**)$_2$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 152.6 (**C$_{Ar}$**-OMe), 147.3 (**C$_{Ar}$**-O), 134.3 (**C**=CH), 131.2 (**C$_{Ar}$3**-H), 129.2 (C=C**H**), 124.9 (**C$_{Ar}$4**-H), 112.6 (**C$_{Ar}$5**-H), 93.8 (**C$_{Ar}$**-I), 76.8 (ArO**C**H), 62.9 (**C**H$_2$OTBS), 55.6 (O**C**H$_3$), 37.6 (**C**H$_2$CH$_2$OTBS), 28.5 (ArOCH**C**H$_2$), 26.0 (C(**C**H$_3$)$_3$), 25.6 (C=CH-**C**H$_2$), 18.9 (CH$_2$**C**H$_2$CH$_2$), 18.3 (**C**(CH$_3$)$_3$), -5.2 (Si(**C**H$_3$)$_2$) ppm

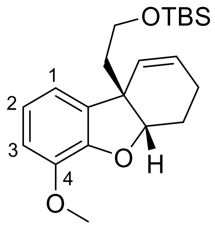
LR MS (ESI$^+$) m/z: 510.9 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{21}H_{33}IO_3SiNa$]$^+$ 511.1136, found 511.1147 Da.

FT-IR (neat) *ν*$_{max}$ (cm^{-1}): 2929 (m), 2855 (m), 1578 (w), 1463 (s), 1445 (m), 1254 (s), 1032 (s)

[α]$_D$: –55.66 (c 0.945, MeCN, 22 °C)

tert-Butyl(2-((5a*R*,9a*R*)-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)ethoxy)dimethylsilane (3.48)



$C_{21}H_{32}O_3Si$

MW: 360.57 gmol^{-1}

To a solution of TBS ether **3.47** (0.75 g, 1.53 mmol, 1.0 equiv.) in toluene (50 mL) was added Pd(dppf)Cl$_2$ (0.11 g, 0.15 mmol, 0.1 equiv.) and Cs_2CO_3 (1.63 g, 4.61 mmol, 3.0 equiv.). The solution was degassed with nitrogen for 20 min. The reaction mixture was then stirred at 70 °C for 65 h. Upon completion, the solution was cooled to rt and filtered through a silica pad, washing with 1:4 EtOAc/Hexane. The solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (1:99 EtOAc/Hexane), affording the product as a colourless oil (0.55 g, 1.51 mmol, 99 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ (ppm) 6.82 (dd, *J*=8.3, 7.2 Hz, 1H, Ar$_2$-**H**), 6.74 (dd, *J*=8.2, 1.0 Hz, 1H, Ar-**H**), 6.71 (dd, *J*=7.5, 1.2 Hz, 1H, Ar-**H**), 5.84 (m, 1H, CH=C**H**-CH$_2$), 5.50 (dt, *J*=10.1, 1.1 Hz, 1H, C**H**=CH-CH$_2$), 4.99 (m, 1H, ArOC**H**), 3.88 (s, 3H, OC**H$_3$**), 3.64-3.77 (m, 2H, C**H$_2$**OTBS), 2.16-2.32 (m, 2H, ArOCHC**H$_2$**), 1.80-2.08 (m, 4H, C**H$_2$**CH$_2$OTBS, CH=CH-C**H$_2$**), 0.84-0.91 (m, 9H, C(C**H$_3$**)$_3$), 0.03 (s, 6H, Si(C**H$_3$**)$_2$) ppm

^{13}C NMR (101MHz, CHLOROFORM-d) δ = 147.0 (**C$_{Ar}$**-OMe), 144.6 (**C$_{Ar}$**-O), 135.8 (**C**$_{Ar}$-C$_{quart}$), 130.6 (**C**=CH-CH$_2$), 127.3 (C=**C**H-CH$_2$), 121.0 (**C$_{Ar}$**H), 115.2 (**C$_{Ar}$**H), 110.9 (**C$_{Ar}$**H), 86.7 (ArO**C**H), 59.8 (**C**H$_2$OTBS), 55.8 (O**C**H$_3$), 47.5 (**C$_{quart}$**), 41.1 (**C**H$_2$CH$_2$OTBS), 25.9 (C(**C**H$_3$)$_3$), 24.0 (ArOCH**C**H$_2$), 19.1 (C=C-**C**H$_2$), 18.2 (**C**(CH$_3$)$_3$), -5.4 (Si(**C**H$_3$)$_2$) ppm

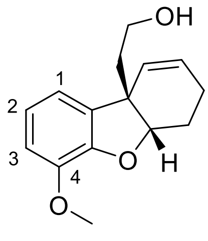
LR MS (ESI$^+$) m/z: 361.3 [M+H]$^+$, [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{21}H_{32}O_3SiNa$]$^+$ 383.2013, found 383.2015 Da.

FT-IR (neat) *v*max (cm^{-1}): 2928 (b,w), 2855 (w), 1740 (w), 1617 (w), 1491 (m), 1455 (m), 1252 (m), 1088 (s), 832 (s), 773 (s), 730 (s)

[α]$_D$: –36.71 (c 1.05, MeCN, 22 °C)

2-(5a*R*,9a*R*)-4-Methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)ethan-1-ol (3.40)



$C_{15}H_{18}O_3$

MW: 246.31 gmol^{-1}

To a solution of Heck product **3.48** (1.005 g, 2.79 mmol, 1.0 equiv.) in THF (50 mL) at 0 °C was added TBAF (1 M in THF, 4.2 mL, 4.18 mmol, 1.5 equiv.), dropwise. The solution was stirred for 15 min then warmed to rt and stirred for 2 h. The reaction mixture was then quenched with H$_2$O and diluted with EtOAc. The layers were separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude residuewas purified by column chromatography (1:1 EtOAc/Hexane) affording the product as a clear oil (0.671 g, 2.73 mmol, 97 %).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ = 6.84 (dd, *J*=8.30, 7.46 Hz, 1H, Ar$_2$-**H**), 6.72 - 6.78 (m, 2H, Ar-**H**), 5.86 (ddd, *J*=9.90, 5.44, 2.63 Hz, 1H, C=C**H**-CH$_2$), 5.59 (dt, *J*=10.03, 1.04 Hz, 1H, C**H**=C-CH$_2$), 4.91 (m, 1H, ArOC**H**), 3.88 (s, 3H, OC**H$_3$**), 3.69-3.82 (m, 2H, C**H$_2$**OH), 2.19 - 2.33 (m, 2H, ArOCHC**H**$_{\mathbf{ax}}$H$_{eq}$, C=C-CH**H**), 2.13 (m, 1H, C**H**HCH$_2$OH), 1.94 - 2.06 (m, 2H, C**H**HCH$_2$OH, C=C-CH**H**), 1.87 (m, 1H, ArOCHCH$_{ax}$**H**$_{\mathbf{eq}}$), 1.45 (br. S, 1H, O**H**) ppm

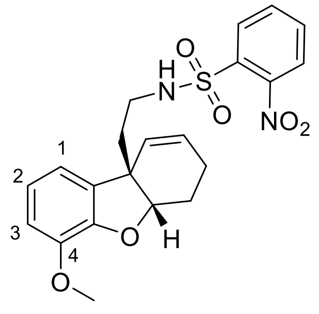
^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ = 146.8 (**C**$_{\mathbf{Ar}}$-O), 144.7 (**C**$_{\mathbf{Ar}}$-O), 135.3 (**C**$_{Ar}$-C$_{quart}$), 130.5 (**C**=CH-CH$_2$), 127.5 (C=**C**H-CH$_2$), 121.3 (**C**$_{\mathbf{Ar}}$H), 115.2 (**C**$_{\mathbf{Ar}}$H), 111.1 (**C**$_{\mathbf{Ar}}$H), 86.6 (ArO**C**H), 59.6 (**C**H$_2$OH), 55.8 (O**C**H$_3$), 47.4 (C$_{quart}$), 41.2 (**C**H$_2$CH$_2$OH), 24.4 (ArOCH**C**H$_2$), 19.2 (C=C-**C**H$_2$) ppm

LR MS (ESI$^+$) m/z: 229.2 [M-OH]$^+$, 247.3 [M+H]$^+$, 269.2 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [C$_{15}$H$_{18}$O$_3$Na]$^+$ 269.1148, found 269.1153 Da.

