A New Strategy Towards the Fawcettimine Core of *Lycopodium* Alkaloids

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A dissertation presented in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

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Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between September 2015 and September 2018. The dissertation is the result of my own work and includes no results obtained through collaboration.

Minh Thao Tran

Acknowledgement

Words cannot convey my gratitude for Professor Martin Smith, who has supported me from the very first time we talked about my application to SBM, through to the end of my DPhil. His constant guidance, tireless assurance, and wisdoms on goldfish have been lights at the end of the tunnels on numerous occasions. I am grateful for the time he has put aside amidst his busy schedule to dispel my concerns, big or small, academic or personal. Thank you, Martin, for having faith, and forcing me to have faith, in my abilities.

I am eternally grateful for my family, their ever-present support and love, and constant picture updates of my mischievous niece and nephew.

My thanks go to CB, Roly, Yao, Glenn and Liam for proof-reading my thesis. Your eagle eyes are invaluable in helping me put this thesis together. Yao, you have always had time for my questions and rants - thank you.

Thank you to all past and present MDS group members who have touched my life. Your terrible music taste, tacky Christmas decorations, unhealthy addictions of checked shirt, and general shenanigans have made gruesome days tolerable, and mundane days memorable. I must mention Alison, Kat and Ben R who were my chief partners in crime when it comes to cheeky businesses such as extended tea breaks and spontaneous ice cream trips.

Thank you to the SBM 2014 cohort. We were ‘lab rats’ together, and together we persevered and thrived. Thank you Rachel, Lara, Laura and Maitane, the incredible Spice Girls of SBM, who have supported us with all their might and inexhaustible supply of teas and biscuits.

Steve, you are a great friend, and I value all the moments we spend together, either to dance around the Rex Richards while rehearsing our talk, or to support one another at difficult times.

Finally, thank you, Dr Glenn Archibald, my irreplaceable housemate. You have always believed in my best, and kept me going through my worst. My memories of every corner of Oxford will ever be sweeter because you were simply there with me. PS: your crock-pot meals are a-ma-zing.

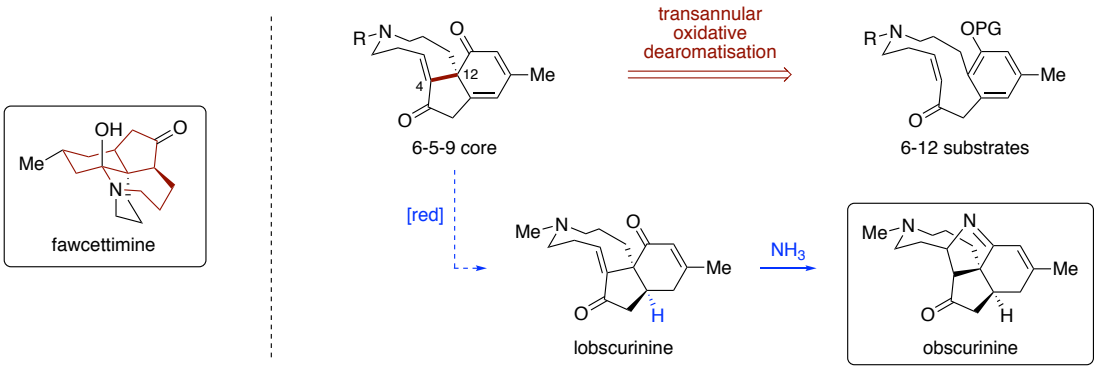
List of Abbreviations

Å	Ångström(s)
Ac	Acetyl
Ar	Aryl (generic)
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
Bu	Butyl
°C	degrees Celsius
Cbz	Carboxybenzyl
COSY	Correlation spectroscopy
m-CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphor-10-sulfonic acid
Cy	Cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	*N*,*N*′-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dr	Diastereoisomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Et	ethyl
eq	Equivalent(s)
EWG	Electron Withdrawing Group
FTIR	Fourier-transform Infrared Spectroscopy
g	gram(s)
HFIP	Hexafluoroisopropanol
IBX	2-iodoxybenzoic acid
IUPAC	International Union of Pure and Applied Chemistry
h	hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
Hz	Hertz
KHMDS	Potassium bis(trimethylsilyl)amide
L	litre(s)
LDA	Lithium diisopropylamide
µ	micro-
m	milli-

M	moles per litre
Me	Methyl
MeCN	Acetonitrile
mol	moles
m.p.	Melting point
M.S.	Molecular sieves
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PMB	4-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
PTS	Polyoxyethanyl α-tocopheryl sebacate
R	Substituent (generic)
rt	Room temperature
SET	Single Electron Transfer
TBAC	*tert*-Butylammonium chloride
TBAF	*tert*-Butylammonium fluoride
TBAI	*tert*-Butylammonium iodide
TBS	*tert*-Butyldimethylsilyl
Temp.	Temperature
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
py	Pyridine

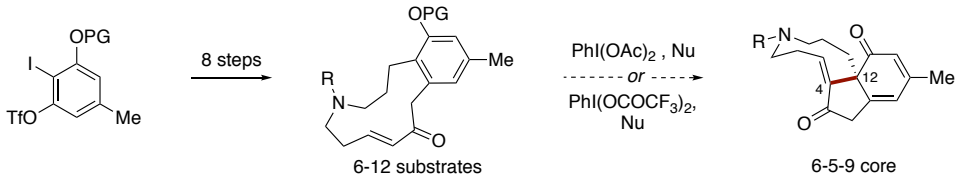
Abstract

This project aims to develop a new strategy towards the fawcettimine core of *Lycopodium* alkaloids with application to the synthesis of obscurinine (Scheme I). Chapter 1 introduces the *Lycopodium* alkaloids, the fawcettimine family, and previous synthetic strategies towards the 6-5-9 fawcettimine core. We proposed a transannular oxidative dearomatisation approach to access this tricyclic core and described literature examples of phenolic dearomatisations in the presence of hypervalent iodine.



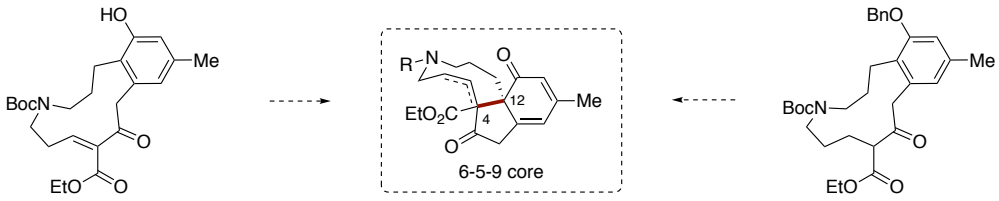
Scheme I Structure of fawcettimine, and the proposed transannular oxidative dearomatisation approach towards obscurinine *via* the 6-5-9 core.

Chapter 2 details the design and execution of the synthetic route to access the 6-12 bicyclic substrates, and outcomes of the proposed transannular oxidative dearomatisation step (Scheme II).



Scheme II Synthesis of the 6-12 bicyclic substrate and the proposed transannular oxidative dearomatisation.

Finally, Chapter 3 describes the synthetic efforts to alternative 6-12 bicyclic substrates, which could be transformed into analogues of the desired 6-5-9 core under oxidative conditions (Scheme III).



Scheme III Alternative 6-12 bicyclic substrates leading to analogues of the 6-5-9 core.

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Chapter 1. Introduction

1.1. *Lycopodium* Alkaloids

To date, almost 300 *Lycopodium* natural products have been isolated from over 50 species of *Lycopodium* club mosses.[1] *Lycopodium* alkaloids display a wide variety of structural scaffolds, including but not limited to quinolizine, pyridine or α-pyridine cores. Ayer categorises the *Lycopodium* alkaloids into four classes according to their structural features,[1] the first three of which are typified by the natural product bearing the name of the class, and the fourth, the miscellaneous class, comprises of a variety of skeletal arrangements (Figure 1.1).

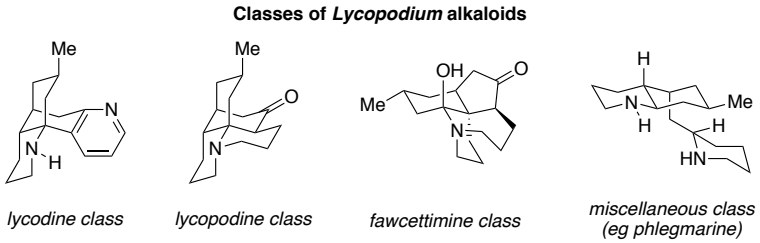
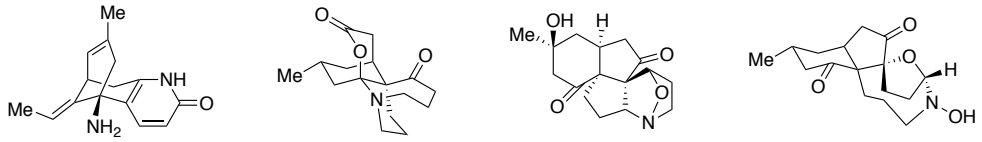


Figure 1.1 The four classes of *Lycopodium* alkaloids.

Besides their complex structures, the biological values of *Lycopodium* alkaloids have also been reported. The club moss *Lycopodium* s. l., for example, has been used in Chinese folk medicine to alleviate various symptoms.[1] From pharmacological studies, huperzine A **1** was identified to be a selective acetylcholinesterase inhibitor, and has been approved as a treatment for Alzheimer's disease in China (Figure 1.2). More recently, biological studies into other members of the *Lycopodium* alkaloids have also revealed properties such as anti-HIV-1 activity (lycojapodine A **2**), inhibition of lipopolysaccharide (LSP)-induced pro-inflammatory factors (lycojaponicumins A **3**), and cytotoxicity against murine lymphoma L1210 cells (siebolidine A **4**).[2]



huperzine A **1**

acetylcholinesterase inhibitor

lycojapodine A **2**

anti-HIV-1 activity

lycojaponicumins A **3**

inhibition of (LSP)-induced pro-inflammatory factors

siebolidine A **4**

cytotoxic against murine lymphoma L1210 cells

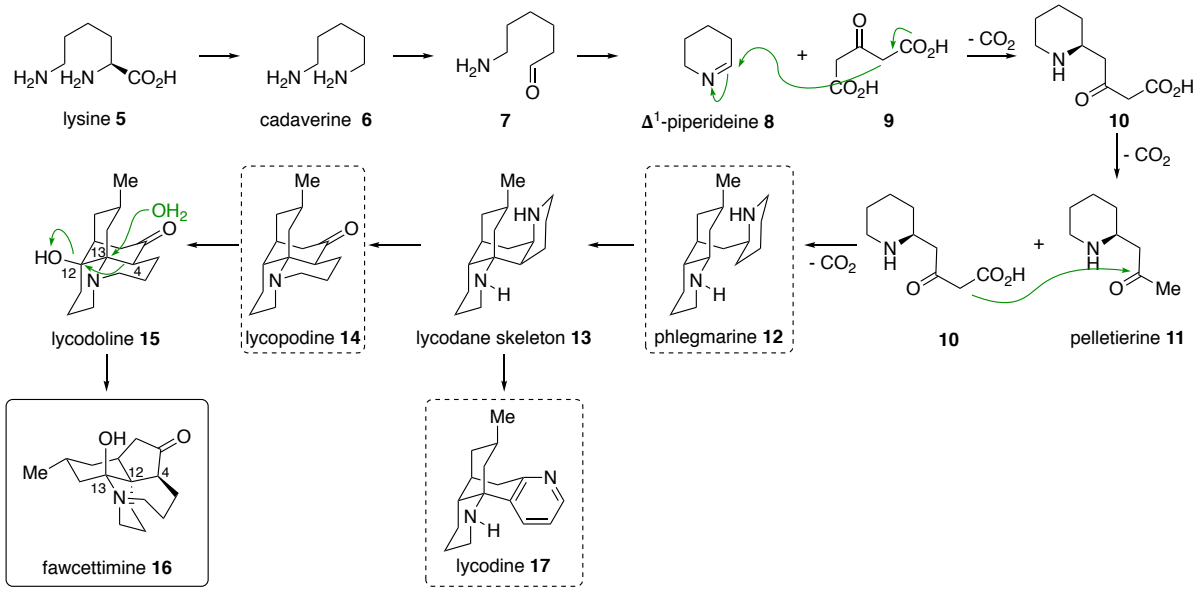
Figure 1.2 Examples of *Lycopodium* alkaloids displaying biological activities.

Extensive biological studies of *Lycopodium* alkaloids have been restricted by the low abundance and slow growth of the parent plants in nature, and lack of successful cultivation and tissue cultures.[1] The limited contents of these natural products in the parent plants further complicates access to the desired compounds, for example, 100 kg of whole plant was needed to isolate 40 mg of lycojaponicumins A-C.[3]

1.2. The Fawcettimine Class

1.2.1. Biogenesis of Fawcettimine

The low abundance of *Lycopodium* alkaloids has also impeded investigations into the biosynthetic pathway. Feeding experiments have shown lysine **5** to be the starting point of the biogenesis,[4,5] which undergoes decarboxylation to form cadaverine **6** (Scheme 1.1).[6] An oxidation and condensation of **7** gives Δ^1-piperideine **8**. Labelling experiments by Hemscheidt and Spenser show that the condensation of Δ^1-piperideine **8** with acetonedicarboxylic acid **9** forms **10**, whose subsequent condensation with pelletierine **11** yields phlegmarine **12**.[7] Cyclisation of phlegmarine **12** completes the lycodane skeleton **13**, whose modifications give rise to the lycodine and lycopodine classes. Oxidation of lycopodine **14** forms lycodoline **15**, which rearranges to yield fawcettimine **16**.[8]



Scheme 1.1 Biogenesis of *Lycopodium* alkaloids from lysine **5**.

1.3. Structures of the Fawcettimine Class

Fawcettimine **16** exists as an equilibrium mixture between its carbinolamine form and the cleaved N-C13 form, keto-amine **20** (Figure 1.3). Within the carbinolamine form, there exist two sub-classes depending on the connectivity between C12-C13, as exemplified by fawcettidine **18** and phlegmariurine B **19**.

The keto-amine form, on the other hand, lacks the N-C13 bond, and is typified by lobscurinol **21**. A bond between N-C4 of these alkaloids, however, can be made to form a distinct subclass, as represented by serratinine **22**.

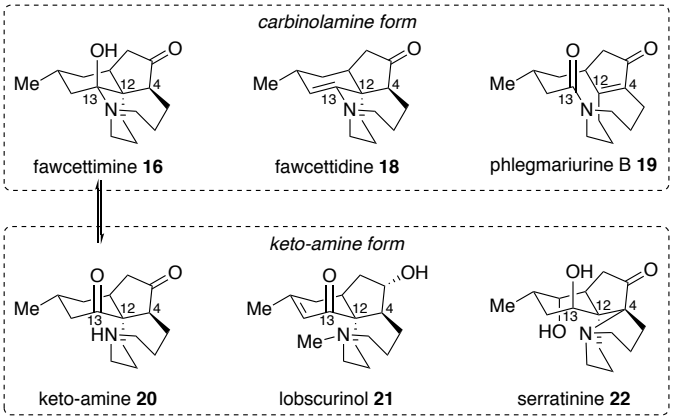
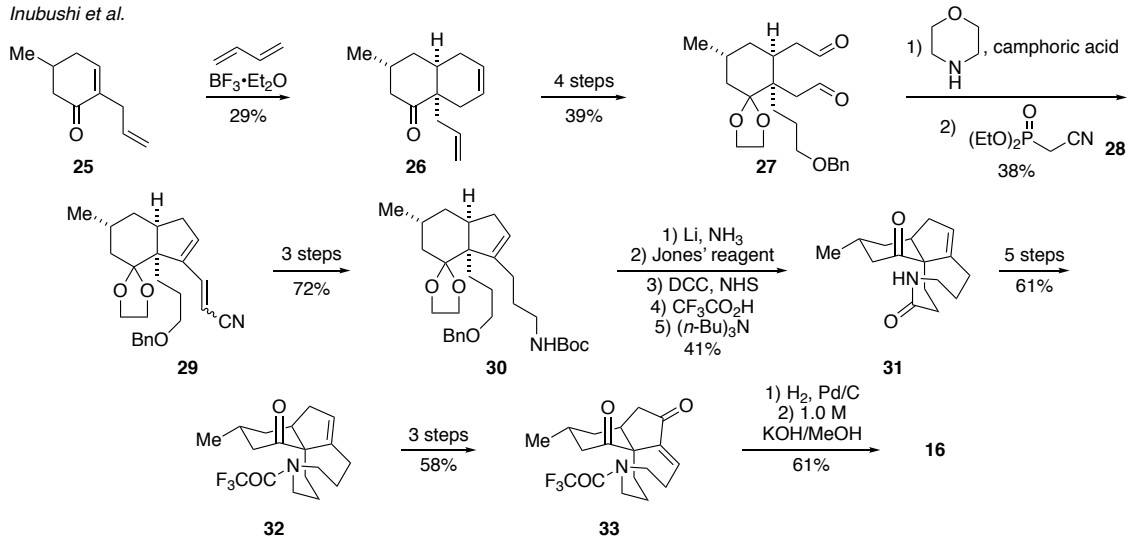


Figure 1.3 The two carbinolamine and keto-amine forms of fawcettimine alkaloids.

1.4. Previous Synthetic Strategy

1.4.1. Heathcock-Inspired Approach to the Fawcettimine Core

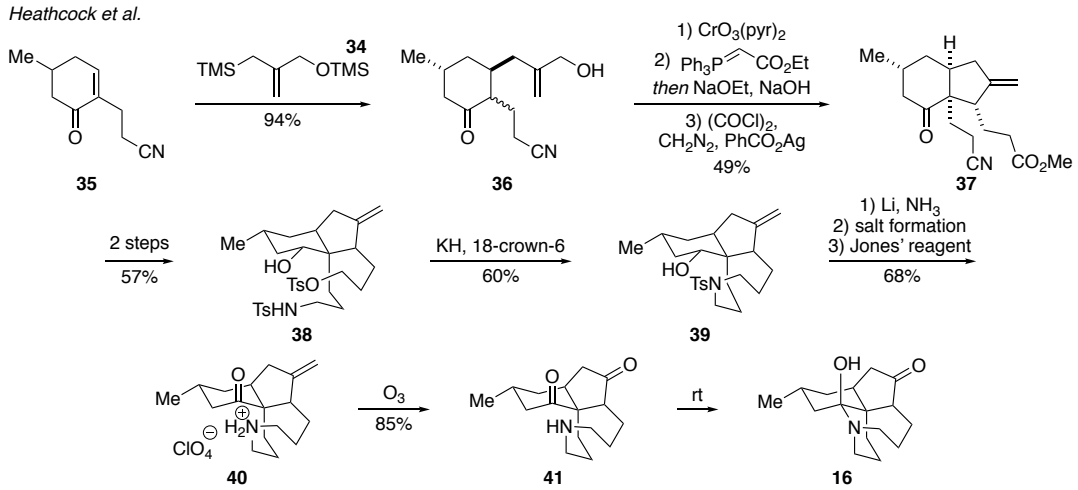
Fawcettimine **16** was first isolated in 1959 as the perchlorate salt from *Lycopodium fawcetti* by Burnell *et al*.,[9] and the first total synthesis of which was reported in 1979 by Inubushi *et al*. (Scheme 1.2).[10] In this seminal synthesis, the relative chemistry around the six-membered ring was set by a Diels-Alder reaction of **25** with 1,3-butadiene. The fused 6-5 bicyclic core was then completed by judicious choice of excess morpholine-camphoric acid mixture to effect regioselective condensation of di-aldehyde **27**, followed by a Wittig reaction to form **29**. After several steps, ketal **30** was transformed into the 6-5-9 core **31**. Modification of this 6-5-9 intermediate **31** then yielded **33**, whose hydrogenation followed by carbinol-amine formation completed the first total synthesis of racemic fawcettimine **16**. The stereochemistry at C4 was, however, neither confirmed in this synthesis nor the isolation paper.



Scheme 1.2 The first total synthesis of (±)-fawcettimine **16**. NHS = *N*-hydroxysuccinimide.

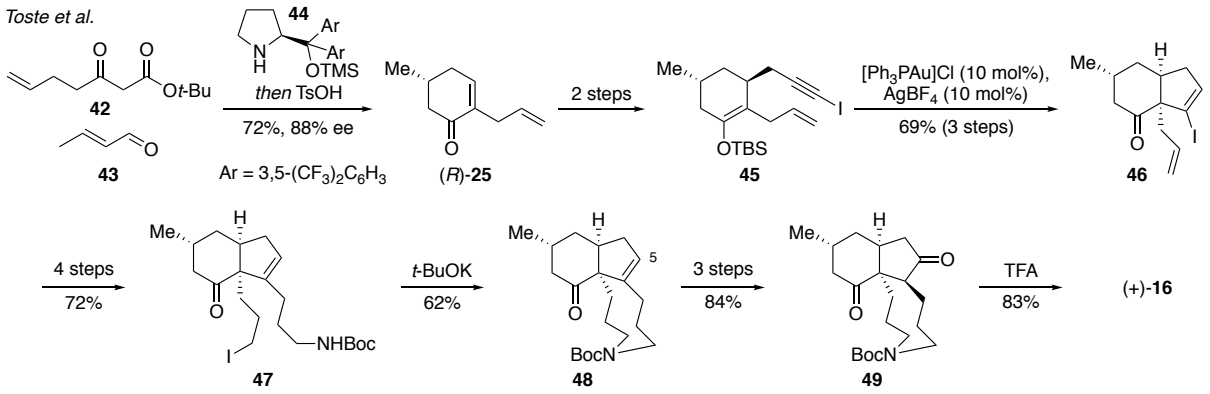
Not until 1986 did a paper by Heathcock *et al*. unequivocally confirm the keto amine/carbinolamine tautomerisation and the C4 stereochemistry of fawcettimine **16** (Scheme 1.3).[11] The synthesis commenced with a Sakurai reaction between cyclohexenone **35** and **34** to form **36** in 94% yield. The fused 6-5 ring system **37** was then formed in a three-step sequence in 49% yield. Modifications of the

sidechains on the 5-membered ring led to secondary alcohol **38**, whose alkylation to form the azonine ring **39** was achieved by treatment with potassium hydride and 18-crown-6. Tosyl-removal followed by oxidation at C13 yielded ketone **40**, which did not show carbinolamine formation. Ozonolysis of the perchlorate or bisulphate salt of **40**, however, formed amino di-ketone **41**, which spontaneously isomerised to **16** at room temperature after a few hours. The stereochemistry at C4 was confirmed by X-ray crystal analysis of the hydrobromide salt of **16**.



Scheme 1.3 Total synthesis of (±)-fawcettimine **16**.

The first asymmetric synthesis of fawcettimine was reported in 2007 by the Toste group (Scheme 1.4).[12] An organocatalytic Robinson ring annulation of **42** and **43** set the stereochemistry on cyclohexenone (*R*)-**25**, whose modification gave enol ether **45**. The 6-5 fused ring **46** was then installed by a gold-catalysed cyclisation. Finally, alkylation of **47** furnished the azonine ring, completing the 6-5-9 tricyclic core **48**. Oxidation at C5 followed by TFA-mediated deprotection then completed the first asymmetric synthesis of fawcettimine **16**.

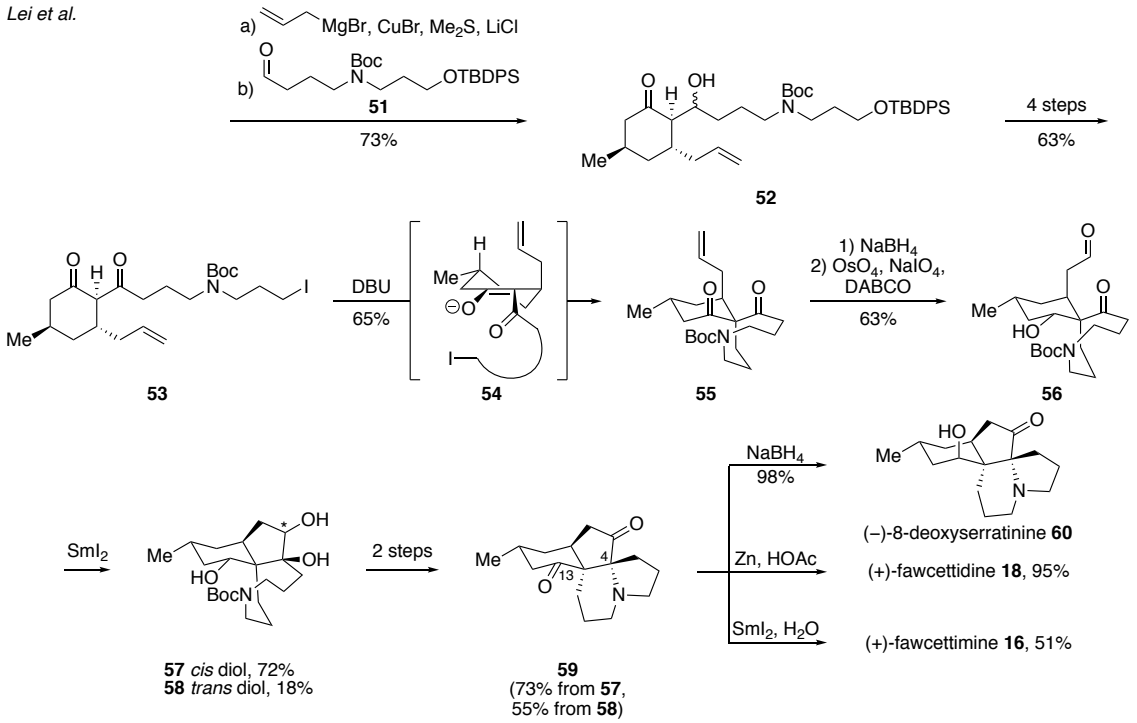


Scheme 1.4 The first asymmetric total synthesis of fawcettimine **16**.

The success of the Inubushi-Heathcock approach, namely the formation of the heavily decorated 6-5 bicycle followed by instalment of the azonine ring, has been further demonstrated in a number of syntheses, and summarised in published reviews.[2,8]

1.4.2. A Different Approach

In 2012, the Lei group disclosed their collective asymmetric syntheses of (+)-fawcettimine **16**, (+)-fawcettidine **18**, and (–)-8-deoxyserratinine **60**, which did not rely on the Inubushi-Heathcock approach (Scheme 1.5).[13] The syntheses started with a tandem conjugate addition/aldol reaction of known enone **50** to form **52** as a mixture of diastereoisomers. The spiro-azonine ring **55** was assembled by an intramolecular alkylation of **53** with complete stereocontrol, presumably *via* transition state **54** which avoided steric clashing with the axial allylic group. Selective reduction of di-ketone and subsequent Lemieux-Johnson oxidation formed **56**. SmI_2-mediated pinacol coupling of **56** yielded the *cis*- and *trans*-diol **57** and **58**, respectively. A two-step sequence then afforded the common intermediate **59**, from which (–)-8-deoxyserratinine **60**, (+)-fawcettidine **18**, and (+)-fawcettimine **16** were synthesised.



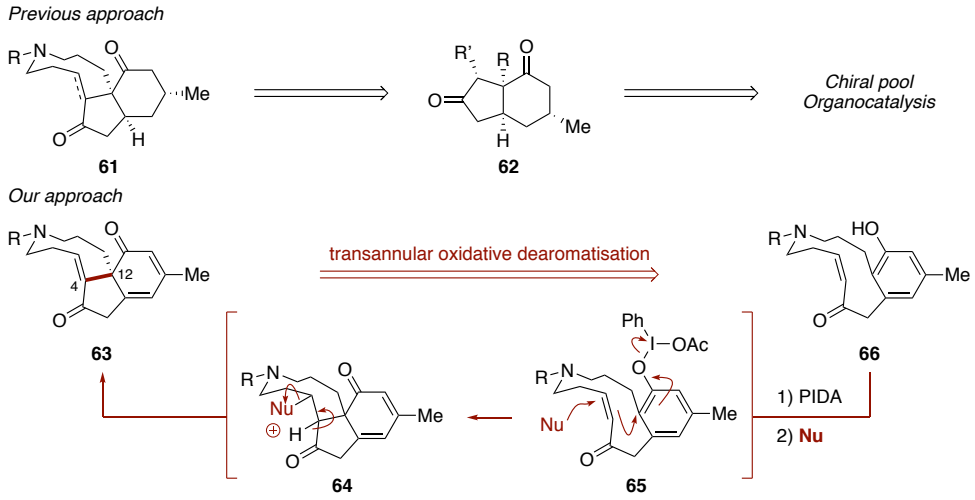
Scheme 1.5 Total syntheses of (–)-8-deoxyserratinine **60**, (+)-fawcettidine **18**, and (+)-fawcettimine **16**.

1.5. Synthetic Strategy

The universality of the Inubushi-Heathcock approach piqued our interest in developing a new strategy to access the 6-5-9 tricyclic core, with potential application to the synthesis of obscurinine (*vide infra*). To the best of our knowledge, previous syntheses of the tricyclic core have mostly relied on the formation of heavily-decorated and enantioenriched *cis*-fused 6-5 systems **62**, with the stereocentres coming from the chiral pool, or, in one example, organocatalysis (Scheme 1.6).[12]

We envisaged a transannular oxidative dearomatisation to form this fused system bearing a quaternary centre from achiral substrate **66**. Oxidation of the phenol moiety in the presence of a hypervalent iodine reagent (See section 1.6.3) could form a phenoxy-λ^3-iodane species **65**.[14] A reversible nucleophilic attack into the pendant enone could effect a Rauhut-Currier type addition into intermediate **64**, which after elimination of the nucleophile could generate the desired tricyclic core **63**.

Asymmetry could be induced in the phenoxy-λ^3-iodane species **65** in the presence of a chiral hypervalent iodine, or alternatively, by applying an appropriate chiral nucleophile (See section 1.6.4).

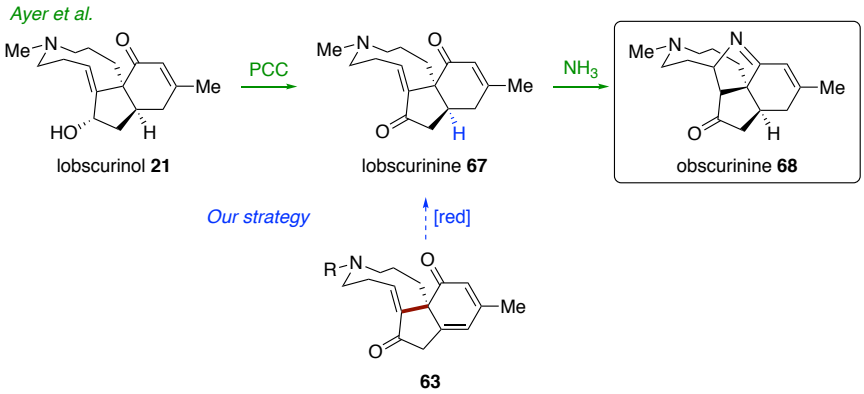


Scheme 1.6 Proposed transannular oxidative dearomatisation approach. PIDA = (diacetoxyiodo)benzene.

1.5.1. Application to the Total Synthesis of Obscurinine

Tricyclic core **63** contains the carbon skeleton of obscurinine **68** (Scheme 1.7), a *Lycopodium* alkaloid belonging to the fawcettimine class. Obscurinine was isolated from *Lycopodium obscurum* L. clubmoss, which has been used to treat rheumatic pain in traditional medicine in East and Southeast Asia.[15,16]

The unusual imino-nitrogen was observed to be inconsistent with the biogenesis of *Lycopodium* alkaloid, and thus, obscurinine was suggested to be an artefact from the isolation process.[16] To test this hypothesis, Ayer *et al*. oxidised lobscurinol **21**, a natural product isolated from the same plant extract, with PCC to form lobscurinine **67**, which under treatment with ammonia readily formed obscurinine **68** (Scheme 1.7). Due to limited materials, the authors were not able to prove the existence of lobscurinine in the plant extract, and the question of whether obscurinine is a genuine natural product remains open.



Scheme 1.7 Top line: oxidation of lobscurinol **21** to form lobscurinine **67** and subsequent treatment with ammonia to form obscurinine **68** by Ayer *et al*.; bottom line: our synthetic plan to transform tricyclic core **63** into obscurinine **68**.

Nonetheless, we were intrigued by the uncommon tetracyclic structure of obscurinine, thus, taking into account Ayer *et al*.'s observation, planned to transform tricyclic core **63** into lobscurinine **68** by a chemoselective reduction, followed by treatment with ammonia to complete the first total synthesis of obscurinine **68**.

1.6. Oxidative Dearomatisation of Phenol Using Hypervalent Iodine Reagents

1.6.1. Structure of Hypervalent Iodine Compounds

The two main classes of organohypervalent iodine are shown in Figure 1.4, namely, trivalent iodine compounds **70** (λ^3-iodanes), and pentavalent iodine compounds **71** (λ^5-iodanes).[17] The former is exemplified by PIDA **72** and PIFA **73**, and the latter by IBX **74** and DMP **75**. Comprehensive reviews of organohypervalent iodine reagents can be found in references 18 and 19.[18,19]

λ^3-iodanes **70** have pseudo-trigonal bipyramidal geometry around the iodine atom, with the ligands in the apical positions, and the R group and two lone pairs of electrons in the equatorial positions. The hypervalent bond in the linear L-I-L bond contains two electrons from the 5p orbital of iodine and one electron from each ligand L, resulting in longer bonds than the expected covalent bond length between L-I. The stability of this 3c-4e centre is heavily influenced by the *trans* effect, requiring either two moderately *trans*-influencing ligands ($PhI(OAc)_2$), or combinations of ligands with weak and strong *trans*-influences (Ph[I(OH)(OTs)]).[20]

λ^5-iodanes **71**, on the other hand, have square-pyramidal geometry, with the ligands in the basal positions, and the R group and the lone pair of electrons in the apical positions. The R group is covalently bound to the iodine atom, whereas the ligands are bound by two 3c-4e hypervalent bonds.

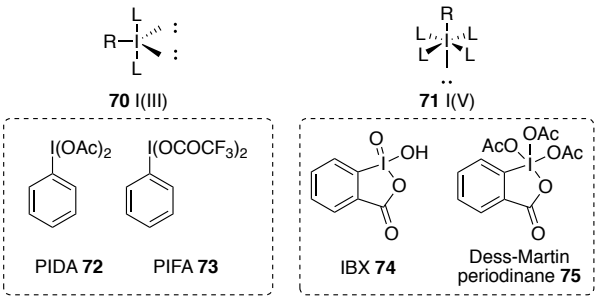


Figure 1.4 Structures and examples of iodine(III) and iodine(V) compounds. L = heteroatom ligands, R = carbon ligands.

In the solid state, PIDA **72** has a pentagonal planar geometry at the iodine atom (Figure 1.5).[21] Two primary I-O bonds are present, whose length is 1.99 Å, shorter than the 2.16 Å value from the sum of the covalent radii. Two secondary intramolecular I---O bonds are also present, which are shorter than the sum of the van der Waals radii of iodine and oxygen.

In contrast, PIFA **73** shows a T-shaped geometry around the iodine centre, two intramolecular bonds I---O, and also two further intermolecular bonds.[22] One intermolecular bond forms a dimer via an I_2O_2 trapezoidal ring, and the other links the dimers into chains.

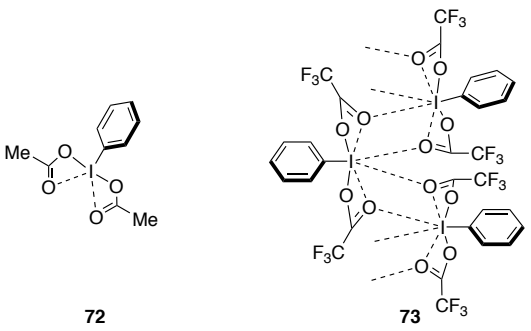


Figure 1.5 Structures of PIDA **72** and PIFA **73** derived from single-crystal X-ray structures.

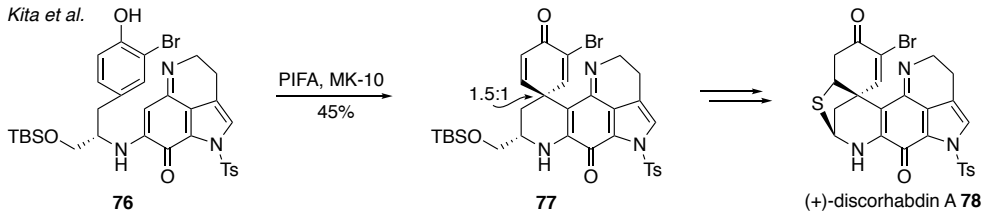
1.6.2. C-C Bond Formation by Oxidative Dearomatisation of Phenols

The long and polarised hypervalent R-I-R bond in λ^3-iodanes is responsible for their high electrophilic reactivity. Thus, a range of organohypervalent iodine reagents has been applied to various transformations, such as oxidation, α-functionalisation of ketones, functionalisation of alkenes, and arylation reactions.[17-19]

As outlined in Scheme 1.6, this thesis is concerned with the formation of a carbon-carbon bond by nucleophilic trapping of an oxidised phenol in the presence of hypervalent iodine.

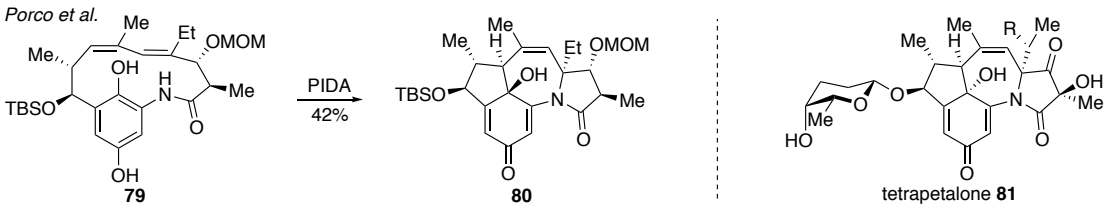
Phenols are electron-rich systems that could be oxidised *via* the loss of one or two electrons to form decorated cyclohexadienones. The oxidation of phenols transforms sp^2 systems into scaffolds amenable to asymmetric induction to form quaternary centres, and allows access to a range of complex structural motifs, some of which will be highlighted below. Applications of phenol dearomatisations in natural product syntheses have also been described in a review by Porco and Roche.[23]

In the first total synthesis of (+)-discorhabdin A **78**, Kita and co-workers used PIFA activated with Montmorrillonite K-10 (MK-10) to construct the spiro-cyclohexadienone **77** in 45% yield, as a 1.5:1 diastereomeric mixture (Scheme 1.8).[24] The major isomer (*S* configuration) was then transformed into the natural product **78**.



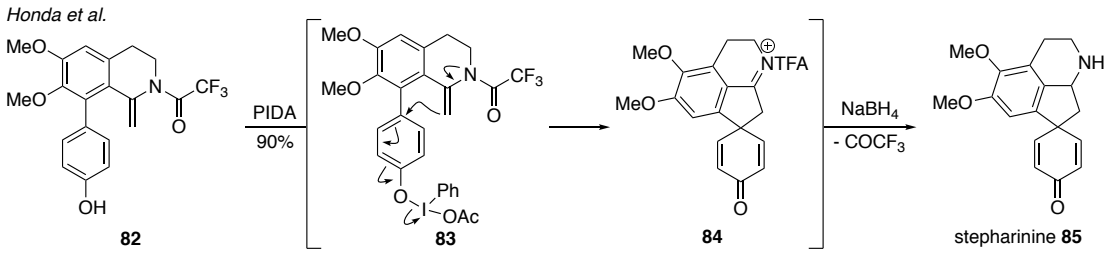
Scheme 1.8 Total synthesis of (+)-discorhabdin A **78**.

By using a PIDA-mediated transannular oxidative [4+3] cyclisation of **79**, Porco and co-workers accessed the tetracyclic core **80** of the tetrapetalones (Scheme 1.9).[25] Molecular magnetic force field studies showed this cyclisation to be a stepwise process *via* formation of an arene-derived oxonium ion, then diene addition, and finally, C-N bond formation.