[α]$_{\mathbf{D}}$: –55.10 (c 0.96, MeCN, 22 °C)

***N*-((2-(5a*R*,9a*R*)-4-Methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)ethyl)-2-nitrobenzenesulfonamide (3.42)**



$C_{21}H_{22}N_2O_6S$

MW: 430.47 gmol^{-1}

To a solution of alcohol **3.40** (0.665 g, 2.70 mmol, 1.0 equiv.), 2-nitrobenzenesulfonamide (1.638 g, 8.10 mmol, 3.0 equiv.) and PPh$_3$ (1.062 g, 4.05 mmol, 1.5 equiv.) in THF (50 mL) at 0 °C was added DIAD (0.8 mL, 4.05 mmol, 1.5 equiv.) dropwise. The solution was allowed to reach rt then stirred for 72 h. The reaction mixture was added further 2-nitrobenzenesulfonamide (0.54 g, 2.70 mmol, 1.0 equiv.) and PPh$_3$ (1.06 g, 4.05 mmol, 1.5 equiv.), cooled to 0 °C, and added DIAD (0.8 mL, 4.05 mmol, 1.5 equiv.). The solution was warmed to rt and stirred for 4 h. Upon completion the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (1:9 – 1:3 EtOAc/Hexane), affording the product as a yellow foam, which was dried to give a crystalline solid (0.890 g, 2.07 mmol, 77 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.05-8.18 (m, 1H, **NsH**), 7.81-7.90 (m, 1H, **NsH**), 7.67-7.79 (m, 2H, **NsH**), 6.83 (t, *J*=7.9 Hz, Ar$_2$-**H**), 6.75 (dd, *J*=8.1, 1.0 Hz, 1H, Ar-**H**), 6.66 (dd, *J*=7.5, 1.0 Hz, 1H, Ar-**H**), 5.87 (ddd, *J*=9.8, 5.2, 2.9 Hz, 1H, C=C**H-**CH$_2$), 5.55 (d, *J*=10.0 Hz, 1H, C**H**=C-CH$_2$), 5.37 (br t, *J*=6.0 Hz, 1H, CH$_2$N**H**Ns), 4.73 (t, *J*=3.6 Hz, 1H, ArOC**H**), 3.86 (s, 3H, OC**H$_3$**), 3.07-3.23 (m, 2H, C**H$_2$**NHNs), 2.14-2.26 (m, 2H, C=C-CH**H,** ArOCHC**H**$_{\mathbf{ax}}$H$_{eq}$), 1.90-2.11 (m, 3H, C**H$_2$**CH$_2$NHNs, C=C-CH**H**), 1.74 (m, 1H, ArOCHCH$_{ax}$**H**$_{\mathbf{eq}}$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 148.0 (**C$_{ArNs}$**-NO$_2$), 146.7 (**C$_{Ar}$**-O), 144.8 (**C$_{Ar}$**-O), 134.3 (**C**$_{Ar}$-C$_{quart}$), 133.7 (**C$_{ArNs}$**-H), 133.6 (**C$_{ArNs}$**-H), 132.8 (**C$_{ArNs}$)**, 131.0 (**C$_{ArNs}$**-H), 129.7 (**C**=CH-CH$_2$), 128.2 (C=**C**H-CH$_2$), 125.4 (**C$_{ArNs}$**-H), 121.5 (**C$_{Ar}$2**-H), 115.0 (**C$_{Ar}$**-H), 111.3 (**C$_{Ar}$**-H), 85.9 (ArO**C**H), 55.8 (O**C**H$_3$), 47.4 (C$_{quart}$), 40.2 (**C**H$_2$NHNs), 38.7 (**C**H$_2$CH$_2$NHNs), 24.7 (ArOCH**C**H$_2$), 19.3 (C=C-**C**H$_2$) ppm

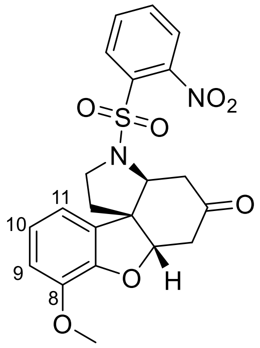
LR MS (ESI$^+$) m/z: 431.3 [M+H]$^+$, 453.2 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{21}H_{22}N_2O_6SNa$]$^+$ 453.1091, found 453.1101 Da.

FT-IR (neat) *v*max (cm^{-1}): 3246 (b, w), 2957 (w), 2160 (w), 2015 (w), 1540 (s), 1492 (m), 1334 (m), 727 (s), 587 (s)

[α]$_D$: –29.13 (c 1.035, MeCN, 22 °C)

(3a*S*,6a*S*,11b*R*)-8-Methoxy-3-((2-nitrophenyl)sulfonyl)-2,3,3a,4,6,6a-hexahydrobenzofuro[3,2-d]indol-5(1H)-one (3.82)



$C_{21}H_{20}N_2O_7S$

MW: 444.46 gmol^{-1}

To a solution of nosyl amide **3.42** (0.150 g, 0.35 mmol, 1.0 equiv.) in anhydrous EtOAc (10 mL) was added molecular sieves (3 Å, 0.2 g) and tbhp (5.5 M in decane, 0.2 mL, 1.04 mmol, 3.0 equiv.). The mixture was stirred for 30 min, then added Mn(OAc)$_3$.2H$_2$O (0.009 g, 0.04 mmol, 0.1 equiv.) and stirred for 24 h. The reaction mixture was then added further tbhp (5.5 M in decane, 0.2 mL, 1.04 mmol, 3.0 equiv.), stirred for 72 h then added Mn(OAc)$_3$.2H$_2$O (0.093 g, 0.35 mmol, 1.0 equiv.) and tbhp (5.5 M in decane, 0.2 mL, 1.04 mmol, 3.0 equiv.) and stirred at 50 °C for 12 h. The reaction mixture was filtered through a celite pad, washing with EtOAc and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:1 EtOAc/hexane), yielding the product as a viscous colourless oil (0.044 g, 0.10 mmol, 28 %).

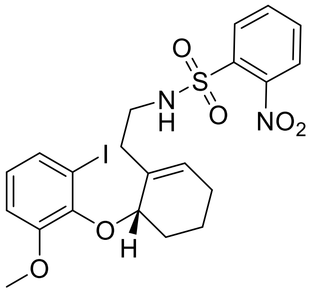
^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.15 (br d, *J*=7.0 Hz, 1H, **NsH**), 7.83-8.07 (m, 3H, **NsH**), 6.90 (br d, *J*=7.6 Hz, 1H, Ar-**H**), 6.80 (t, *J*=7.8 Hz, 1H, Ar$_{10}$-**H**), 6.56 (br d, *J*=6.8 Hz, 1H, Ar-**H**), 5.02 (br s, 1H, ArOC**H**), 3.93 (br s, 1H, C**H**NNs), 3.87 (br d, *J*=8.1 Hz, 1H, C**H$_2$**NNs), 3.75 (s, 3H, OC**H$_3$**), 3.68 (m, 1H, C**H$_2$**NNs), 2.67-2.91 (m, 3H, OCHC**H$_2$**, NCHC**H$_2$**), 2.21 (br d, *J*=2.6 Hz, 3H, C**H$_2$**CH$_2$NNs, NCHC**H$_2$**) ppm

^{13}C NMR (101 MHz , DMSO-d$_6$) δ = 205.7 (**C**=O), 148.4 (**C$_{ArNs}$-**NO$_2$), 147.3 (**C$_{Ar}$**-O), 144.7 (**C$_{Ar}$**-O), 135.7 (**C$_{ArNs}$**-H), 133.1 (**C$_{ArNs}$**-H), 131.0 (**C$_{ArNs}$**-H), 130.7 (**C$_{ArNs}$**), 129.7 (**C**$_{Ar}$-C$_{quart}$), 124.7 (**C$_{ArNs}$**-H), 122.6 (**C$_{Ar}$10**-H), 115.4 (**C$_{Ar}$**-H), 113.5 (**C$_{Ar}$**-H), 86.5 (ArO**C**H), 64.5 (**C**HNNs), 56.1 (O**C**H$_3$), 54.7 (C$_{quart}$), 48.6 (**C**H$_2$NNs), 42.0 (OCH**C**H$_2$**)**, 40.7 (NCH**C**H$_2$**)**, 34.9 (**C**H$_2$CH$_2$NNs) ppm

LR MS (ESI$^+$) m/z: 445.1 [M+H]$^+$, 467 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{21}H_{20}N_2O_7SNa$]$^+$ 467.0883, found 467.0881 Da.

(*S*)-N-(2-(6-(2-Iodo-6-methoxyphenoxy)cyclohex-1-en-1-yl)ethyl)-2-nitrobenzenesulfonamide (3.41)

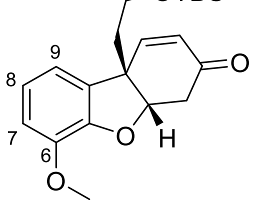


$C_{21}H_{23}IN_2O_6S$

MW: 558.39 gmol^{-1}

To a solution of alcohol **3.39** (0.150 g, 0.40 mmol, 1.0 equiv.) in THF (20 mL) was added PPh$_3$ (0.157 g, 0.60 mmol, 1.5 equiv.), 2-nitrobenzenesulfonamide (0.243 g, 1.20 mmol, 3.0 equiv.) then DIAD (0.12 mL, 0.60 mmol, 1.5 equiv.), the solution was then stirred at rt for 24 h. Upon completion the solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:9 – 1:4 EtOAc:Hexane) affording the product as a pale yellow oil (0.133 g, 0.24 mmol, 59 %). The product still contained inseparable impurities, but was used in the subsequent heck reaction after further drying under reduced pressure and without further purification.

9b-(2-(4a*R*,9b*R*)-((tert-Butyldimethylsilyl)oxy)ethyl)-6-methoxy-4a,9b-dihydrodibenzo[b,d]furan-3(4H)-one (3.76)



$C_{21}H_{30}O_4Si$

MW: 374.55 gmol^{-1}

To a solution of tricycle **3.48** (0.076 g, 0.21 mmol, 1.0 equiv.) in anhydrous EtOAc (2 mL) was added molecular sieves (3 Å, 0.200 g) and $Mn(OAc)_3.2H_2O$ (0.006 g, 0.02 mmol, 0.1 equiv.). The mixture was stirred for 10 min then added tbhp (5.5 M in decane, 0.2 mL, 1.06 mmol, 5.0 equiv.) and stirred at rt for 72 h. Upon completion the reaction mixture was filtered through a thin pad of celite, washing with EtOAc. The solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:9 EtOAc/hexane), affording the product as a gummy white solid. (0.327 g, 0.09 mmol, 42 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 6.92 (dd, *J*=8.2, 7.3 Hz, 1H, Ar$_8$-**H**), 6.78-6.83 (m, 2H, Ar-**H**), 6.43 (dd, *J*=10.3, 1.8 Hz, 1H, CH=C**H**-C=O), 6.02 (d, *J*=10.3 Hz, 1H, C**H**=CH-C=O), 5.14 (m, 1H, ArOC**H**), 3.87 (s, 3H, OC**H$_3$**), 3.73-3.84 (m, 2H, C**H$_2$**OTBS), 3.11 (dd, *J*=17.7, 3.1 Hz, 1H, ArOCHC**H$_{ax}$**H$_{eq}$), 3.08 (dd, *J*=17.9, 3.8 Hz, 1H, ArOCHCH$_{ax}$**H$_{eq}$**), 3.02 (m, 1H), 2.24 (m, 1H, C**H$_2$**CH$_2$OTBS), 2.15 (m, 1H, C**H$_2$**CH$_2$OTBS), 0.87 (s, 9H, SiC(C**H$_3$**)$_3$), -0.03-0.07 (m, 6H, SiC**H$_3$**) ppm

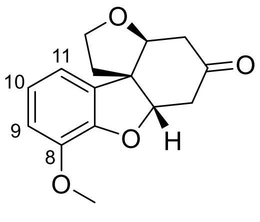
^{13}C NMR (101 MHz , CHLOROFORM-d) δ = 195.6 (**C**=O), 148.3 (C=**C**-C=O), 147.17 (**C$_{Ar}$**-OMe), 144.9 (**C$_{Ar}$**-O), 132.8 (**C**$_{Ar}$-C$_{quart}$), 127.3 (**C**=C-C=O), 122.1 (**C$_{Ar}$8** -H), 114.9 (**C$_{Ar}$**-H), 112.2 (**C$_{Ar}$**-H), 85.9 (ArO**C**H), 59.4 (**C**H$_2$OTBS), 56.0 (O**C**H$_3$), 48.6 (C$_{quart}$), 39.0 (**C**H$_2$CH$_2$OTBS, 38.3 (**C**H$_2$C=O), 25.8 (C(**C**H$_3$)$_3$), 18.1 (**C**(CH$_3$)$_3$), -5.5 ppm (Si**C**H$_3$) ppm

LR MS (ESI$^+$) m/z: 375.2 $[M+H]^+$, 397 $[M+Na]^+$

HRMS (ES$^+$): Calculated for $[C_{21}H_{30}O_4SiNa]^+$ 397.1806. found 397.1815 Da.