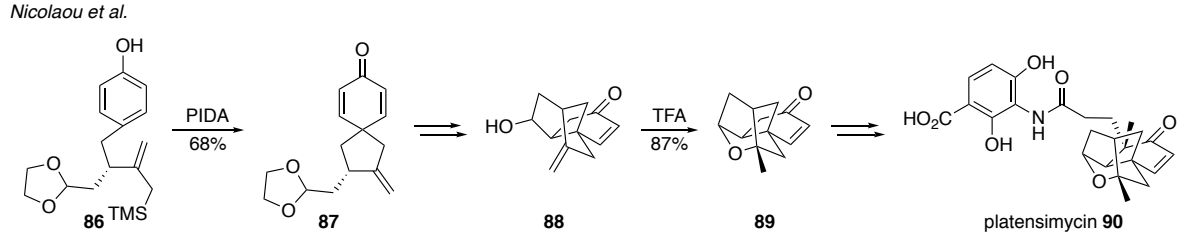
Scheme 1.9 Synthesis of the tetracyclic core **80** of tetrapetalone.

Stepharinine **85**, a proaporphine alkaloid with antihypertensive activity, also posseses a spiro-cyclohexadienone core (Scheme 1.10). The synthesis of **85** was reported in 2006 by Honda and co-workers where the key carbon-carbon bond was formed by aromatic oxidation of **82** with PIDA, followed by iminium reduction with $NaBH_4$ to form the natural product in 90% yield.[26]



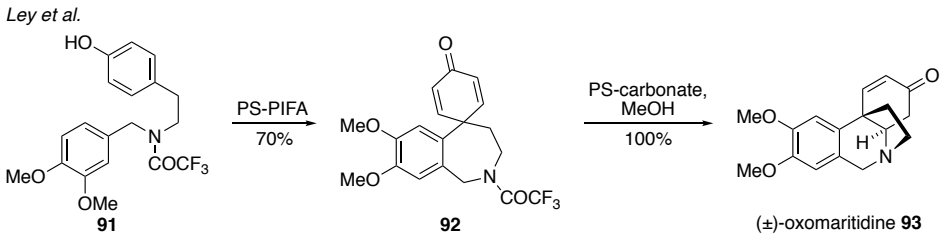
Scheme 1.10 Total synthesis of (±)-stepharinine **85**.

Spirocyclic dienone **87** was a key intermediate in the total synthesis of (–)-platensimycin **90** by the Nicolaou group, whose synthesis relied on a dearomatisation of phenol **86** in the presence of PIDA and an allylsilane intramolecular nucleophile (Scheme 1.11).[27] The cyclodearomatisation reaction proceeded in 68% yield without loss of enantiopurity. The acetal **87** was then transformed into platensimycin **90** as described in their 2006 report.[28]



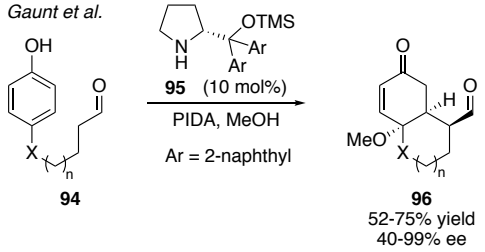
Scheme 1.11 Phenol dearomatisation by PIDA in the total synthesis of (–)-platensimycin **90**.

The utility of this strategy has also been demonstrated in a flow process for the total synthesis of (±)-oxomaritidine **93**, as developed by Ley and co-workers (Scheme 1.12).[29] Phenol **91** underwent an oxidative phenolic coupling when added to a column containing polymer-supported PIFA (PS-PIFA) to form spiro-cyclohexeneone product **92**. The synthesis of (±)-oxomaritidine **93** was then completed by passing compound **92** through a column containing polymer-supported carbonate to remove the protecting group and allow a subsequent conjugate addition.



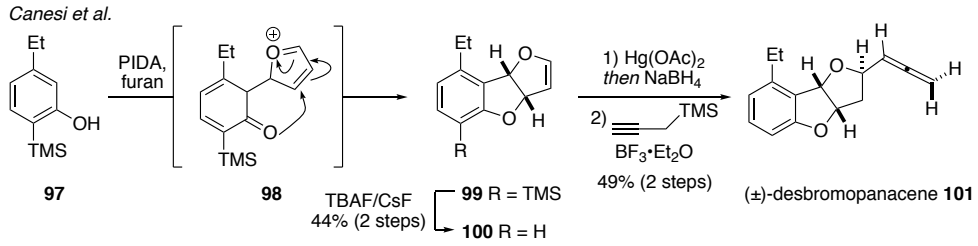
Scheme 1.12 Oxidative coupling in the flow process for the total synthesis of (±)-oxomaritidine **93**.

An enantioselective oxidative dearomatisation to form fused ring systems was reported in 2008 by Gaunt and co-workers (Scheme 1.13).[30] In this report, *meso*-cyclohexadienones **94** were oxidised in the presence of PIDA, and subsequent desymmetrisation by a Michael addition yielded **96**. The three newly formed stereocentres were controlled by pyrrolidine catalyst **95**.



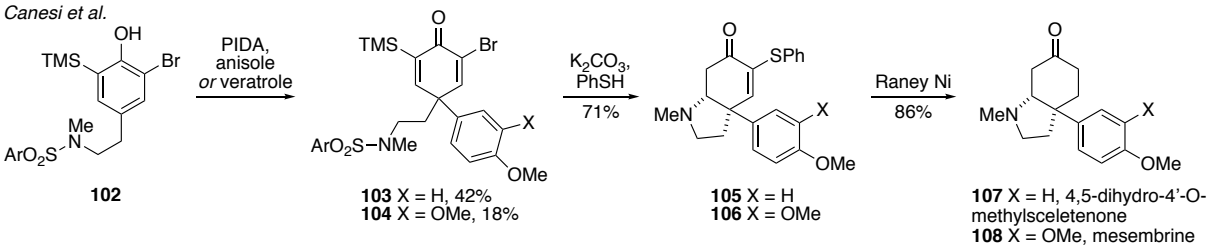
Scheme 1.13 Enantioselective oxidative dearomatisation reaction.

Another application in natural product synthesis was the stereocontrolled synthesis of (±)-desbromopanacene **101** by Canesi *et al*. (Scheme 1.14).[31] An 'aromatic ring umpolung' of phenol **97** in the presence of PIDA as an oxidant, and furan as a nucleophile, allowed formation of **99**. Deprotection followed by an oxymercuration/demercuration sequence and subsequent Sakurai reaction yielded the natural product **101**.



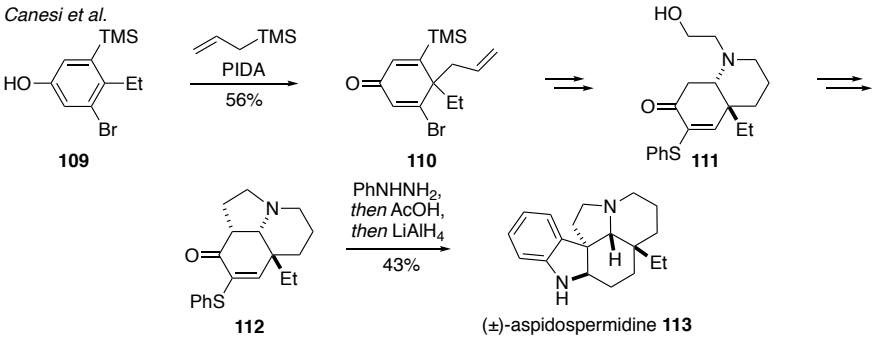
Scheme 1.14 'Aromatic ring umpolung' in the synthesis of natural allenic products.

An extension of this methodology is present in the total syntheses of *Amaryllidaceae* alkaloids (Scheme 1.15).[32] An oxidative Friedel-Crafts reaction of **102** with either anisole or veratrole in the presence of PIDA yielded dienone **103** and **104**, respectively. Tandem removal of the protecting group, conjugate addition of the secondary amine, and formation of the thioenol ether were then achieved in a one-pot process. Treatment of the products **105** and **106** with Raney nickel then afforded the natural products **107** and **108**, respectively.



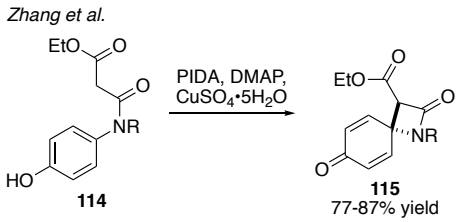
Scheme 1.15 Oxidative Friedel-Crafts reaction in the total syntheses of *Amaryllidaceae* alkaloids; Ar = *p*-$NO_2C_6H_4$.

The Canesi group has also exploited an oxidative Hosomi-Sakurai reaction to form substituted spiro-dienone **110** (Scheme 1.16).[33] Elaboration of **110** gave tricyclic core **112**, whose exposure to Fischer indole conditions completed the synthesis of aspidospermidine **113**.



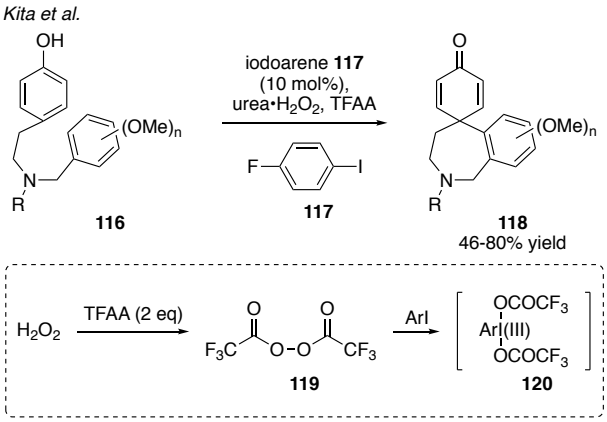
Scheme 1.16 Oxidative Hosomi-Sakurai reaction in the total synthesis of (±)-aspidospermidine **113**.

A different structural motif, spiro-β-lactams, can also be accessed by dearomatisation of phenols.[34] Zhang and co-workers described an intramolecular radical oxidative coupling between phenol and the α-carbon of the 1,3-dicarbonyl moiety in **114** to yield **115** in the presence of PIDA (Scheme 1.17). The copper salt was hypothesised to be a co-oxidising agent and an electron acceptor.



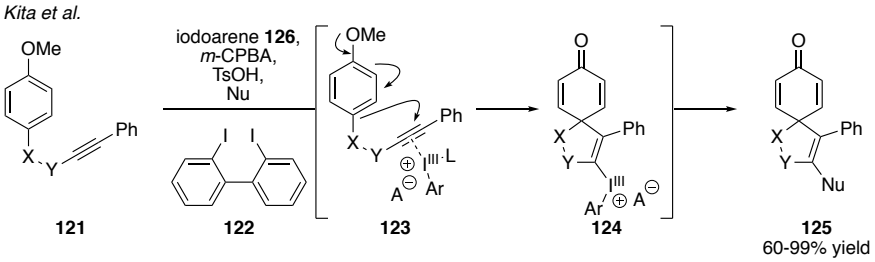
Scheme 1.17 Synthesis of spiro-β-lactams by radical oxidative coupling.

The examples discussed so far have used PIDA or PIFA as an oxidising reagent. However, iodine(III) species can also be formed *in situ* for the dearomatisation of phenols. Iodoarene-catalysed syntheses of spirocyclic dienones have been reported by Kita and co-workers in 2008 (Scheme 1.18).[35] The group observed the formation of bis(trifluoroacetyl) peroxide **119** by treatment of H_2O_2 with excess TFAA, which reacted with iodoarene **117** to catalytically form the reactive oxidant iodine(III) species **120**. The corresponding oxidised intermediate generated from **116** underwent concomitant C-C bond formation in the presence of **120** to yield spirocyclised products **118**.



Scheme 1.18 Iodoarene-catalysed spirocyclic dienone formation.

The spiro-cyclisation transformation has been further expanded in a paper published in 2011 by the same group (Scheme 1.19).[36] In the presence of *m*-CPBA and an acid (HA), iodoarene **122** formed a cationic hypervalent iodine(III) species which activated alkyne **121** towards nucleophilic attack by the neighbouring anisole group. The iodonium(III) salt **124** was then functionalised by reductive coupling with a range of nucleophiles to form spiro-cycles **125**.



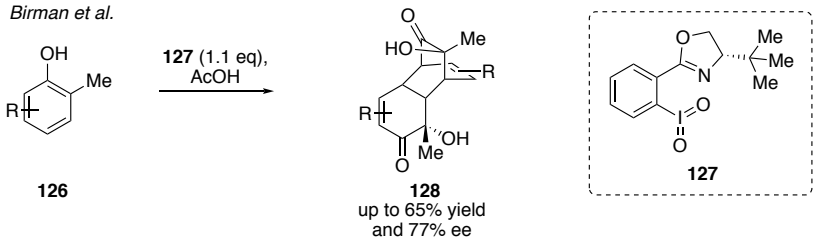
Scheme 1.19 Iodine(III)-mediated spiro-cyclisation.

1.6.3. Chiral Hypervalent Iodine Reagents for the Enantioselective Oxidative Dearomatisation of Phenols

Having described examples of carbon-carbon bond formation facilitated by hypervalent iodine-oxidised phenols, this section will next introduce chiral hypervalent iodine compounds which can induce enantioselective dearomatisation of phenols.

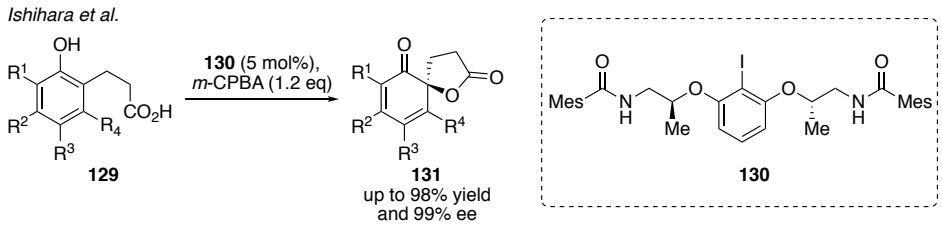
Whilst asymmetric oxidative dearomatisations of naphthols have been extensively studied, the equivalent reactions for phenols have been less developed.[14] Birman *et al*. reported an asymmetric synthesis of *o*-quinol **128** by oxidative dimerization of *o*-alkylphenols **126** in the presence of a chiral

iodine(V) species **127** in 2009 (Scheme 1.20).[37] An equivalent of acetic acid improved the yields, in line with reports by Barton *et al*. wherein acid catalysts were found to complex to the iodine-oxygen bond, reducing the kinetic activation energy barrier.[38]



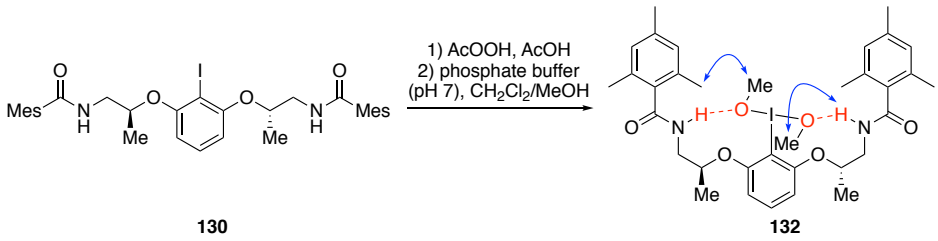
Scheme 1.20 Synthesis of enantioenriched *o*-quinol dimer **128**.

In 2013, Ishihara *et al*. reported an asymmetric oxidative dearomatisation of phenols **129** to form cyclohexadienones **131** in the presence of **130** (Scheme 1.21).[39] Experimental results underlined the importance of methanol and HFIP as additives to improve reactivities of electron-rich and electron-deficient phenols, respectively.



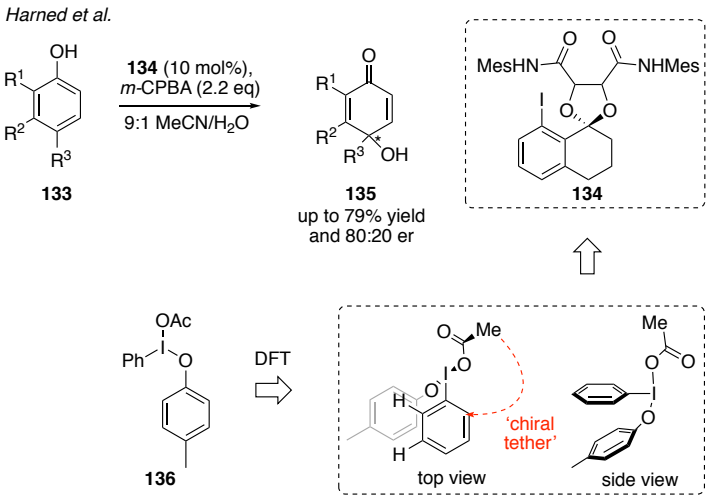
Scheme 1.21 Asymmetric oxidative dearomatisation of phenol.

Catalyst screening revealed the importance of C2 symmetry and amido protons in improving asymmetric induction and reaction yields, both of which are featured in their best catalyst **130**. In order to understand the active iodine(III) species generated *in-situ* under the reaction conditions, iodosylarene dimethoxide **132** was made from catalyst **130** (Scheme 1.22). Whilst X-ray diffraction analysis showed the linear conformation of **130**, intramolecular hydrogen-bondings were observed between the amido protons and the methoxy ligands (red lines) in **132**. This folding conformation in solution was also confirmed by nOe analysis (blue arrows).



Scheme 1.22 Formation of iodosylarene dimethoxide **132** from **130**; red line: hydrogen bonding observed in X-ray crystal structure; blue arrows: observed nOe correlations.

In 2013, Harned *et al*. reported a rational design of an aryl iodide catalyst for the synthesis of *para*-quinols based on DFT calculations of iodine(III) intermediates.[40] The minimised structure of **136** showed the phenolate ring lying below the phenyl ring of the iodane, prompting the author to consider a 'chiral tether' between the *ortho*-position of the aryl iodide and the carboxylate to induce asymmetry in an oxidative dearomatisation reaction (Scheme 1.23). Catalyst **134** was thus designed and applied to the dearomatisation of phenol **133** with a range of R^1, R^2 and R^3 substituents to form **135**. *Ortho*-substituents were required for enantioselectivity, and the e.r. obtained were moderate (63:37 to 80:20). The authors attributed the moderate e.r. to the difficult task of controlling the approach of water, a small external nucleophile.

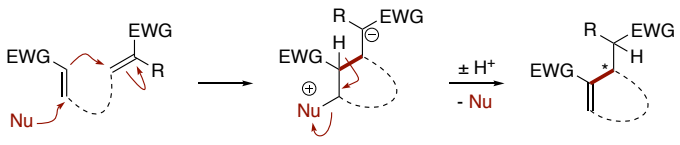


Scheme 1.23 Top line: asymmetric oxidative dearomatisation of phenol; bottom line: rational design of chiral catalyst **134** through DFT calculations.

1.6.4. Enantioselective Intramolecular Rauhut-Currier Reaction Using Chiral Nucleophiles

In our proposed transannular strategy towards the tricyclic 6-5-9 core in Scheme 1.6, a Rauhut-Currier reaction was envisaged to couple the neighbouring enone to the oxidised phenol, with the facial selectivity of the nucleophilic addition dictated by either a chiral hypervalent iodine ligand, or a chiral nucleophile. This section will now explore examples of asymmetric intramolecular Rauhut-Currier (IRC) reactions using chiral nucleophiles.

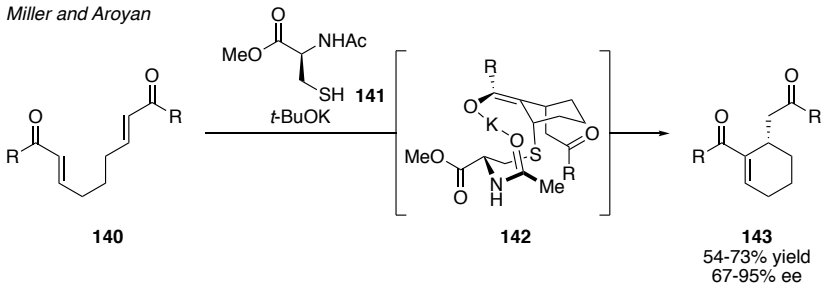
The Rauhut-Currier reaction is a vinylogous Morita-Baylis-Hillman reaction for the formation of a carbon-carbon bond between two reacting alkenes.[41] The reaction involves the alpha-carbon on an alkene partner undergoing a conjugate addition into a Michael acceptor, enabled by a catalytic amount of an appropriate nucleophile (Scheme 1.24). Proton transfers and elimination of the nucleophile generates an olefin and a new carbon-carbon bond which may bear a newly formed quaternary centre.



Scheme 1.24 Schematic mechanism for a Rauhut-Currier reaction.

1.6.4.1 Chiral Thiolate

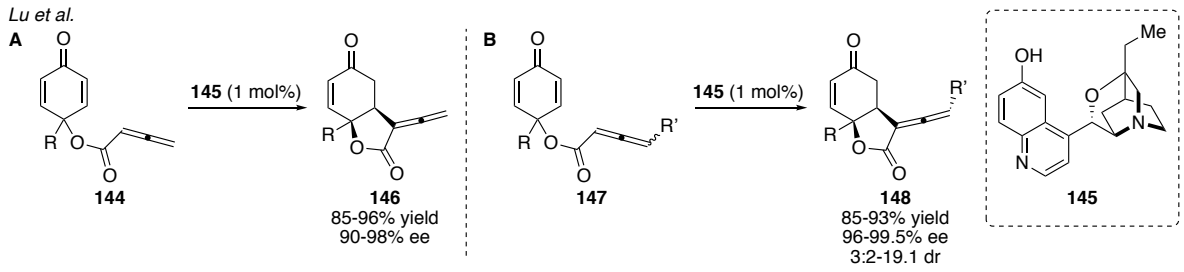
An example of such a transformation was reported by Miller and Aroyan[42] by using the thiolate of protected cysteine **141** to form cyclic enones **143** (Scheme 1.25). Control experiments showed the involvement of the potassium counterion, and the elimination of the catalyst to be the rate-determining step. The proposed model **142** takes into account the orbital overlap between the enolate and σ*(C-S), and a more stable amide-chelated complex over an ester-chelated complex to explain the observed stereochemistry.



Scheme 1.25 Asymmetric IRC by chiral thiolate.

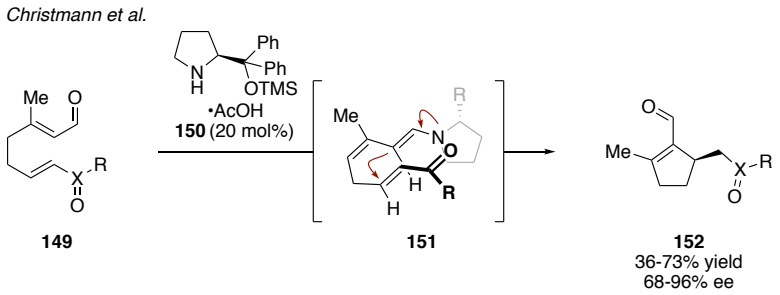
1.6.4.2 Chiral Amines

In an allene-dienone system studied by Lu *et al.*,[43] cinchona alkaloid-derived catalyst **145** mediated an asymmetric (IRC) reaction to form bicyclic allenes **146** in 85 to 96% yield and 90 to 98% ee (Scheme 1.26, A). Dynamic kinetic resolutions of racemic allenoates were also possible, and yielded enones **148** in good yields and enantioselectivities (Scheme 1.26, B), affording a new method to synthesise optically active allenes.



Scheme 1.26 A) IRC of allenoates; B) dynamic kinetic resolutions of racemic allenoates.

The group of Christmann has reported the use of dienamine activation to transform aldehydes such as **149** into enantioenriched iridoid aldehydes **152** using catalyst **150** (Scheme 1.27).[44] The utility of this methodology has been applied to the synthesis of (+)-rotundial, a known mosquito repellent (where X = C and R = H in **152**). The β-methyl substituent of the aldehyde was found to be necessary for fast reaction rate and good enantioselectivity, presumably due to the stabilising effect on the reactive configuration **151**.

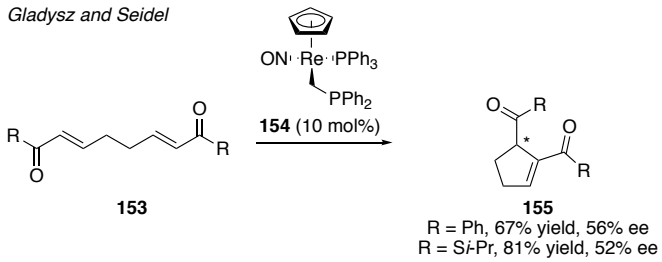


Scheme 1.27 Dienamine activation in an asymmetric IRC reaction.

1.6.4.3 Chiral Phosphines

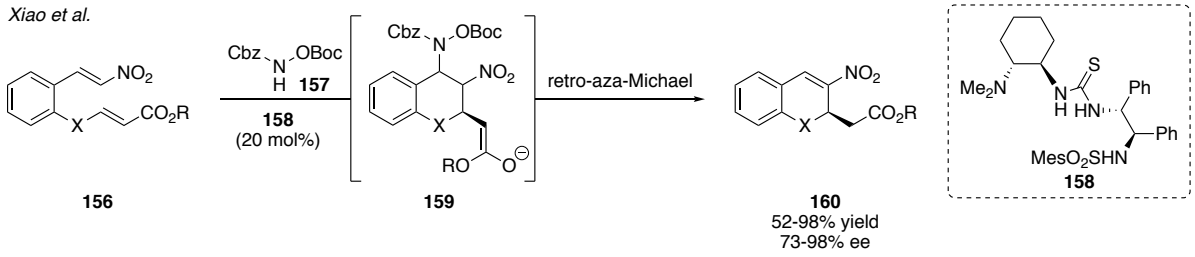
Chiral phosphines have been extensively developed for asymmetric IRC reactions to generate a plethora of structural motifs, a selection of which will now be discussed (a detailed review on asymmetric IRC reactions and the related Morita-Baylis-Hillman reactions was published by Bahradwaj in 2015).[41]

The group of Gladysz have a long-standing interest in transition-metal Lewis bases, in particular, their enhanced nucleophilicities due to the eighteen-electron metal species. In a report in 2007, the group reported one of the first examples of an asymmetric IRC reaction wherein rhenium-containing phosphine **154** was used to induce enantioselectivity in the formation of cyclopentenes **155** (Scheme 1.28).[45]



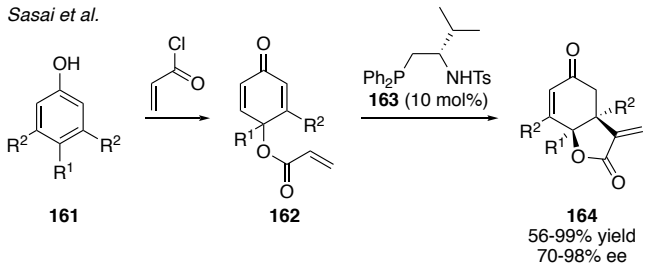
Scheme 1.28 The first example of an asymmetric IRC reaction.

Chromenes such as **160** have been recognised as an important scaffold in medicinal compounds. Amongst various methodologies to construct this privileged motif is an asymmetric IRC reaction of precursors **156** using hydrogen-bonding catalyst **158**, as reported by Xiao and co-workers (Scheme 1.29).[46] Computational studies by the authors have shown the enantio-inducing step to be the Michael addition, whilst the final retro-aza-Michael addition was the rate-determining step.



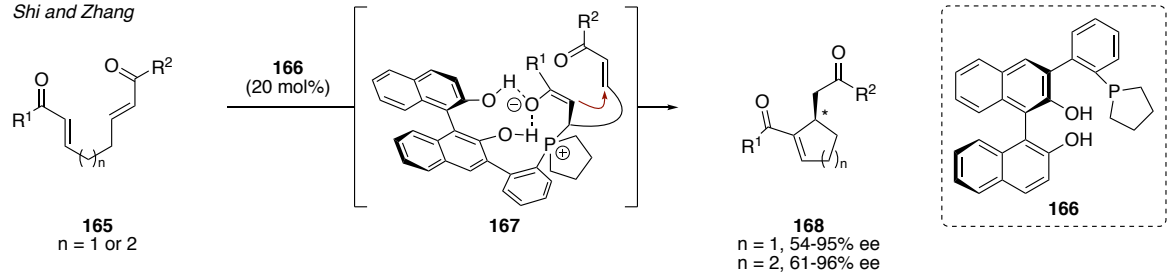
Scheme 1.29 Synthesis of enantioenriched chromenes **160** by an asymmetric IRC reaction.

Another prevalent motif in natural products is α-alkylidene-γ-butyrolactone, which can be accessed directly by an asymmetric IRC reaction of dearomatised phenol **162**. To this end, the group of Sasai developed an acid/base organocatalytic procedure to afford enantioenriched α-alkylidene-γ-butyrolactones such as **164** bearing two contiguous stereocentres (Scheme 1.30).



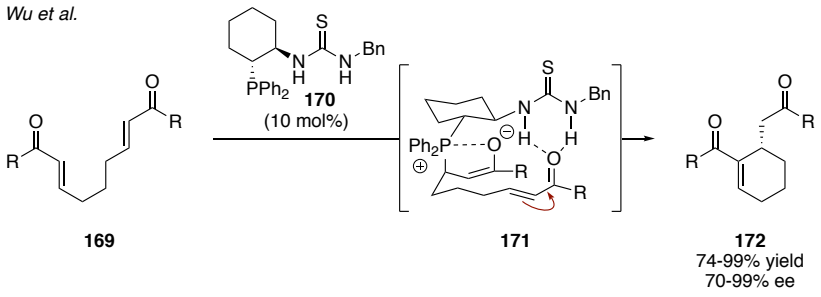
Scheme 1.30 An asymmetric IRC reaction using acid/base organocatalysis.

The most common mode of enantioinduction by chiral nucleophiles is *via* conformational restriction due to hydrogen bonding between the formed enolate after the initial nucleophilic attack and the catalyst. This is exemplified in the work of Shi and Zhang, whose use of chiral phosphine **166** transformed bis(enones) **165** into enantioenriched **168** *via* an IRC reaction (Scheme 1.31).[47] The proposed transition state **167** rationalises the conjugate addition of the enolate into the Michael acceptor to happen on the *Re*-face, resulting in *R*-products, as controlled by hydrogen bonding between the catalyst and the enolate.



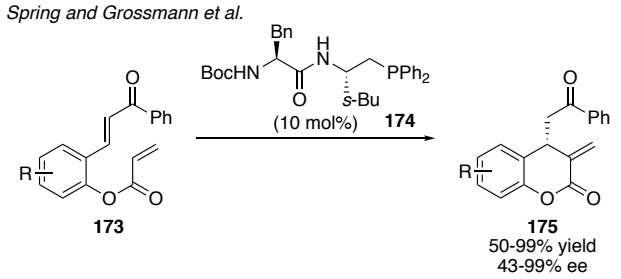
Scheme 1.31 An asymmetric IRC reaction using chiral phosphine catalyst.

In a similar fashion, thiourea-phosphine **170**, as studied by Wu *et al*., mediated the asymmetric cyclisation of bis(enone) **169** to yield cyclohexenone **172** (Scheme 1.32).[48] When the R groups were electron-rich aryl substituents, the enantioselectivity was much improved. This observation helped the group propose transition state **171** to explain the stereochemistry in the obtained products: initially, phosphine catalyst **170** attacks bis(enone) **169**, whose enolate intermediate **171** undergoes a conjugate addition from the *Si* face as dictated by the hydrogen bonding network to generate the *S*-product **172**.



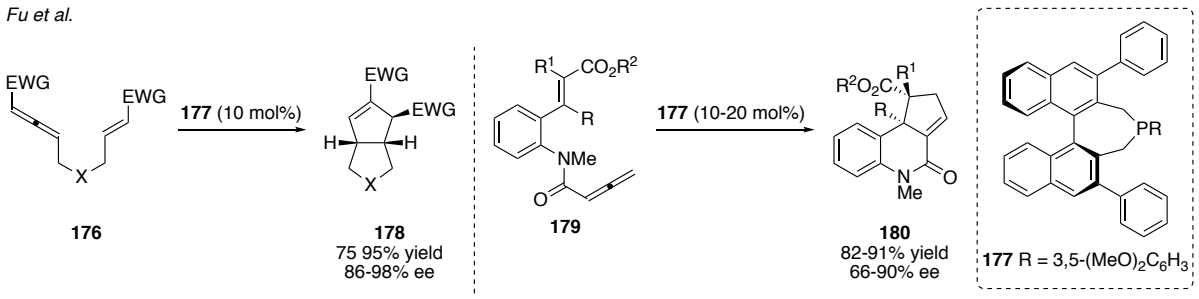
Scheme 1.32 Thiourea-phosphine catalyst in an asymmetric IRC reaction.

Chromanones are motif commonly found in medicinally-relevant compounds, and have been of interest to the Spring and Grossmann group.[49] In 2015, the group reported an asymmetric IRC cyclisation of chalcone **173** using dipeptidic phosphine catalyst **174** to synthesise chromanone **175** (Scheme 1.33). In this system, the intramolecular Michael addition was found to be the rate-determining step. The enantioselectivity was dictated by hydrogen bonding between the acyl nitrogen with the enolate forcing conjugate addition on the *Si*-face. Elimination of the catalyst then completed the catalytic cycle and formed enantioenriched chromanone **175**.



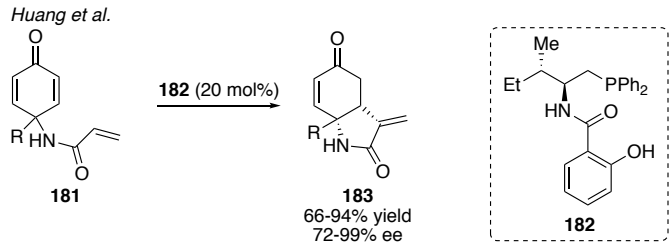
Scheme 1.33 Synthesis of enantioenriched chromanones by an asymmetric IRC reaction.

A different class of chiral phosphine is phosphepine such as **177** (Scheme 1.34), which has found application in asymmetric [3+2] ring annulations of allenes **176** and **179** to synthesise diquinanes **178** and quinolin-2-one derivatives **180**, respectively, in good yields and enantioselectivities.[50] ^{31}P NMR experiment showed that initial addition of the phosphine nucleophile into the allene was the rate-determining step, and mechanistic investigations confirmed a concerted process.



Scheme 1.34 Asymmetric synthesis of diquinanes and quinolin-2-one derivatives by chiral phosphepine.

The first report of an asymmetric synthesis of nitrogen-containing cyclic compounds by an IRC reaction was published in 2017 (Scheme 1.35).[51] A range of enantioenriched hydro-*2H*-indole substrates **183** were made from precusors **181** in the presence of catalyst **182** bearing both Brønsted acidic and Lewis basic moieties. Experimental results highlighted hydrogen bonding from the Brønsted acidic portions to be important in the enantio-inducing step.

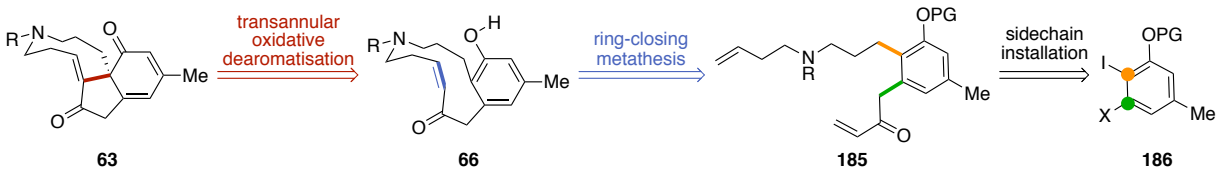


Scheme 1.35 The first asymmetric IRC to synthesise nitrogen-containing cyclic compounds.

Chapter 2. Synthesis of the Precursors for the Rauhut-Currier Approach

2.1. Retrosynthesis

We envisaged that the requisite bicyclic precursor **66** for the transannular oxidative dearomatisation step could be formed *via* a ring-closing metathesis of diene **185** (Scheme 2.1). The sidechains of **185** could be introduced by two transition-metal catalysed coupling reactions of protected phenol **186** bearing two carbon-(pseudo)halide bonds.

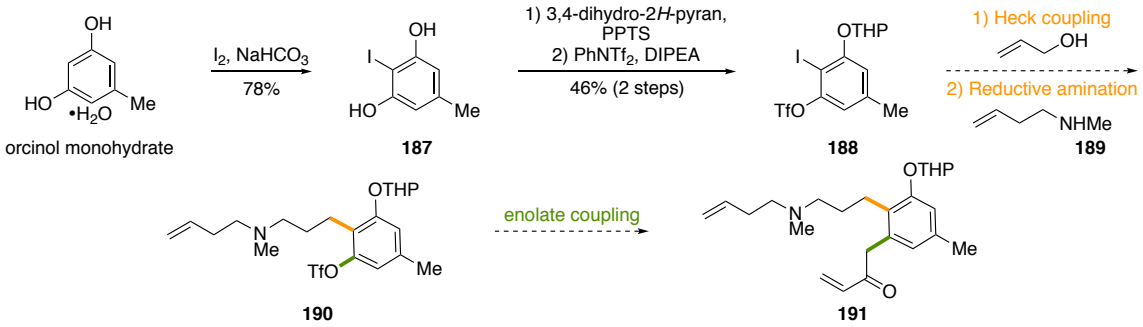


Scheme 2.1 Retrosynthesis for the transannular oxidative dearomatisation precursor **66**.

2.2. 1st Generation Synthesis

2.2.1. Synthesis of Starting Material

Since bicycle **66** was envisaged to be the key substrate for the transannular oxidative dearomatisation step, our aim was to design a streamlined approach to this intermediate that was amenable to scale-up. Thus, a starting material such as **188** (Scheme 2.2) was required on multi-gram scale from easily accessed materials. To this end, commercially available orcinol monohydrate underwent iodination to yield **187** in 78% yield. A mono-THP protection followed by triflation then transformed **187** into **188** in 46% yield over two steps on gram scale. The THP protecting group was expected to be orthogonal to the remaining chemistry employed in the synthesis, namely, a Heck coupling of **188** with allyl alcohol followed by *in situ* isomerisation, and subsequent reductive amination of the resulting aldehyde with **189** to form **190**. Finally, α-arylation of a suitable carbonyl should yield diene **191**.

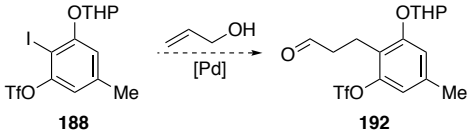


Scheme 2.2 Synthesis of diene **191** from orcinol monohydrate.

2.2.2. Palladium-Catalysed Coupling of 188

The Heck reaction is a metal-mediated vinylation of aryl (pseudo)halides in the presence of a palladium source to form a C-C bond. The reaction can be controlled *via* a combination of ligands and reaction conditions to be rendered regio- and/or enantioselective.[52]

In our synthesis, we intended to carry out a Heck coupling of **188** with allyl alcohol, followed by palladium-mediated isomerisation to yield the desired aldehyde **192** (Scheme 2.3), ready for further functionalisation as described in Scheme 2.2.



Scheme 2.3 Intended Heck coupling/isomerisation of **188** with allyl alcohol to yield **192**.

This coupling, however, was more challenging than expected, likely due to the steric hindrance around the C-I bond and the electron-donating *ortho*-OTHP group (Table 2.1). Under a series of different conditions, starting material was recovered with the C-I bond unchanged. Palladium(II) acetate in the presence of a quarternary ammonium salt (conditions first reported by Jeffrey)[53] (entries 1 to 3) did not yield any products. The use of Herrmann-Beller palladacyle **194**[54] (entry 4) showed improved conversion but only 18% of *trans*-alkene **193** and 20% of the starting material were isolated.