FT-IR (neat) *v*max (cm^{-1}): 2928 (b, m), 2856 (w), 1674 (s), 1489 (s), 1283 (s), 1248 (s), 1082 (s), 831 (s), 774 (s)

(3a*S*,6a*S*,11b*R*)-8-Methoxy-2,3,3a,4,6,6a-hexahydrobenzofuro[3,2-d]benzofuran-5-one (3.78)



Chemical Formula: $C_{15}H_{16}O_4$

MW: 260.29 gmol^{-1}

To a solution of enone **3.76** (0.070 g, 0.19 mmol, 1.0 equiv.) in THF (4 mL) at 0 °C was added TBAF (1 M in THF, 0.3 mL, 0.28 mmol, 1.5 equiv.) dropwise. The solution was allowed to warm to rt and stirred for 1 h. Upon completion the reaction as quenched with water and diluted with EtOAc. The layers were separated and the aqueous layers extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/hexane) affording the product a colourless powder (0.037 g, 0.14 mmol, 74 %).

^{1}H NMR (CHLOROFORM-d, 400 MHz) δ = 6.95 (t, *J*=7.8 Hz, 1H, Ar$_{10}$-**H**), 6.84 (br t, *J*=7.4 Hz, 2H, Ar-**H**), 4.85 (br s, 1H, ArOC**H**), 4.13 (m, 1H, C**H$_2$**OCH), 4.03 (m, 1H, C**H$_2$**OCH), 3.96 (br s, 1H, CH$_2$OC**H**), 3.84-3.92 (m, 3H, OC**H$_3$**), 3.04 (dd, *J*=18.2, 2.8 Hz, 1H, ArOCHC**H$_{ax}$**H$_{eq}$), 2.74-2.83 (m, 2H, ArOCHCH$_{ax}$**H$_{eq}$,** C**H$_2$**CH$_2$O), 2.70 (dd, *J*=18.0, 3.2 Hz, 1H, CH2OCHC**H$_{ax}$**H$_{eq}$C=O), 2.35 (br dd, *J*=17.7, 2.4 Hz, 1H, CH2OCHCH$_{ax}$**H$_{eq}$**C=O), 2.18 (ddd, *J*=13.4, 7.9, 6.7 Hz, 1H, C**H$_2$**CH$_2$O) ppm

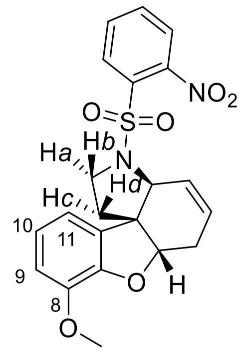
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 205.5 (**C**=O), 147.7 (**C$_{Ar}$**-OMe), 144.8 (**C$_{Ar}$**-O), 130.9 (**C**$_{Ar}$-C$_{quart}$), 122.4 (**C$_{Ar}$10**-H), 115.0 (**C$_{Ar}$**-H), 112.2 (**C$_{Ar}$**-H), 88.5 (ArO**C**H), 83.4 (CH$_2$O**C**HCH$_2$), 67.3 (**C**H$_2$OCH), 56.0 (O**C**H$_3$), 53.2 (C$_{quart}$), 39.4 (CH$_2$OCH**C**H$_2$C=O), 39.4 (ArOCH**C**H$_2$), 38.6 (**C**H$_2$CH$_2$O) ppm

LR MS (ESI$^+$) m/z: 261.2 [M+H]$^+$, 283.2 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{15}H_{16}O_4Na$]$^+$ 283.0941, found 283.0939 Da.

FT-IR (neat) *v*max (cm^{-1}): 2905 (b, w), 2871 (w), 1716 (s), 1494 (s), 1045 (s), 1019 (s), 777 (s), 736 (s)

(3a*S*,6a*S*,11b*R*)-(8-Methoxy-3-((2-nitrophenyl)sulfonyl)-1,2,3,3a,6,6a-hexahydrobenzofuro[3,2-d]indole (3.82)



Chemical Formula: $C_{21}H_{20}N_2O_6S$

MW: 428.46 gmol^{-1}

A solution of Pd(OAc)$_2$ (0.005 g, 0.024 mmol, 0.1 equiv.) and benzoquinone (0.005 g, 0.049 mmol, 0.2 equiv.) in AcOH (3 mL) was stirred for 15 min, then added MnO_2 (0.043 g, 0.490 mmol, 2.0 equiv.) and nosyl amide **3.42** (0.100 g, 0.230 mmol, 1.0 equiv.) and stirred at 50 °C for 20 h. Upon completion the reaction mixture was partitioned between EtOAc and H_2O. The layers were separated and the organic layer washed with H_2O (3 times), saturated Na_2SO_3 (aq) and brine then dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (1:4 EtOAc/Hexane), affording the product as a colourless residue (0.080 g, 0.186 mmol, 80%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.01 (d, *J*=7.6 Hz, 1H, **NsH**), 7.62-7.85 (m, 3H, **NsH**), 6.73 (dd, *J*=8.1, 1.1 Hz, 1H, Ar$_9$-**H**), 6.66 (t, *J*=7.9 Hz, 1H, Ar$_{10}$-**H**), 6.36 (dd, *J*=7.6, 1.1 Hz, 1H, Ar$_{11}$-**H**), 5.96 (ddt, *J*=9.9, 3.4, 1.7 Hz, 1H, NCHC**H**=CH-CH$_2$), 5.82 (dtd, *J*=9.8, 4.7, 1.5 Hz, 1H, NCHCH=C**H**-CH$_2$), 4.67 (t, *J*=5.4 Hz, 1H, ArOC**H**), 4.32 (m, 1H, NC**H**CH=CH-CH$_2$), 3.93 (dt, *J*=10.3, 7.3 Hz, 1H, CH$_2$C**H$_a$**H$_b$NNs), 3.85 (s, 3H, OC**H$_3$**), 3.66 (m, 1H, CH$_2$CH$_a$**H$_b$**NNs), 2.52 (m, 2H, ArOCHC**H$_2$**), 2.29 (ddd, *J*=12.9, 7.3, 5.9 Hz, 1H, C**H$_c$**H$_d$CH$_2$NNs), 2.13 (dt, *J*=12.8, 7.2 Hz, 1H, CH$_c$**H$_d$**CH$_2$NNs) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 148.2 (**C$_{ArNs}$**-NO$_2$), 147.0 (**C$_{Ar}$**-OMe), 144.6 (**C$_{Ar}$**-O), 133.6 (**C$_{ArNs}$**-H), 132.9 (**C**$_{Ar}$-C$_{quart}$), 132.7 (**C$_{ArNs}$**), 131.5 (**C$_{ArNs}$**-H), 131.0 (**C$_{ArNs}$**-H), 129.0 (NCH**C**H=CH-CH$_2$), 126.1 (NCHCH=**C**H-CH$_2$), 124.0 (**C$_{ArNs}$**-H), 121.9 (**C$_{Ar}$10**-H), 114.6 (**C$_{Ar}$11**-H), 111.7 (**C$_{Ar}$9**-H), 85.8 (ArO**C**H), 62.0 (N**C**HCH=CH-CH$_2$), 55.9 (O**C**H$_3$), 55.3 (C$_{quart}$), 47.6 (**C**H$_2$NNs), 37.6 (**C**H$_2$CH$_2$NNs), 27.5 (ArOCH**C**H$_2$**)** ppm

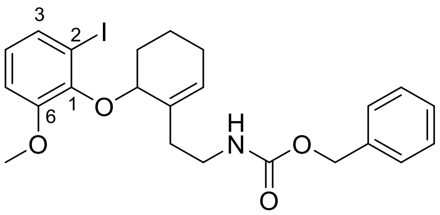
LR MS (ESI$^+$) m/z: 429.3 [M+H]$^+$, 451 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{21}H_{21}N_2O_6S$]$^+$ 429.1115, found 429.1123 Da.

FT-IR (neat) *v*max (cm^{-1}): 2939 (b, w), 1733 (w), 1541 (s), 1354 (m), 1164 (s), 567 (s)

[α]$_D$: –27.86 (c 0.70, MeCN, 22 °C)

(±)-Benzyl (2-(6-(2-iodo-6-methoxyphenoxy)cyclohex-1-en-1-yl)ethyl)carbamate (3.92)



Chemical Formula: $C_{23}H_{26}INO_4$

MW: 507.37 gmol^{-1}

To a solution of 2-iodo-6-methoxyphenol **3.17** (0.086 g, 0.34 mmol, 1.2 equiv.) in THF (5 mL) was added ^{n}Bu$_3$P (0.15 mL, 0.58 mmol, 2.0 equiv.), cyclohexenol **2.78** (0.079 g, 0.29 mmol, 1.0 equiv.) then DBAD (0.134 g, 0.58 mmol, 2.0 equiv). The solution was stirred at rt for 18 h. Upon completion the solvent was removed under reduced pressure and the crude residue was purified by column chromatography (1:9 EtOAc/Hexane with 0.5% Et$_3$N) affording the product as a colourless oil (0.121 g, 0.24 mmol, 82 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.29-7.41 (m, 6H, Ar$_{cbz}$-**H**, Ar-**H**), 6.87 (d, *J*=7.3 Hz, 1H, Ar-**H**), 6.76 (t, *J*=8.1 Hz, 1H, Ar$_4$-**H**), 5.76 (br s, 1H, C=C**H**-CH$_2$), 5.09 (d, *J*=1.5 Hz, 2H, C**H$_2$**Ph), 5.02 (m, 1H, N**H**), 4.95 (br s, 1H, ArOC**H**), 3.81 (s, 3H, OC**H₃**), 3.40-3.50 (m, 2H, C**H₂**NHCbz), 2.63 (m, 1H, C**H₂**CH_2NHCbz), 2.34 (dt, *J*=14.2, 7.0 Hz, 1H, C**H₂**CH_2NHCbz), 2.16 (m, 1H, C=CH-C**H₂**), 1.90 (m, 1H, ArOCHC**H₂**), 1.40-1.58 (m, 4H, C=CH-C**H₂**, ArOCHC**H₂**, CH_2C**H₂**CH_2) ppm

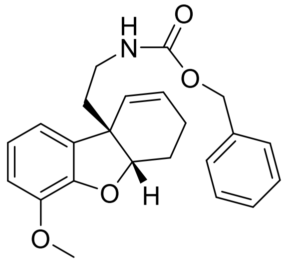
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 156.4 (**C**=O), 152.5 (**C**$_{\text{Ar}}$-O), 146.6 (**C**$_{\text{Ar}}$-OMe), 136.8 (**C**$_{\text{ArCbz}}$), 134.2 (**C**=CH-CH_2), 131.2 (**C**$_{\text{Ar}}$-H), 129.9 (C=**C**H-CH_2), 128.5 (**C**$_{\text{ArCbz}}$-H), 128.1 (**C**$_{\text{ArCbz}}$-H), 125.1 (**C**$_{\text{Ar}}$**4**-H), 112.5 (**C**$_{\text{Ar}}$-H), 93.9 (**C**$_{\text{Ar}}$-I), 76.4 (ArO**C**H), 66.4 (**C**H_2Ph), 55.6 (O**C**H_3), 39.9 (**C**H_2NHCbz), 34.6 (**C**H_2CH_2NHCbz), 28.2 (ArOCH**C**H_2), 25.5 (C=CH-**C**H_2), 18.6 (CH_2**C**H_2CH_2) ppm

LR MS (ESI$^+$) m/z: 530.3 $[M+Na]^+$

HRMS (ES$^+$): Calculated for $[C_{23}H_{26}INO_4Na]^+$ 530.0799, found 530.0802 Da.

FT-IR (neat) *v*max (cm^{-1}): 3336 (b, w), 2933 (m), 1700 (s), 1461 (s), 1253 (s), 1026 (s), 762 (m), 696 (m)

(±)-Benzyl-(2-5a*R*,9a*R*)-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)ethyl)carbamate (3.93)



Chemical Formula: $C_{23}H_{25}NO_4$

MW: 379.46 gmol^{-1}

To a solution of ether **3.92** (0.096 g, 0.19 mmol, 1.0 equiv.) in toluene (10 mL) was added Pd(dppf)Cl_2 (0.013 g, 0.02 mmol, 0.1 equiv.) and Cs_2CO_3 (0.201 g, 0.57 mmol, 3.0 equiv.) The solution was degassed with N_2 for 30 min then stirred at 80 °C for 18 h, added Pd(dppf)Cl_2 (0.013 g, 0.02 mmol, 0.1 equiv.) and Cs_2CO_3 (0.201 g, 0.57 mmol, 3.0 equiv.) and stirred at 80 °C for a further 7 h. Upon completion the reaction mixture was filtered through a thin pad of celite, washing with Et_2O. The solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:9 EtOAc/Hexane with 0.5% Et_3N) affording the product as a colourless solid (0.052 g, 0.14 mmol, 72 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.29-7.44 (m, 5H, Ar$_{\text{Cbz}}$-**H**), 6.84 (m, 1H, Ar-**H**), 6.63-6.78 (m, 2H, Ar-**H**), 5.84 (br d, *J*=2.7 Hz, 1H, C=C**H**-CH_2), 5.58 (br d, *J*=10.0 Hz, 1H, C**H**=C-CH_2), 5.03-5.16 (m, 2H, C**H₂**Ph), 4.84 (br s, 1H, ArOC**H**), 4.77 (br s, 1H, N**H**), 3.83-3.90 (m, 3H, OC**H₃**), 3.13-3.31 (m, 2H, C**H₂**NHCbz), 2.11-2.32 (m, 2H, C**H₂**CH₂NHCbz), 1.88-2.06 (m, 3H, ArOCHC**H₂**C**H₂**), 1.83 (m, 1H, ArOCHC**H₂**CH₂) ppm

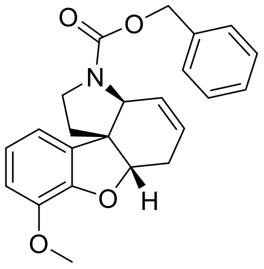
^{13}C NMR (101 MHz , CHLOROFORM-d) δ = 156.2 (**C**=O), 146.7 (**C**$_{Ar}$-OMe), 144.7 (**C**$_{Ar}$-O), 134.9 (**C**$_{Ar}$-C$_{quart}$), 130.0 (**C**=CH-CH₂), 128.5 (C=**C**H-CH₂), 128.1 (**C**$_{ArCbz}$), 127.7 (**C**$_{ArCbz}$), 126.0 (**C**$_{ArCbz}$), 121.4 (**C**$_{Ar}$-H), 115.1 (**C**$_{Ar}$-H), 111.1 (**C**$_{Ar}$-H), 86.2 (ArO**C**H), 66.7 (**C**H₂Ph), 55.8 (O**C**H₃), 47.4 (C$_{quart}$), 38.7 (**C**H₂NHCbz), 37.5 (**C**H₂CH₂NHCbz), 24.7 (ArOCH**C**H₂), 19.2 (C=C-**C**H₂) ppm

LR MS (ESI$^+$) m/z: 380.4 [M+H]$^+$, 402.3 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{23}H_{25}NO_4Na$]$^+$ 402.1676, found 402.1673 Da.