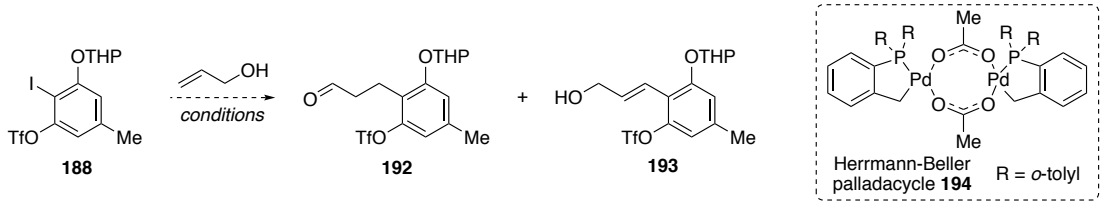
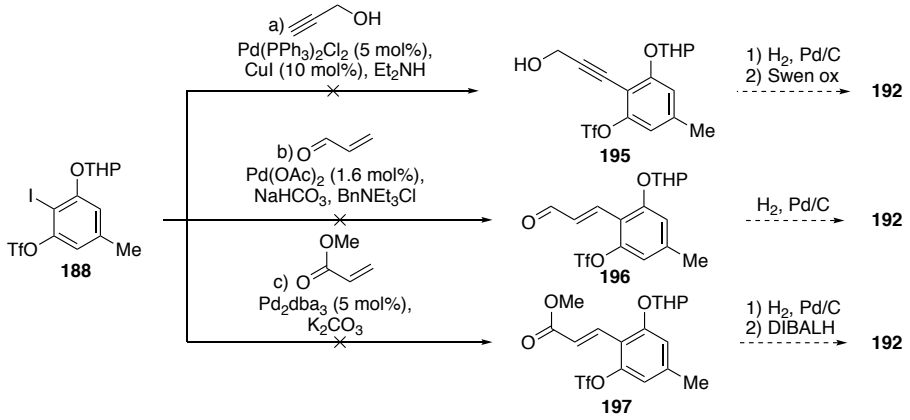


Table 2.1 Unsuccessful conditions for the Heck coupling of **188** with allyl alcohol.

Entry	[Pd]	Base	Ligand	Solvent	Temp. (°C)	Remarks
1	$Pd(OAc)_2$	$NaHCO_3$	$PhCH_2NEt_3^+Cl^-$	DMF	40	**188** recovered
2	$Pd(OAc)_2$	$NaHCO_3$	$PhCH_2NEt_3^+Cl^-$	DMF	55	**188** recovered
3	$Pd(OAc)_2$	$NaHCO_3$	$Bu_4N^+Cl^-$	NMP	55	**188** recovered
4	**194**	$NaHCO_3$	$Bu_4N^+Cl^-$	DMF/MeCN/H_2O (5:5:1, v:v:v)	120	**188** (20%), **193** (18%)

We were hopeful that other coupling partners might be successful. Thus, palladium-catalysed couplings to yield **195**, **196** and **197** were attempted, since these products could be transformed into aldehyde **192** by oxidation state manipulations (Scheme 2.4). Unfortunately, Sonogashira coupling of **188** with prop-2-yn-1-ol (condition a), or Heck couplings with acrolein and methyl acrylate (conditions b and c, respectively) gave solely returned starting materials.

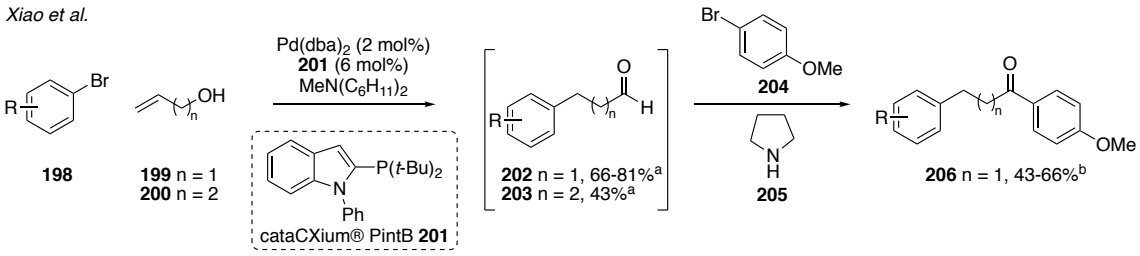


Scheme 2.4 Unsuccessful palladium-catalysed couplings of **188**.

The lack of conversion in the cases above suggested a sluggish oxidative addition into the sterically-encumbered C-I bond. The formation of *trans*-alkene **193** in the presence of Herrmann-Beller palladacycle **194** hinted at the need for not only bulky phosphine ligands to stabilise the low-valent

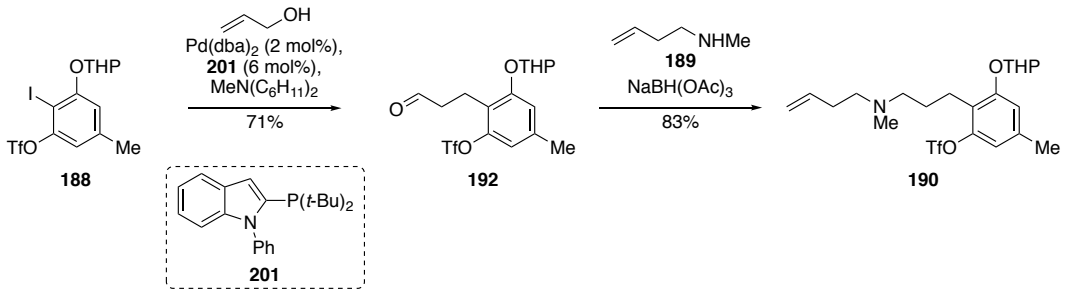
palladium(0) species, but also ones with appropriate electronic properties to allow complete isomerisation to the desired aldehyde **192**.

While searching for a suitable phosphine ligands, we came across cataCXium® PintB **201**, originally developed by Beller *et al*. for the amination of aryl chlorides.[55] Furthermore, ligand **201** has been successfully employed in a one-pot Heck arylation/isomerisation/acylation sequence by Xiao *et al*.,[56] to couple aryl bromides **198** with allyl alcohols **199**-**200** and aryl bromide **204** to yield functionalised ketones **206** (Scheme 2.5). In their initial studies of the Heck arylation/isomerisation step, the authors discovered ligand **201** to be effective at coupling a range of substituted alcohol partners with aryl bromides, followed by isomerisation, to yield the desired aldehyde products **202**. A notable example was 3-buten-1-ol **200**, which also underwent complete isomerisation in the presence of ligand **201** to yield aldehyde **203** in 43% yield (R = H). The use of Cy_2NMe as a base improved the yields, perhaps due to the efficient regeneration of the active palladium(0) species from the Pd(II)-H intermediate.[57]



Scheme 2.5 One-pot Heck arylation/isomerisation/acylation cascade; [a] isolated yield of the Heck product; [b] isolated yield of the product from the one-pot procedure.

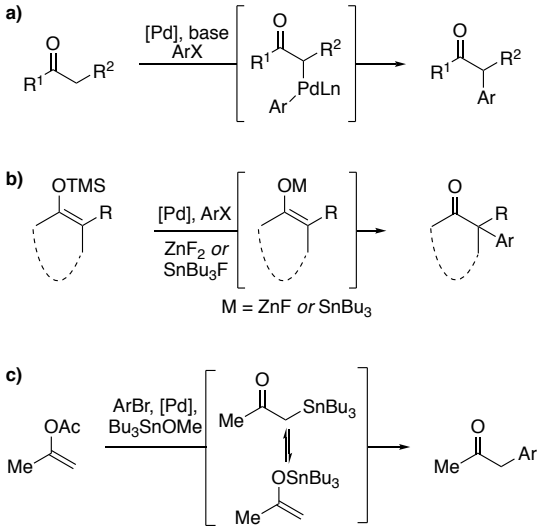
Using these reported conditions, we were pleased to find that ligand **201** was indeed effective at overcoming our previous problem with functionalising the C-I bond: Heck coupling of allyl alcohol and **188** proceeded smoothly to form **192** in 71% yield (Scheme 2.6). The subsequent reductive amination with amine **189** using sodium triacetoxyborohydride afforded **190** in 83% yield, ready for the envisaged enolate coupling.



Scheme 2.6 Successful Heck coupling of **188** using ligand **201** and subsequent reductive amination to yield **190**.

2.2.3. Enolate coupling of aryl triflate 190

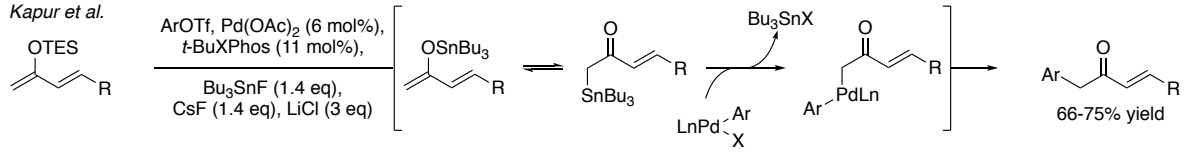
Palladium-catalysed α-arylation of ketones requires judicious choices of reagents and conditions to suppress side reactions such as aldol condensation and di-arylation; moreover, regioselectivity can also be a problem when there are two enolisable sites.[58] Current approaches to these issues can be divided into three main categories: a) *via in situ* formation of the enolate using strong bases such as NaO*t*-Bu or KHMDS; b) using a silyl enol ether as a masked enolate, with *in situ* generation of the corresponding zinc or tin enolate to promote the transmetallation step; or c) using vinyl acetate with *in situ* formation of a tributylstannyl enolate (Scheme 2.7).



Scheme 2.7 Literature strategies for α-arylation of ketones using a) *in situ* formation of enolates; b) silyl enol ethers; and c) vinyl acetates.

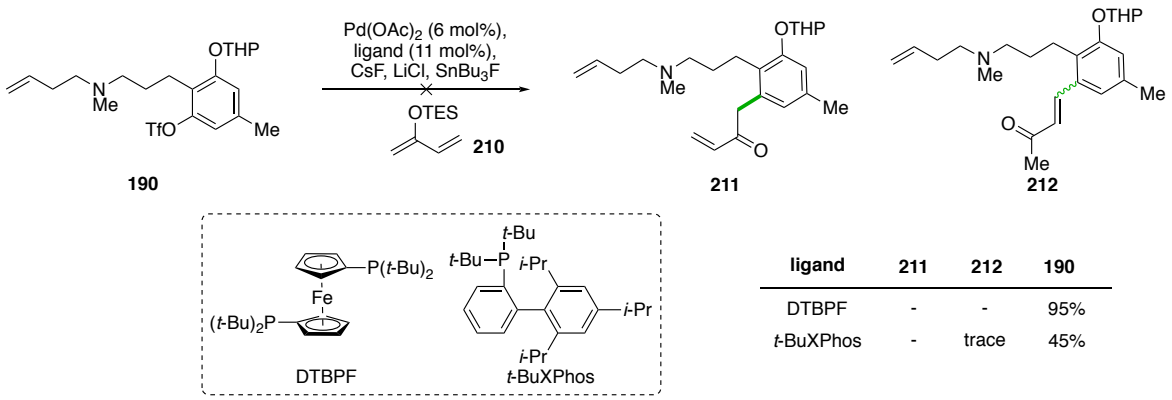
Whilst the enolate coupling of carbonyls such as esters,[59] amides[60] and 1,3-dicarbonyls[61,62] have been well developed, the α-arylation of enones have been less studied, where Heck reaction of the olefin is

a competing pathway. Work by Kapur *et al*.[63] provided an elegant solution by employing a modified Kuwajima-Uribe protocol, where the silyl-stannyl exchange and subsequent transmetallation outcompeted migratory insertion of the olefin to give excellent regioselectivity (Scheme 2.8). Lithium chloride was proposed to produce an aryl palladium chloride species that underwent transmetallation,[64] and the combination of tributyltin fluoride and cesium fluoride is known to improve yields in the coupling of enol ethers with aryl halides due to a currently unexplained synergistic effect.[65]



Scheme 2.8 Reported α-arylation of enones.

Despite a range of successful substrates reported in the paper, including *ortho*-substituted and electron-rich aryl triflates, in our hands, the coupling of silyl enol ether **210** with aryl triflate **190** was unsuccessful (Scheme 2.9). In the presence of ligand DTBPF, only starting material was recovered, whereas ligand *t*-BuXPhos gave trace amounts of the undesired Heck product **212** alongside 45% recovered starting material.

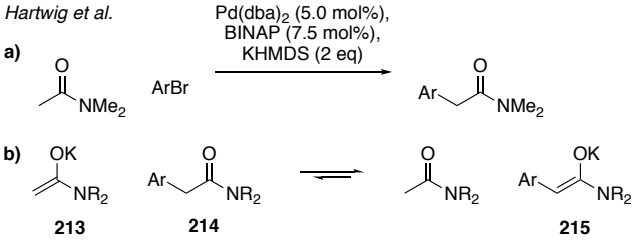


ligand	211	212	190
DTBPF	-	-	95%
t-BuXPhos	-	trace	45%

Scheme 2.9 Unsuccessful enolate coupling of aryl triflate **190** with silyl enol ether **210**.

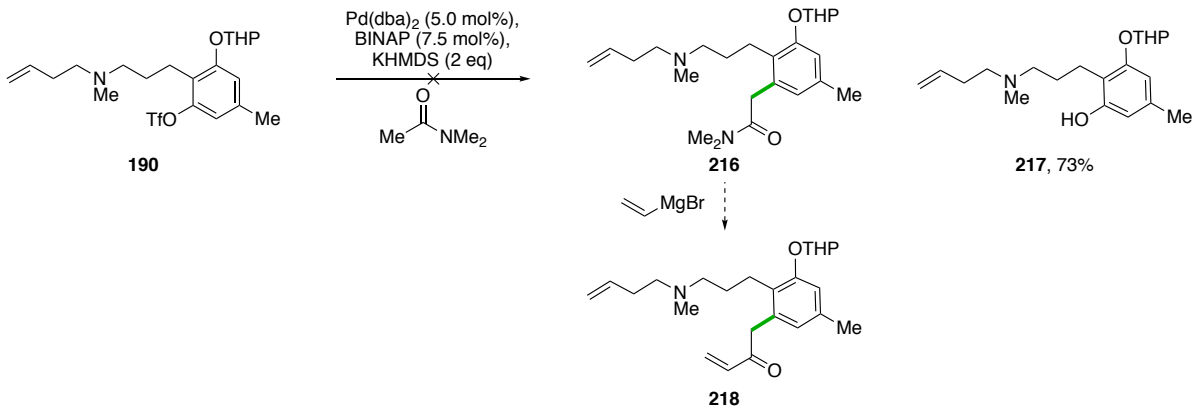
The trace formation of **212** nonetheless showed reactivity at the C-OTf bond, and thus investigations into other coupling partners were conducted.

The coupling of dimethylacetamide with aryl halides has been reported by Hartwig *et al.*[66] (Scheme 2.10, a)). The authors noted the need for two equivalents of KHMDS to reduce di-arylated products: without the second equivalent of base, the concentration of enolate **215** would be higher than that of enolate **213**, causing a competing di-arylation pathway (Scheme 2.10, b)).



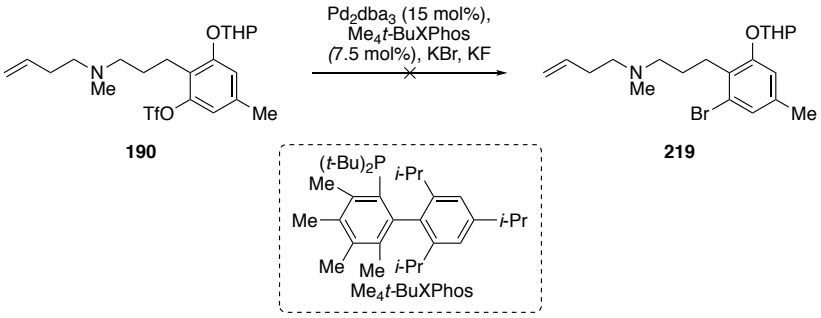
Scheme 2.10 a) α-arylation of DMA; b) equilibrium of DMA enolate **213** and mono-arylamide enolate **215** without a second equivalent of KHMDS.

We were hopeful that this methodology would form amide **216**, whose treatment with vinylmagnesium bromide would yield **218**[67] (Scheme 2.11). Unfortunately, the presence of KHMDS at elevated temperature (100 °C) simply led to hydrolysis of the triflate group to give **217** in 73% yield.



Scheme 2.11 Unsuccessful coupling of **190** with dimethylacetamide to form amide **216**.

Recognising the lability of the triflate group, attempts to convert the C-OTf bond into C-Br were made using conditions published by Buchwald *et al.*,[68] but this resulted only in decomposition of the starting material (Scheme 2.12).



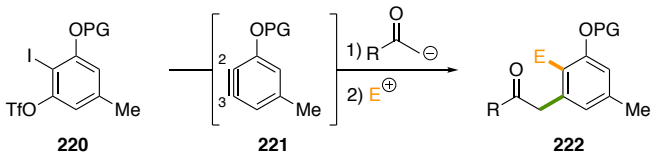
Scheme 2.12 Unsuccessful attempt to transform **190** into **219**.

The inability to activate the C-OTf bond in **190** towards metal-mediated coupling reactions necessitated a change in strategy to install the enone.

2.3. 2nd Generation Synthesis

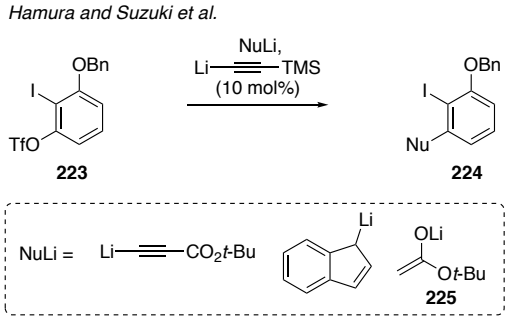
2.3.1. Nucleophilic Addition/Iodination of Benzyne

By installing two carbon-(pseudo)halide bonds, namely C-I and C-OTf, in starting material **220** for our intended metal-catalysed coupling reactions (Scheme 2.13), we had also formed a potential aryne precursor. The reactivity of arenes allows nucleophilic attack at C3 followed by electrophile trapping at C2. In fact, this chemistry has been exploited for three-component coupling reactions to rapidly access multi-functionalised arenes by changing the nucleophile/electrophile combination.[69-72] Generally, this strategy suffers from poor regioselectivity, but the presence of an alkoxy group capable of an inductive effect in **221** should direct the site of the initial nucleophilic attack.



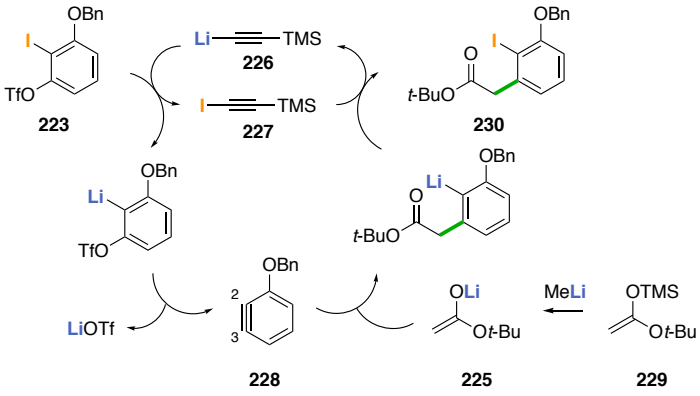
Scheme 2.13 Functionalisation of starting material **220** using aryne chemistry.

Hamura and Suzuki reported the nucleophilic addition/iodination of arynes in the presence of a catalytic amount of lithiated TMS-acetylene to afford aryl iodide **224** (Scheme 2.14).[73] The reaction proceeded in good yields and with good regioselectivity, across a range of substrates and nucleophiles, with nucleophile **225** being of particular interest to our synthesis.



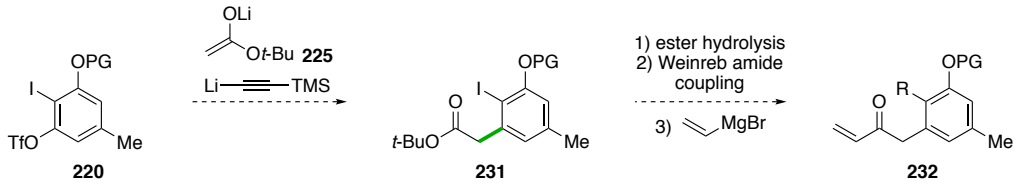
Scheme 2.14 Nucleophilic addition/iodination of arynes **223**.

The reaction relied on catalytic formation of aryne species **228** by initial slow and unfavourable lithium-halogen exchange between **226** and starting material **223**, driven by triflate being a good leaving group and concomitant formation of lithium triflate (Scheme 2.15). Nucleophile **225** was formed *in situ* in the presence of methyl lithium,[74] whose addition into the C3 position of **228** was governed by the inductive effect of the benzyl ether. Finally, a favourable lithium-halogen exchange completed the catalytic cycle and generated product **230**.



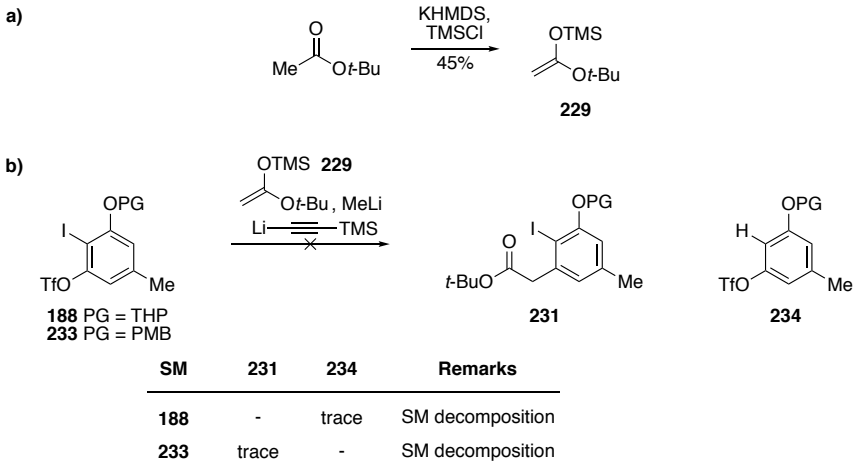
Scheme 2.15 Mechanism of the nucleophilic addition/iodination reaction.

We anticipated that *tert*-butyl ester **231** would allow the installation of the required enone **232** *via* a three-step sequence: 1) ester hydrolysis, 2) Weinreb amide coupling, and 3) addition of vinyl magnesiumbromide (Scheme 2.16).



Scheme 2.16 Incorporation of Hamura and Suzuki's nucleophilic addition/iodination methodology into our synthetic route and proposed completion of the enone sidechain.

To this end, silyl enol ether **229** was synthesised from *tert*-butyl acetate in 45% yield (Scheme 2.17, a)), whose treatment with methyl lithium would form nucleophile **225** *in situ*.[74] Unfortunately, when THP was the phenol protecting group (**188**), only trace amounts of proto-deiodination product **234** were observed amongst decomposed starting material and nucleophile (Scheme 2.17, b)). Changing the protecting group to PMB (**233**) gave a complex mixture, with only trace amounts of the desired product **231** observed in the crude NMR spectrum.



SM	231	234	Remarks
188	-	trace	SM decomposition
233	trace	-	SM decomposition

Scheme 2.17 a) Synthesis of silyl enol ether **229**; b) unsuccessful nucleophilic addition/iodination reactions with THP and PMB as the phenol protecting groups.

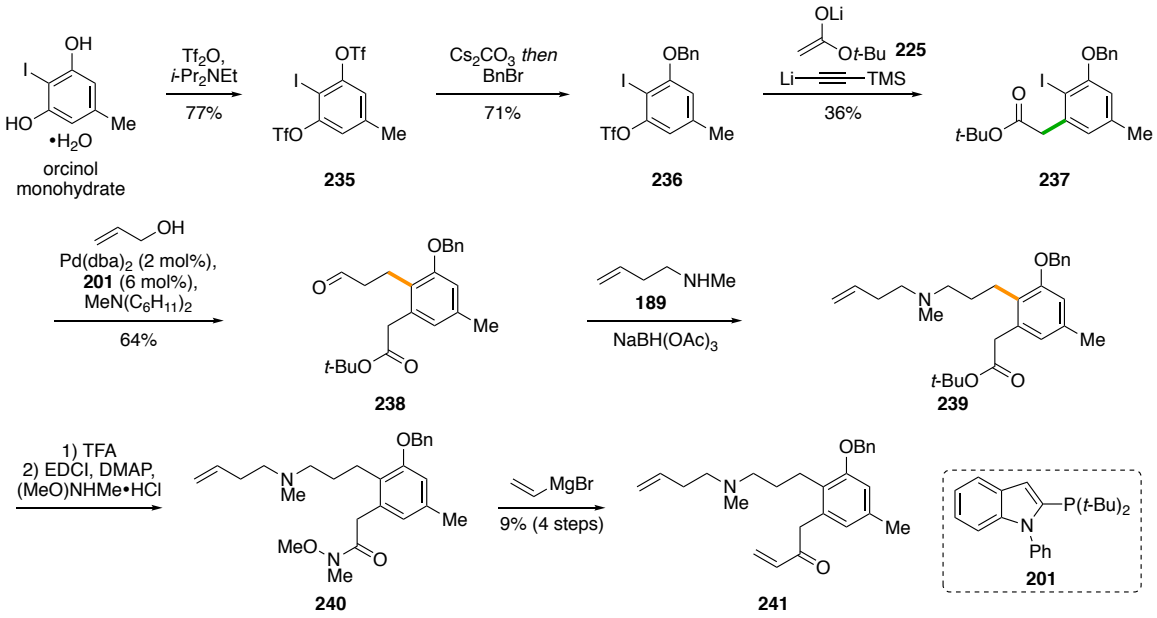
These difficulties led us to choose benzyl as the ether protecting group, as originally used in Hamura and Suzuki's paper, in order to move forward in the synthesis, despite potential complications associated with the *O*-deprotection step later in our route.[75]

Thus, starting material **236** was synthesised on gram-scale from orcinol monohydrate in two steps (Scheme 2.18). Firstly, a double triflation in CH_2Cl_2 at –78 °C formed **235** in 77% yield. Heating **235** at reflux in dimethoxyethane in the presence of cesium carbonate removed one triflate group, and

upon addition of benzyl bromide at 0 °C in the same pot, **236** was formed in 71% yield. When **236** was subjected to the nucleophilic addition/iodination conditions, we were delighted to isolate *tert*-butyl ester **237** in 36% yield, with the C-I bond intact and ready for the installation of the top side chain.

Here, as previously described, a Heck coupling/isomerisation sequence of **237** with allyl alcohol was facilitated by ligand **201** to give aldehyde **238** in 64% yield. Subsequent reductive amination with **189** and sodium triacetoxyborohydride yielded tertiary amine **239**. Ester hydrolysis of **239** revealed the corresponding carboxylic acid, which was difficult to handle and purify. The crude residue was hence telescoped through an amide coupling with *N*,*O*-dimethylhydroxylamine hydrochloride to afford **240**. The crude Weinreb amide was sufficiently clean based on NMR analysis, and was treated with vinylmagnesium bromide at −10 °C to yield **241** in 9% yield over 4 steps.

Having succeeded in reaching the ring-closing metathesis precursor **241**, two problems arose during this synthetic route that required in-depth studies: a) the low yield and unreliability of the vinylmagnesium bromide addition to **240**, and b) the proposed ring-closing metathesis of **241** in the presence of an electron rich tertiary amine. Model substrates were thus synthesised to investigate these steps.

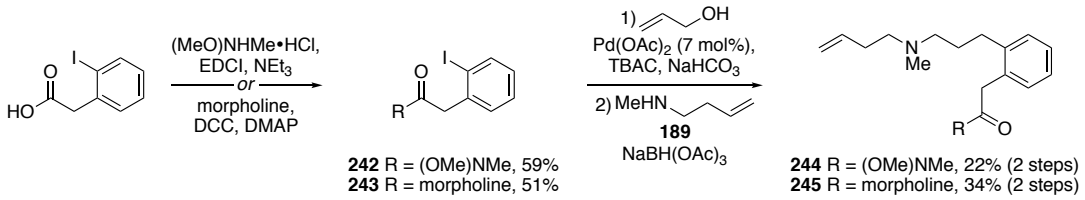


Scheme 2.18 Synthesis of **241** from orcinol monohydrate with benzyl as the phenol protecting group.

2.3.2. Model System

2.3.2.1 Studies of the Grignard Addition

Model compounds **244** and **245** were accessed in three steps from 2-iodophenylacetic acid (Scheme 2.19). The synthesis commenced with amide coupling of 2-iodophenylacetic acid with *N*,*O*-dimethylhydroxylamine hydrochloride and morpholine to yield **242** and **243**, respectively, in moderate yields. Subsequently, Heck coupling/isomerisation in the presence of palladium(II) acetate yielded the corresponding aldehydes, which underwent reductive amination with **189** and sodium triacetoxyborohydride to afford **244** and **245**. The lack of steric hindrance around the C-I bond in **242** and **243** here allowed successful Heck coupling with allyl alcohol under conventional Jeffery conditions,[53] without the need for ligand **201**.



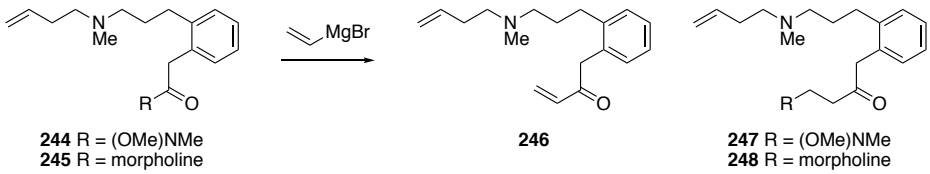
Scheme 2.19 Synthesis of model substrates **244** and **245**.

With model substrates **244** and **245** in hand, the Grignard addition was first investigated. The yields and reproducibility of the vinylmagnesium bromide addition step were limited by low mass recovery and side-product formation. Amongst the obtained complex mixtures, the major side-product was identified to originate from a second conjugate addition by the released amine to form **247** and **248** (from **244** and **245**, respectively) (Table 2.2). All side-products co-eluted with the desired enone **246** under our purification conditions, thus side reactions needed to be fully suppressed.

To this end, different equivalents of vinylmagnesium bromide and quenching methods were investigated. With R = Weinreb amide, a slight excess of the Grignard reagent (1.2 equivalents, entry 1) coupled with quenching by aqueous 1.0 M solution of HCl at 0 °C gave a mixture of the desired product and **247**. Quenching the reaction with acetic anhydride at –5 °C[76] gave 19% yield of the desired product **246** without the formation of **247** (entry 2). Hoping to increase the yield, the

equivalents of vinylmagnesium bromide were raised (entries 3 and 4) but this led to increased formation of inseparable and unidentified impurities. The best result (entry 5, 34% yield of **246**) was obtained with 1.5 equivalents of vinylmagnesium bromide, and by quenching with saturated aqueous solution of ammonium chloride at –78 °C.

Changing R to morpholine in starting material **245** did not suppress the formation of **248** (entry 6), and whilst increased equivalents of vinylmagnesium bromide (3.0 equivalents, entry 7) gave product **246** in comparable yield to entry 5, upon scaling up, the formation of inseparable impurities was once again observed (entry 8).



244 R = (OMe)NMe
245 R = morpholine

246

247 R = (OMe)NMe
248 R = morpholine

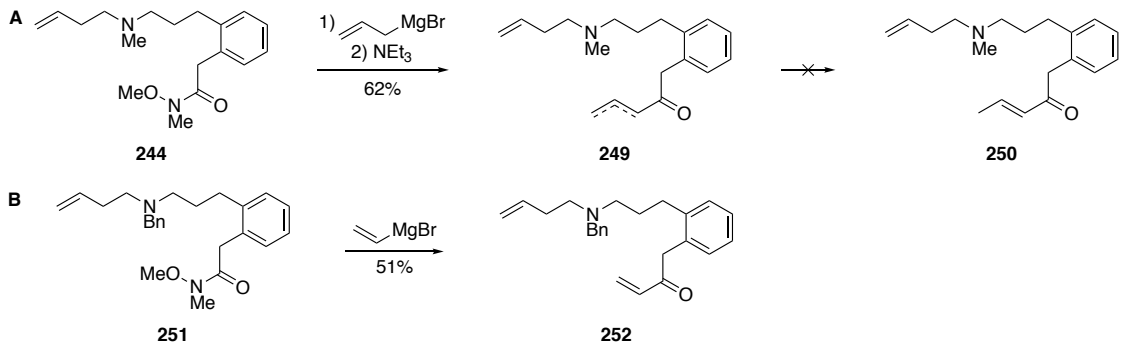
Table 2.2 Conditions screened for the Grignard addition.

Entry	R	MgBr (eq.)	Quenching method	Remarks
1	(OMe)NMe	1.2	1.0 M HCl at 0 °C	**246** + **247**
2	(OMe)NMe	1.2	Ac_2O at –5 °C	**246** (19%)
3	(OMe)NMe	1.5	Ac_2O at –5 °C	**246** + impurity
4	(OMe)NMe	2.0	Ac_2O at –5 °C	**246** + impurity
5	(OMe)NMe	1.5	Sat. aq. NH_4Cl at –78 °C	**246** (34%)
6	morpholine	1.2	Ac_2O at –5 °C	**248** + impurity
7[a]	morpholine	3.0	Ac_2O at –5 °C	**246** (30%)
8[b]	morpholine	3.0	Ac_2O at –5 °C	**246** + impurity

All reactions were carried out in THF at 0 °C; [a] reaction performed on 0.055 mmol; [b] reaction performed on 0.15 mmol.

At this stage, two observations gave us potential solutions to this troublesome step. Theorising that a crotyl group would prevent the second conjugate addition of the released Weinreb amine, **244** was subjected to allylmagnesium bromide addition followed by isomerisation (Scheme 2.20, A). However, a mixture of alkene regioisomers **249** was observed even with excess triethylamine (up to 10 equivalents) and prolonged reaction time (48 h). Although complete isomerisation to the desired crotyl enone **250** could not be obtained, the mass recovery of this reaction was much improved (62%).

Changing the amino-protecting group to benzyl (Scheme 2.20, B) also improved the Grignard addition to afford **252** in 51% yield. Since the benzyl protecting group was hoped to aid the ring-closing metathesis step (*vide infra*), method B was employed to improve the Grignard addition in the model substrate.



Scheme 2.20 A) Grignard addition of allylmagnesium bromide followed by isomerisation; B) benzyl as the amino-protecting group in **251**.

2.3.2.2 Studies of the Ring-Closing Metathesis

Concurrently, experiments were performed to investigate the ring-closing metathesis to form the requisite bicycle **253** — a precursor for the transannular Rauhut-Currier reaction. Whilst the methylamine group was desired due to its presence in the natural product obscurinine **68**, ruthenium-catalysed ring-closing metathesis is difficult in the presence of electron-rich and sterically-exposed alkylamines due to catalyst poisoning.[77] Nonetheless, we were encouraged by reports in the literature where protection of the amine as an ammonium salt could allow the ring-closing metathesis to proceed.[78]

Molybdenum-based catalysts, whilst generally more compatible with amines,[79] suffer setbacks such as moisture- and air-sensitivity, high cost, and intolerance of α,β-unsaturated carbonyl functionalities.[80] Thus, substrate **241** was subjected to ruthenium-catalysts in the presence of Lewis and Brønsted acids, under high dilution conditions (Table 2.3). Unfortunately, no desired product **253** was observed, only starting materials were recovered (entries 1 and 2), or decomposition occurred (entry 3).

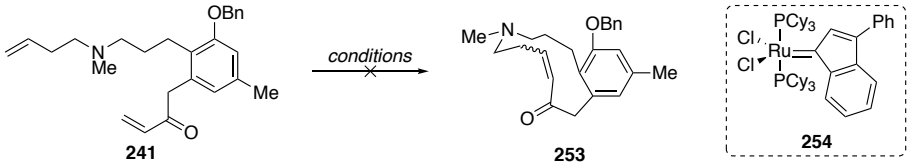


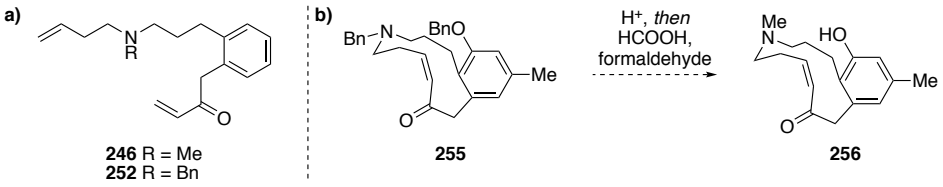
Table 2.3 Conditions tested for the ring-closing metathesis of **241**.

Entry	[Ru]	Acid	Concentration (M)	Remarks
1	Grubbs I (15 mol%)	CSA	0.002	SM recovered
2	**254** (20 mol%)	TFA	0.005	SM recovered
3	Hoveyda-Grubbs II (5 mol%)	$TsOH•H_2O$	0.01	Decomposition

All reactions were carried out in freshly freeze-pump thawed CH_2Cl_2, at 40 °C for 24 h.

Model substrate **246** and **252** (Scheme 2.21, a)) were therefore employed to study the ring-closing metathesis without exhausting the supply of **241**.

Benzyl was chosen as the amino-protecting group in **252** to increase the steric bulk around the amine to disfavour catalyst coordination.[78] In addition, if the benzyl amine group was incorporated into our bicyclic substrate **255**, an acidic deprotection followed by an Eschweiler-Clarke reaction could form **256** with the methyl amine moiety that is present in obscurinine **68** (Scheme 2.21, b)).



Scheme 2.21 a) Model substrates **246** and **252** for investigating the ring-closing metathesis; b) planned acidic deprotection followed by Eschweiler-Clarke reaction to yield bicyclic substrate **256**.

Unfortunately, under a variety of reaction conditions, **246** did not yield any desired product but only decomposed (Table 2.4, entries 1 and 2). In the presence of various combinations of ruthenium-catalysts and acids, **252** also only decomposed (entries 3 and 4), or was recovered unchanged (entries 5 to 7).

The lack of product formation suggested catalyst poisoning, despite our attempt at *in situ* protection of the amine as ammonium salts. We therefore resorted to an electron-withdrawing *tert*-

butoxylcarbamate protecting group in **257** to facilitate this ring-closing metathesis, and were pleased to observe the desired product **260** being formed as a single *E*-isomer in 13% yield (entry 8).

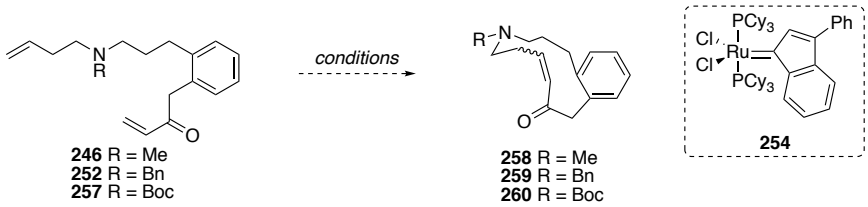


Table 2.4 Selected conditions screened for ring-closing metathesis.

Entry	R	[Ru]	Acid	Concentration (M)	Remarks
1	Me	Grubbs II	HCl	0.008	**246** + decomposition
2	Me	Grubbs II	Ti(O*i*-Pr)$_4$	0.005	Decomposition
3	Bn	Grubbs II	Ti(O*i*-Pr)$_4$	0.008	Decomposition
4	Bn	**254**	HCl	0.002	Decomposition
5	Bn	Grubbs I	Ti(O*i*-Pr)$_4$	0.002	**252** recovered
6	Bn	Grubbs I	CSA	0.002	**252** recovered
7	Bn	Grubbs I	TFA	0.002	**252** recovered
8	Boc	Grubbs II	-	0.002	13% *E*-**260**

All reactions were carried out in CH_2Cl_2 at 40 °C for 24 h at 20 mol% catalyst loading. Full details of conditions tested are described in Appendix 5.1.

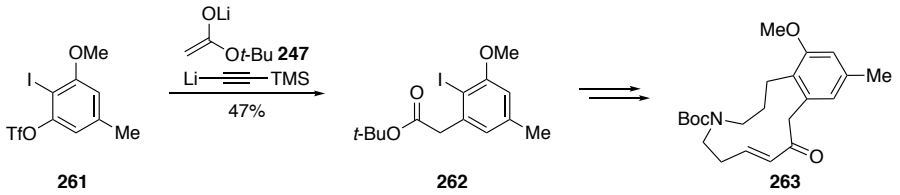
The yield for the ring-closing metathesis remained to be optimised, but having found a successful substrate for this challenging macrocyclisation event, we returned to the original synthetic route to incorporate the required carbamate protecting group into the alkyl amine sidechain.