FT-IR (neat) *v*max (cm^{-1}): 3343 (b, m), 2929 (m), 1699 (s), 1489 (s), 1244 (s), 734 (s)

(±)-(3a*S*,6a*S*,11b*R*)-Benzyl-8-methoxy-1,2,6,6a-tetrahydrobenzofuro[3,2-d]indole-3(3aH)-carboxylate (3.94)



Chemical Formula: $C_{23}H_{23}NO_4$

MW: 377.44 gmol^{-1}

A solution of Pd(OAc)₂ (0.002 g, 0.008 mmol, 0.1 equiv.) and benzoquinone (0.002 g, 0.016 mmol, 0.2 equiv.) in AcOH (1 mL) was stirred for 15 min then added MnO₂ (0.014 g, 0.158 mmol, 2.0 equiv.) followed by a solution of tricycle **3.93** (0.030 g, 0.079 mmol, 1.0 equiv.) in AcOH (2 mL). The mixture was stirred at 50 °C for 20 h. Upon completion the reaction mixture was partitioned between H₂O and Et₂O and the layers separated. The organic layer was washed with H₂O (3 times) then saturated Na₂SO₃ (aq) and dried (MgSO₄). The solvent was then removed under reduced pressure and the crude residue purified using column chromatography (1:4 EtOAc/Hexane with 0.5 % Et₃N) affording the product as a viscous colourless oil (0.016 g, 0.041 mmol, 52%).

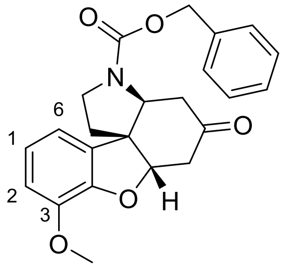
^{1}H NMR (400 MHz, ACETONITRILE-d₃) δ = 7.29-7.45 (m, 5H, Ar$_{Cbz}$-**H**), 6.80-6.85 (m, 2H, Ar-**H**), 6.73 (m, 1H, Ar-**H**), 5.98 (m, 1H, CH=C**H**-CH₂), 5.82 (ddd, *J*=9.7, 4.8, 1.3 Hz, 1H, C**H**=CH-CH₂), 5.12 (s, 2H, C**H₂**Ph), 4.67 (t, *J*=5.7 Hz, 1H, ArOC**H**), 4.11 (br s, 1H, NC**H**-C=C), 3.80 (s, 3H, OC**H₃**), 3.77 (br d, *J*=4.9 Hz, 1H, C**H₂**NCbz), 3.55 (br s, 1H, C**H₂**NCbz), 2.59 (dt, *J*=16.7, 5.4 Hz, 1H, ArOCHC**H₂**), 2.35 (br d, *J*=15.7 Hz, 1H, ArOCHC**H₂**), 2.13-2.29 (m, 2H, C**H₂**CH₂NCbz) ppm

^{13}C NMR (101 MHz, ACETONITRILE-d$_3$) δ = 155.5 (**C**=O), 148.2 (**C$_{Ar}$**-OMe), 145.6 (**C$_{Ar}$**-O), 135.5 (**C**$_{Ar}$-C$_{quart}$), 131.5 (**C**=CH-CH$_2$), 131.0 (C=**C**H-CH$_2$), 129.5 (**C$_{ArCbz}$**), 129.0 (**C$_{ArCbz}$**), 128.6 (**C$_{ArCbz}$**), 125.5 (**C$_{ArCbz}$**-CH$_2$), 122.9 (**C$_{Ar}$**-H), 116.0 (**C$_{Ar}$**-H), 113.3 (**C$_{Ar}$**-H), 86.4 (ArO**C**H), 67.4 (**C**H$_2$Ph), 56.5 (O**C**H$_3$), 46.1 (C$_{quart}$), 38.2 (**C**H$_2$NCbz), 37.4 (**C**H$_2$CH$_2$NCbz), 28.7 (C=C-**C**H$_2$) ppm

LR MS (ESI$^+$) m/z: 378.3 [M+H]$^+$, 400.3 [M+Na]$^+$

HRMS (ES$^+$): Calculated for [$C_{23}H_{23}NO_4Na$]$^+$ 400.1519, found 400.1516 Da.

(±)-(3a*S*,6a*S*,11b*R*)-Benzyl-8-methoxy-5-oxo-1,2,4,5,6,6a-hexahydrobenzofuro[3,2-d]indole-3(3aH)-carboxylate (3.95)



Chemical Formula: $C_{23}H_{23}NO_5$

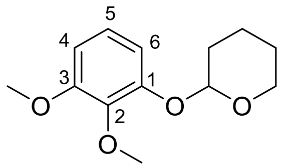
MW: 393.44 gmol^{-1}

To a solution of tetracycle **3.94** (0.015 g, 0.040 mmol, 1.0 equiv.) in MeCN/H_2O (4:1, 5 mL) was added $PdCl_2$ (0.001 g, 0.004 mmol, 0.1 equiv.) and CrO_3 (0.004 g, 0.040 mmol, 1.0 equiv.). The solution was stirred at rt for 18 h. Upon completion the reaction mixture was partitioned between EtOAc and H_2O, the layers separated, and the organic layer filtered through a thin pad of celite, washing with EtOAc. The crude residue was purified using column chromatography (1:1 EtOAc/Hexane with 0.5%) affording the product as a colourless viscous oil (0.006 g, 0.015 mmol, 38%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.33-7.41 (m, 5H, Ar$_{Cbz}$-**H**), 6.94 (t, *J*=7.7 Hz, 1H, Ar-**H**), 6.85 (d, *J*=7.9 Hz, 1H, Ar-**H**), 6.79 (d, *J*=7.5 Hz, 1H, Ar-**H**), 5.15 (br d, *J*=9.9 Hz, 2H, C**H$_2$**Ph), 4.93 (t, *J*=3.6 Hz, 1H, ArOC**H**), 4.02 (br s, 1H, NC**H**CH$_2$), 3.89 (m , 5H, OC**H$_3$**, CH$_2$C**H$_2$**NCbz), 3.51 (dt, *J*=11.2, 6.9 Hz, 1H, C**H$_2$**CH$_2$NCbz), 3.06 (dd, *J*=18.3, 3.7 Hz, 1H, ArOCHC**H$_2$**), 2.63 (dd, *J*=18.3, 3.7 Hz, 1H, ArOCHC**H$_2$**), 2.53 (m, 1H, C**H$_2$**CH$_2$NCbz), 2.40 (dd, *J*=17.5, 2.9 Hz, 1H, NCHC**H$_2$**), 2.09 (m, 1H, NCHC**H$_2$**) ppm

LR MS (ESI$^+$) m/z: 394.3 [M+H]$^+$, 416.3 [M+Na]$^+$

2-(2,3-Dimethoxyphenoxy)tetrahydro-2H-pyran (3.18)