2.3.3. *tert*-Butoxylcarbonate as an Amino Protecting Group

2.3.3.1 Protecting Group Consideration for the Phenol

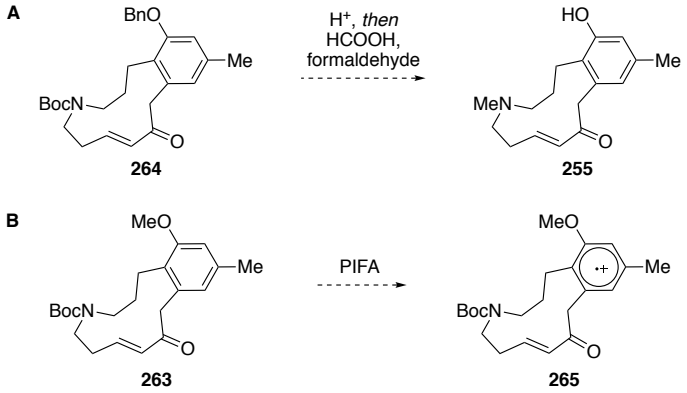
Having decided on *tert*-butoxylcarbonate as the amino protecting group, we also reconsidered the phenolic protecting group. As previously discussed, protecting group choices for the phenol moiety were limited to benzyl ether due to the nucleophilic addition/iodination methodology by Hamura and Suzuki (see Scheme 2.18). Whilst a plan for the benzyl ether deprotection was in place (*vide infr*a), a test reaction revealed successful nucleophilic addition/iodination of aryne precursor **261** bearing a

methyl ether to form *tert*-butyl ester **262** in 47% yield, giving us a potential alternative substrate **263** (Scheme 2.22).



Scheme 2.22 Successful nucleophilic addition/iodination of aryne **261** bearing a methyl ether.

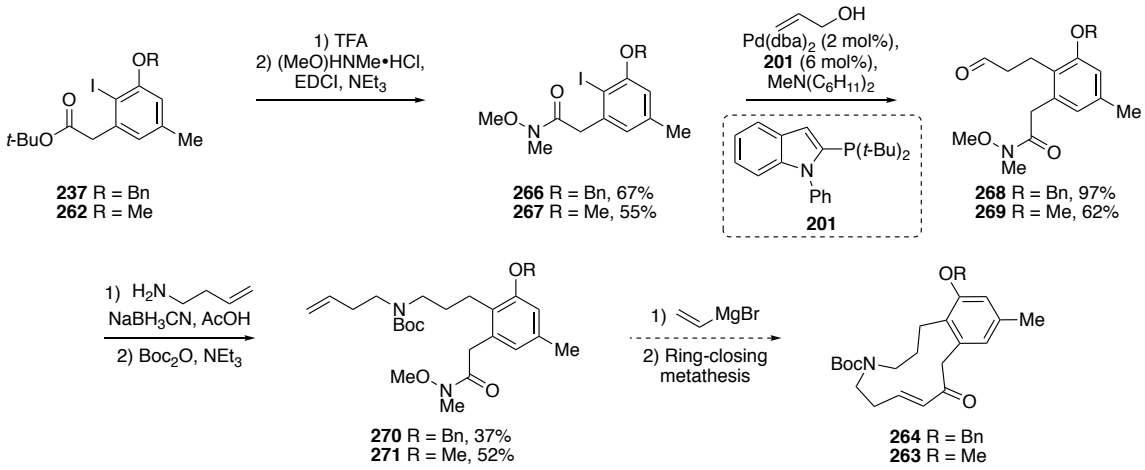
In order to reveal phenol **255** as required for the oxidative Rauhut-Currier reaction, the benzyl ether group in **264** could be removed in tandem with *N*-Boc cleavage under acidic conditions. Subsequent reaction under Eschweiler-Clarke conditions[81] should install the methylamine as required for the natural product obscurinine **68** (Scheme 2.23, A). Bicycle **263**, on the other hand, could directly undergo single-electron-transfer in the presence of PIFA in HFIP to generate a radical cation.[82] Such an intermediate could be susceptible to nucleophilic attack (Scheme 2.23, B). Thus, both bicyclic substrates **255** and **265** could be amenable to our proposed transannular oxidative Rauhut-Currier approach.



Scheme 2.23 Two possible protecting groups on the phenol: a) benzyl ether **264** may be deprotected under acidic conditions to reveal phenol **255**; b) anisole **263** may be oxidised to radical cation **265** in the presence of PIFA.

*2.3.3.2 Synthesis of Weinreb amides **270** and **271***

Thus, **237** and **262** underwent a sequence of reactions similar to those used in the synthesis of **241** (*vide supra*, Scheme 2.18). Firstly, ester hydrolysis of **237** and **262** with trifluoroacetic acid revealed the corresponding carboxylic acids, which were subjected to amide coupling conditions with *N*,*O*-dimethylhydroxylamine hydrochloride to furnish **266** and **267** in 67% and 55% yield after two steps, respectively (Scheme 2.24). Subsequently, a Heck coupling/isomerisation cascade with allyl alcohol in the presence of ligand **201** gave aldehydes **268** and **269** in good yields. The reductive amination with 3-buten-1-amine in the presence of sodium cyanoborohydride then afforded the corresponding secondary amines in poor yields (around 30%), whose *tert*-butylcarbamate protection completed the synthesis of amides **270** and **271** in 37% and 52% yield over two steps, respectively. The stage was set for a Grignard addition followed by a ring-closing metathesis to form **264** and **263**.



Scheme 2.24 Syntheses of **270** and **271**.

However, the low yields of the reductive amination steps were a concern, and detailed studies were conducted to solve this problem.

2.3.3.3 Reductive Amination

The reaction of an aldehyde or ketone with an amine forms an imine, which is then typically protonated to form an iminium cation. This species can then be reduced with either transition metals or hydride reducing reagents.[83] The reaction can be carried out either *step-wise*, *i.e.* the reducing

reagent is added after the iminium formation, or *directly*, *i.e.* all reagents are added at the same time. Reductive amination of aldehydes and primary amines, however, are prone to forming di-alkylated side-products.

The reductive amination step outlined in Table 2.5 was in fact optimised throughout the different generations of the synthesis, on substrate **A** bearing different protecting groups and sidechains; the results are summarised here for comparison. Applying conditions as reported by Abdel-Magid *et al.*,[83] namely, using $NaBH(OAc)_3$ as the reductant, unfortunately yielded a complex mixture (entry 1), with trace amounts of aldol condensation products observed in the crude NMR spectrum. The *step-wise* procedure was next tested, where the aldehyde and amine were stirred at room temperature overnight, before the addition of $NaBH_4$ (entry 2), to give only di-alkylated product **C**. In order to encourage iminium cation formation, 3 Å molecular sieves were added (entry 3), and $NaBH_3CN$ was used, which at pH $\approx$ 6 should selectively reduce the iminium intermediate over aldehyde **A**.[83] Here, the desired product **B** was isolated in 31% yield. Changing to a polar protic solvent (MeOH, entry 4), reduced the yield due to formation of the di-alkylated product **C**.

When the conditions in entry 3 were applied to a different substrate (entry 5), comparable yields for the desired product **B** were obtained. A different desiccant ($MgSO_4$, entry 6), however, only gave the di-alkylated product **C**. The step-wise procedure proved to be successful for this substrate (entry 7), to give 44% yield, although upon scale-up (entry 8), the yield was reduced and the formation of **C** was again observed. Finally, we were able to create a reliable and reproducible protocol by using the hydrochloride salt of the amine reagent (entry 9) to give 67% of the desired product **B**. We hypothesise that the iminium intermediate is slowly formed at a low steady state concentration due to the reduced nucleophilicity of the amine hydrochloride salt. Then, rapid reduction by $NaBH_3CN$ yield product **B**, whose protonation by one equivalent of hydrochloric acid minimises the formation of di-alkylated product **C**.

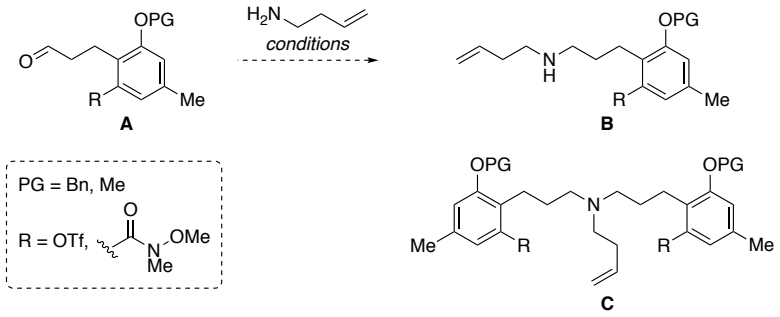


Table 2.5 Conditions tested for the reductive amination.

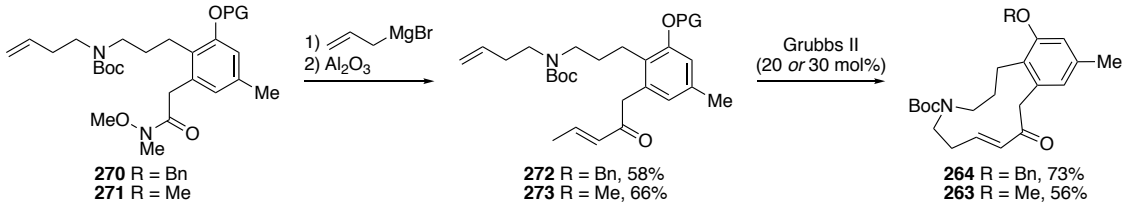
Entry	PG	R	Reductant	Additive	Solvent	Remarks
1[a]	Bn	C(O)NMeOMe	$NaBH(OAc)_3$	-	CH_2Cl_2	Complex mixture
2[b]	Bn	C(O)NMeOMe	$NaBH_4$	-	CH_2Cl_2	**C** + impurity
3[a]	Bn	C(O)NMeOMe	$NaBH_3CN$	AcOH, 3 Å M.S.	CH_2Cl_2	**B** (31%)
4[a]	Bn	C(O)NMeOMe	$NaBH_3CN$	AcOH, 3 Å M.S.	MeOH	**B** (13%) + **C** + impurity
5[a]	Me	OTf	$NaBH_3CN$	AcOH, 3 Å M.S.	CH_2Cl_2	**B** (22%)
6[a]	Me	OTf	$NaBH(OAc)_3$	$MgSO_4$	CH_2Cl_2	**C** + impurity
7[b,c]	Me	OTf	$NaBH_4$	-	MeOH	**B** (44%)
8[b,d]	Me	OTf	$NaBH_4$	-	MeOH	**B** (32%) + **C** + impurity
9[a]	Me	C(O)NMeOMe	$NaBH_3CN$	HCl•amine, 3 Å M.S.	MeOH	**B** (67%)

[a] *Direct* procedure: aldehyde, amine and additives were added to a solution of starting material in solvent (0.15 M), the mixture was stirred for 30 minutes at room temperature, the reductant was then added and the reaction was stirred at room temperature for 16 h; [b] *Step-wise* procedure: amine and additives were added to a solution of starting material in solvent (1.6 M) and the mixture was stirred at room temperature overnight until complete imine formation was determined by NMR analysis, the reductant was then added and the reaction was stirred at room temperature until complete consumption of the imine; [c] 0.15 mmol of starting material; [d] 0.51 mmol of starting material,

2.3.3.4 Grignard Addition and Ring-closing Metathesis

As previously discovered in the model substrate (see Section 2.3.2.1), the Grignard addition of allylmagnesium bromide followed by isomerisation to the requisite crotyl enone was found to reliably and cleanly produce the desired products **272** and **273** in 58% and 66% yield, respectively (Scheme 2.25). Alumina was found to be a mild but effective basic medium to effect this isomerisation.

We were delighted to find that ring-closing metathesis using modified conditions from the model studies in Section 2.3.2.2 (at 0.005 M concentration) gave bicyclic substrates **264** and **263** in 73% (at 30 mol% catalyst loading) and 56% yield (at 20 mol% catalyst loading), respectively.

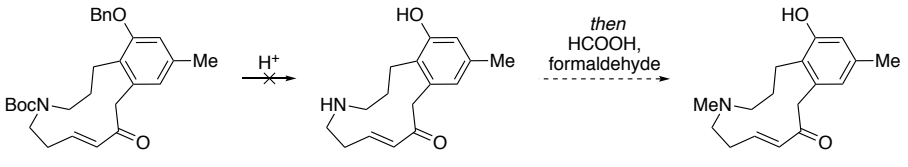


Scheme 2.25 Completion of bicycles **264** and **263**.

With the bicyclic substrates **264** and **263** in hand, attention was turned to the deprotection of benzyl ether **264**, and subjecting both its corresponding phenol and anisole substrate **263** to the proposed transannular oxidation Rauhut-Currier reaction.

*2.3.3.5 Attempts to Form Bicyclic Substrate **256***

In order to form bicyclic phenol **256** for the oxidation in the presence of hypervalent iodine, we intended to carry out an acidic global deprotection of **264** followed by an Eschweiler-Clarke reaction to install the methyl amine (Scheme 2.26).[81] Unfortunately, whilst the carbamate group could be removed under acidic conditions (as observed by Mass Spectrometry and NMR spectra), attempts to simultaneously cleave the benzyl ether to form **274** were not successful. The presence of the enone moiety complicated common reductive methods to remove the benzyl group. Faced with these difficulties, we discontinued our investigation with **264**.

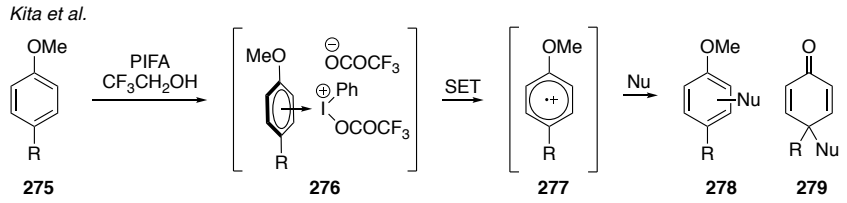


H^+	Temp. (° C)
$AlCl_3$	0
$TiCl_4$	0
TFA	60
HCl/Et_2O	0
$AlCl_3$, anisole	0

Scheme 2.26 Unsuccessful acidic deprotection to form **274**, and the intended Eshweiler-Clarke reaction to afford **256**.

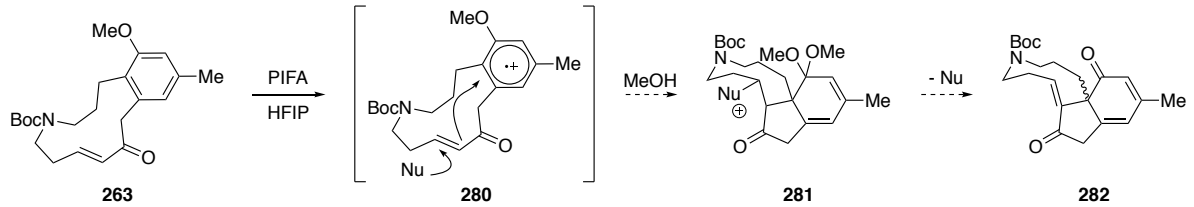
*2.3.3.5.1 Oxidation of Anisole Substrate **263***

Work by Kita *et al*. has shown that phenol ethers such as **275** readily form charge-transfer complexes **276** in the presence of PIFA in CF_3CH_2OH (Scheme 2.27), which then undergo single-electron transfer to generate radical cation intermediates **277**. This intermediate can be trapped by a range of nucleophiles to form either re-aromatised products **278**, or benzoquinones **279**.[82,84]



Scheme 2.27 Nucleophilic substitution of substituted phenol ethers.

Looking at our system, we were hopeful that a nucleophile would add reversibly to enone **263** to form an intramolecular carbon nucleophile to trap radical cation intermediate **280** (Scheme 2.28). Elimination of the nucleophile in a Rauhut-Currier fashion should then give the desired tricycle **282**. Electron spin density calculations by Kita *et al*. concluded that the cation radical was concentrated *ortho-* to the methoxy group, the position at which we wanted the addition to occur. We were also aware of the extended reaction time typical for Rauhut-Currier reactions, and were delighted to find reports of the reactive intermediate's lifetime being extended to a few hours in $(CF_3)_2CHOH$.[82]



Scheme 2.28 Proposed transannular Rauhut-Currier reaction *via* a cation radical intermediate.

When substrate **263** was subjected to PIFA in methanol, no conversion of the starting material was observed (Scheme 2.29). We found that either $(CH_3)_2CHOH$ or CF_3CH_2OH were required as solvent to effect any conversion, presumably due to the hydrogen-bonding ability of these solvents increasing

the oxidating ability of PIFA.[85] $(CH_3)_2CHOH$ was chosen for our studies because of the increased liftetime of the reactive intermediate in this solvent.[82]

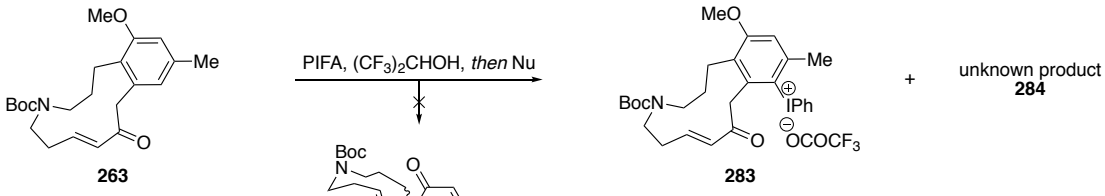
In the absence of any nucleophile, iodonium salt **283** was isolated in 48% yield, a product commonly observed when *meta*-substituted phenyl ethers were oxidised the absence of strong nucleophiles.[84] The isolation of **283** suggested charge transfer complex **276** was the intermediate.

263 **283**

solvent	263	283
MeOH	quant.	-
CF_3CH_2OH	-	29%
$(CF_3)_2CHOH$	-	48%

Scheme 2.29 Oxidation of **263** in the presence of PIFA in HFIP as solvent.

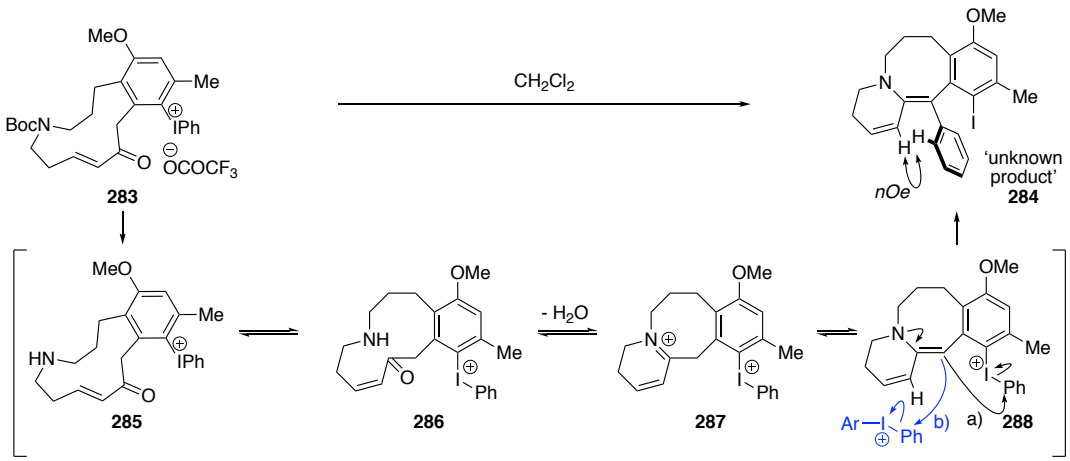
Thus, bicyclic anisole **263** was re-subjected to the above condition, but now with added nucleophiles common for Rauhut-Currier reactions: DMAP, DABCO, PPh_3, and *n*-Bu_3P (Scheme 2.30). After 2 h, in the presence of DMAP and DABCO, complete starting material consumption was observed, and only iodonium salt **283** was isolated from a complex mixture in 7% and 33% yield, respectively. In the presence of triphenylphosphine, extensive decomposition was observed after 2 h, and we could only isolate a 4:1 mixture of triphenylphosphine:triphenylphosphine oxide in 40% combined yield. Interestingly, when the reaction with tri *n*-butylphosphine was left for 24 h, an unknown product **284** was isolated as an inseparable mixture with tri *n*-butylphosphine and tri *n*-butylphosphine oxide.



Nu	Time (h)	283	284
DMAP	2	7%	-
DABCO	2	33%	-
PPh_3	2	-	-
n-Bu_3P	24	-	**284** + *n*-Bu_3P + *n*-Bu_3P=O

Scheme 2.30 Unsuccessful trapping of radical cation intermediate to form tricycle **282**.

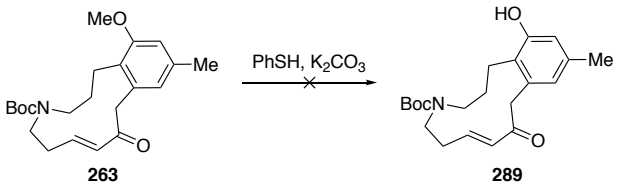
We wondered if aryliodonium salt **283** itself could undergo nucleophilic substitution, thus, **283** was isolated and stirred with *n*-Bu_3P at room temperature in CH_2Cl_2 (Scheme 2.31). Starting material was consumed after 24 h and, to our surprise, the previously observed unknown product was formed, which, after isolation, was identified to be tricycle **284**. In a control experiment, **284** was also formed when **283** was simply stirred in CH_2Cl_2 at room temperature without *n*-Bu_3P. We thus proposed the following mechanism for the formation of **284**: cleavage of the *N*-carbamate bond due to trace amounts of trifluoroacetic acid, followed by olefin isomerisation and iminium condensation, tautomerisation, and enamine attack on the adjacent phenyl group, either a) intramolecularly, or b) intermolecularly. The position of the pendant phenyl group was determined by 2D NMR experiments showing nOe correlations between the marked protons (detailed structural determination can be found in the Experimental Section).



Scheme 2.31 Proposed mechanism for the formation of rearranged product **284**.

Since the desired reactivity could not be effected on anisole substrate **263**, we sought to access the unprotected phenol **289** which should undergo oxidation to a cationic species in the presence of hypervalent iodine.[86]

To this end, **263** were subjected to deprotection (Scheme 2.32),[87] but unfortunately only decomposition was observed. At the time, we were not aware of other methyl ether deprotection conditions that would be orthogonal to the functional groups present in **263** (i.e. a *tert*-butoxycarbamate and an enone), thus, no further studies were conducted with this anisole substrate.



263 **289**

Scheme 2.32 Attempt to deprotect aryl methyl ether **263**.

Due to the instability of the deprotected intermediate generated from **264**, and the unsuitability of **263** towards the desired reactivity, we decided to change the protecting group strategy earlier on in the synthesis.

2.4. Unprotected Bicyclic Phenol as the Target Precursor

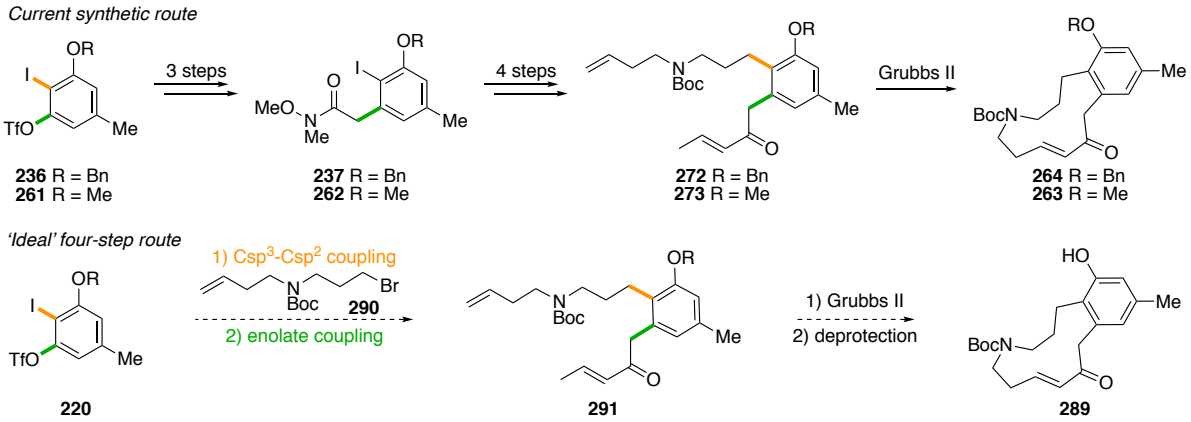
2.4.1. Revision of Synthetic Route: Attempts to Reduce the Step Count

From starting materials **236** and **261**, bicyclic substrates **264** and **263** could be accessed in eight steps using the previously described synthetic route (Scheme 2.33). The synthesis could be carried out on gram-scale, including a nucleophilic addition/iodination of an aryne, a sterically-demanding Heck coupling, and a ring-closing metathesis.

However, given that the key transannular oxidative dearomatisation step was planned at the end of the synthesis, a more concise synthetic route was still desirable for faster access to ample quantities of the bicyclic precursor **289**.

During this revision stage of our synthetic route, we entertained the idea of an 'ideal' four-step synthesis. Starting material **220** could be subjected two sets of carbon-carbon bond formation *via*

metal-mediated couplings. First, an sp^3-sp^2 coupling with alkyl bromide **290** could directly install the tertiary amine side chain. Then, an enolate coupling of the remaining aryl triflate should install the enone sidechain to complete **291**. Finally, a ring-closing metathesis and a deprotection would yield the desired bicyclic precursor **289**.



Scheme 2.33 Comparison between current synthetic route and an 'ideal' four-step synthesis to bicyclic substrates.

2.4.1.1 Csp^3-Csp^2 coupling

At this stage, we had in hand a large amount of **261** remaining from the previous synthetic route and thus provisionally used **261** to screen conditions for the two metal-catalysed carbon-carbon bond formation steps in the revised route.

The reactivity of primary alkyl halides in metal-catalysed cross-coupling reactions has been detailed in several reviews,[88-90] but in our case, we were interested in their ability to undergo alkyl/aryl coupling to form Csp^3-Csp^2 bonds. Such a transformation can be effected by rhodium,[91,92] iron,[93,94] copper,[95] palladium,[96-99] and nickel catalysis.[100-103]

Amongst the many possibilities, we thought the Negishi reaction or cross-electrophile coupling would be most suitable for our substrates. The Negishi reaction is a metal-catalysed coupling between an aryl halide and a nucleophilic alkyl metal species.[103] Reversing the electronics of the coupling partners, *i.e.* using an alkyl halide and an aryl metal reagent, often risks β-elimination of the alkyl-transition metal complex. Cross-electrophile coupling, on the other hand, avoids the formation of carbon nucleophiles which are typically difficult to handle, but requires the metal (commonly

palladium or nickel) to preferentially undergo oxidative addition with one electrophile over the other.[104]

Thus, **261** was subjected to Negishi and cross-electrophile couplings and selected conditions are summarised in Table 2.6 (see Appendix 2 for full details of conditions and substrates tested).

Under nickel-catalysed Negishi coupling conditions[105] with fluorostyrene acting as the ligand (entry 1),[106] only starting material **261** was recovered, alongside **290** and proto-debrominated amine **293**. Using Lipshutz conditions wherein PTS surfactant was used to form catalytic nanoreactors (entry 2),[107] we only recovered both **261** and **290** unchanged. We had hoped that when the Pd-N heterocyclic carbene was used with LiCl as an additive (entry 3),[108] a more soluble RZnX•LiCl complex should be generated.[109] However, once again **261** was observed alongside **290** and **293**. In a report by Knochel *et al*., a mixture of CuCl, $MnBr_2$ and Et_2Zn formed an active catalytic species which underwent oxidative addition with simple alkyl bromides to allow cross-coupling.[110] Although these conditions (entry 4) gave trace amounts of product **292**, side reactions also occurred and the desired product could not be purified.

From preliminary studies with iodobenzene (see Section 5.2.1.1) we had hoped that cross-electrophile coupling conditions would be more successful. Thus, a [Ni^0•2EC•Py] complex was generated *in situ* as described by Peng *et al*. (entry 5) to effect the desired sp^3-sp^2 coupling,[111] but unfortunately only decomposition was observed.

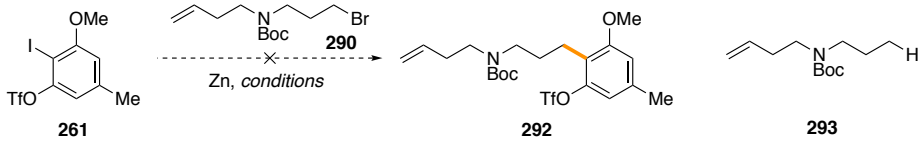


Table 2.6 Conditions screened for the sp^3-sp^2 coupling.

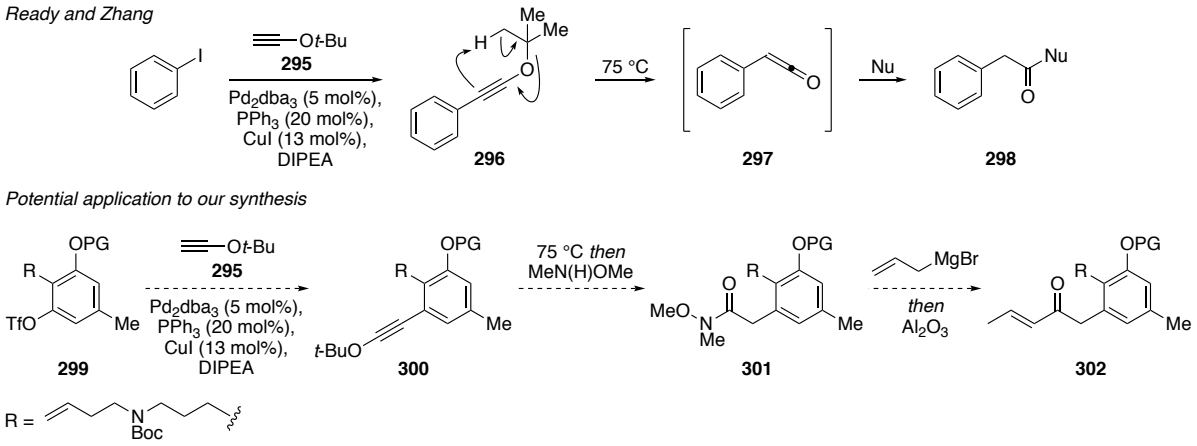
Entry	[M]	Ligand	Other reagents	Temp. (°C)	Remarks
1	$Ni(acac)_2$	4-fluorostyrene	TBAI	RT[-]	**261**, **290** and **293** observed
2	$Pd(Cl_2)$(amphos)	TMEDA	PTS (2% wt. in H_2O)	RT	**261** and **290** recovered
3	PEPPSI	-	LiCl	RT	**261**, **290** and **293** observed
4[a]	$Pd(dppf)Cl_2$	-	CuCl, $MnBr_2$	65	≈ 6% **292** (impure)
5	$NiCl_2$	ethyl crotonate	pyridine	55	decomposition

Zn dust was activated by heating at reflux (60 °C) in a solution of dibromoethane and TMSCl in THF for 5 min;[108] [a] Et_2Zn was used as the zinc source.

Overall, we faced difficulties in fully generating the alkylzinc bromide species, and thus effecting good conversion of the starting material **261** (entries 1 to 3). Furthermore, when **261** was consumed, either low yields (entry 4) or decomposition (entry 5) were observed. These discouraging results were in line with our previous struggles to react the sterically-demanding C-I bond in **261** (see Section 2.2.2), and prompted us to abandon the Csp^3-Csp^2 coupling approach.

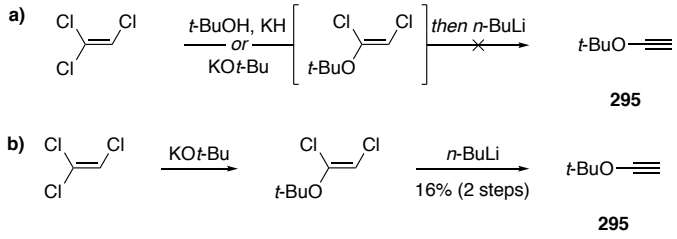
2.4.1.2 Sonogashira Coupling with an Ynol Ether

Having been unsuccessful in performing enolate couplings on our aryl triflate substrates (see section 2.2.3), we envisaged a different approach to directly install the carbonyl, *i.e.* by trapping an aryl ketene with an appropriate nucleophile. Reports by Ready and Zhang[112] have indeed proven the feasibility and applicability of such an approach, wherein an aryl iodide underwent a Sonogashira coupling with ynol ether **295**. The product then thermally rearranged *via* a [1,5]-hydride shift to form aryl ketene **297** (Scheme 2.34, top line). In our case, trapping an aryl ketene such as **297** with *N*,*O*-dimethylhydroxylamine would directly yield Weinreb amide **301** (Scheme 2.34, bottom line), whose treatment with allylmagnesium bromide and alumina would complete the desired product **302**.



Scheme 2.34 Formation of aryl ketene **297** from aryl iodide which can be trapped *in situ* by nucleophiles to generate **298**, and potential application to our current synthetic route.

Initial experiments found difficulties in forming ynol ether **295** according to the procedure reported by Ready and Zhang. The one-pot procedure reported by Minehan and Tran using potassium *tert*-butoxide[113] also did not yield any desired product (Scheme 2.35, a)). Fortunately, a step-wise protocol was found to give ynol ether **295** in 16% yield over two steps, as a 7.7% solution in hexane and diethyl ether (w:w) (Scheme 2.35, b)).

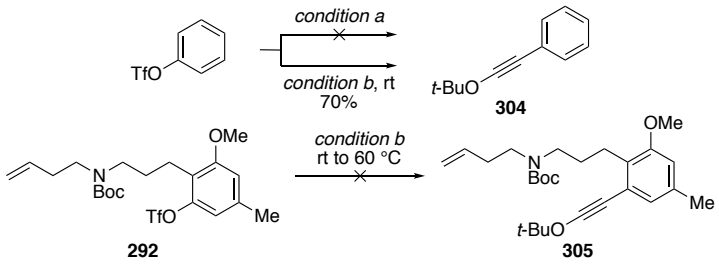


Scheme 2.35 a) Unsuccessful one-pot procedure; b) successful step-wise procedure to make **295**.

Screening of reaction conditions showed that Sonogashira coupling of **295** with simple phenyl trifluoromethanesulfonate in the presence of TBAI as an additive yielded the coupling product **304** in 70% yield at room temperature (Scheme 2.36). Upon subjecting aryl triflate **292** to these conditions, however, only returned starting material was observed, even when warmed to 60 °C. In fact, Sonogashira coupling of literature aryl triflate compounds with similar electronic and steric properties suggested the need for elevated temperature between 70 to 120 °C, which, in our case, would induce

thermal a [1,5] hydride shift of ynol ether, and either cause decomposition of the coupling partner **295**, or of the desired product **305** once formed.

This observation prompted us to discontinue this investigation and return to our previously established synthetic route.

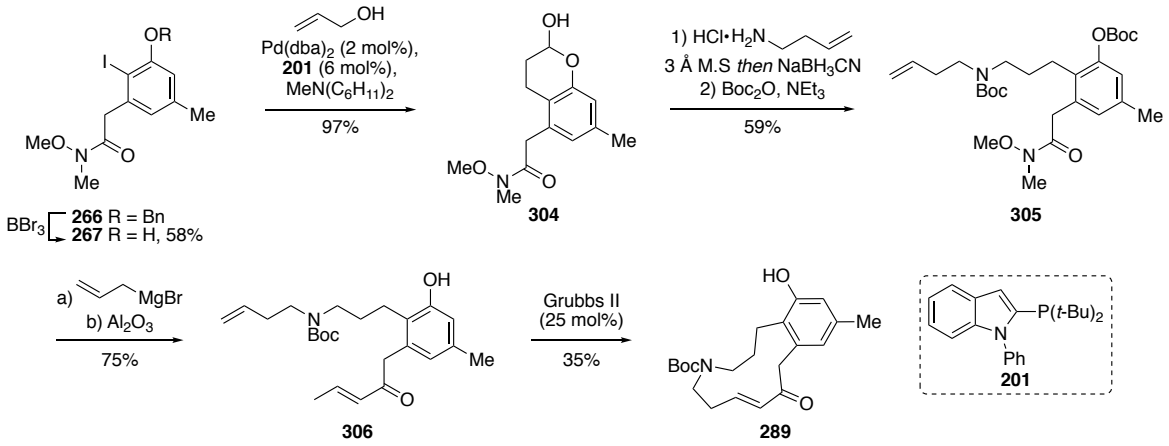


Scheme 2.36 Sonogashira couplings of **295** with phenyl trifluoromethanesulfonate and aryl triflate **292**; *condition a*: **295**, $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), NEt_3, DMF, 4 Å M.S., 40 °C; *condition b*: **295**, $Pd(PPh_3)_4$ (10 mol%), CuI (10 mol%), NEt_3, TBAI, DMF, 4 Å M.S.

2.4.2. Returning to the Orginal Route to Access the Unprotected Phenol Target

In order to avoid potential complications associated with late-stage deprotection in the presence of sensitive groups such as carbamate and enone, phenol deprotection was carried out early on in the synthesis (Scheme 2.37).

Thus, benzyl ether **266** was deprotected with boron tribromide. The free phenol **267** then underwent Heck coupling/isomerisation with allyl alcohol to form acetal **304** in 97% yield. Reductive amination using conditions previously optimised in Section 2.3.3.3 followed by treatment with di-*tert*-butyl carbonate gave doubly protected product **305**. Initially, we only intended to protect the alkyl amine but partial *O*-Boc formation was always observed, thus triethylamine and two equivalents of di-*tert*-butyl carbonate were added to yield **305** cleanly. Fortunately, the *O*-Boc bond was labile in the presence of allylmagnesium bromide, hence two equivalents of this Grignard reagent and subsequent isomerisation provided **306** as the sole product. The ring-closing metathesis step suffered in yield, potentially due to chelation of the naked phenol causing catalyst poisoning,[114] but the synthesis of bicyclic precursor **289** was nonetheless completed in 35% yield.

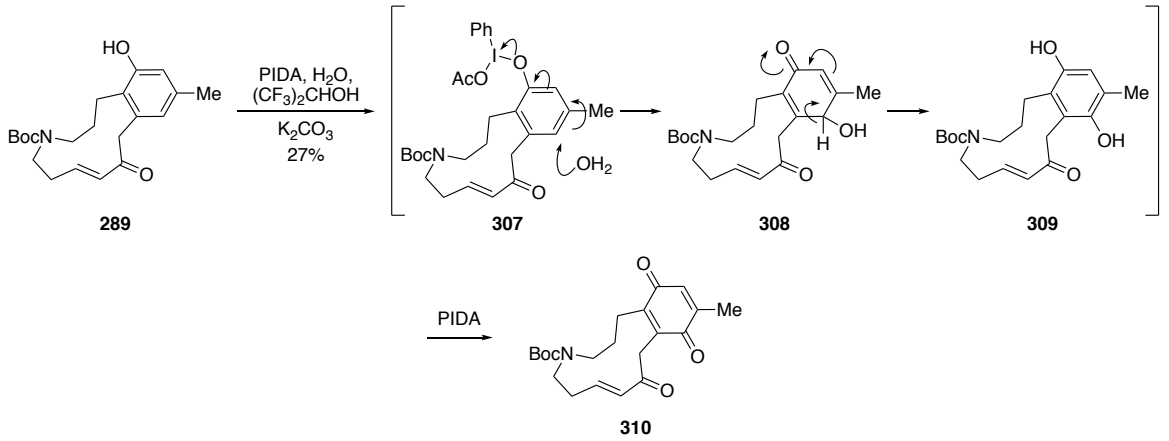


Scheme 2.37 Synthesis of the unprotected bicyclic phenol **289**.

*2.4.2.1 Transannular Oxidative Addition Attempts on **289***

In order to probe the oxidation of phenol **289**, the substrate was subjected to PIDA in the presence of water as a nucleophile (Scheme 2.38). Once again, it was found that the use of HFIP as solvent was required to effect conversion of the starting material. Two equivalents of potassium carbonate were added to the reaction mixture as a buffer to prevent deprotection of the Boc group due to acetic acid released in the course of the reaction.

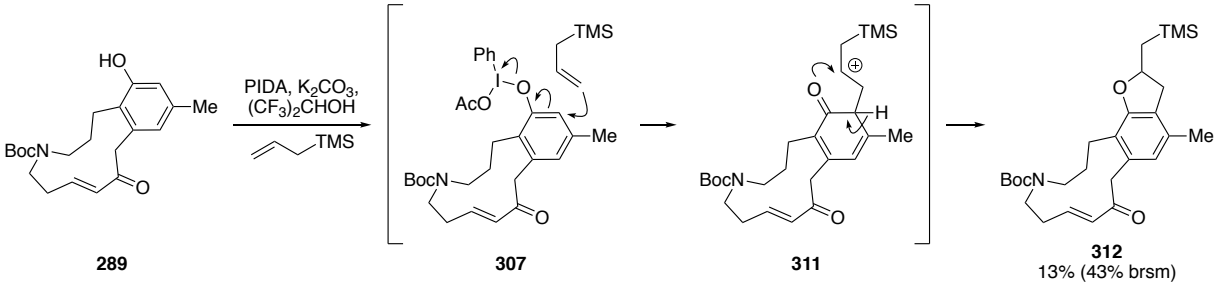
In the presence of water, the oxidised intermediate **307** underwent nucleophilic attack at the *para*-position to generate hydroquinone **309**. A second oxidation then yielded 1,4-benzoquinone **310**.[115]



Scheme 2.38 Oxidation of **289** in the presence of water as a nucleophile.

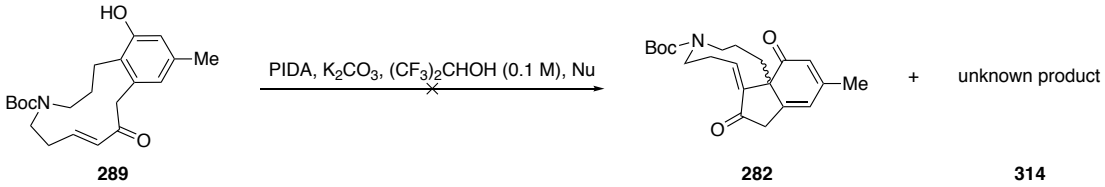
Encouraged by oxidised product **310**, we next subjected **289** to the oxidation in the presence of a known carbon nucleophile, *i.e.* allyltrimethylsilane (Scheme 2.39).[116] A [3+2] product **312** was

observed as expected from work by Canesi *et al.*,[116] confirming the formation of an oxidised intermediate that could be trapped with a nucleophile.



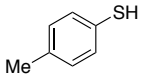
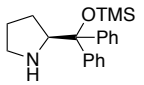
Scheme 2.39 Oxidation of **289** in the presence of allyltrimethylsilane as a nucleophile.

Bicyclic substrate **289** was next subjected to PIDA in HFIP in the presence of nucleophiles known to facilitate the intramolecular Rauhut-Currier reaction (Table 2.7). Triphenylphosphine (entry 1) and tributylphosphine[117] (entry 2) both caused extensive decomposition of the starting material and the PIDA reagent, although the latter also gave trace amounts of an unknown product **314**. Likewise, only decomposition was observed in the presence of 4-methylbenzenethiol (entry 3). When proline-derived catalyst **313** was used (entry 4), alongside decomposition, we again observed trace amounts of the unknown product **314**.



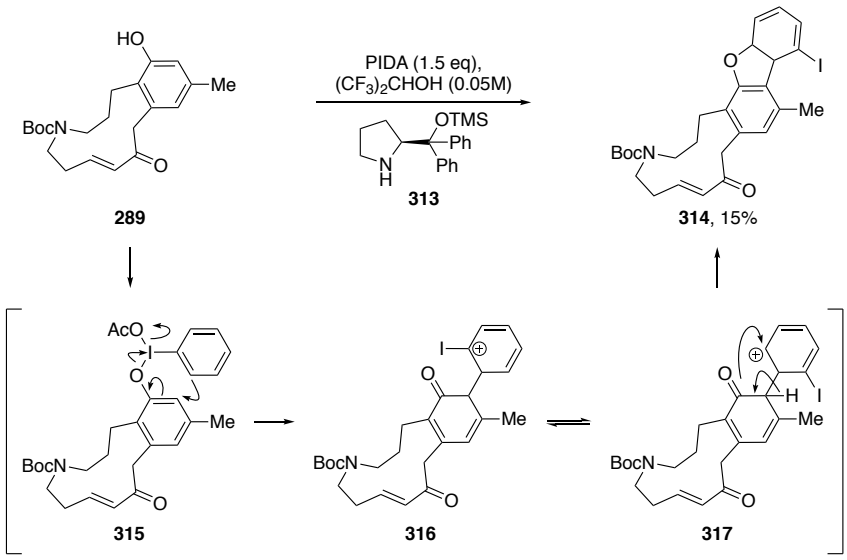
289 282 314

Table 2.7 Testing the oxidative transannular Rauhut-Currier reaction with various nucleophiles.

Entry	Nu	Remarks
1	PPh_3	Decomposition
2	*n*-Bu_3P	Decomposition and **314** (trace)
3		Decomposition
4	 **313**	**289** (5%), **314** (trace) and decomposition

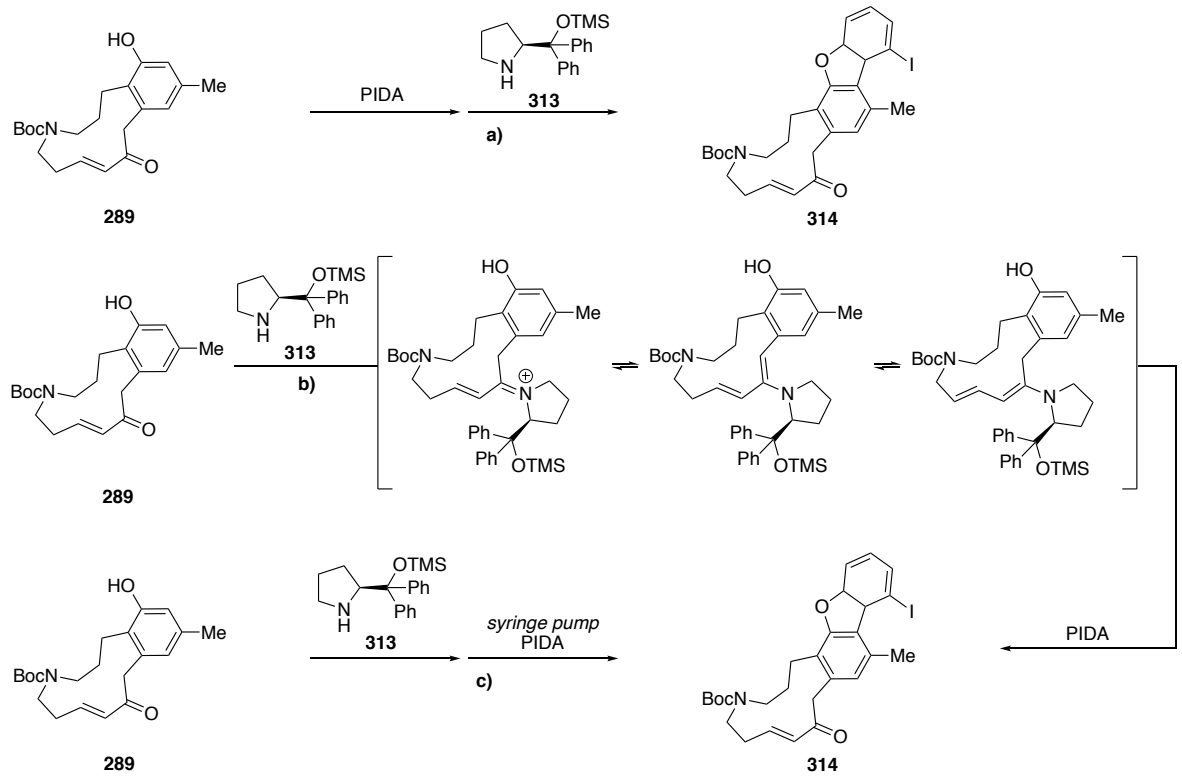
All reactions were carried out at room temperature until complete consumption of the starting material was observed by TLC analysis.

In the presence of **313**, and with a reduced concentration of 0.05 M with respect to starting material **289**, a sufficient amount of **314** was isolated to allow full characterisation (Scheme 2.40, see Section 6.2 for full structural data). A proposed mechanism for the formation of **314** was suggested: oxidation of starting material **289** in the presence of PIDA might facilitate a rearrangement to give intermediate **316** (for a discussion of iodonio-Claisen rearrangement, see Appendix 4),[118] and subsequent rearomatisation followed by attack at the oxidised oxygen centre[119] then formed the tetracycle **314**.



Scheme 2.40 Proposed mechanism for the formation of **314**.

All reactions in Table 2.7 were conducted using procedure a): to a solution of **289** dissolved in $(CH_3)_2CHOH$ was added PIDA, and the reaction mixture was stirred under argon until the yellow solution turned deep red (2 to 3 minutes), before addition of the nucleophile into the reaction vessel (Scheme 2.41, a)). We thus hoped to suppress the formation of **314** by varying the reaction procedure. Since oxidised intermediate **315** was formed almost instantaneously upon the addition of PIDA, we hypothesised that by first stirring the starting material with catalyst **313** (procedure b), we could pre-form the enamine, which should be poised for addition into the cationic species. Slow addition of a solution of PIDA in HFIP using a syringe pump after the enamine formation (procedure c) was also examined, with the hope to prevent the S_EAr reaction. Unfortunately, these efforts were to no avail since **314** was immediately formed in the presence of PIDA.



Scheme 2.41 Unsuccessful attempts to suppress the formation of **314** by changing the reaction procedure.

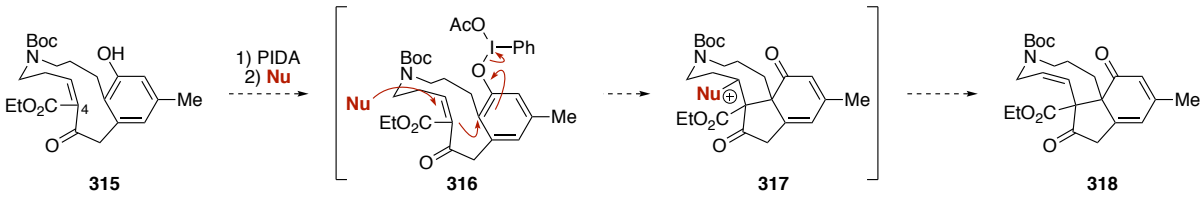
The inability to 'tune' substrate **289** towards the desired reactivity prompted us to investigate alternative substrates that could give rise to the 6-5-9 fawcettimine core using this oxidative approach.

Chapter 3. Synthesis of Alternative Substrates

3.1. Alternative Approaches to the Transannular Oxidative Dearomatisation

3.1.1. A Different Rauhut-Currier Substrate

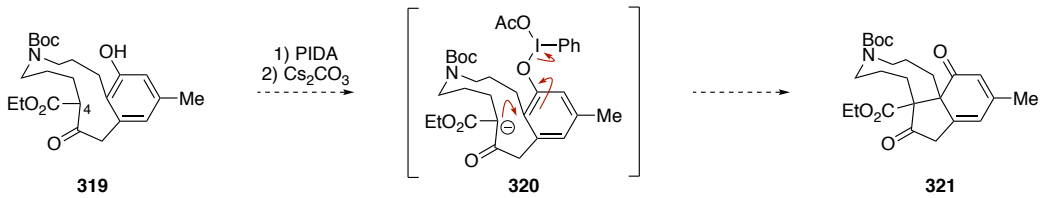
Whilst oxidation of phenolic substrate **289** was possible, no intramolecular nucleophilic attack into the cationic intermediate species was observed. Typical intramolecular Rauhut-Currier reactions initiated by a nucleophilic attack at an unactivated enone require either extended reaction time (> 12 h), elevated temperature (> 40 °C), or a combination of both.[41] With the hope that increased rate of the initial nucleophilic attack would facilitate the addition of the olefin to the oxidised phenol intermediate **316**, we designed substrate **315** with an electron withdrawing group at C4 to, hopefully, form tricycle **318** (Scheme 3.1).



Scheme 3.1 Modified substrate **315** to increase the rate of nucleophilic attack into olefin **316**.

3.1.2. A 1,3-Dicarbonyl Substrate

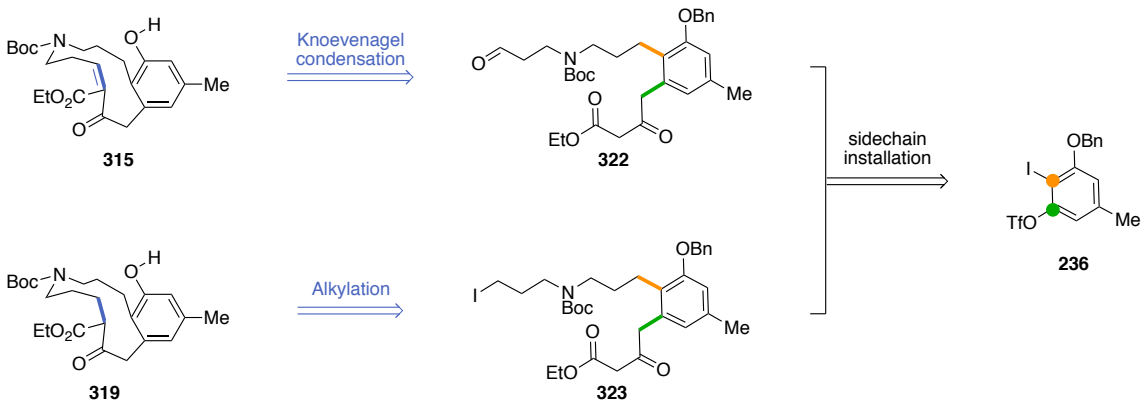
Another strategy to allow a transannular attack into an oxidised phenol intermediate such as **320** would be an enolate addition by deprotonation at C4. By introducing the 1,3-dicarbonyl moiety in **319**, a mild base such as cesium carbonate could effect the formation of the tricyclic core **321** (Scheme 3.2).[120,121]



Scheme 3.2 Proposed formation of tricycle **321** by oxidative transannular enolate addition of **319**.

3.2. Retrosynthetic Analysis for the Alternative Substrates

Using similar retrosynthetic analysis as the previous substrates, bicycles **315** and **319** could be formed from an appropriate macrocyclisation strategy (Scheme 3.3). A Knoevenagel condensation of 1,3-dicarbonyl **322** could yield **315**, whereas an alkylation of alkyl iodide **323** could furnish **319**. The two sidechains in **322** and **323** could come from starting material **236**.



Scheme 3.3 Retrosynthetic analysis of bicyclic substrates **315** and **319**.

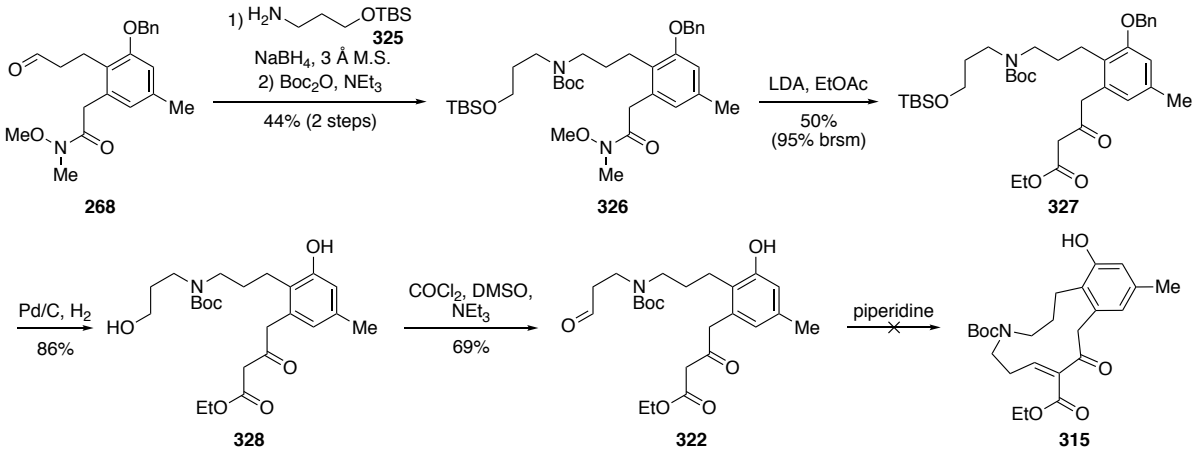
3.3. Synthesis of Alternative Substrates

3.3.1. Synthesis of Substrate 315

The synthesis of substrate **315** commenced with aldehyde **268** (Scheme 3.4), whose synthesis is described in Scheme 2.24. Chain extension of **268** started with a reductive amination in the presence of **325** and sodium borohydride using the *two-step* protocol[83] to yield the corresponding amine, which was protected with *tert*-butylcarbonate to give **326** in 44% yield over two steps. The 1,3-dicarbonyl moiety was then introduced by an enolate addition into Weinreb amide **326** to form **327** in 50% yield

(complete conversion of starting material **326** could not be achieved, even upon addition of 2.3 equivalents of the enolate). Next, deprotection of both ether groups were achieved by hydrogenation to give primary alcohol **328**.[122] Oxidation to form aldehyde **322** was carried out under Swern conditions.

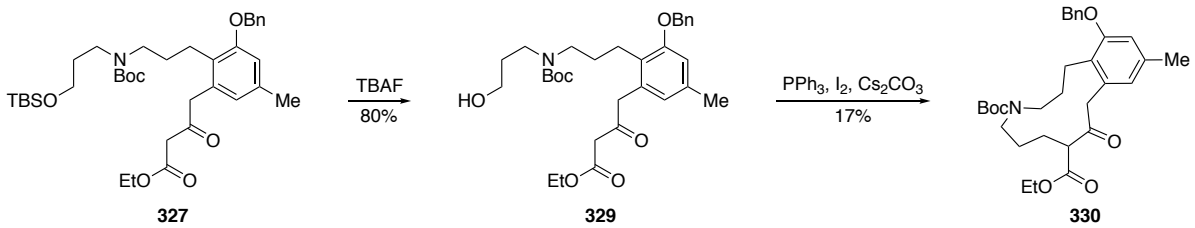
Finally, formation of the macrocycle **315** was attempted *via* a Knoevenagel condensation in the presence of piperidine, but even under high dilution at 0.007 M, only polymeric products were observed by NMR. Perhaps having an unprotected phenol in the presence of an aldehyde in **322** was problematic, but we had, unfortunately, exhausted the material at this stage to conduct further studies.



Schcme 3.4 Synthesis of substrate **315**.

3.3.2. Synthesis of 1,3-Dicarbonyl 319

The synthetic route towards **319** started with protected alcohol **327** (Scheme 3.5). Removal of the *tert*-butyldimethylsilyl ether was achieved by treatment with *tert*-butylammonium fluoride. Next, macrocyclisation of 1,3-dicarbonyl **329** was effected by an Appel/alkylation sequence[123] to afford benzyl ether **330** in 17% yield.



Scheme 3.5 Synthesis of substrate **330**.

A final benzyl-deprotection of **330** would complete the synthesis of bicyclic substrate **319** (Table 3.1). However, under hydrogenation conditions at room temperature (entry 1), no conversion was observed. Warming the reaction mixture to 40 °C (entry 2) for 48 h gave small amount of product **319**. Switching solvents (entries 3 to 4) did not yield any products, with only returned starting material and decomposition observed. These results disappointingly prevented access to **319** and further studies on this substrate.

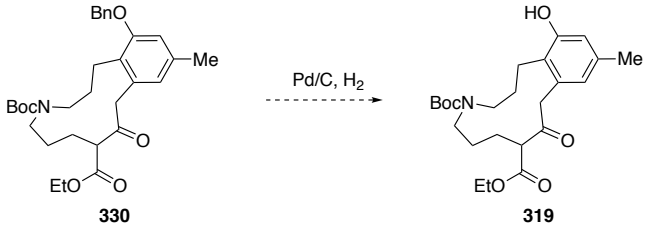


Table 3.1 Conditions tested for the deprotection of benzyl ether **330**.

Entry	Solvent	Temp. (°C)	Time (h)	Remarks
1	EtOAc	RT	18	**330** recovered
2	EtOAc	40	48	**319** (23%, 1 mg)
3	MeOH	40	24	**330** recovered
4	MeOH	50	48	**330** recovered

Chapter 4. Conclusion and Future Work

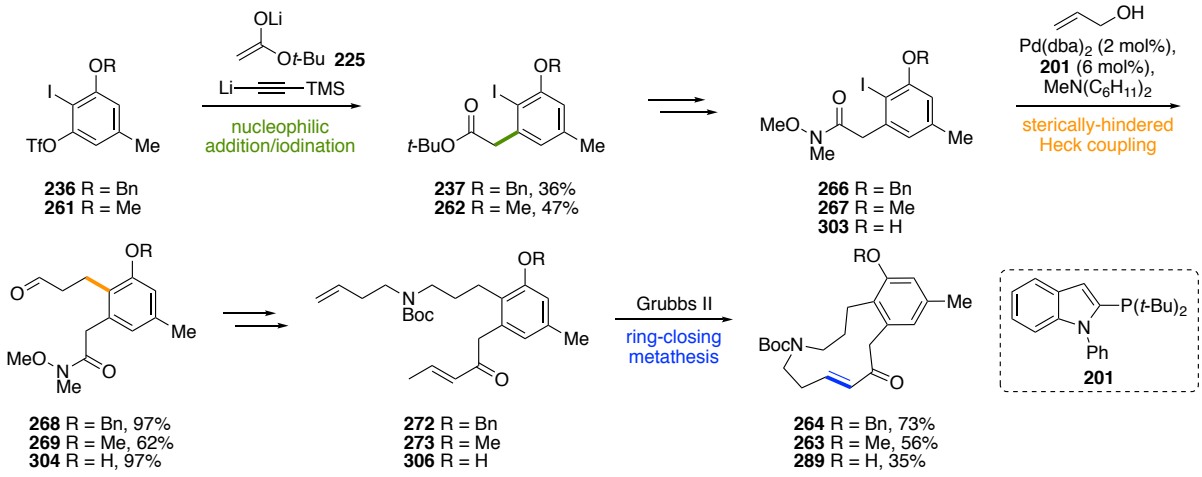
4.1. Conclusion

4.1.1. Transannular Oxidative Dearomatisation

4.1.1.1 Substrate Synthesis

In summary, a short substrate synthesis has been achieved (Scheme 4.1). Starting materials **236** and **261** could be made on multi-gram scale from commercially available orcinol monohydrate, from which bicycles **264**, **263** and **289** were synthesised in eight steps.

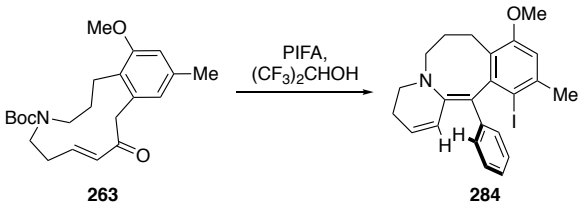
Key transformations included a nucleophilic addition/iodination of aryne precursors **236** and **261**; a sterically-hindered Heck coupling/isomerisation of aryl iodides **266**, **267** and **303** enabled by ligand **201**; and a ring-closing metathesis of **272**, **273** and **306** to assemble the 12-membered ring of bicyclic substrates **264**, **263** and **289**, respectively.



Scheme 4.1 Synthesis of bicyclic substrates **264**, **263** and **289**.

4.1.1.2 Products from the Oxidative Dearomatisations

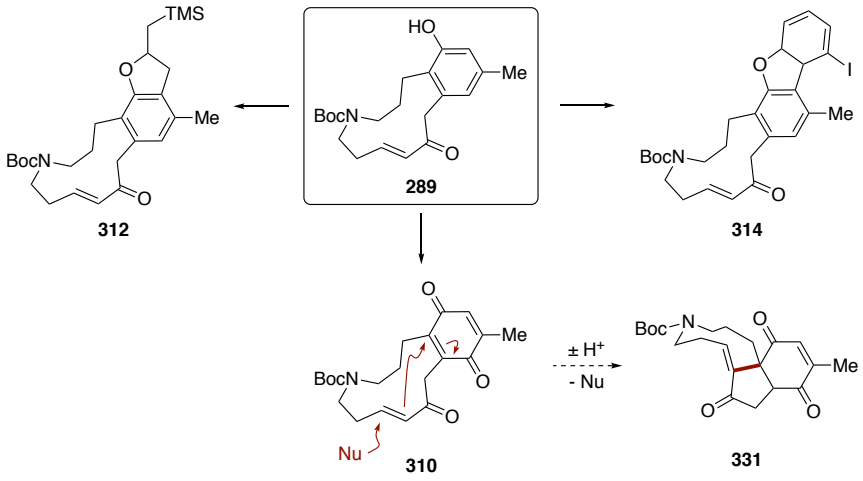
Oxidation of anisole substrate **263** gave tricyclic rearranged product **284**, whose structure has been confirmed by 2D NMR (Scheme 4.2).



Scheme 4.2 Rearranged product from the oxidative dearomatisation of **263**.

Substrate **289**, on the other hand, generated a λ^3-iodane intermediate in the presence of PIDA, which was trapped by water to generate 1,4-benzoquinone **310**, or allyltrimethylsilane to give dihydrobenzofuran **312** (Scheme 4.3, for mechanisms see Section 2.4.2.1). In the absence of nucleophiles, tetracycle **314** was isolated *via* a currently unknown mechanism.

1,4-Benzoquinone **310** could be susceptible towards a Rauhut-Currier reaction to yield tricyclic core **331**, and this avenue will be part of our future work.

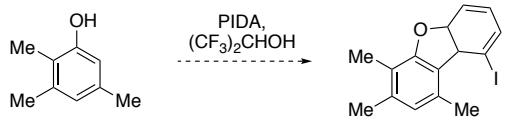


Scheme 4.3 Products from the oxidative dearomatisations of **289**.

4.2. Future Work

4.2.1. Investigations into the Dihydrobenzofuran Formation

The curious formation of dihydrobenzofuran product **314** requires detailed studies. Substituted phenol **332** could be subjected to the reaction conditions to investigate the formation of product **333** (Scheme 4.4).



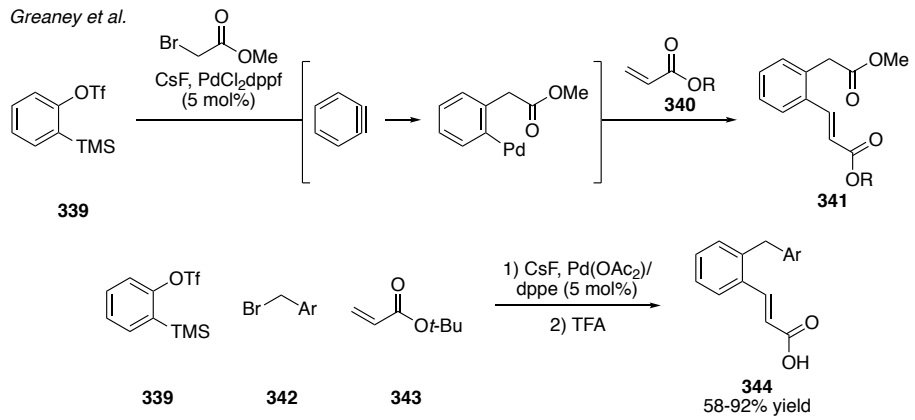
332 **333**

Scheme 4.4 Substituted phenol **332** as test substrate for the dihydrobenzofuran formation.

4.2.2. A Shorter Synthesis Towards the 6-5-9 Tricyclic Core

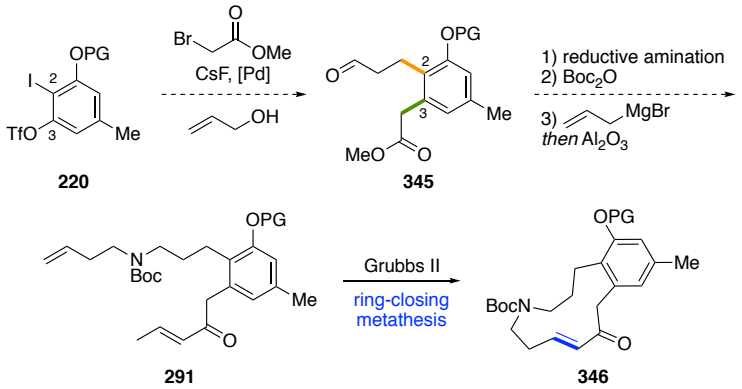
From the outset, we were aware of the need for a concise and reliable synthesis to yield ample quantities of bicyclic substrate **289** for investigating the oxidative dearomatisation step. As outlined in Section 2.3.1, the three-component coupling of benzyne has been explored in the literature,[69-73,124-133] and if successfully incorporated into our route design, could simplify the synthesis. The majority of the reported combinations of nucleophiles and electrophiles, however, are not applicable to our system, with limited examples of regiocontrol.

Nonetheless, a particular report by Greaney and co-workers[71] attracted our attention, whose domino intermolecular carbopalladation methodology yielded a range of di-substituted arenes **341** and **344** (Scheme 4.5).



Scheme 4.5 Three-component couplings of benzyne.

We envisaged an application of such methodology to functionalise aryne precursor **220**, thus introducing two carbon-carbon bonds at C2 and C3 in one operational step (Scheme 4.6). The presence of the ether group at C1 could induce regioselectivity.[73] Elaboration of both sidechains of **345** using previously developed chemistry, followed by a ring-closing metathesis would yield bicyclic substrate **346** in five steps from starting material **220**, instead of eight steps as in the current synthesis.



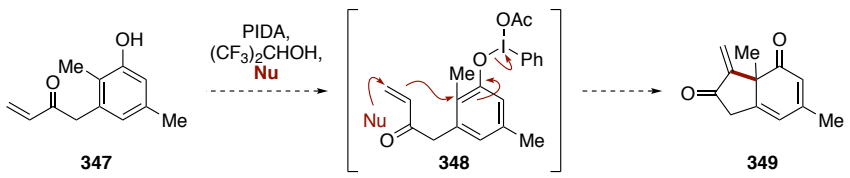
Scheme 4.6 Proposed three-component coupling of benzyne precursor **220** and shortened synthetic route towards bicyclic substrate **346**.

4.2.3. Phenolic Umpolung

4.2.3.1 Model Substrate

Despite numerous examples of nucleophilic alkenyl trapping of dearomatised phenols (see Section 1.6.2), the transformation has commonly been carried out stepwise: *i.e.* dearomatisation of phenols, followed by nucleophilic addition. A model substrate such as **347** would therefore be useful for studying the transformations in tandem (Scheme 4.7).

In bicyclic substrate **289**, the installation of the macrocycle was hoped to bias *ortho*-addition by pre-organisation, combined with electronic argument of δ^+ being concentrated at the more substituted *ortho*-position. The lack of macrocyclic constraints in model substrate **347** should help determine the innate regioselectivity of intermediate **348** towards nucleophilic addition.



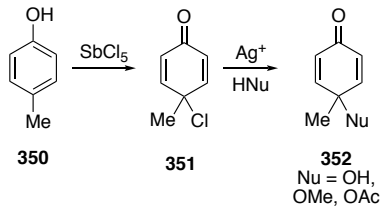
Scheme 4.7 Model substrate **347** to study the oxidative Rauhut-Currier addition.

4.2.3.2 Alternative Oxidants

Besides hypervalent iodine reagents, phenols can also be oxidised by a range of metal salts followed by nucleophilic trapping to generate substituted cyclohexadienones. Most of these methodologies,

however, require *para*-substituted phenols and/or heavily oxygenated arenes. The oxidised intermediates are commonly trapped by nucleophilic solvents, with limited examples of carbon nucleophiles. Most examples with carbon-carbon bond formations have focussed on dimerisation, intramolecular Diels-Alder, and biaryl couplings. Finally, the toxicity of these reagents had prompted our initial decision to focus on hypervalent iodine reagents.

An example of phenolic dearomatisation by metal salts is the use of antimony pentachloride to generate **351** from *para*-cresol **350**. Subsequent silver-induced solvolysis then furnishes cyclohexadienone **352** (Scheme 4.8).[134]

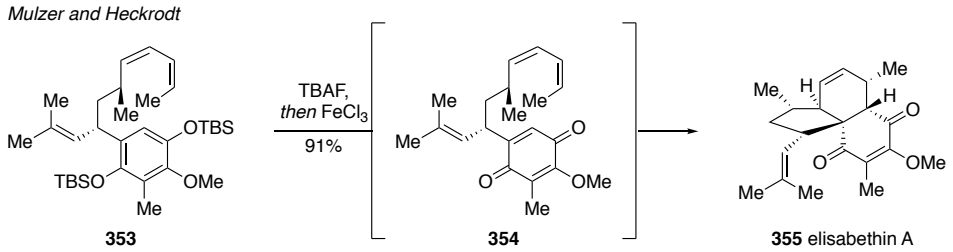


Scheme 4.8 Dearomatisation of *para*-cresol using $SbCl_5$.

Thallium(III) nitrate has also been reported to oxidise phenols into *p*-benzoquinones *via ipso*-thallation.[135] In the presence of thallium(III) trifluoroacetate, phenols can undergo oxidative dimerisation, or intramolecular oxidative coupling.[136]

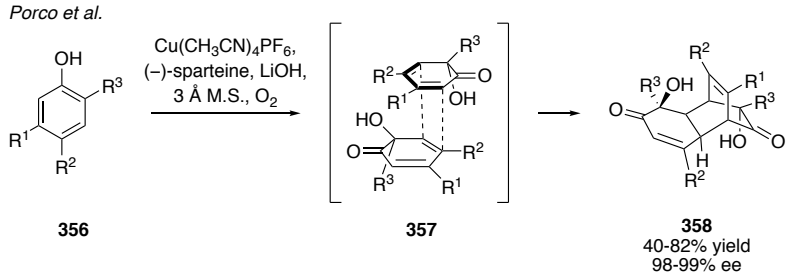
The oxidation of *para*-substituted phenol with peroxides has also been reported in the presence of $RuCl_2(PPh_3)_3$, and was hypothesised to proceed *via* a phenoxy radical-Ru(III)(OH) intermediate.[137]

In 1981, Miller *et al*. reported the use of supported reagent $FeCl_3/SiO_2$ for biaryl intramolecular and intermolecular coupling, and formation of *p*-benzoquinones from disiloxy aromatics.[138] Iron-catalysed oxidation of phenols to *p*-benzoquinones has also been reported.[139] The utility of this reagent has been further demonstrated by Mulzer *et al*. in total synthesis: deprotection and oxidation of **353** in the presence of $FeCl_3$ triggered an intramolecular Diels-Alder (IMDA) reaction to form the fused tricyclic core of elisabethin A **355** (Scheme 4.9).[140]



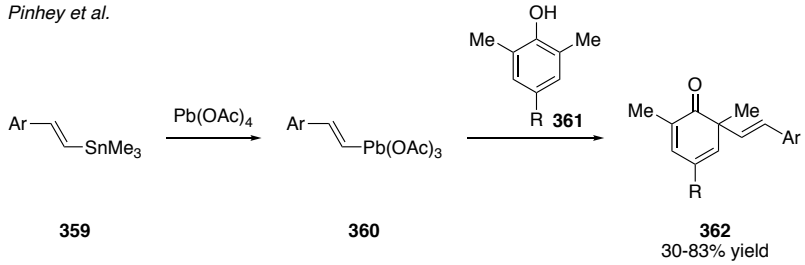
Scheme 4.9 $FeCl_3$-mediated biomimetic IMDA in the total synthesis of elisabethin A **355**.

A strategy towards bicycle[2.2.2]octenone was described by Porco and co-workers in their 2008 report, wherein a copper-mediated oxidative dearomatisation of substituted phenol **356** initiated a [4+2] dimerisation to generate complex scaffolds in one operational step (Scheme 4.10).[141] The combination of enolate pre-formation with LiOH and treatment with the $[(-)\text{-sparteine}]_2Cu_2O_2\text{-}(PF_6)_2$ complex gave product **358** in good yields and enantioselectivities. The authors noted the necessity of *para*-substituents R^2 to avoid biaryl coupling.



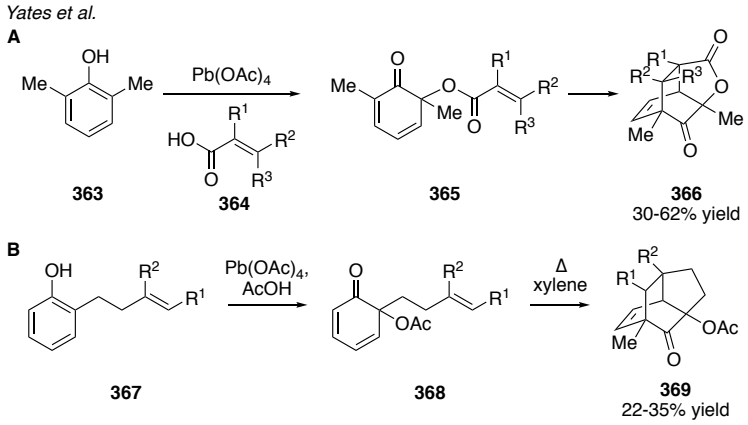
Scheme 4.10 Copper-mediated oxidative dearomatisation/[4+2] cascade developed by the group of Porco.

From their discovery that vinyllead(IV) triacetates behave as vinyl cations, Pinhey and co-workers developed a dearomatisation of phenol **361** in the presence of vinyl stannanes **359** and lead acetate to yield substituted quinones **362** (Scheme 4.11).[142]



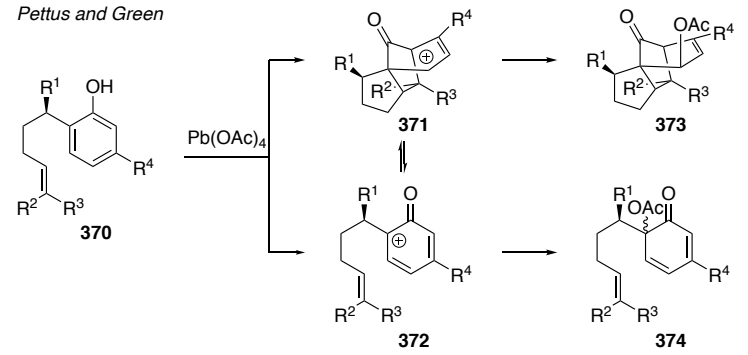
Scheme 4.11 Dearomatisation of substituted phenol **361** in the presence of vinyllead acetate.

The treatment of *ortho*- and *para*-substituted phenols with lead(IV) acetate to form cyclohexadienones is called the Wessely oxidation.[143] The group of Yates have exploited this transformation in tandem with an intramolecular Diels-Alder reaction to generate complex structures, namely, bicycle[2.2.2]octenones **366** and isotwistanes **369** (Scheme 4.12).[144]



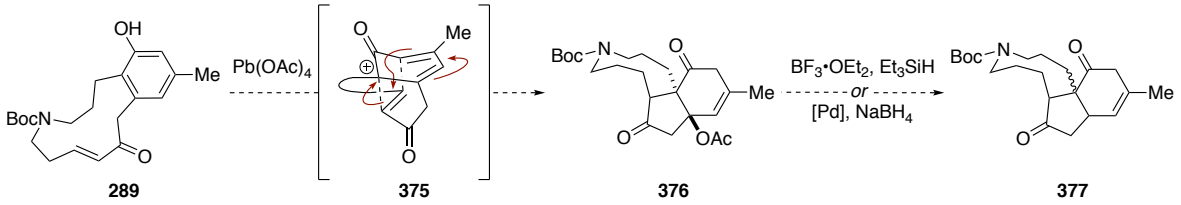
Scheme 4.12 Tandem Wessely oxidation/IMDA to generate A) bicycle[2.2.2]octenones **366** and B) isotwistanes **369**.

More recently, Pettus and Green reported a [5+2] cycloaddition to synthesise α-cedrene, α-pipitzol, and *sec*-cedrenol (Scheme 4.13).[145] The reaction proceeded *via* phenoxonium intermediate **372**, whose acetate trapping to yield side-product **374** was minimised by lowering the reaction to –40 °C. The product **373** was formed as a single diastereoisomer, suggesting the role of the benzylic stereocentre in controlling the ring formation.



Scheme 4.13 Lead(IV) acetate-mediated [5+2] cycloaddition.