Chemical Formula: $C_{13}H_{18}O_4$

MW: 238.28 gmol^{-1}

To a solution of 2,3-dimethoxyphenol (1.00 g, 6.49 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was added dihydropyran (5.50 mL, 64.90 mmol, 10 equiv.) and PPTS (0.33 g, 1.30 mmol, 0.2 equiv.). The solution was stirred at rt for 72 h. Upon completion the reaction mixture was quenched with saturated NaOH (aq) (20 mL), diluted with H_2O, and the layers separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/Hexane) affording the product as a colourless solid (1.47 g, 6.17 mmol, 95 %).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 6.96 (t, *J*=8.3 Hz, 1H, Ar$_5$-**H**), 6.81 (dd, *J*=8.4, 1.3 Hz, 1H, Ar-**H**), 6.61 (dd, *J*=8.3, 1.3 Hz, 1H, Ar-**H**), 5.44 (t, *J*=3.2 Hz, 1H, OC**H**O), 3.99 (m, 1H, OC**H$_2$**), 3.89 (s, 3H, OC**H$_3$**), 3.86 (s, 3H, OC**H$_3$**), 3.62 (m, 1H, OC**H$_2$**), 2.05 (m, 1H, OCHCH$_2$C**H$_2$**), 1.84-1.96 (m, 2H, OCHC**H$_2$**), 1.59-1.76 (m, 3H, OCHCH$_2$C**H$_2$, **OCH$_2$C**H$_2$**) ppm

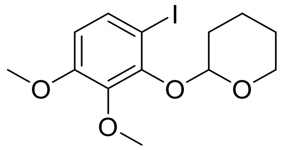
^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 153.6 (C$_{Ar}$O), 150.9 (C$_{Ar}$O), 139.4 (C$_{Ar}$O), 123.5 (**C$_{Ar}$5**H), 110.1 (**C$_{Ar}$**H), 106.1 (**C$_{Ar}$**H), 97.3 (O**C**HO), 62.0 (O**C**H$_2$), 60.9 (O**C**H$_3$), 56.1 (O**C**H$_3$), 30.4 (OCH**C**H$_2$**)**, 25.3 (OCH$_2$**C**H$_2$), 18.8 (OCHCH$_2$**C**H$_2$) ppm

LR MS (ESI$^+$) m/z: 261.2 [M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{13}H_{18}O_4Na]^+$ 261.1097, found 261.1098 Da.

FT-IR (neat) *v*max (cm^{-1}): 2939 (m), 1596 (m), 1473 (s), 1082 (s), 982 (m)

2-(6-Iodo-2,3-dimethoxyphenoxy)tetrahydro-2H-pyran (3.19)



Chemical Formula: $C_{13}H_{17}IO_4$

MW: 364.18 gmol^{-1}

To a solution of THP ether **3.18** (1.00 g, 4.20 mmol, 1.0 equiv.) in THF (20 mL) at 0 °C was added ^{n}BuLi (2.1 M, 2.6 mL, 5.46 mmol, 1.4 equiv.) slowly dropwise. The reaction mixture was warmed to rt and stirred for 2.5 h, during which time the solution turned yellow. The mixture was cooled to – 50 °C and added a solution of iodine (2.13 g, 8.40 mmol, 2.0 equiv.) in THF (40 mL) dropwise via cannula. The reaction mixture was warmed to rt and stirred for 18 h. The mixture was diluted with Et_2O and brine and H_2O. The layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with saturated $Na_2S_2O_3$ (aq) dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (1:9 EtOAc/Hexane) affording the product (with roughly 10% inseparable starting material) as a colourless solid (1.16 g, 3.19 mmol, 76% yield).

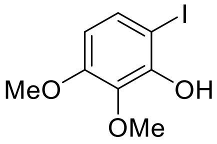
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.46 (d, *J*=8.8 Hz, 1H, Ar-**H**), 6.48 (d, *J*=8.8 Hz, 1H, Ar-**H**), 5.68 (t, *J*=2.9 Hz, 1H, OC**H**O), 4.26 (m, 1H, OC**H₂**), 3.85 (s, 3H, OC**H₃**), 3.83 (s, 3H, OC**H₃**), 3.63 (m, 1H, OC**H₂**), 2.03-2.20 (m, 2H, OCHC**H₂**), 1.89 (m, 1H, OCH_2C**H₂**), 1.62-1.72 (m, 3H, OCH_2C**H₂,** $OCHCH_2C$**H₂**) ppm

LR MS (ESI$^+$) m/z: 387.1 $[M+Na]^+$

HRMS (ES$^+$): Calculated for $[C_{13}H_{17}O_4INa]^+$ 387.0064, found 387.0066 Da.

FT-IR (neat) *v*max (cm^{-1}): 2936 (m), 1568 (m), 1418 (s), 1291 (s), 870 (s), 797 (s), 625 (m)

6-Iodo-2,3-dimethoxyphenol (3.14)



Chemical Formula: $C_8H_9IO_3$

MW: 280.06 gmol^{-1}

To a solution of iodo-THP ether **3.19** (1.10 g, 3.02 mmol, 1.0 equiv.) in MeOH (25 mL) was added AcOH (2 mL) and stirred for 18 h. Upon completion the solvent and methoxy-THP ether by-product were removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ (aq). The solvent was removed under reduced pressure, leaving the product as a colourless solid (0.72 g, 2.57 mmol, 85 %).

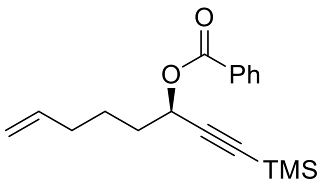
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.35 (d, *J*=8.9 Hz, 1H, Ar-**H**), 6.35 (d, *J*=8.9 Hz, 1H, Ar-**H**), 6.20 (s, 1H, O**H**), 3.91 (s, 3H, OC**H₃**), 3.86 (s, 3H, OC**H₃**) ppm

LR MS (ESI$^+$) m/z: 281.1 $[M+H]^+$, 303.0 $[M+Na]^+$

HRMS (ES$^+$): Calculated for $[C_8H_9IO_3Na]^+$ 302.9489, found 302.9483 Da.

FT-IR (neat) *v*max (cm^{-1}): 3390 (b, m), 3011 (w), 2953 (w), 2830 (w), 1586 (m), 1459 (s), 1208 (s), 1090 (s), 989 (s), 773 (s)

(*R*)-1-(Trimethylsilyl)oct-7-en-1-yn-3-yl benzoate (3.24)



To a solution of (*R*)-propargyl alcohol **2.80** (0.022 g, 0.11 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) at 0 °C was added benzoyl chloride (0.013 mL, 0.11 mmol, 1.0 equiv.) and Et_3N (0.050 mL, 0.34 mmol, 3.0 equiv.). The solution was stirred at rt for 18 h. Upon completion the reaction mixture was diluted with CH_2Cl_2 and H_2O and the layers separated. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified using column chromatography (1:4 EtOAc/Hexane) affording the product as colourless oil (0.012 g, 0.03 mmol, 35 %, 97.4 % ee).