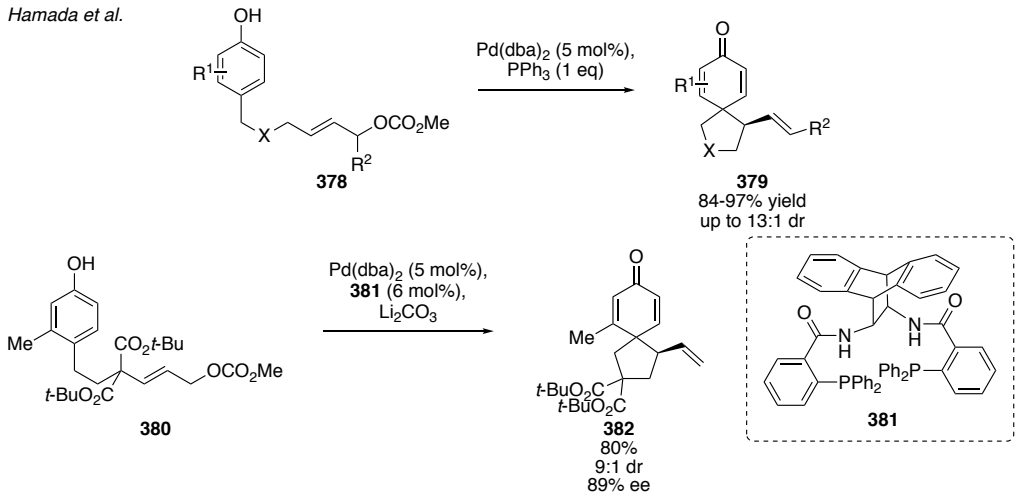
The tandem Wessely oxidation/cycloaddition cascade could potentially be applied to substrate **289** to generate tricyclic core **376** (Scheme 4.14). The flexible macrocycle and the *E*-configuration of the enone should allow formation of the reactive conformation **375**. Reduction of the OAc group would then furnish the 6-5-9 core **377**.



Scheme 4.14 Potential application of the Wessely oxidation/cycloaddition cascade to our system.

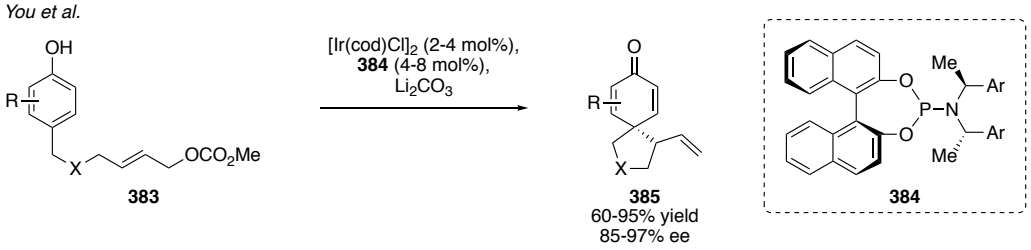
4.2.4. Allylative Dearomatisation

Besides 'phenolic umpolung', dearomatisation of phenols can also be achieved by allylative methods.[146] To this end, an *ipso*-Friedel Crafts alkylation of **378** has been developed by the group of Hamada to synthesise a range of spiro[4.5]cyclohexadienones **379** (Scheme 4.15).[147] The reaction proceeded *via* a π-allylpalladium species, and deprotonation of the phenol was found to be important in increasing the nucleophilicity at the *para*-position. One enantioselective example described the formation of product **382** in good yield, dr and enantioselectively in the presence of ligand **381**.



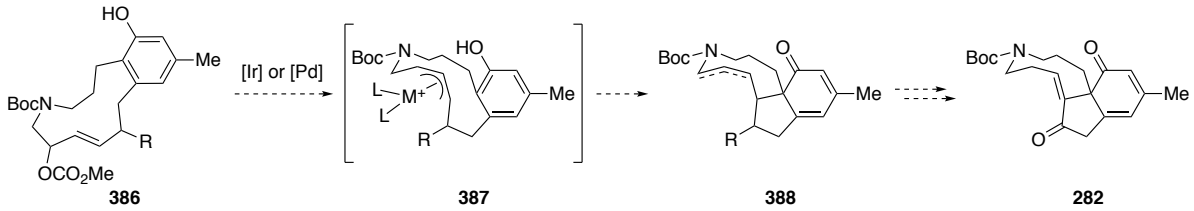
Scheme 4.15 Intramolecular allylative dearomatisation of phenol.

In 2011, You and co-workers reported a similar transformation using iridium catalysis (Scheme 4.16).[148] Here, phosphoramidite ligand **384** was found to generate spirocyclohexadienone product **385** in good yields and enantioselectivities.



Scheme 4.16 Asymmetric intramolecular allylative dearomatisation of phenol.

The success of this intramolecular transformation may offer another avenue towards our desired 6-5-9 tricyclic core **282**. We envisaged allylcarbonate **386** to undergo oxidative addition, forming π-allylmetal species **387** that could be susceptible to phenolic alkylation to yield the 6-5-9 core **388**, a precursor to tricycle **282** (Scheme 4.17).



Scheme 4.17 Proposed transannular allylative dearomatisation to form the 6-5-9 tricyclic core.

Chapter 5. Appendices

5.1. Appendix 1

5.1.1. Conditions Tested for Ring-Closing Metathesis

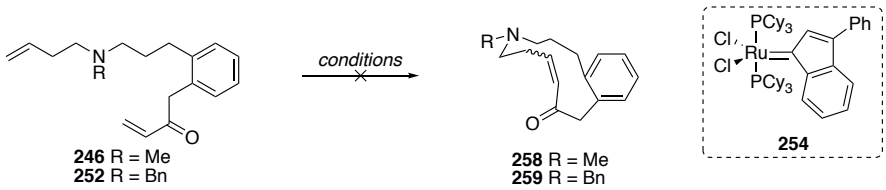


Table 5.1 Conditions screened for the ring-closing metathesis of model substrates **246** and **252**.

Entry	SM	[Ru]	Acid	Concentration (M)	Remarks
1	**246**	Grubbs II	HCl	0.008	SM + decomposition
2	**246**	Grubbs II	HCl	0.01	SM + decomposition
3	**246**	Grubbs II	Ti(O*i*-Pr)$_4$	0.005	Decomposition
4	**252**	Grubbs II	Ti(O*i*-Pr)$_4$	0.008	Decomposition
5[a]	**252**	Grubbs II	HCl	0.002	SM
6[a]	**252**	Grubbs II	Ti(O*i*-Pr)$_4$	0.002	SM
7	**252**	**254**	HCl	0.002	Decomposition
8[a]	**252**	**254**	HCl	0.002	SM
9[a]	**252**	**254**	Ti(O*i*-Pr)$_4$	0.002	SM
10	**252**	Grubbs I	Ti(O*i*-Pr)$_4$	0.002	SM
11	**252**	Grubbs I	CSA	0.002	SM
12	**252**	Grubbs I	TFA	0.002	SM
13[a]	**252**	Grubbs I	HCl	0.002	SM
14[a]	**252**	Grubbs I	Ti(O*i*-Pr)$_4$	0.005	SM

Reactions were carried out in freshly freeze-pump thawed CH_2Cl_2, at 40 °C for 24 h unless otherwise stated; [a] reactions were carried out in freshly freeze-pump thawed toluene, at 110 °C for 24 h.

5.2. Appendix 2

5.2.1. Conditions Tested for Csp^3-Csp^2 Coupling

5.2.1.1 Intitial Screening on Iodobenzene

As mentioned in Section 2.4.1.1, we attempted to install the top sidechain in one operational step *via* a Csp^3-Csp^2 cross-coupling. In order to study this transformation, Negishi (Table 5.2, entries 1 to 3) and cross-electrophile coupling conditions (entries 4 to 6) were initially tested on iodobenzene.

In the presence of $NiCl_2(PPh_3)_2$ and zinc dust (entry 1), only decomposition of the starting material was observed. When we switched to zinc powder (entry 2), starting material was recovered in 62% yield, with both alkyl bromide **290** and proto-debrominated species **293** isolated, indicating formation of the alkylzinc bromide species. However, no coupling product **390** was observed. Palladium catalysis (entry 3) showed improved starting material conversion but, again, no desired product **390** was observed.

Initial results obtained using cross-electrophile coupling conditions were not promising (entry 4), however, when manganese was used as the reducing agent[149] (entry 5), the desired product **390** was obtained as an inseparable 1:6 mixture with **293** (37% combined yield). Here, TMSCl was used as an additive to remove the tightly bound metal-oxide layer on the surface of the metal.[150] Finally, we were delighted to find a dual ligand system (entry 6) which delivered **390** in 46% yield. Experimental data from Weix *et al*. suggested two distinct catalysis modes in this transformation to explain the need for both ligands, but further mechanistic details were not discussed.[151]

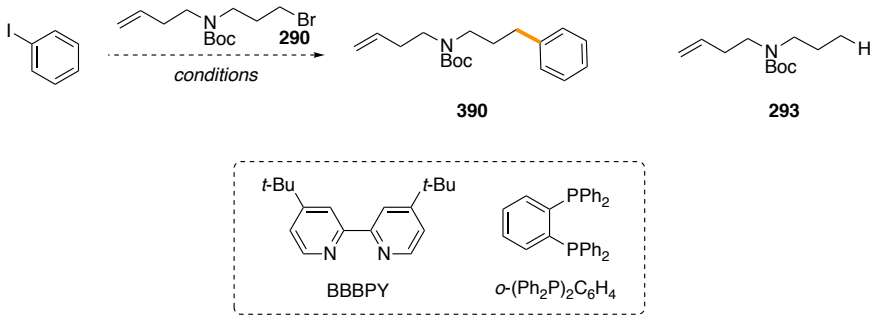


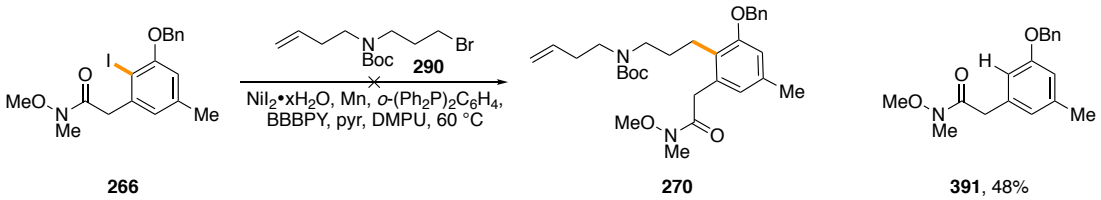
Table 5.2 Conditions screened for the Negishi and cross-electrophile couplings with iodobenzene.

Entry	Catalyst	[M]	Reagents	390	SM	290/293
1[a]	$NiCl_2(PPh_3)_2$	Zn dust	I_2	decomposition	-	-
2[a]	$NiCl_2(PPh_3)_2$	Zn powder	I_2	-	62%	**290** (9%), **293** (8%)
3[a]	$Pd(PPh_3)_4$	Zn powder	I_2	-	20%	**293** (14%)
4[b]	(bpy)NiI_2	Zn dust	NaI, pyridine	decomposition	-	-
5[b]	(bpy)NiI_2	Mn	NaI, TMSCl	37% (1:6 mixture **390**:**293**, 4% yield based on ^{1}H NMR)	-	-
6[c]	NiI_2•xH_2O	Mn	BBBPY, *o*-$(Ph_2P)_2C_6H_4$, pyridine	43%	-	-

Zn dust and powder were activated by heating at reflux (60 °C) in a solution of dibromoethane and TMSCl in THF for 5 min; [a] reactions were carried out in DMA at rt for 3 h; [b] reactions were carried out in DMPU at rt for 3 h; [c] reactions were carried out in DMPU at 60 °C for 3 h.

*5.2.1.2 Attempted Cross-Electrophile Coupling with Aryl Iodide **266***

Despite the positive results obtained with iodobenzene, the above conditions could not be applied to our substrate **266** to form **270** in one operational step. Under these reaction conditions, only proto-deiodinated product **391** were obtained in 48% yield.



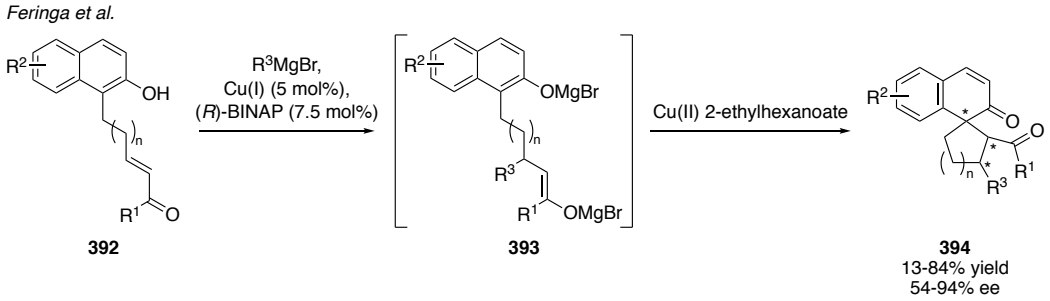
Scheme 5.1 Unsuccessful cross-electrophile coupling with **266**.

5.3. Appendix 3

5.3.1. Alternative Phenol Dearomatisation Methods

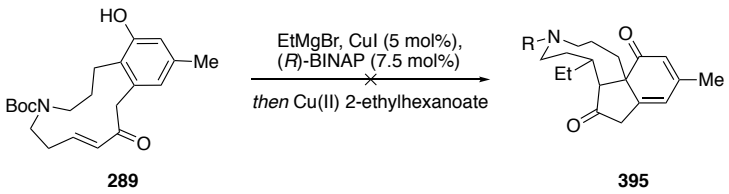
5.3.1.1 Asymmetric Conjugate Addition/Oxidative Dearomatisation of Naphthols

In 2011, the group of Feringa reported an asymmetric conjugate addition/oxidative dearomatisation of naphthols to generate enantioenriched spirocyclic five- or six-membered ring **394** with three contiguous stereocentres (Scheme 5.2).[152] The reaction commenced with the conjugate addition of a Grignard reagent to **392** to form intermediate **393**, whose oxidation with a copper(II) source generated the desired product **394** *via* a currently unknown mechanism.



Scheme 5.2 Asymmetric conjugate addition/oxidative dearomatisation of naphthols.

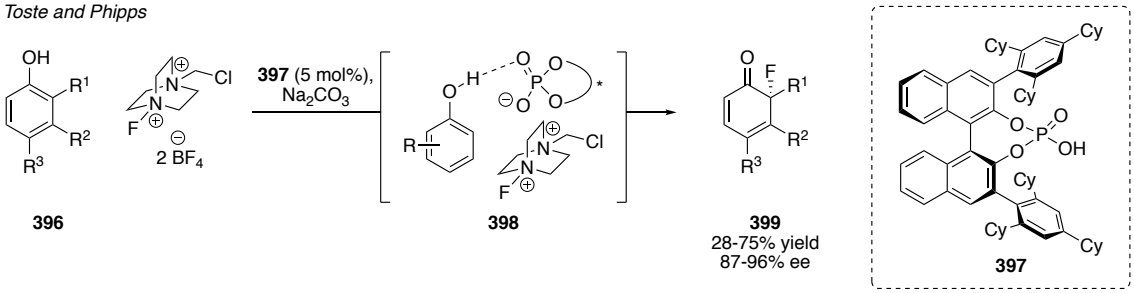
We were attracted to the carbon-carbon bond formation between the α-position of a carbonyl and the *ortho*-position of the naphthol, and thought our system **289** could be activated towards such a transformation to yield tricyclic core **395** (Scheme 5.3). Unfortunately, in our hands, these conditions led to extensive decomposition of the starting material.



Scheme 5.3 Unsuccessful conjugate addition/oxidative dearomatisation of phenol **289**.

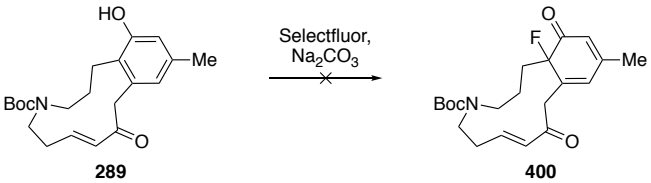
5.3.1.2 Enantioselective Fluorinative Dearomatisation of Phenols

A chiral anion phase transfer catalysis was developed for the enantioselective fluorinative dearomatisation of substituted phenol **396** by Toste and Phipps (Scheme 5.4),[153] whose facial selectivity in the fluorination step was controlled by hydrogen bonding between the chiral phosphate **397**-Selectfluor ion pair with the phenol OH group. Thus, a range of 2,3-di and 2,3,4-trisubstituted phenols were subjected to the reaction conditions to yield cyclohexadienones **399** with good enantioselectivities.



Scheme 5.4 Enantioselective fluorinative dearomatisation of phenols.

We were interested in an alternative method to activate the *ortho*-position of our phenolic system, thus **289** was subjected to racemic fluorinative conditions (Scheme 5.5). Unfortunately even after 48 h, we only recovered 73% of the starting material, with no fluorinated product **400** observed.

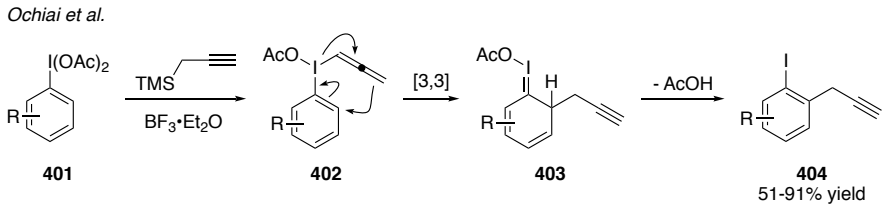


Scheme 5.5 Attempted fluorinative dearomatisation of phenol substrate **289**.

5.4. Appendix 4

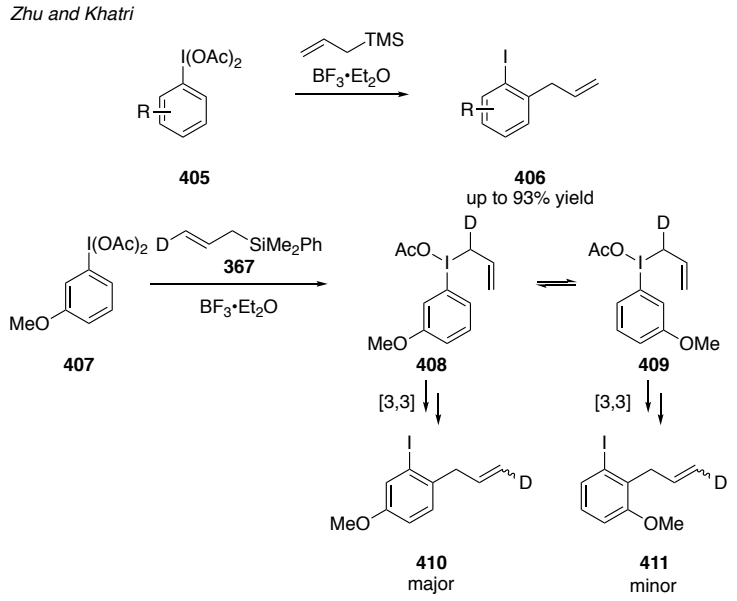
5.4.1. Iodonio-Claisen Rearrangement

The iodonio-Claisen rearrangement was reported by Ochiai in 1991, wherein propargylation of a range of aryliodinanes **401** afforded products **404**, with complete regioselectivity at the *ortho*-position (Scheme 5.6).[154] The mild temperatures (–30 °C to rt) contrasted with typical conditions required for the Claisen rearrangements of the nitrogen and sulfur variants (150 to 250 °C), and were attributed to the low bond energy of the apical I(III)-carbon bond.



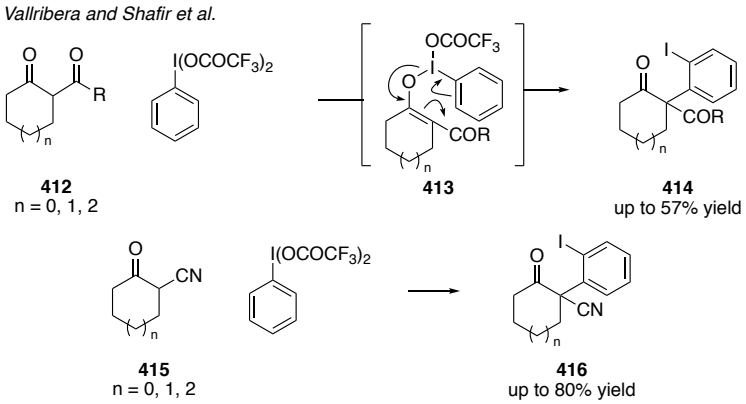
Scheme 5.6 Propargylation of aryliodinanes *via* an iodonio-Claisen rearrangement.

A report by Zhu and Khatri in 2012 described a reductive iodonio-Claisen rearrangement of aromatic λ^3-iodanes **405** and allyltrimethylsilane in the presence of a Lewis acid to form *ortho*-allyliodoarenes **406** (Scheme 5.7). Deuterium labelling experiments of **407** and deuterated dimethylphenylsilane **367** showed the major product to be **410**, with the deuterium fully incorporated at the terminal position, and scrambling of the alkene stereochemistry. The conformational isomer **409** leading to the minor product **411** was hypothesised to be disfavoured due to steric clashing, and electronic effect caused by the methoxy group. The isolation of **410** as the major product was consistent with a [3,3] sigmatropic rearrangement mechanism.



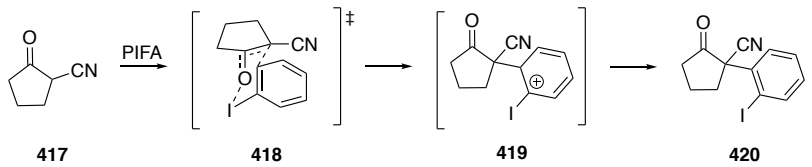
Scheme 5.7 Reductive iodonio-sigmatropic rearrangement and deuterium labelling experiments.

A similar transformation has been adapted to α-arylation of ketone by the group of Vallribera and Shafir (Scheme 5.8).[155] β-keto esters **412** and α-cyanoketones **415** were transformed into the products **414** and **416**, respectively, upon exposure to PIFA.



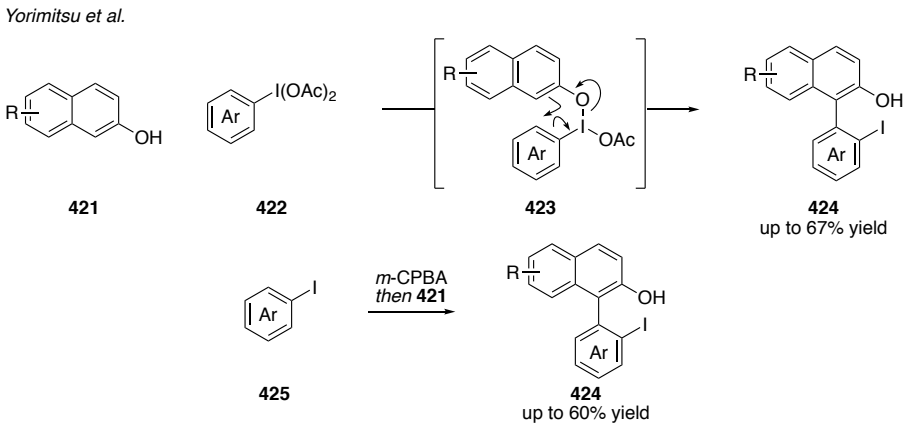
Scheme 5.8 α-arylation of cyclic ketones by PIFA.

In a 2015 report by Shafir *et al*., DFT calculations for the arylation of 2-cyanocyclohexanone **417** supported a [3,3] rearrangement mechanism *via* chair-like transition state **418** leading to cationic species **419** and thus product **420** (Scheme 5.9).[156]



Scheme 5.9 DFT calculations for the arylation of **417** *via* a chair-like transition state.

The iodonio-sigmatropic rearrangement has also been used in a metal-free method to synthesise biaryls, as developed by Yorimitsu *et al*.[157] To this end, a range of binaphthyls **424** were synthesised from naphthol **421** and aryliodanes **422** (Scheme 5.10). A one-pot protocol was also developed wherein iodoarenes **425** were oxidised *in situ* with *m*-CPBA, followed by dehydrogenative coupling with naphthol partners **421** to yield binaphthyls **424**.



Scheme 5.10 Metal-free biaryl synthesis *via* an iodonio-sigmatropic rearrangement.

Chapter 6. Experimental

6.1. General Experimental Procedures

Solvents and Reagents

Acetonitrile (MeCN), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), methanol (MeOH), and tetrahydrofuran (THF) were purified by filtration through activated alumina columns employing the method of Grubbs *et al*.[158] $(CF_3)_2CHOH$ was stored over activated 3 Å molecular sieves for at least seven days and kept under argon.

Water was purified by a Millipore Elix® UV-10 system. Reagents were used directly as supplied by major chemical suppliers, or following purification procedures described by Chai and Armarego.[159] Petroleum ether (pet. ether) refers to the fraction of petroleum ether which boils in the range 40 – 60 °C unless otherwise stated. Brine refers to a saturated aqueous solution of sodium chloride.

Chromatography

Flash column chromatography was carried out using Merck Geduran® Si 60 silica gel (40 – 63 μm particle size). Analytical thin layer chromatography (TLC) was carried out using pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}). Visualisation was achieved with ultraviolet irradiation (254 nm) and staining with aqueous basic $KMnO_4$ solution.

Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopy was carried out using Bruker Avance spectrometers in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference (^{1}H NMR: $CDCl_3$ 7.26 ppm; toluene-d_8 7.01 ppm; MeCN-d_3 2.13 ppm; ^{13}C NMR: $CDCl_3$ 77.16 ppm; toluene-d_8 137.86 ppm; MeCN-d_3 118.26 ppm). Chemical shifts are quoted in ppm, and coupling constants, *J*, are rounded to the nearest 0.1 Hz. Signal patterns are interpreted based on appearance rather than interpretation, and are indicated as: br, broad; s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet. Assignments were determined either on the basis of unambiguous chemical shift

or coupling patterns, 2D NMR experiments (COSY, HSQC, HMBC, NOESY), or by analogy to fully interpreted spectra for structurally related compounds.

Infrared Spectroscopy

Infrared spectra were prepared as neat films and were recorded with a Bruker Tensor 27 FTIR spectrometer using an ATR module.

Mass Spectrometry

Low-resolution mass spectroscopy (MS) was carried out under electrospray ionisation (ESI) using an Agilent 6120 Quadrupole mass spectrometer, or a Waters LCT Premier XE mass spectrometer. High-resolution mass spectroscopy (HRMS) was carried out using Bruker MicroToF mass spectrometer, or on a Thermo Exactive Orbitrap mass spectrometer under ESI or APCI (atmospheric-pressure chemical ionisation) conditions, or an Agilent 7200 Quadrupole Q-ToF mass spectrometer under chemical ionisation (CI) or electron impact ionisation (EI) conditions.

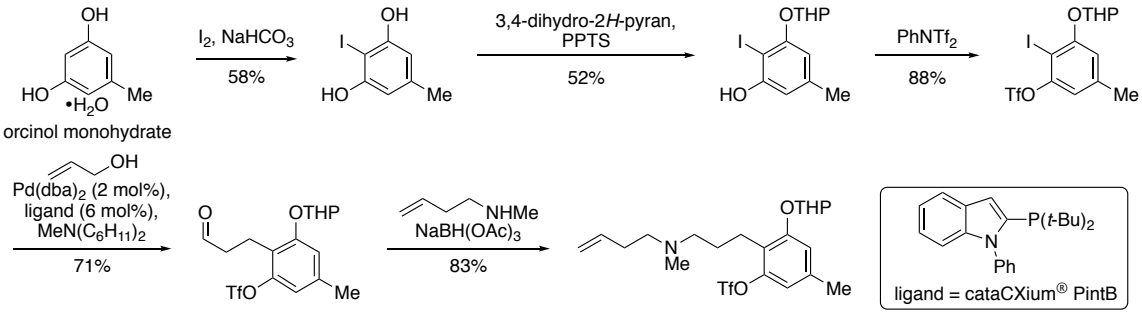
Melting Points

Melting points were determined using a Reichert melting point apparatus and are uncorrected.

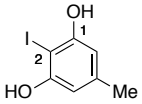
Naming and Numbering of Compounds

Compounds are named according to IUPAC guidelines. The atoms on the compounds are numbered for ease of referencing between similar compounds.

6.2. Experimental Procedures



2-Iodo-5-methylbenzene-1,3-diol (187)



Following a modified procedure from Suzuki *et al.*,[160] to a round-bottomed flask equipped with a stirrer bar was charged a solution of orcinol monohydrate (10.0 g, 70.3 mmol, 1.0 eq) in H_2O (400 mL) and THF (400 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added $NaHCO_3$ (6.00 g, 71.4 mmol, 1.1 eq) portion-wise, and iodine (20.0 g, 78.8 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to rt, and was stirred for further 30 min at rt until complete consumption of the starting material, as indicated by TLC. The reaction was quenched with $Na_2S_2O_3$ (9.00 g), and then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was passed through a plug of silica (eluting with EtOAc, 500 mL), and the eluent was concentrated *in vacuo*. To the residue was added hexane (500 mL), and the mixture was heated at reflux. The clear layer was decanted while hot into a round-bottomed flask, cooled to 0 °C to form crystals, and the solvent was removed by filtration to afford the title compound as a colourless solid (10.3 g, 41.2 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.40 (s, 2H, 2 × Ar*H*), 5.29 (s, 2H, 2 × O*H*), 2.25 (s, 3H, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.3 (*C*1, *C*3), 141.2 (*C*5), 108.4 (*C*4, *C*6), 73.7 (*C*2), 21.3 (*C*H_3).

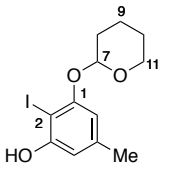
MS (ESI) calcd for $C_7H_6IO_2^-$ $[M-H]^-$ 249.0, found 248.9.

ν_{max} (film)/cm^{-1} 3453, 1587, 1452, 1413, 1342, 1271, 1184, 1045, 1022, 987, 820.

m.p. 100 – 102 °C.

These data are consistent with those previously published for this compound.[160]

2-Iodo-5-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenol (S1)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **187** (9.18 g, 36.7 mmol, 1.0 eq) in CH_2Cl_2 (108 mL), PPTS (923 mg, 3.67 mmol, 0.10 eq), and 3,4-dihydro-2*H*-pyran (3.40 mL, 36.7 mmol, 1.0 eq). The reaction mixture was stirred at rt for 3 h until complete consumption of the starting material, as indicated by TLC. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as a colourless wax (6.40 g, 19.1 mmol, 52%).

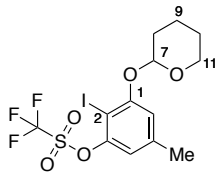
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.54 – 6.50 (m, 1H, *H*4), 6.49 – 6.47 (m, 1H, *H*6), 5.53 (t, *J* = 2.9 Hz, 1H, *H*7), 5.35 (s, 1H, O*H*), 3.89 – 3.82 (m, 1H, *H*11$_a$), 3.66 – 3.57 (m, 1H, *H*11$_b$), 2.28 (s, 3H, ArC*H*$_3$), 2.21 – 1.59 (m, 6H, 2 × *H*8, 2 × *H*9, 2 × *H*10).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 155.9 (*C*1), 155.8 (*C*3), 140.9 (*C*5), 109.3 (*C*4), 108.0 (*C*6), 96.5 (*C*7), 75.7 (*C*2), 61.9 (*C*11), 30.3 (*C*8), 25.4 (*C*10), 21.6 (*C*H$_3$), 18.4 (*C*9).

HRMS (CI) calcd for $C_{12}H_{16}IO_3^+$ $[M+H]^+$ 335.1609, found 335.0145.

ν_{max} (film)/cm^{-1} 3236, 2941, 1587, 1440, 1411, 1269, 1180, 1020, 900, 817.

2-Iodo-5-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl trifluoromethanesulfonate (188)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **S1** (6.42 g, 19.2 mmol, 1.0 eq) in CH_2Cl_2 (64.0 mL), *N*,*N*-diisopropylethylamine (3.30 mL, 19.2 mmol, 1.0 eq), 4-(dimethylamino)pyridine (235 mg, 1.92 mmol, 0.1 eq), and $PhNTf_2$ (6.90 g, 19.2 mmol, 1.0 eq). The reaction was stirred at rt arbitrarily for 16 h. To the reaction mixture was added brine (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as a colourless viscous oil (7.90 g, 16.9 mmol, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.83 (s, 1H, *H*4), 6.72 (s, 1H, *H*6), 5.49 (t, *J* = 3.0 Hz, 1H, *H*7), 3.74 (td, *J* = 11.0, 3.0 Hz, 1H, $H11_a$), 3.62 – 3.50 (m, 1H, $H11_b$), 2.29 (s, 3H, ArCH_3), 2.13 – 1.53 (m, 6H, 2 × *H*8, 2 × *H*9, 2 × *H*10).

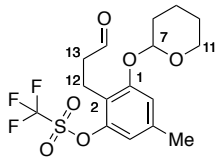
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 157.4 (*C*1), 150.7 (*C*3), 141.3 (*C*5), 118.9 (q, *J* = 319 Hz, CF_3), 115.6 (*C*4), 115.0 (*C*6), 96.9 (*C*7), 79.6 (*C*2), 61.8 (*C*11), 30.1 (*C*8), 25.1 (*C*10), 21.6 (ArCH_3), 18.1 (*C*9).

^{19}F NMR ($CDCl_3$, 377 MHz) δ_F −73.2.

HRMS (CI) calcd for $C_{13}H_{18}F_3INO_5S^+$ $[M+NH_4]^+$ 484.2481, found 483.9902.

ν_{max} (film)/cm^{-1} 2949, 1597, 1568, 1425, 1219, 1139, 1115, 1035, 1019, 976, 901, 873, 837.

5-Methyl-2-(3-oxopropyl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl trifluoromethanesulfonate (192)



Following a modified procedure of Xiao *et al.*,[56] to a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged **188** (2.00 g, 4.29 mmol, 1.0 eq), cataCXium® PintB (86.9 mg, 0.257 mmol, 0.060 eq), and $Pd(dba)_2$ (49.3 mg, 8.58 μmol, 0.020 eq). The Schlenk tube was

evacuated and refilled with argon three times. To the Schlenk tube was added DMF (17.0 mL), distilled allyl alcohol (0.320 mL, 4.72 mmol, 1.1 eq) and distilled *N*,*N*-dimethylcyclohexylamine (1.00 mL, 4.72 mmol, 1.1 eq). The reaction mixture was stirred at 100 °C for 3 h until complete consumption of the starting material, as indicated by TLC. The reaction vessel was then cooled to rt. To the reaction flask was added H_2O (20 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as an orange viscous oil (1.21 g, 3.00 mmol, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.81 (t, *J* = 1.5 Hz, 1H, C*H*O), 6.97 (s, 1H, *H*4), 6.73 (s, 1H, *H*6), 5.47 – 5.42 (m, 1H, *H*7), 3.81 (td, *J* = 11.4, 3.1 Hz, 1H, $H11_a$), 3.69 – 3.61 (m, 1H, $H11_b$), 3.05 – 2.98 (m, 2H, 2 × *H*13), 2.77 – 2.70 (m, 2H, 2 × *H*12), 2.33 (s, 3H, ArCH_3), 1.93 – 1.61 (m, 6H, 2 × *H*8, 2 × *H*9, 2 × *H*10).

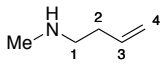
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 201.4 (*C*HO), 156.1 (*C*1), 147.8 (*C*3), 139.1 (*C*5), 120.2 (*C*2), 118.6 (q, *J* = 320 Hz, CF_3), 114.9 (*C*4), 114.8 (*C*6), 96.6 (*C*7), 62.2 (*C*11), 43.2 (*C*13), 30.4 (*C*8), 25.2 (*C*10), 21.7 (ArCH_3), 18.8 (*C*9), 17.3 (*C*12).

^{19}F NMR ($CDCl_3$, 377 MHz) δ_F –73.9.

HRMS (CI) calcd for $C_{16}H_{23}F_3NO_6S^+$ $[M+NH_4]^+$ 414.4157, found 414.1198.

ν_{max} (film)/cm^{-1} 2950, 1726, 1622, 1417, 1209, 1138, 1022, 970, 817.

N-Methylbut-3-en-1-amine (189)



Following a modified procedure by Dull *et al.*,[161] methylamine gas (7.00 mL, 125 mmol, 12.5 eq) was condensed at –78 °C from a solution of methylamine (40 wt. % in H_2O, dried over sodium hydroxide pellets) into a flame-dried, argon-flushed high-pressure vessel equipped with a stirrer bar. To this reaction vessel was charged DMF (7.00 mL), anhydrous potassium carbonate (1.38 g, 100 mmol, 1.0 eq) and 4-bromobut-1-ene (1.00 mL, 100 mmol, 1.0 eq). The resulting suspension was allowed to

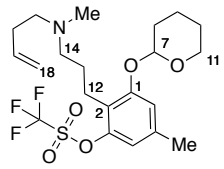
warm to rt and was stirred arbitrarily for 18 h. To the reaction vessel was added H_2O (10 mL), and the reaction mixture extracted with Et_2O (5 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* fractional distillation afforded the title compound as a colourless liquid (389 mg, 46.0 mmol, 46%, bp = 85 – 87 °C at 1 bar, the boiling point is consistent with that previously reported for this compound).[162]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.73 – 5.68 (m, 1H, *H*3), 5.11 – 4.94 (m, 2H, 2 × *H*4), 2.59 (t, *J* = 6.8 Hz, 2H, 2 × *H*1), 2.37 (s, 3H, C*H*$_3$), 2.20 (qt, *J* = 7.0, 1.5 Hz, 2H, 2 × *H*2), 1.79 (br s, N*H*).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 136.4 (*C*3), 116.4 (*C*4), 50.9 (*C*1), 36.3 (*C*H$_3$), 34.1 (*C*2).

HRMS (CI) calcd for $C_5H_{12}N^+$ $[M+H]^+$ 86.1575, found 86.0965.

2-(3-(But-3-en-1-yl(methyl)amino)propyl)-5-methyl-3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl trifluoromethanesulfonate (190)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **192** (361 mg, 0.911 mmol, 1.0 eq) in CH_2Cl_2 (4.60 mL), sodium triacetoxyborohydride (270 mg, 1.28 mmol, 1.4 eq), and **189** (85.4 mg, 1.00 mmol, 1.1 eq). The reaction mixture was stirred at rt arbitrarily for 16 h. The reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution (5.00 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) then EtOAc afforded the title compound as a colourless viscous oil (350 mg, 0.756 mmol, 83%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.95 (s, 1H, *H*4), 6.70 (s, 1H, *H*6), 5.86 – 5.71 (m, 1H, *H*17), 5.45 (t, *J* = 3.0 Hz, 1H, *H*7), 5.07 – 4.96 (m, 2H, 2 × *H*18), 3.88 – 3.78 (m, 1H, *H*11$_a$), 3.67 – 3.61 (m, 1H,

*H*11$_b$), 2.71 – 2.63 (m, 2H, 2 × *H*12), 2.45 – 2.39 (m, 4H, 2 × *H*15, 2 × *H*14), 2.32 (s, 3H, ArC*H*$_3$), 2.27 – 2.19 (m, 5H, NC*H*$_3$, 2 × *H*16), 2.03 – 1.66 (m, 8H, 2 × *H*9, 2 × *H*8, 2 × *H*13, 2 × *H*10).

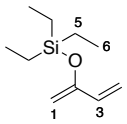
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C 156.2 (*C*1), 148.1 (*C*3), 138.2 (*C*5), 136.9 (*C*17), 121.7 (*C*2), 118.7 (q, J_{CF} = 320 Hz, *C*F$_3$), 115.6 (*C*18), 114.8 (*C*4), 114.5 (*C*6), 96.4 (*C*7), 62.0 (*C*11), 57.6 (*C*15), 57.0 (*C*14), 42.2 (N*C*H$_3$), 31.8 (*C*16), 30.5 (*C*8), 26.7 (*C*12), 25.3 (*C*10), 22.5 (*C*13), 21.6 (Ar*C*H$_3$), 18.7 (*C*9).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F –74.1.

HRMS (ESI) calcd for $C_{21}H_{31}F_3NO_5S^+$ $[M+H]^+$ 466.1870, found 466.1850.

ν_{max} (film)/cm^{-1} 2950, 1622, 1456, 1417, 1209, 1141, 1020, 970, 839, 825.

Buta-1,3-dien-2-yloxytriethylsilane (210)



Following a modified procedure by Woerpel *et al*.,[163] to a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of diisopropylamine (0.400 mL, 3.14 mmol, 1.1 eq) in THF (5.70 mL). The reaction vessel was cooled to –78 °C, and *n*-BuLi (2.5 M in hexanes, 1.20 mL, 3.14 mmol, 1.1 eq) was added to the reaction mixture. The reaction was stirred for 10 min at –78 °C. To the reaction mixture was added dropwise methyl vinyl ketone (0.230 mL, 2.85 mmol, 1.0 eq) followed by the dropwise addition of triethylsilylchloride (0.530 mL, 3.14 mmol, 1.1 eq). The resulting solution was warmed to rt and was stirred arbitrarily for 18 h. To the reaction was added H_2O (2 mL) and the layers were separated. The aqueous layers were extracted with pet. ether (3 × 5 mL). The combined organic layers were washed with H_2O (2 mL), brine (2 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Flash chromatography (100% pet. ether) afforded the title compound as a colourless liquid (264 mg, 1.43 mmol, 50%).

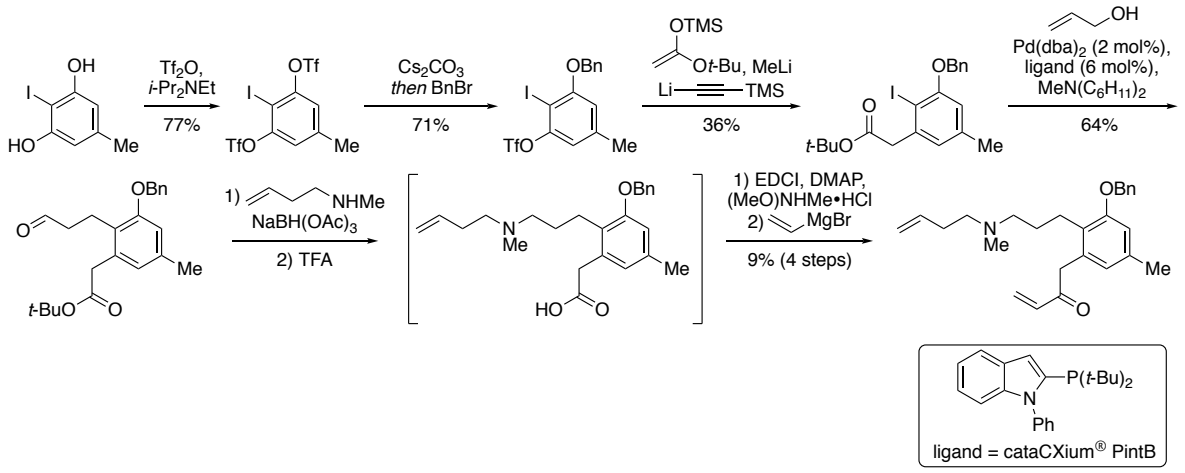
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.20 (dd, J = 16.9, 10.5 Hz, 1H, *H*3), 5.59 – 5.41 (m, 1H, *H*1$_a$), 5.14 – 5.02 (m, 1H, *H*4$_a$), 4.36 – 4.34 (m, 1H, *H*1$_b$), 4.32 – 4.30 (m, 1H, *H*4$_b$), 1.00 (t, J = 8.0 Hz, 9H, 9 × *H*6), 0.73 (q, J = 8.0 Hz, 6H, 6 × *H*5).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 155.5 (*C*2), 135.2 (*C*3), 114.8 (*C*4), 96.2 (*C*1), 7.2 (*C*5), 5.4 (*C*6).

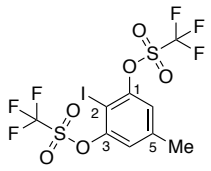
HRMS (CI) calcd for $C_{10}H_{21}OSi^+$ $[M+H]^+$ 185.3615, found 185.1352.

ν_{max} (film)/cm^{-1} 2958, 2877, 1460, 1240.

These data are consistent with those previously published for this compound.[163]



2-Iodo-5-methyl-1,3-phenylene bis(trifluoromethanesulfonate) (235)



Following the modified procedure of Suzuki and Matsumoto *et al*.,[160] to a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **187** (10.3 g, 41.1 mmol, 1.0 eq) in CH_2Cl_2 (82.0 mL). The reaction flask was cooled to −78 °C. To the cooled reaction mixture was added triethylamine (12.6 mL, 90.4 mmol, 2.2 eq), and trifluoromethanesulfonic anhydride dropwise (15.2 mL, 90.4 mmol, 2.2 eq). The resulting solution was warmed to 0 °C, and was stirred for 30 min. The reaction was quenched with H_2O (40 mL). The reaction mixture was then allowed to warm to rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was passed through a plug of silica, eluting with CH_2Cl_2/pet. ether (500 mL, 1:9, v:v). The eluent was concentrated to afford the title compound as a colourless crystalline solid (16.3 g, 31.6 mmol, 77%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.18 (s, 2H, *H*4, *H*6), 2.45 (s, 3H, Ar*CH*$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 151.3 (*C*1, *C*3), 142.7 (*C*5), 122.4 (*C*4, *C*6), 118.8 (q, J_{CF} = 320 Hz, *C*F_3), 83.1 (*C*2), 21.5 (Ar*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ −72.9.

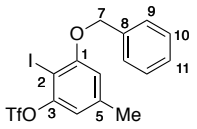
HRMS (EI) calcd for $C_9H_5F_6IO_6S_2$ $[M]^+$ 513.8446. found 513.8441.

ν_{max} (film)/cm^{-1} 1610, 1566, 1427, 1354, 1207, 1134, 1022, 966, 858, 827, 792, 756.

m.p. 60 – 61 °C.

These data are consistent with those previously published for this compound.[160]

3-(Benzyloxy)-2-iodo-5-methylphenyl trifluoromethanesulfonate (236)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **235** (7.90 g, 15.4 mmol, 1.0 eq) in anhydrous DME (51.2 mL), and anhydrous cesium carbonate (7.51 g, 23.1 mmol, 1.5 eq) in one portion. The reaction mixture was heated at 80 °C over 3 h until complete consumption of the starting material, as indicated by TLC. The reaction mixture was allowed to cool to rt. The reaction mixture was cooled to 0 °C and to the cooled reaction was added benzyl bromide (2.50 mL, 20.9 mmol, 1.4 eq). The reaction was allowed to warm to rt and stirred arbitrarily for 18 h. The reaction mixture was cooled to 0 °C, and diethylamine (1.60 mL) was added to the reaction vessel to quench excess benzyl bromide. After stirring at 0 °C for 30 min, the reaction mixture was allowed to warm to rt. To the reaction was added H_2O (50 mL), and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 2.0 M aqueous HCl solution (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as an off-white wax (5.1 mg, 10.9 mmol, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.56 – 7.30 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.85 – 6.78 (m, 1H, *H*4), 6.69 (s, 1H, *H*6), 5.16 (s, 2H, 2 × *H*7), 2.37 (s, 3H, ArCH_3).

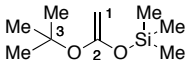
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 159.2 (*C*1), 151.2 (*C*3), 141.5 (*C*5), 135.9 (*C*8), 128.8 (*C*10), 128.3 (*C*11), 127.1 (*C*9), 118.8 (q, J_{CF} = 321 Hz, CF_3), 115.5 (*C*4), 112.9 (*C*6), 79.3 (*C*2), 71.6 (*C*7), 21.7 (ArCH_3).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F −73.2.

HRMS (CI) calcd for $C_{15}H_{16}F_3INO_4S^+$ $[M+NH_4]^+$ 490.2551, found 489.9799.

ν_{max} (film)/cm^{-1} 1597, 1570, 1419, 1205, 1134, 1066, 970, 838, 812, 696.

((1-(*tert*-Butoxy)vinyl)oxy)trimethylsilane (229)



Following the procedure of Tanabe *et al.*,[164] to a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of KHMDS (0.5 M in toluene, 36.0 mL, 18.0 mmol, 1.2 eq) in cyclopentyl methyl ether (11.0 mL). The reaction vessel was cooled to 0 °C. To this cooled solution was added a solution of *tert*-butyl acetate (2.00 mL, 15.0 mmol, 1.0 eq) in cyclopentyl methyl ether (3.50 mL) over 4 min. The resulting solution was stirred at 0 °C for 30 min, then chlorotrimethylsilane (2.50 mL, 19.4 mmol, 1.3 eq) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, then warmed to rt and stirred arbitrarily for further 2 h. After this time, the reaction mixture was poured onto crushed ice. The reaction mixture was extracted with hexane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* fractional distillation under argon atmosphere afforded the title compound as a colourless liquid (1.28 g, 675 mmol, 45%, bp = 67 – 69 °C at 40 mbar).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.42 (dd, J = 9.9, 1.4 Hz, 2H, 2 × *H*1), 1.34 (s, 9H, C(CH_3)$_3$), 0.22 (s, 9H, Si(CH_3)$_3$).

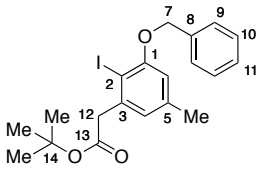
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 157.7 (*C*2), 78.2 (*C*3), 71.9 (*C*1), 28.7 C(*C*H$_3$)$_3$, 0.0 (Si(*C*H$_3$)$_3$).

HRMS (CI) calcd for $C_9H_{21}O_2Si^+$ $[M+H]^+$ 189.3495, found 189.1311.

ν_{max} (film)/cm^{-1} 2959, 2900, 1708, 1251, 1172, 1093, 846.

These data are consistent with those previously published for this compound.[164]

***tert*-Butyl 2-(3-(benzyloxy)-2-iodo-5-methylphenyl)acetate (237)**



Following the procedure of Suzuki *et al*.,[73] to a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **229** (307 mg, 1.63 mmol, 3.9 eq) in THF (5.80 mL). The reaction flask was cooled to 0 °C. To the cooled reaction mixture was added methyllithium (1.6 M in Et_2O, 0.990 mL, 1.58 mmol, 3.7 eq). The resulting solution was stirred at 0 °C for further 30 min, and was then further cooled to –78 °C. To the cooled reaction mixture was added a solution of **236** (200 mg, 0.424 mmol, 1.0 eq) in THF (5.80 mL), and ((trimethylsilyl)ethynyl)lithium (0.40 M in THF, 0.105 mL, 0.0424 mmol, 0.10 eq, prepared by stirring a solution of ethynyltrimethylsilane (0.100 mL, 0.722 mmol) in THF (1.40 mL) with *n*-BuLi (2.5 M in hexane, 0.290 mL) at –78 °C for 30 min). The resulting solution was warmed to –30 °C and was stirred at this temperature for further 2 h until complete consumption of the starting material, as indicated by TLC. After this time, the reaction was quenched with H_2O (5 mL) and was allowed to warm to rt. The layers were separated and the aqueous layers were extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (5:95, v:v) afforded the title compound as a yellow oil (67.4 mg, 0.152 mmol, 36%).

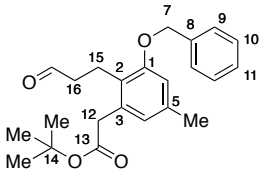
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.55 – 7.51 (m, 2H, 2 × *H*9), 7.43 – 7.37 (m, 2H, 2 × *H*10), 7.35 – 7.30 (m, 1H, *H*11), 6.78 – 6.74 (m, 1H, *H*4), 6.60 – 6.58 (m, 1H, *H*6), 5.12 (s, 2H, 2 × *H*7), 3.74 (s, 2H, 2 × *H*12), 2.30 (s, 3H, ArCH_3), 1.48 (s, 9H, C(CH_3)$_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C 170.2 (*C*13), 157.5 (*C*1), 140.0 (*C*3), 139.3 (*C*5), 136.8 (*C*8), 128.6 (*C*10), 127.9 (*C*11), 127.1 (*C*9), 124.6 (*C*4), 112.2 (*C*6), 90.3 (*C*2), 81.2 (*C*14), 71.2 (*C*7), 47.8 (*C*12), 28.2 (C(CH_3)$_3$), 21.4 (ArCH_3).

HRMS (CI) calcd for $C_{20}H_{27}INO_3^+$ $[M+NH_4]^+$ 456.3439, found 456.1040.

ν_{max} (film)/cm^{-1} 2979, 2930, 1716, 1575, 1366, 1306, 1137, 1087, 1067, 958, 804, 741, 665.

tert-Butyl 2-(3-(benzyloxy)-5-methyl-2-(3-oxopropyl)phenyl)acetate (238)



Following a modified procedure of Xiao *et al*.,[56] to a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged **237** (65.1 mg, 0.148 mmol, 1.0 eq), cataCXium® PintB (3.0 mg, 8.90 μmol, 0.060 eq) and $Pd(dba)_2$ (1.7 mg, 2.97 μmol, 0.020 eq). The Schlenk tube was evacuated and refilled with argon three times. To the Schlenk tube was added DMF (0.590 mL), distilled allyl alcohol (0.0110 mL, 0.463 mmol, 1.1 eq) and distilled *N*,*N*-dimethylcyclohexylamine (0.0350 mL, 0.163 mmol, 1.1 eq). The reaction mixture was stirred at 100 °C for 3 h, and after this time was cooled to rt. To the reaction mixture was added H_2O (2 mL), and the reaction mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with H_2O (3 × 2 mL) and brine (2 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as a yellow oil (35.1 mg, 0.0947 mmol, 64%).

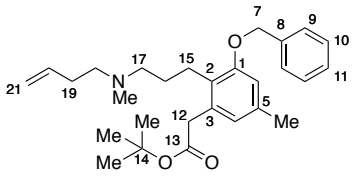
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 9.75 (t, *J* = 1.5 Hz, 1H, C*H*O), 7.44 – 7.37 (m, 4H, 2 × *H*9, 2 × *H*10), 7.37 – 7.30 (m, 1H, *H*11), 6.69 – 6.68 (m, 2H, *H*4, *H*6), 5.05 (s, 2H, 2 × *H*7), 3.55 (s, 2H, 2 × *H*12), 2.93 – 2.84 (m, 2H, 2 × *H*15), 2.66 – 2.57 (m, 2H, 2 × *H*16), 2.30 (s, 3H, ArCH_3), 1.44 (s, 9H, $C(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C 202.6 (*C*HO), 171.2 (*C*13), 156.9 (*C*1), 137.3 (*C*8), 137.1 (*C*5), 134.2 (*C*3), 128.7 (*C*10), 128.0 (*C*11), 127.2 (*C*9), 125.1 (*C*2), 124.1 (*C*4), 111.7 (*C*6), 81.1 (*C*14), 70.1 (*C*7), 43.9 (*C*16), 40.2 (*C*12), 28.2 ($C(CH_3)_3$), 21.6 (ArCH_3), 19.4 (*C*15).

HRMS (ESI) calcd for $C_{23}H_{28}NaO_4^+$ $[M+Na]^+$ 391.1880, found 391.1866.

ν_{max} (film)/cm^{-1} 2977, 2928, 1724, 1612, 1580, 1454, 1367, 1294, 1146, 1092, 837, 737, 698.

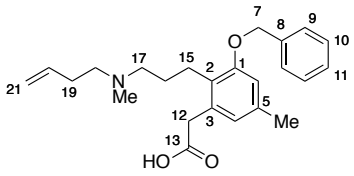
***tert*-Butyl 2-(3-(benzyloxy)-2-(3-(but-3-en-1-yl(methyl)amino)propyl)-5-methylphenyl)acetate (239)**



To a flame-dried, argon flushed vial equipped with a stirrer bar was charged **238** (23.8 mg, 0.0646 mmol, 1.0 eq). To the reaction vial was added a solution of **189** (6.0 mg, 0.0710, 1.1 eq) in CH_2Cl_2 (0.320 mL), and sodium triacetoxyborohydride (19.2 mg, 0.0904 mmol, 1.4 eq). The reaction mixture was stirred at rt arbitrarily for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL), and extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The crude residue (25.0 mg) was used in subsequent chemistry without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.48 – 7.27 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.68 (s, 2H, *H*4, *H*6), 5.80 – 5.65 (m, 1H, *H*20), 5.09 – 4.95 (m, 4H, 2 × *H*21, 2 × *H*7), 3.54 (s, 2H, 2 × *H*12), 2.73 – 2.59 (m, 2H, NCH_2), 2.59 – 2.46 (m, 4H, 2 × *H*15, NCH_2), 2.34 – 2.20 (m, 8H, 2 × *H*19, NCH_3, ArCH_3), 1.82 – 1.69 (m, 2H, 2 × *H*16), 1.44 (s, 9H, C(CH_3)$_3$).

2-(3-(Benzyloxy)-2-(3-(but-3-en-1-yl(methyl)amino)propyl)-5-methylphenyl)acetic acid (S2)

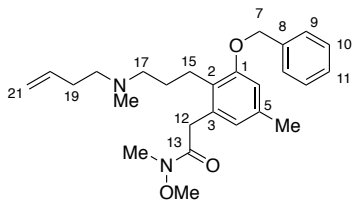


To a flame-dried, argon flushed vial equipped with a stirrer bar was charged a solution of **239** (25.0 mg) in CH_2Cl_2 (0.0360 mL). The reaction flask was cooled to 0 °C. To the cooled reaction mixture was added dropwise trifluoroacetic acid (0.0360 mL). The reaction was allowed to warm to rt and was stirred for 2 h until complete consumption of starting material, as indicated by TLC. The reaction mixture was diluted with EtOAc (1 mL), washed with saturated aqueous $NaHCO_3$ solution (1 mL). The combined aqueous layers were extracted with EtOAc (4 × 1 mL), dried over anhydrous

magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude residue (19.0 mg) was used in subsequent chemistry without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.45 – 7.28 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.73 – 6.56 (m, 2H, *H*4, *H*6), 5.72 – 5.50 (m, 1H, *H*20), 5.09 – 4.94 (m, 4H, 2 × *H*21, 2 × *H*7), 3.53 (s, 2H, 2 × *H*12), 2.91 – 2.62 (m, 6H, 2 × *H*15, 2 × *H*17, 2 × *H*18), 2.45 (s, 3H, ArCH_3), 2.35 – 2.22 (m, 5H, NCH_3, 2 × *H*19), 1.90 – 1.79 (m, 2H, 2 × *H*16).

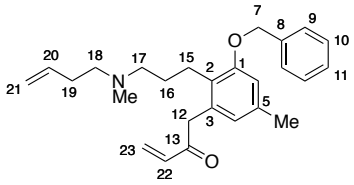
2-(3-(Benzyloxy)-2-(3-(but-3-en-1-yl(methyl)amino)propyl)-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (S3)



To a round-bottomed flask was charged a solution of **S2** (19.0 mg, assumed to be 0.0498 mmol, 1.0 eq) in CH_2Cl_2 (0.300 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (7.30 mg, 0.0747 mmol, 1.5 eq), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (14.3 mg, 0.0747 mmol, 1.5 eq), and 4-(dimethylamino)pyridine (9.10 mg, 0.0747 mmol, 1.5 eq). The reaction mixture was stirred at rt arbitrarily for 18 h. To the reaction mixture was added H_2O (1 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were washed brine (1 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The crude residue (7.0 mg) was used in subsequent chemistry without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.48 – 7.28 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.72 – 6.62 (m, 2H, *H*4, *H*6), 5.69 – 5.54 (m, 1H, *H*20), 5.08 – 4.94 (m, 4H, 2 × *H*21, 2 × *H*7), 3.78 (s, 2H, 2 × *H*12), 3.64 (s, 3H, N(Me)OCH_3), 3.20 (s, 3H, N(OMe)CH_3), 2.70 – 2.62 (m, 2H, 2 × *H*15), 2.59 – 2.45 (m, 4H, 2 × *H*17, 2 × *H*18), 2.34 – 2.20 (m, 8H, ArCH_3, NCH_3, 2 × *H*19), 1.82 – 1.72 (m, 2H, 2 × *H*16).

1-(3-(Benzyloxy)-2-(3-(but-3-en-1-yl(methyl)amino)propyl)-5-methylphenyl)but-3-en-2-one (241)



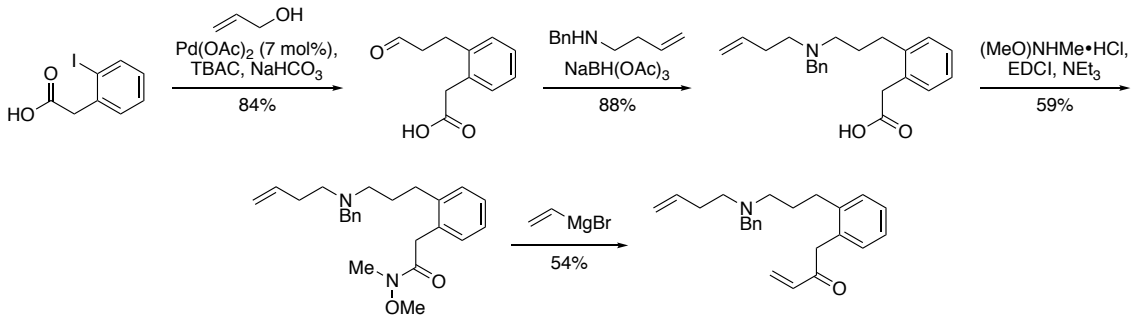
To a flame-dried, argon flushed vial equipped with a stirrer bar was charged a solution of **S3** (7.0 mg, assumed to be 0.0165 mmol, 1.0 eq) in THF (0.0250 mL). The reaction flask was cooled to −10 °C. To the cooled reaction mixture was added vinylmagnesium bromide (1.0 M in THF, 0.0600 mL, 0.0598 mmol, 1.2 eq). The resulting solution was stirred for 30 min at −10 °C. After this time, the reaction mixture was quenched with 1.0 M aqueous HCl (1 mL), allowed to warm to rt, and extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (1 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with $MeOH/CH_2Cl_2$ (5:95, v:v) afforded the title compound as a yellow oil (2.3 mg, 6.10 μmol, 9% from **239**).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.51 – 7.29 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.69 (s, 1H, *H*4), 6.58 (s, 1H, *H*6), 6.44 (dd, *J* = 17.5, 10.3 Hz, 1H, *H*22), 6.32 (dd, *J* = 17.5, 1.4 Hz, 1H, $H23_a$), 5.84 – 5.68 (m, 2H, *H*20, $H23_b$), 5.04 (s, 2H, *H*7), 5.01 – 4.95 (m, 2H, 2 × *H*21), 3.89 (s, 2H, 2 × *H*12), 2.62 – 2.53 (m, 2H, 2 × *H*15), 2.49 – 2.36 (m, 4H, 2 × H*17*, 2 × H18), 2.29 (s, 3H, ArCH_3), 2.23 – 2.21 (m, 5H, NCH_3, 2 × *H*19), 1.73 – 1.58 (m, 2H, 2 × *H*16).

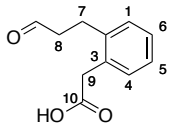
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 198.2 (*C*13), 157.1 (*C*1), 137.6 (*C*5), 136.7 (*C*8), 136.5 (*C*3), 135.6 (*C*23), 133.6 (*C*20), 128.8 (*C*22), 128.7 (*C*10), 127.9 (*C*11), 127.3 (*C*9), 127.2 (*C*2), 124.1 (*C*4), 115.9 (*C*21), 111.7 (*C*6), 70.1 (*C*7), 57.4 (*C*18), 56.7 (*C*17), 45.3 (*C*12), 41.9 (NCH_3), 29.9 (*C*19), 26.7 (*C*16), 24.5 (*C*15), 21.6 (ArCH_3).

HRMS (ESI) calcd for $C_{26}H_{34}NO_2^+$ $[M+H]^+$ 392.2584, found 392.2573.

ν_{max} (film)/cm^{-1} 2952, 2921, 1698, 1613, 1578, 1456, 1418, 1292, 1147, 1083, 913, 741.



2-(2-(3-Oxopropyl)phenyl)acetic acid (S4)



To a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged (2-iodophenyl)acetic acid (2.00 g, 7.62 mmol, 1.0 eq), $Pd(OAc)_2$ (123 mg, 0.548 mmol, 0.072 eq), $NaHCO_3$ (2.30 g, 27.6 mmol, 3.6 eq) and tetrabutylammonium chloride (3.10 g, 11.0 mmol, 1.5 eq). The Schlenk tube was evacuated and refilled with argon three times. To the Schlenk tube was added DMF (35.0 mL) and distilled allyl alcohol (1.10 mL, 16.6 mmol, 2.2 eq). The reaction mixture was stirred at 40 °C for 3 h until complete consumption of starting material, as indicated by TLC. The reaction flask was cooled to rt. To the reaction mixture was added 1.0 M aqueous HCl (20 mL), and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with $MeOH/CH_2Cl_2/AcOH$ (5:95:0.1, v:v:v) afforded the title compound as a brown oil (1.23 g, 6.40 mmol, 84%).

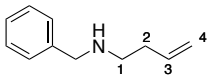
^{1}H NMR (400 MHz, $CDCl_3$) δ_H (t, J = 1.1 Hz, 1H, C*H*O), 7.32 – 7.13 (m, 4H, *H*1, *H*4, *H*5, *H*6), 3.72 (s, 2H, 2 × *H*9), 3.04 – 2.94 (m, 2H, 2 × *H*7), 2.84 – 2.74 (m, 2H, 2 × *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.6 (*C*HO), 177.8 (*C*10), 139.2 (*C*2), 131.7 (*C*3), 131.0 (*C*4), 129.3 (*C*1), 128.1 (*C*6), 126.9 (*C*5), 44.7 (*C*8), 38.5 (*C*9), 24.9 (*C*7).

HRMS (ESI) calc for $C_{11}H_{11}O_3^-$ $[M–H]^-$ 191.0714, found 191.0714.

ν_{max} (film)/cm^{-1} 3024, 2929, 1718 (broad signal), 1493, 1413, 1388, 1237, 1162, 755.

N-Benzylbut-3-en-1-amine (S5)



Following a procedure by van de Weghe *et al*.,[165] to a round-bottomed flask equipped with a stirrer bar was charged a solution of benzylamine (8.00 mL, 73.2 mmol, 5.0 eq) in ethanol (29 mL), 4-bromo-1-butene (1.50 mL, 14.6 mmol, 1.0 eq), and sodium iodide (220 mg, 1.46 mmol, 0.10 eq). The resulting mixture was stirred at 80 °C for 4 h arbitrarily. The reaction mixture was then cooled to rt and concentrated *in vacuo*. To the residue was added 1.0 M aqueous NaOH (20 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether/NEt_3 (2:8:0.1, v:v:v) afforded the title compound as a golden liquid (2.08 g, 12.8 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H, 5 × Ar*H*), 5.89 – 5.68 (m, 1H, *H*3), 5.14 – 5.01 (m, 2H, 2 × *H*4), 3.80 (s, 2H, NC*H*$_2$Ph), 2.71 (t, *J* = 6.8 Hz, 2H, 2 × *H*1), 2.36 – 2.27 (m, 2H, 2 × *H*2), 1.46 (br s, 1H, N*H*).

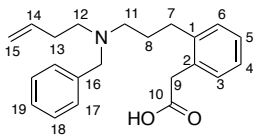
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (CH_2*C*), 136.5 (*C*3), 128.4 (Ar*C*), 128.2 (Ar*C*), 126.9 (Ar*C*), 116.4 (*C*4), 53.9 (N*C*H$_2$C), 48.3 (*C*1), 34.4 (*C*2).

MS (ESI) calcd for $C_{11}H_{16}N^+$ $[M+H]^+$ 162.2, found 162.1.

ν_{max} (film)/cm^{-1} 3076, 2975, 2814, 1639, 1604, 1454, 1118, 912, 697, 668.

These data are consistent with those previously published for this compound.[165]

2-(2-(3-(Benzyl(but-3-en-1-yl)amino)propyl)phenyl)acetic acid (S6)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S4** (1.19 g, 6.21 mmol, 1.0 eq) in CH_2Cl_2 (31.0 mL), **S5** (1.20 g, 7.45 mmol, 1.2 eq), and

sodium triacetoxyborohydride (1.84 g, 8.69 mmol, 1.4 eq). The resulting mixture was stirred at rt for 4 h until complete consumption of starting material, as indicated by TLC. After this time, the solvent was removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2/AcOH (10:90:0.1, v:v:v) afforded the title compound as a yellow oil (1.77 g, 5.46 mmol, 88%).

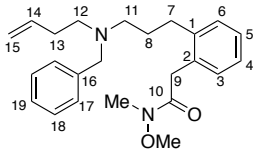
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.11 (br s, 1H, O*H*), 7.39 – 7.00 (m, 9H, 9 × Ar*H*), 5.71 – 5.54 (m, 1H, *H*14), 5.10 – 4.96 (m, 2H, 2 × *H*15), 4.01 (s, 2H, NCH_2Ph), 3.62 (s, 2H, 2 × *H*9), 2.93 – 2.72 (m, 4H, 2 × *H*11, 2 × *H*12), 2.63 (t, *J* = 7.6 Hz, 2H, 2 × *H*7), 2.42 – 2.28 (m, 2H, 2 × *H*13), 2.03 – 1.91 (m, 2H, 2 × *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.6 (*C*10), 139.1 (Ar*C*), 134.7 (Ar*C*), 133.5 (*C*14), 131.4 (overlapping signals, 2 × Ar*C*), 131.0 (Ar*C*), 130.9 (Ar*C*), 129.2 (Ar*C*), 129.1 (Ar*C*), 127.1 (Ar*C*), 126.7 (Ar*C*), 117.8 (*C*15), 56.2 (N*C*H_2Ph), 51.4 (*C*12), 50.9 (*C*11), 40.8 (*C*9), 30.1 (*C*13), 28.4 (*C*7), 21.8 (*C*8).

HRMS (ESI) calcd for $C_{22}H_{28}NO_2^+$ $[M+H]^+$ 338.2115, found 338.2117.

ν_{max} (film)/cm^{-1} 3062, 2940, 1694, 1452, 1261, 1075, 738.

2-(2-(3-(Benzyl(but-3-en-1-yl)amino)propyl)phenyl)-*N*-methoxy-*N*-methylacetamide (S7)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **S6** (1.70 g, 5.48 mmol, 1.0 eq) in CH_2Cl_2 (32.0 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (802 mg, 8.23 mmol, 1.5 eq), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.58 g, 8.23 mmol, 1.5 eq), and *N*,*N*-diisopropylethylamine (2.90 mL, 16.5 mmol, 3.0 eq). The reaction mixture was stirred at rt arbitrarily for 18 h. To the reaction mixture was added H_2O (20 mL) and the layers were separated. The aqueous layers were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the

solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with $MeOH/CH_2Cl_2$ (3:97, v:v) afforded the title compound as a yellow oil (1.22 g, 3.23 mmol, 59%).

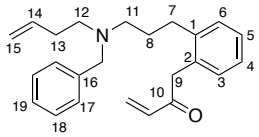
^1H NMR (400 MHz, $CDCl_3$) δ_H 7.29 – 7.03 (m, 9H, 9 × Ar*H*), 5.79 – 5.64 (m, 1H, *H*14), 4.99 – 4.86 (m, 2H, 2 × *H*15), 3.70 (s, 2H, *H*9), 3.51 (s, 2H, NCH_2Ph), 3.46 (s, 3H, OCH_3), 3.11 (s, 3H, NCH_3), 2.58 – 2.40 (m, 6H, 2 × *H*7, 2 × *H*11, 2 × *H*12), 2.21 – 2.12 (m, 2H, *H*13), 1.73 – 1.62 (m, 2H, *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.8 (*C*10), 141.1 (Ar*C*), 140.0 (Ar*C*), 137.2 (*C*14), 133.1 (Ar*C*), 130.2 (Ar*C*), 129.3 (Ar*C*), 128.9 (Ar*C*), 128.2 (Ar*C*), 127.2 (Ar*C*), 126.8 (Ar*C*), 126.1 (Ar*C*), 115.5 (*C*15), 61.3 (OCH_3), 58.5 (NCH_2Ph), 53.5 (*C*11), 53.3 (*C*12), 36.6 (*C*9), 32.5 (NCH_3), 31.6 (*C*13), 30.8 (*C*7), 28.2 (*C*8).

HRMS (ESI) calcd for $C_{24}H_{32}N_2O_2^+$ $[M+H]^+$ 381.2537, found 381.2535.

ν_{max} (film)/cm^{-1} 3063, 2936, 2801, 1653, 1451, 1417, 1377, 1027, 913, 738.

1-(2-(3-(Benzyl(but-3-en-1-yl)amino)propyl)phenyl)but-3-en-2-one (252)



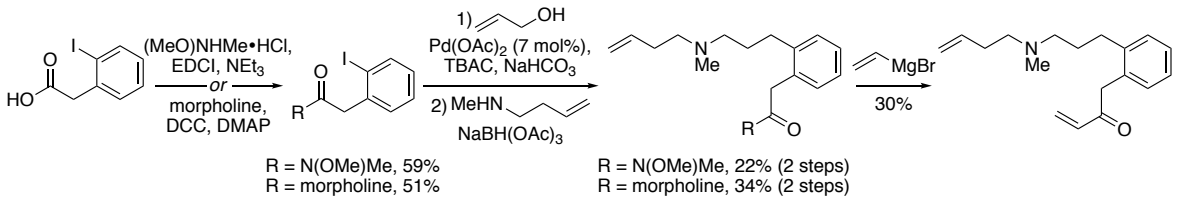
To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S7** (123 mg, 0.323 mmol, 1.0 eq) in THF (0.500 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added vinylmagnesium bromide (1.0 M in THF, 0.390 mL, 0.388 mmol, 1.2 eq). The resulting solution was stirred at 0 °C for 4 h until complete consumption of starting material, as indicated by TLC. After this time, the reaction mixture was quenched with 1.0 M aqueous HCl (0 mL), allowed to warm to rt, and extracted with Et_2O (3 × 1 mL). The aqueous layer was basified with 2.0 M aqueous NaOH solution until pH paper indicated that pH > 12, and was further extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with $MeOH/CH_2Cl_2/NEt_3$ (1:99:0.1, v:v:v) afforded the title compound as a yellow oil (60.6 mg, 0.174 mmol, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.07 (m, 9H, 9 × Ar*H*), 6.42 (dd, *J* = 17.5, 10.3 Hz, 1H, *H*20), 6.29 (dd, *J* = 17.5, 1.4 Hz, 1H, *H*21$_a$), 5.87 – 5.72 (m, 2H, *H*14, *H*21$_b$), 5.08 – 4.94 (m, 2H, 2 × *H*15), 3.89 (s, 2H, 2 × *H*9), 3.59 (s, 2H, NC*H*$_2$Ph), 2.60 – 2.45 (m, 6H, 2 × *H*7, 2 × *H*11, 2 × *H*12), 2.29 – 2.17 (m, 2H, 2 × *H*13), 1.80 – 1.64 (m, 2H, 2 × *H*8).

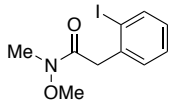
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 197.9 (*C*10), 141.3 (Ar*C*), 140.0 (Ar*C*), 137.1 (*C*14), 135.5 (*C*20), 132.4 (Ar*C*), 130.8 (Ar*C*), 129.5 (Ar*C*), 128.9 (*C*21), 128.8 (Ar*C*), 128.3 (Ar*C*), 127.5 (Ar*C*), 126.9 (Ar*C*), 126.3 (Ar*C*), 115.5 (*C*15), 58.5 (N*C*H$_2$Ph), 53.4 (*C*12), 53.3 (*C*11), 45.1 (*C*9), 31.6 (*C*13), 30.8 (*C*7), 28.3 (*C*8).

HRMS (ESI) calcd for $C_{24}H_{30}NO^+$ $[M+H]^+$ 348.2322, found 348.2325.

ν_{max} (film)/cm^{-1} 3062, 3025, 2940, 2800, 1693, 1639, 1614, 1414, 1075, 986, 911, 669.



2-(2-Iodophenyl)-*N*-methoxy-*N*-methylacetamide (242)



To a round-bottomed flask was charged a solution of 2-(2-iodophenyl)acetic acid (1.31 g, 4.99 mmol, 1.0 eq) in CH_2Cl_2 (10.0 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added 1,1′-carbonyldiimidazole (890 mg, 5.49 mmol, 1.1 eq) and the reaction mixture was stirred at 0 °C for 30 min. After this time, *N*,*O*-dimethylhydroxylamine hydrochloride (584 mg, 5.99 mmol, 1.2 eq) and triethylamine (2.20 mL, 16.0 mmol, 3.2 eq) were added to the reaction mixture at 0 °C. The resulting mixture was allowed to warm to rt, and was stirred arbitrarily for further 18 h. To the reaction mixture was added saturated aqueous NH_4Cl solution (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (10 mL), 1.0 M aqueous HCl solution (10 mL), H_2O (10 mL), and brine (10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (3:97, v:v) afforded the title compound as a yellow oil (1.22 g, 2.94 mmol, 59%).

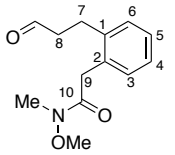
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89 – 7.82 (m, 1H, Ar*H*), 7.38 – 7.24 (m, 2H, 2 × Ar*H*), 7.01 – 6.92 (m, 1H, Ar*H*), 3.95 (s, 2H, ArCH_2), 3.74 (s, 3H, OCH_3), 3.24 (m, 3H, NCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.4 (*C*(O)N(Me)OMe), 139.4 (Ar*C*), 138.5 (Ar*C*), 130.5 (Ar*C*), 128.6 (Ar*C*), 128.4 (Ar*C*), 101.4 (Ar*C*), 61.5 (OCH_3), 44.5 (ArCH_2), 32.5 (NCH_3).

HRMS (ESI) calcd for $C_{10}H_{12}INO_2Na^+$ $[M+Na]^+$ 327.9805, found 327.9803.

ν_{max} (film)/cm^{-1} 3051, 2936, 1658, 1563, 1304, 1013, 743.

_N_-Methoxy-_N_-methyl-2-(2-(3-oxopropyl)phenyl)acetamide (S8)



To a flame-dried, argon-flushed round-bottomed flask was charged **242** (540 mg, 1.77 mmol, 1.0 eq), $Pd(OAc)_2$ (28.0 mg, 0.127 mmol, 0.072 eq), $NaHCO_3$ (538 mg, 6.41 mmol, 3.6 eq) and tetrabutylammonium chloride (713 mg, 2.57 mmol, 1.5 eq). The reaction flask was evacuated and refilled with argon three times. To the reaction flask was added DMF (8.00 mL) and distilled allyl alcohol (0.260 mL, 3.86 mmol, 2.2 eq). The reaction mixture was stirred at 40 °C for 4 h until complete consumption of starting material, as indicated by TLC. The reaction flask was cooled to rt. The reaction was quenched with 1.0 M aqueous HCl solution (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (3:7 to 1:0, v:v) afforded the title compound as a yellow oil (312 mg, 1.33 mmol, 75%).

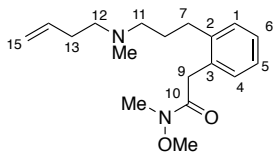
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.83 (t, *J* = 1.3 Hz, 1H, C*H*O), 7.24 – 7.13 (m, 4H, 4 × Ar*H*), 3.82 (s, 2H, 2 × *H*9), 3.65 (s, 3H, OCH_3), 3.21 (s, 3H, NCH_3), 2.99 – 2.93 (m, 2H, 2 × *H*7), 2.82 – 2.76 (m, 2H, 2 × *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.7 (*C*HO), 172.5 (*C*10), 139.2 (Ar*C*), 133.3 (Ar*C*), 130.8 (Ar*C*), 129.1 (Ar*C*), 127.5 (Ar*C*), 126.7 (Ar*C*), 61.4 (O*C*H_3), 44.8 (*C*8), 36.6 (*C*9), 32.5 (N*C*H_3), 25.1 (*C*7).

HRMS (ESI) calcd for $C_{13}H_{18}NO_3^+$ $[M+H]^+$ 236.1281, found 236.1284.