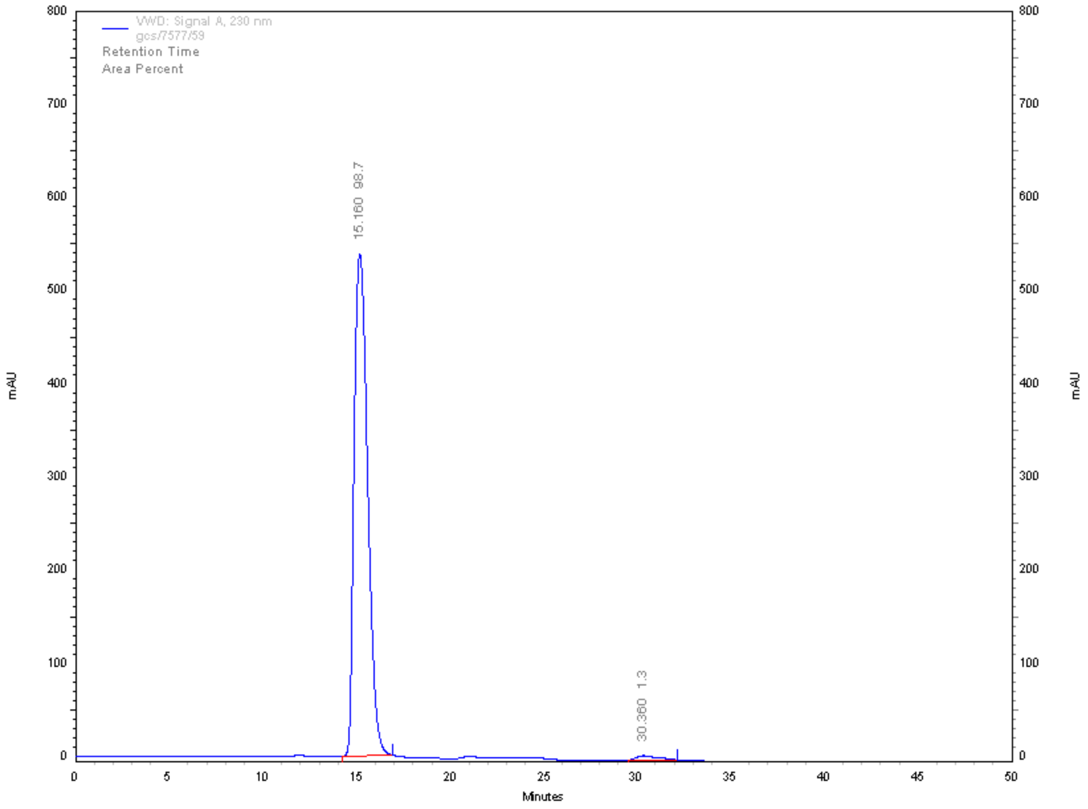
^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 8.09 (d, *J*=7.7 Hz, 2H, Ar-**H**), 7.58 (tt, *J*=7.2, 1.1 Hz, 1H, Ar-**H**), 7.46 (t, *J*=7.5 Hz, 2H, Ar-**H**), 5.82 (ddt, *J*=17.0, 10.3, 6.6 Hz, 1H, H$_2$C=C**H**), 5.66 (t, *J*=6.6 Hz, 1H, C**H**OBz), 5.05 (dq, J=17.1, 1.7 Hz, 1H, **H$_{trans}$**H$_{cis}$C=CH), 4.99 (ddt, *J*=10.1, 2.1, 1.2 Hz, 1H, H$_{trans}$**H$_{cis}$**C=CH), 2.10-2.18 (m, 2H, H$_2$C=CH-C**H$_2$**), 1.84-1.99 (m, 2H, BzOCHC**H$_2$**), 1.61-1.68 (m, 2H, CH$_2$C**H$_2$**CH$_2$), 0.15-0.21 (m, 9H, Si(C**H$_3$**)$_3$) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 165.4 (**C**=O), 138.1 (H$_2$C=C**H**), 133.1 (**C$_{Ar}$**-H), 130.0 (**C$_{Ph}$**-C=O), 129.8 (**C$_{Ar}$**-H), 128.3 (**C$_{Ar}$**-H), 115.0 (**H$_2$**C=CH), 102.6 (**C**ΞC-TMS), 90.5 (CΞ**C**-TMS), 64.7 (**C**HOBz), 34.3 (BzOCH**C**H$_2$), 33.1 (H$_2$C=CH-**C**H$_2$**)**, 24.3 (CH$_2$**C**H$_2$CH$_2$), -0.2 (Si(**C**H$_3$)$_3$) ppm

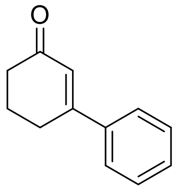
LR MS (ESI$^+$) m/z: 301.3 [M+H]$^+$, 323.3 [M+Na]$^+$

HRMS (ES$^+$): Calculated for $[C_{18}H_{24}O_2SiNa]^+$ 323.1438, found 323.1437 Da.

FT-IR (neat) *v*max (cm^{-1}): 2956 (w), 1249 (s), 1095 (m), 839 (s), 709 (s)



3-phenylcyclohex-2-enone (3.73)



$C_{12}H_{12}O$

MW: 172.23 $gmol^{-1}$

Rhodium allylic oxidation method

To a solution of Rh_2cap_4 (0.002 g, 2.70 µmol, 0.1 mol%) in CH_2Cl_2 (10 mL) was added 1-phenylcyclohexene (0.43 mL, 2.70 mmol, 1.0 equiv.) and K_2CO_3 (0.187 g, 1.35 mmol, 0.5 equiv.). The mixture was stirred for 5 min then added tbhp (5.5 M, 2.45 mL,. 13.50 mmol, 5.0 equiv.) in one portion, causing significant release of O_2, which was captured using a rubber balloon. The reaction mixture was stirred at rt for 90 min. Upon completion the mixture was filtered through a short pad of silica, washing with CH_2Cl_2 and the solvent removed under reduced pressure. The crude residue was purified using column chromatography (1:4 EtOAc/Hexane), affording the product as an off white low melting solid (0.184 g, 1.07 mmol, 40 %). Spectroscopic data are consistent with those reported.[190]

Chromium allylic oxidation method

To a solution of 1-phenylcyclohexene (0.206 g, 1.30 mmol, 1.0 equiv.) and *N*-hydroxyphthalimide (0.294 g, 1.80 mmol, 1.4 equiv.) in acetone/H_2O (9:1, 10 mL) was added pyridinium dichromate (0.752 g, 2.00 mmol, 1.5 equiv.). The solution was stirred at rt for 20 h. Upon completion the reaction mixture was concentrated under reduced pressure and diluted with EtOAc/H_2O then filtered through a pad of celite, washing with EtOAc. The layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was then purified by column chromatography (1:4 EtOAc/Hexane), affording the product as an off white low melting solid (0.118 g, 0.68 mmol, 53 %). Spectroscopic data are consistent with those reported.[190]

^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.52-7.56 (m, 2H, Ph-**H**), 7.39-7.44 (m, 3H, Ph-**H**), 6.42 (t, *J*=1.4 Hz, 1H, C=C**H**), 2.78 (td, *J*=6.0, 1.3 Hz, 2H, C**H₂**), 2.46-2.52 (m, 2H, C**H₂**), 2.12-2.20 (m, 2H, C**H₂**) ppm

^{13}C NMR (101 MHz, CHLOROFORM-d) δ = 199.8 (**C**=O), 159.7 (**C**=CH), 138.7 ($\mathbf{C_{Ph}}$-C=CH), 129.9 (**C**H), 128.7 (**C**H), 126.0 (**C**H), 125.4 (**C**H), 37.2 (**C**H_2), 28.0 (**C**H_2), 22.8 (**C**H_2) ppm

FT-IR (neat) *v*max (cm^{-1}): 3058 (w), 2940 (w), 2867 (w), 1713 (m), 1650 (s), 1602 (m), 1446 (m), 1348 (m), 751 (s)

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