ν_{max} (film)/cm^{-1} 3063, 2938, 2823, 2726, 1721, 1662, 1383, 1173, 1001, 749.

2-(2-(3-(But-3-en-1-yl(methyl)amino)propyl)phenyl)-_N_-methoxy-_N_-methylacetamide (244)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S8** (434 mg, 1.84 mmol, 1.0 eq) in CH_2Cl_2 (9.20 mL), and **189** (173 mg, 2.03 mmol, 1.1 eq). The resulting solution was stirred at rt for 30 min. After this time, sodium triacetoxybrorohydride (547 mg, 2.58 mmol, 1.4 eq) was added in one portion. The reaction mixture was stirred at rt arbitrarily for 18 h. The reaction was quenched by the addition of H_2O (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (1:9 then 1:4, v:v) afforded the title compound as a yellow oil (161 mg, 0.533 mmol, 29%).

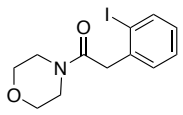
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.11 (br s, 4H, 4 × Ar*H*), 5.77 – 5.60 (m, 1H, *H*14), 5.11 – 4.92 (m, 2H, 2 × *H*15), 3.74 (s, 2H, 2 × *H*9), 3.56 (s, 3H, OCH_3), 3.12 (s, 3H, C(O)NCH_3), 2.67 – 2.50 (m, 6H, 2 × *H*11, 2 × *H*12, 2 × *H*7), 2.50 – 2.23 (m, 5H, CH_2NCH_3, 2 × *H*13), 1.93 – 1.78 (m, 2H, 2 × *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.4 (*C*10), 139.7 (Ar*C*), 134.7 (*C*14), 133.0 (Ar*C*), 130.5 (Ar*C*), 129.1 (Ar*C*), 127.1 (Ar*C*), 126.2 (Ar*C*), 116.7 (*C*15), 61.2 (O*C*H_3), 56.2 (*C*12), 55.8 (*C*11), 40.9 (CH_2N*C*H_3), 36.4 (*C*9), 32.2 (C(O)N*C*H_3), 30.3 (*C*7), 30.2 (*C*13), 26.3 (*C*8).

HRMS (ESI) calcd for $C_{18}H_{29}N_2O_2^+$ $[M+H]^+$ 305.2223, found 305.2220.

ν_{max} (film)/cm^{-1} 2938, 1664, 1640, 1464, 1413, 1380, 999, 916, 771.

2-(2-Iodophenyl)-1-morpholinoethan-1-one (243)



To a round-bottomed flask equipped with a stirrer bar was added a solution of 2-(2-iodophenyl)acetic acid (1.00 g, 3.81 mmol, 1.0 eq) in CH_2Cl_2 (15.0 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added a solution of *N*,*N*′-dicyclohexylcarbodiimide (786 mg, 3.81 mmol, 1.0 eq) and 4-(dimethylamino)pyridine (4.60 mg, 0.0381 mmol, 0.010 eq) in CH_2Cl_2 (7.60 mL). The resulting solution was stirred at 0 °C for 2 h until complete consumption of starting material, as

indicated by TLC. After this time, the reaction mixture was warmed to rt, filtered (eluting with CH_2Cl_2, 15 mL) and concentrated *in vacuo*. The residue was diluted with EtOAc (10 mL), and washed with saturated aqueous NH_4Cl solution (10 mL). The inorganic layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (3:97, v:v) afforded the title compound as a colourless paste (642 mg, 1.94 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.37 – 7.24 (m, 2H, 2 × Ar*H*), 6.96 – 6.85 (m, 1H, Ar*H*), 3.80 (s, 2H, CH_2CO), 3.69 (q, *J* = 2.0 Hz, 4H, CH_2OCH_2), 3.65 – 3.58 (m, 2H, NCH_2), 3.51 – 3.41 (m, 2H, NCH_2).

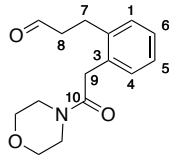
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.0 (*C*=ON), 139.6 (CH_2*C*), 138.4 (Ar*C*), 129.9 (Ar*C*), 128.9 (Ar*C*), 128.7 (Ar*C*), 101.1 (I*C*), 67.0 (O*C*H_2), 66.7 (O*C*H_2), 46.6 (*C*H_2Ph), 45.6 (N*C*H_2), 42.4 (N*C*H_2).

MS (ESI) calcd for $C_{12}H_{15}INO_2$ $[M+H]^+$ 332.0, found 332.0.

ν_{max} (film)/cm^{-1} 2924, 1645 (broad), 1436, 1230, 1170, 1113, 1035, 1013, 746.

These data are consistent with those previously published for this compound.[166]

3-(2-(2-Morpholino-2-oxoethyl)phenyl)propanal (S9)



To a flame-dried, argon-flushed round-bottomed flask was charged **243** (592 mg, 1.79 mmol, 1.0 eq), $Pd(OAc)_2$ (28.9 mg, 0.129 mmol, 0.072 eq), $NaHCO_3$ (544 mg, 6.47 mmol, 3.6 eq), and tetrabutylammonium chloride (720 mg, 2.59 mmol, 1.5 eq). The reaction flask was evacuated and refilled with argon three times. To the reaction flask was added DMF (8.10 mL) and distilled allyl alcohol (0.270 mL, 3.90 mmol, 2.2 eq). The reaction mixture was stirred at 40 °C for 4 h until complete consumption of the starting material, as indicated by TLC. The reaction flask was cooled to rt. The reaction was quenched with 1.0 M aqueous HCl solution (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine (10 mL),

dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (5:95, v:v) afforded the title compound as a brown oil (187 mg, 0.716 mmol, 40%).

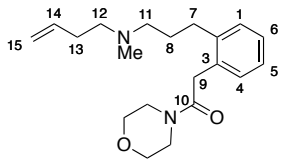
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.83 (t, *J* = 1.2 Hz, 1H, C*H*O), 7.24 – 7.11 (m, 4H, 4 × Ar*H*), 3.74 (s, 2H, 2 × *H*9), 3.72 – 3.56 (m, 6H, 2 × NCH_2, 4 × OCH_2), 3.54 – 3.44 (m, 2H, 2 × NCH_2), 2.96 – 2.86 (m, 2H, 2 × *H*7), 2.86 – 2.76 (m, 2H, 2 × *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.5 (*C*HO), 169.7 (*C*10), 138.8 (Ar*C*), 133.3 (Ar*C*), 129.7 (Ar*C*), 129.1 (Ar*C*), 127.6 (Ar*C*), 126.9 (Ar*C*), 67.0 (OCH_2), 66.7 (OCH_2), 46.5 (NCH_2), 44.6 (*C*8), 42.3 (NCH_2), 37.9 (*C*9), 24.9 (*C*7).

HRMS (ESI) calcd for $C_{15}H_{20}NO_3^+$ $[M+H]^+$ 262.1438, found 262.1439.

ν_{max} (film)/cm^{-1} 2854, 1719, 1643, 1453, 1272, 1114, 1036, 849, 748.

2-(2-(3-(But-3-en-1-yl(methyl)amino)propyl)phenyl)-1-morpholinoethan-1-one (245)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S9** (171 mg, 0.654 mmol, 1.0 eq) in MeOH (3.90 mL), *N*-methylbut-3-en-1-amine (111 mg, 1.31 mmol, 2.0 eq), and glacial acetic acid (0.190 mL, 3.27 mmol, 5.0 eq). The reaction mixture was stirred at rt for 1 h. After this time, sodium cyanoborohydride (82.2 mg, 1.31 mmol, 2.0 eq) was added to the reaction flask, and the resulting mixture was stirred at rt arbitrarily for 18 h. The reaction was quenched with 1.0 M aqueous NaOH solution (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2/NEt (5:95:0.1, v:v:v) afforded the title compound as a colourless oil (183 mg, 0.556 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24 – 7.06 (m, 4H, 4 × Ar*H*), 5.88 – 5.71 (m, 1H, *H*14), 5.11 – 4.95 (m, 2H, 2 × *H*15), 3.72 (s, 2H, 2 × *H*9), 3.67 (br s, 4H, 2 × C(O)NCH_2, 2 × OCH_2), 3.58 – 3.52 (m,

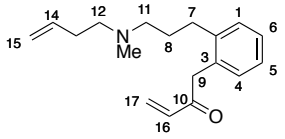
2H, 2 × OCH_2), 3.43 – 3.37 (m, 2H, 2 × C(O)NCH_2), 2.66 – 2.56 (m, 2H, 2 × *H*7), 2.49 – 2.39 (m, 4H, 2 × *H*12, 2 × *H*11), 2.27 – 2.19 (m, 5H, NCH_3, 2 × *H*13), 1.80 – 1.71 (m, 2H, 2 × *H*8).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.1 (*C*10), 140.2 (Ar*C*), 136.5 (*C*14), 133.0 (Ar*C*), 129.5 (Ar*C*), 129.1 (Ar*C*), 127.3 (Ar*C*), 126.5 (Ar*C*), 115.9 (*C*15), 67.0 (O*C*H_2), 66.6 (O*C*H_2), 57.3 (*C*12), 57.0 (*C*11), 46.5 (C(O)N*C*H_2), 42.2 (N*C*H_3), 42.1 (C(O)N*C*H_2), 37.8 (*C*9), 31.6 (*C*13), 30.7 (*C*7), 27.9 (*C*8).

HRMS (ESI) calcd for $C_{20}H_{31}N_2O_2^+$ $[M+H]^+$ 331.2380, found 331.2379.

ν_{max} (film)/cm^{-1} 2922, 2853, 1643, 1431, 1229, 1115, 1068, 955, 848, 747.

1-(2-(3-(But-3-en-1-yl(methyl)amino)propyl)phenyl)but-3-en-2-one (246)



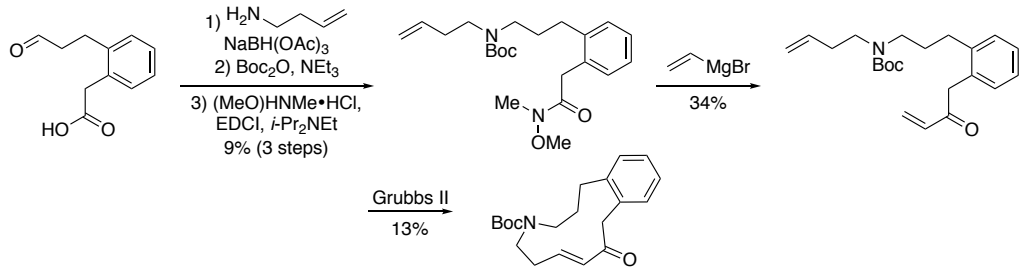
To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **245** (18.0 mg, 54.5 μmol, 1.0 eq) in THF (0.540 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added dropwise a solution of vinylmagnesium bromide (1.0 M in THF, 0.160 mL, 0.163 mmol, 3.0 eq). The reaction was stirred at 0 °C for 1.5 h until complete consumption of starting material, as indicated by TLC. The reaction was quenched at 0 °C by the addition of acetic anhydride (6.0 μL), and H_2O (0.50 mL). The resulting mixture was allowed to warm to rt, and extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2/NEt_3 (5:95:0.1, v:v:v) afforded the title compound as a yellow oil (5.0 mg, 16.4 μmol, 30%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.32 – 7.11 (m, 4H, 4 × Ar*H*), 6.46 (dd, *J* = 17.5, 10.3 Hz, 1H, *H*16), 6.30 – 6.20 (m, 1H, *H*17$_a$), 5.89 – 5.75 (m, 2H, *H*14, *H*17$_b$), 5.13 – 4.99 (m, 2H, 2 × *H*15), 3.95 (s, 2H, 2 × *H*9), 2.65 – 2.54 (m, 2H, 2 × *H*7), 2.54 – 2.37 (m, 4H, 2 × *H*11, 2 × *H*12), 2.37 – 2.22 (m, 5H, NCH_3, 2 × *H*13), 1.83 – 1.72 (m, 2H, 2 × *H*8).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 198.0 (*C*10), 141.0 (Ar*C*), 136.6 (*C*14), 135.5 (*C*16), 132.5 (Ar*C*), 131.0 (Ar*C*), 129.6 (Ar*C*), 128.9 (*C*17), 127.6 (Ar*C*), 126.4 (Ar*C*), 115.9 (*C*15), 57.2 (*C*12), 57.0 (*C*11), 45.1 (*C*9), 42.1 (N*C*H_3), 31.6 (*C*13), 30.7 (*C*7), 28.2 (*C*8).

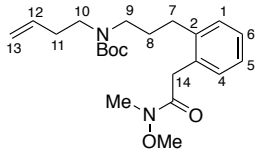
HRMS (ESI) calcd for $C_{18}H_{26}NO^+$ $[M+H]^+$ 272.2009, found 272.2008.

ν_{max} (film)/cm^{-1} 2943, 1692, 1640, 1491, 1454, 1329, 1119, 1076, 987, 751.



***tert*-Butyl but-3-en-1-yl(3-(2-(2-(methoxy(methyl)amino)-2-oxoethyl)phenyl)propyl)carbamate**

(S10)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S4** (273 mg, 1.42 mmol, 1.0 eq), in CH_2Cl_2 (7.10 mL), 3-buten-1-amine (0.160 mL, 1.70 mmol, 1.2 eq), and sodium triacetoxyborohydride (420 mg, 1.99 mmol, 1.4 eq). The resulting mixture was stirred at rt arbitrarily for 16 h. The reaction mixture was concentrated, filtered through Celite® (eluting with MeOH, 10 mL) and the solvent removed *in vacuo*. The crude amine residue (216 mg) was used in subsequent chemistry without further purification.

To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of the crude amine residue (216 mg, assumed to be 0.873 mmol, 1.0 eq) in CH_2Cl_2 (8.70 mL), triethylamine (0.240 mL, 1.75 mmol, 2.0 eq), and di-*tert*-butyl-dicarbonate (286 mg, 1.31 mmol, 1.5 eq). The resulting mixture was stirred at rt arbitrarily for 16 h. To reaction mixture was added H_2O (10 mL) and the layers were separated. The aqueous layer was acidified by the addition of 1.0 M aqueous HCl solution until pH paper indicated pH < 5. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude carboxylic acid residue (133 mg) was used in subsequent chemistry without further purification.

To a round-bottomed flask equipped with a stirrer bar was charged a solution of the crude carboxylic acid residue (133 mg, assumed to be 0.383 mmol, 1.0 eq) in CH_2Cl_2 (2.30 mL), *N*,*O*-

dimethylhydroxylamine hydrochloride (56.0 mg, 0.574 mmol, 1.5 eq), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (110 mg, 0.574 mmol, 1.5 eq), and *N*,*N*-diisopropylethylamine (0.200 mL, 1.15 mmol, 3.0 eq). The resulting mixture was stirred at rt arbitrarily for 16 h. To reaction mixture was added H_2O (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (2:98, v:v) afforded the title compound as a yellow viscous oil (52.6 mg, 0.128 mmol, 9% over three steps).

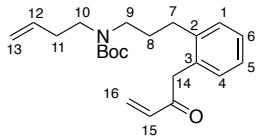
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.20 – 7.07 (m, 4H, 4 × Ar*H*), 5.81 – 5.57 (m, 1H, *H*12), 5.09 – 4.89 (m, 2H, 2 × *H*13), 3.81 – 3.70 (m, 2H, 2 × *H*14), 3.64 – 3.43 (m, 3H, OCH_3), 3.38 – 2.94 (m, 7H, 2 × *H*9, 2 × *H*10, NCH_3), 2.66 – 2.46 (m, 3H, 2 × *H*7, *H*11$_a$), 2.41 – 2.07 (m, 2H, *H*8$_a$, H11$_b$), 1.82 – 1.75 (m, 1H, *H*8$_b$), 1.42 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.5 (*C*(O)NCH$_3$), 155.4 (N*C*(O)O*t*-Bu), 140.2 (*C*2), 135.4 (*C*13), 132.9 (*C*3), 130.1 (*C*4), 128.9 (*C*1), 127.0 (*C*5), 126.1 (*C*6), 116.4 (*C*12), 79.1 (O*C*(CH$_3$)$_3$), 61.1 (O*C*H$_3$), 51.5 (*C*10), 47.1 (*C*9), 36.3 (*C*14), 33.3 (*C*11), 32.2 (N*C*H$_3$), 30.2 (*C*7), 29.6 (*C*8), 28.4 (OC(*C*H$_3$)$_3$).

HRMS (ESI) calcd for $C_{22}H_{34}N_2O_4Na^+$ $[M+Na]^+$ 413.2410, found 413.2388.

ν_{max} (film)/cm^{-1} 2973, 2934, 1686, 1676, 1604, 1465, 1415, 1379, 1365, 1300, 1248, 1226, 1167, 1002, 918, 770.

tert-Butyl but-3-en-1-yl(3-(2-(2-oxobut-3-en-1-yl)phenyl)propyl)carbamate (257)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S10** (64.5 mg, 0.165 mmol, 1.0 eq) in THF (0.270 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added dropwise vinylmagnesium bromide (1.0 M in THF, 0.200 mL, 0.198 mmol, 1.2 eq) and the resulting mixture was stirred at 0 °C for 2 h until complete

consumption of starting material, as indicated by TLC. The reaction was quenched at 0 °C by the addition of 1.0 M aqueous HCl solution (1 mL) and was warmed to rt. The reaction mixture was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as a colourless oil (20.1 mg, 0.0561 mmol, 34% yield).

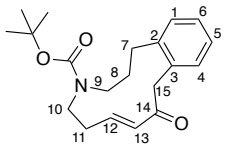
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.23 – 7.06 (m, 4H, 4 × Ar*H*), 6.43 (dd, *J* = 17.5, 10.3 Hz, 1H, *H*15), 6.34 – 6.32 (m, 1H, $H16_a$), 5.87 – 5.65 (m, 2H, $H13_a$, $H16_b$), 5.12 – 4.90 (m, 2H, *H*12, $H13_b$), 3.89 (s, 2H, 2 × *H*14), 3.35 – 3.09 (m, 4H, 2 × *H*10, 2 × *H*9), 2.52 (t, *J* = 8.1 Hz, 2H, 2 × *H*7), 2.35 – 2.13 (m, 2H, 2 × *H*11), 1.84 – 1.70 (m, 2H, 2 × *H*8), 1.44 (s, 9H, $OC(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 197.8 ($CH_2C(O)CHCH_2$), 155.6 (N*C*(O)O*t*-Bu), 140.6 (*C*2), 135.6 (*C*12), 135.5 (*C*15), 132.3 (*C*3), 131.0 (*C*4), 129.3 (*C*1), 128.9 (*C*16), 127.6 (*C*5), 126.5 (*C*6), 116.6 (*C*13), 79.4 ($OC(CH_3)_3$), 47.3 (*C*10), 46.9 (*C*9), 45.1 (*C*14), 33.0 (*C*11), 30.4 (*C*7), 29.5 (*C*8), 28.6 ($OC(CH_3)_3$).

HRMS (ESI) calcd for $C_{22}H_{31}NO_3Na^+$ $[M+Na]^+$ 380.2196, found 380.2196.

ν_{max} (film)/cm^{-1} 2924, 1692 (broad), 1468, 1416, 1302, 1249, 1164, 988, 753.

tert-Butyl (*E*)-14-hydroxy-9-oxo-2,3,5,6,9,10-hexahydrobenzo[*e*][1]azacyclododecine-4(1*H*)-carboxylate (260)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **257** (10.0 mg, 0.0280 mmol, 1.0 eq) in freeze-pump thawed CH_2Cl_2 (4.00 mL). The reaction vessel was warmed to 40 °C. To the heated reaction flask was added a solution of Grubbs' 2nd Generation catalyst (4.7 mg, 5.59 μmol, 0.20 eq) in freeze-pump thawed CH_2Cl_2 (2.00 mL). Upon complete addition of the catalyst solution, the resulting mixture was stirred at 40 °C arbitrarily over 16 h. The reaction was cooled to rt and was directly concentrated *in vacuo*. Purification of the residue

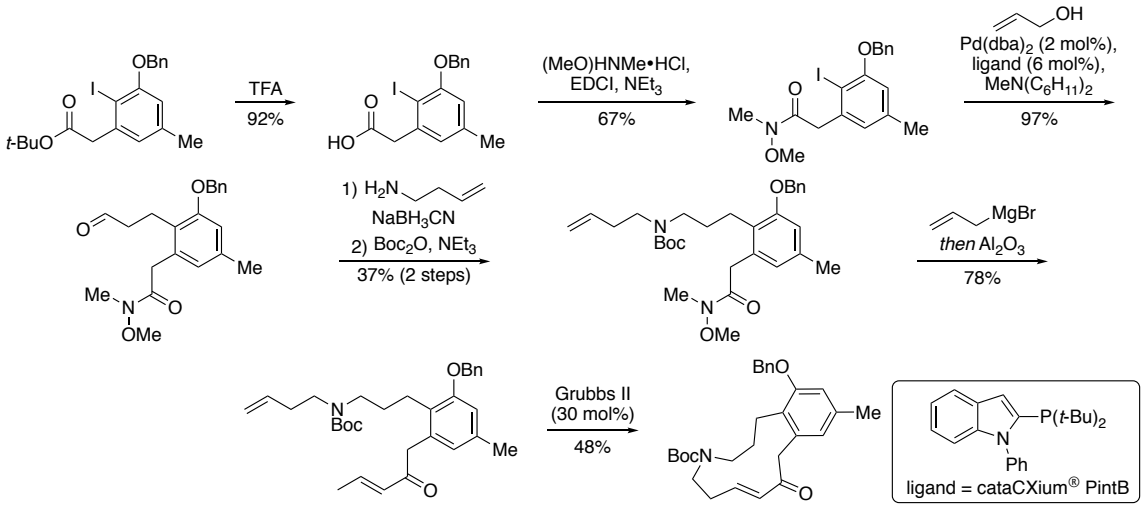
via flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as a yellow oil (1.20 mg, 3.64 μmol, 13% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.39 – 7.29 (m, 1H, Ar*H*), 7.21 – 7.09 (m, 3H, 3 × Ar*H*), 7.07 – 6.94 (m, 1H, *H*12), 6.20 (dd, *J* = 16.1, 9.8 Hz, 1H, *H*13), 3.86 (s, 2H, 2 × *H*15), 3.44 – 3.26 (m, 4H, 2 × *H*9, 2 × *H*10), 2.79 – 2.53 (m, 4H, 2 × *H*11, 2 × *H*7), 1.57 – 1.49 (m, 11H, 2 × *H*8, OC(CH_3)$_3$).

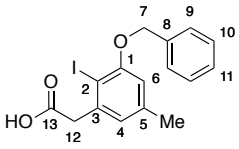
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 199.4 (*C*14, minor rotamer), 199.3 (*C*4, major rotamer), 156.7 (N*C*(O)O*t*-Bu), 156.1 (*C*1), 146.9 (*C*12, major rotamer), 146.2 (*C*12, minor rotamer), 140.5 (*C*2, minor rotamer), 140.2 (*C*2, major rotamer), 134.0 (*C*13), 133.4 (*C*3, major rotamer), 133.0 (*C*3, minor rotamer), 132.3 (*C*4, major rotamer), 132.1 (*C*4, minor rotamer), 130.6 (*C*6, minor rotamer), 130.5 (*C*6, major rotamer), 126.7 (*C*5, major rotamer), 126.6 (*C*5, minor rotamer), 80.1 (O*C*(CH_3)$_3$, minor rotamer), 80.0 (O*C*(CH_3)$_3$, major rotamer), 50.6 (*C*10, major rotamer), 50.4 (*C*9, major rotamer), 50.0 (*C*10, minor rotamer), 49.6 (*C*9, minor rotamer), 42.7 (*C*15, major rotamer), 42.5 (*C*15, minor rotamer), 32.5 (*C*7), 31.2 (*C*8, minor rotamer), 31.1 (*C*8, major rotamer), 29.9 (*C*11, major rotamer), 29.8 (*C*11, minor rotamer), 28.7 (OC(*C*H_3)$_3$, minor rotamer), 28.6 (OC(*C*H_3)$_3$, major rotamer).

HRMS (ESI) calcd for $C_{20}H_{28}NO_3^+$ $[M+H]^+$ 330.2064, found 330.2065.

ν_{max} (film)/cm^{-1} 2923, 1691, 1629, 1467, 1411, 1365, 1297, 1243, 1169, 1108, 1086, 977, 689.



2-(3-(Benzyloxy)-2-iodo-5-methylphenyl)acetic acid (S11)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **237** (1.99 g, 4.54 mmol) in CH_2Cl_2 (2.80 mL). The reaction vessel was cooled to 0 °C. To the reaction flask was added trifluoroacetic acid (2.80 mL). The resulting mixture was stirred at 0 °C for 30 min, warmed to rt, and further stirred for 30 min. The reaction was quenched at 0 °C by the dropwise addition of saturated aqueous $NaHCO_3$ solution (3 mL). The reaction mixture was allowed to warm to rt and was then extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether/acetic acid (1:1:0.1, v:v:v) afforded the title compound as an off-white solid (1.60 g, 4.18 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 – 7.29 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.79 (s, 1H, *H*4), 6.61 (s, 1H, *H*6), 5.13 (s, 2H, 2 × *H*7), 3.89 (s, 2H, 2 × *H*12), 2.31 (s, 3H, ArC*H*$_3$).

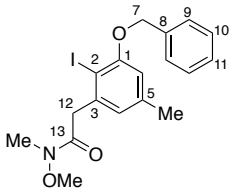
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.5 (*C*13), 139.6 (*C*1), 138.6 (*C*3), 136.7 (*C*8), 128.7 (overlapping signals, *C*5, *C*10), 128.0 (*C*11), 127.1 (*C*9), 124.5 (*C*4), 112.6 (*C*6), 90.3 (*C*2), 71.1 (*C*7), 46.4 (*C*12), 21.4 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{16}H_{15}IO_3^+$ $[M+H]^+$ 383.0139, found 383.0140.

ν_{max} (film)/cm^{-1} 3030, 1706, 1574, 1412, 1307, 734.

m.p. 108 – 110 °C.

2-(3-(Benzyloxy)-2-iodo-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (266)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S11** (1.60 g, 4.20 mmol, 1.0 eq) in CH_2Cl_2 (25 mL), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.21 g, 6.30 mmol, 1.5 eq), *N*,*O*-dimethylhydroxylamine hydrochloride (614 mg, 6.30 mmol, 1.5 eq), and *N*,*N*-diisopropylethylamine (2.20 mL, 12.6 mmol, 3.0 eq). The resulting reaction mixture was stirred at rt arbitrarily for 16 h. To the reaction mixture was added H_2O (20 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1.0 M aqueous HCl solution (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as an off-white solid (1.19 g, 2.81 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.30 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.77 (m, 1H, *H*4), 6.59 (s, 1H, *H*6), 5.12 (s, 2H, 2 × *H*7), 3.98 (s, 2H, 2 × *H*12), 3.74 (s, 3H, OCH_3), 3.24 (s, 3H, NCH_3), 2.30 (s, 3H, ArCH_3).

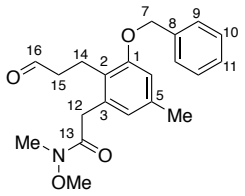
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.7 (*C*13), 157.3 (*C*1), 139.9 (*C*3), 139.2 (*C*8), 136.7 (*C*5), 128.5 (*C*10), 127.8 (*C*11), 127.0 (*C*9), 124.2 (*C*4), 112.1 (*C*6), 90.5 (*C*2), 71.0 (*C*7), 61.5 (OCH_3), 44.8 (*C*12), 32.5 (NCH_3), 21.4 (ArCH_3).

HRMS (ESI) calcd for $C_{18}H_{21}INO_3^+$ $[M+H]^+$ 426.0561, found 426.0556.

ν_{max} (film)/cm^{-1} 3031, 1664, 1573, 1411, 1380, 1176, 1091, 735.

m.p. 100 – 103 °C.

2-(3-(Benzyloxy)-5-methyl-2-(3-oxopropyl)phenyl)-*N*-methoxy-*N*-methylacetamide (268)



Following a modified procedure of Xiao *et al*.,[56] to a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged **266** (1.19 g, 2.80 mmol, 1.0 eq), cataCXium® PintB (56.7 mg, 0.17 mmol, 0.060 eq) and $Pd(dba)_2$ (32.2 mg, 0.0560 mmol, 0.020 eq). The Schlenk tube was evacuated and refilled with argon three times. To the Schlenk tube was added DMF (11.0 mL), distilled allyl alcohol (0.210 mL, 3.08 mmol, 1.1 eq) and distilled *N*,*N*-dimethylcyclohexylamine (0.660 mL, 3.08 mmol, 1.1 eq). The reaction mixture was stirred at 100 °C for 3 h until complete consumption of starting material, as indicated by TLC. The reaction vessel was then cooled to rt. To the reaction mixture was added H_2O (20 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as a yellow oil (0.969 mg, 2.72 mmol, 97%).

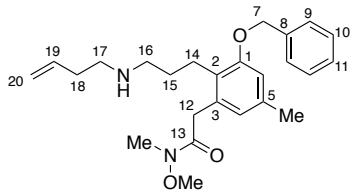
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (br s, 1H, *H*16), 7.46 – 7.29 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.68 – 6.67 (m, 2H, *H*4, *H6*), 5.05 (s, 2H, 2 × *H*7), 3.79 (s, 2H, 2 × *H*12), 3.68 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 2.96 (t, *J* = 7.5 Hz, 2H, 2 × *H*14), 2.69 (t, *J* = 7.5 Hz, 2H, *H*15), 2.29 (s, 3H, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 202.8 (*C*16), 156.9 (*C*13), 137.4 (*C*1), 137.0 (*C*8), 134.4 (*C*3), 128.7 (*C*5), 128.0 (*C*10), 127.2 (overlapping signals, *C*9, *C*11), 125.3 (*C*2), 124.0 (*C*4), 111.5 (*C*6), 70.1 (*C*7), 61.5 (O*C*H_3), 43.8 (*C*15), 36.7 (*C*12), 32.5 (N*C*H_3), 21.6 (Ar*C*H_3), 19.3 (*C*14).

HRMS (ESI) calcd for $C_{21}H_{25}NO_4Na^+$ $[M+Na]^+$ 378.1676, found 378.1670.

ν_{max} (film)/cm^{-1} 2936, 2724, 1721, 1663, 1580, 1454, 1415, 1381, 1279, 1143, 1029, 739.

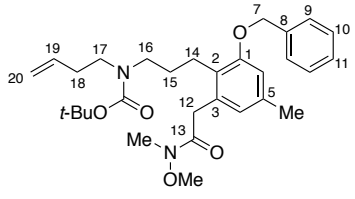
2-(3-(Benzyloxy)-2-(3-(but-3-en-1-ylamino)propyl)-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (S12)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution a solution of **268** (1.06 g, 2.98 mmol, 1.0 eq) in MeOH (18.0 mL), but-3-en-1-amine (0.550 mL, 5.96 mmol, 2.0 eq), and acetic acid (0.850 mL, 14.9 mmol, 5.0 eq). The reaction mixture was stirred at rt for 30 min, and then cooled to 0 °C. To the cooled reaction mixture was added sodium cyanoborohydride (375 mg, 5.96 mmol, 2.0 eq) in one portion, and the reaction mixture was allowed to warm to rt and stirred arbitrarily for 16 h. The reaction was quenched by the addition of 1.0 M aqueous NaOH solution until pH paper indicated pH 11 was reached, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The crude residue (1.07 g) was used in subsequent chemistry without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 – 7.32 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.75 (s, 1H, *H*4), 6.64 (s, 1H, *H*6), 5.67 – 5.54 (m, 1H, *H*19), 5.10 – 5.03 (m, 4H, 2 × *H*20, 2 × *H*7), 3.79 (s, 2H, 2 × *H*12), 3.72 (s, 3H, OCH_3), 3.24 (s, 3H, NCH_3), 2.89 – 2.83 (m, 2H, 2 × *H*16), 2.83 – 2.72 (m, 4H, 2 × *H*14, 2 × *H*17), 2.34 – 2.22 (m, 5H, 2 × *H*18, ArCH_3), 2.13 – 1.99 (m, 2H, 2 × *H*15).

***tert*-Butyl (3-(2-(benzyloxy)-6-(2-(methoxy(methyl)amino)-2-oxoethyl)-4-methylphenyl)propyl)(but-3-en-1-yl)carbamate (270)**



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of crude **S12** (1.07 g, assumed to be 2.61 mmol, 1.0 eq) in CH_2Cl_2 (26.0 mL), and

triethylamine (0.440 mL, 3.31 mmol, 1.2 eq). The resulting solution was cooled to 0 °C. To the cooled reaction mixture was added di-*tert*-butyl-dicarbonate (683 mg, 3.31 mmol, 1.2 eq). The reaction mixture was allowed to warm to rt and stirred arbitrarily for 16 h. To the reaction mixture was added H_2O (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as a colourless viscous oil (1.61 g, 1.10 mmol, 37% from **S12**).

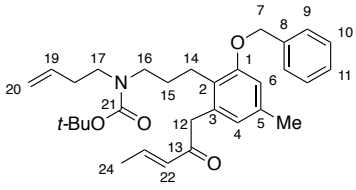
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.45 – 7.28 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.66 (s, 2H, *H*4, *H*6), 5.70 (br s, 1H, *H*19), 5.08 – 4.93 (m, 4H, 2 × *H*7, 2 × *H*20), 3.75 (s, 2H, 2 × *H*12), 3.68 – 3.59 (m, 3H, OCH_3), (3.26 – 3.04, m, 7H, NCH_3, 2 × *H*16, 2 × *H*17), 2.66 – 2.59 (m, 2H, 2 × *H*14), 2.28 (s, 3H, ArCH_3), 2.23 – 2.15 (m, 2H, 2 × *H*18), 1.75 – 1.64 (m, 2H, 2 × *H*15), 1.44 – 1.36 (m, 9H, C(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.8 (*C*13), 156.8 (*C*1), 155.6 (*C*O(O*t*-Bu), 137.6 (*C*8), 136.3 (*C*3), 135.7 (*C*19), 134.1 (*C*5), 128.6 (*C*10), 127.8 (*C*11), 127.2 (*C*9), 126.6 (*C*2), 123.5 (*C*4), 116.4 (*C*20), 111.4 (*C*6), 79.0 (O*C*(CH$_3$)$_3$), 70.0 (*C*7), 61.4 (NO*C*H$_3$), 47.1 (N*C*H$_2$), 46.4 (N*C*H$_2$), 36.5 (*C*12), 32.7 (*C*18), 32.4 (ON*C*H$_3$), 28.7 (*C*15), 28.5 (OC(*C*H$_3$)$_3$), 23.9 (*C*14), 21.5 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{30}H_{42}N_2O_5Na^+$ $[M+Na]^+$ 533.2986, found 533.2993.

ν_{max} (film)/cm^{-1} 2921, 1688 (broad), 1580, 1455, 1416, 1365, 1302, 1248, 1164, 914.

tert-Butyl (*E*)-(3-(2-(benzyloxy)-4-methyl-6-(2-oxopent-3-en-1-yl)phenyl)propyl)(but-3-en-1-yl)carbamate (272)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a cooled solution of **270** (53.0 mg, 0.104 mmol, 1.0 eq) in THF (2.60 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added allylmagnesium bromide (1.0 M solution in

THF, 0.210 mL, 0.208 mmol, 2.0 eq). The ice-bath was removed and the resulting solution was stirred for 20 min until complete consumption of starting material, as indicated by TLC. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) at 0 °C. The resulting reaction mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*.

A stirrer bar was added to the crude residue in a round-bottomed flask. The reaction flask was then flushed with argon, and was charged with Et_2O (1 mL), and alumina (20.0 mg). The reaction mixture was stirred at rt arbitrarily for 16 h, before being filtered through a pad of Celite® (eluting with EtOAc, 5 mL), and the solvents were removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (5:95, v:v) afforded the title compound as a yellow oil (40.3 mg, 0.0811 mmol, 78%).

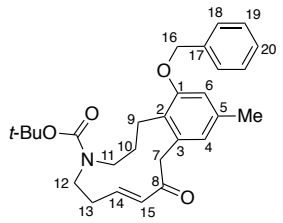
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.49 – 7.35 (m, 4H, 2 × *H*9, 2 × *H*10), 7.35 – 7.29 (m, 1H, *H*11), 7.00 – 6.89 (m, 1*H*, *H*23), 6.69 (br s, 1H, *H*4), 6.58 (br s, 1H, *H*6), 6.27 – 6.19 (m, 1H, *H*22), 5.78 – 5.61 (m, 1H, *H*19), 5.05 (s, 2H, 2 × *H*7), 5.04 – 4.94 (m, 2H, 2 × *H*20), 3.80 (br s, 2H, 2 × *H*12), 3.27 – 3.03 (m, 4H, 2 × *H*16, 2 × *H*17), 2.60 – 2.51 (m, 2H, 2 × *H*14), 2.29 (s, 3H, ArCH_3), 2.26 – 2.12 (m, 2H, 2 × *H*18), 1.89 (dd, *J* = 6.9, 1.7 Hz, 3H, 3 × *H*24), 1.72 – 1.60 (m, 2H, 2 × *H*15), 1.48 – 1.38 (m, 9H, $C(CH_3)_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7 (*C*13, minor rotamer), 197.4 (*C*13, major rotamer), 157.0 (*C*1), 155.6 (*C*21), 143.4 (*C*23), 137.6 (*C*8), 136.6 (*C*5), 135.8 (*C*19), 133.9 (*C*3), 131.0 (*C*22, minor rotamer), 130.7 (*C*22, major rotamer), 128.6 (*C*9), 127.9 (*C*10), 127.2 (*C*11), 126.8 (*C*2), 124.1 (*C*4, minor rotamer), 124.0 (*C*4, major rotamer), 116.4 (*C*20), 111.6 (*C*6), 79.1 ($OC(CH_3)_3$), 70.0 (*C*7), 47.6 (major rotamer, *C*16), 47.2 (minor rotamer, *C*16), 46.5 (*C*17), 45.6 (*C*12, major rotamer), 45.2 (*C*12, minor rotamer), 33.3 (*C*18, minor rotamer), 32.8 (*C*18, major rotamer), 28.7 (*C*15, major rotamer), 28.5 ($C(CH_3)_3$), 28.2 (*C*15, minor rotamer), 24.1 (*C*14), 21.5 ($ArCH_3$), 18.4 (*C*24).

HRMS (ESI) calcd for $C_{31}H_{42}NO_4^+$ $[M+H]^+$ 492.3108, 492.3087.

ν_{max} (film)/cm^{-1} 2973, 1687 (broad), 1628, 1578, 1270, 1162, 1145, 772.

tert-Butyl (_E_)-14-(benzyloxy)-12-methyl-9-oxo-2,3,5,6,9,10-hexahydrobenzo[_e_][1]azacyclododecine-4(1_H_)-carboxylate (264)



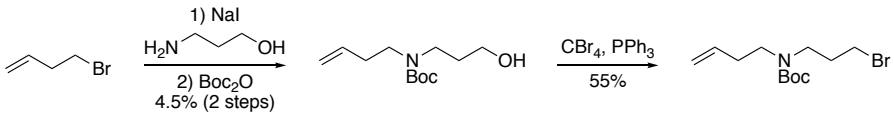
To a flame-dried, argon-flushed 2-necked round-bottomed flask equipped with a condenser was added a solution of **272** (20.0 mg, 0.0407 mmol, 1.0 eq) in freshly freeze-pump thawed CH_2Cl_2 (7.00 mL), and a solution of Grubbs' 2nd Generation catalyst (8.5 mg, 0.0102 mmol, 0.25 eq) in CH_2Cl_2 (1.10 mL). The reaction was stirred at 40 °C arbitrarily for 16 h. The reaction mixture was allowed to cool to rt before being filtered through a pad of Celite® (eluting with EtOAc, 5 mL), and the solvents removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:5, v:v) afforded the title compound as a yellow oil (8.8 mg, 0.0195 mmol, 48%).

^{1}H NMR (500 MHz, toluene-d_8) δ_H 7.33 – 7.27 (m, 2H, 2 × *H*18), 7.26 – 7.16 (m, 2H, 2 × *H*19), 7.07 – 7.04 (m, 2H, *H*4, *H*20), 6.84 – 6.70 (m, 1H, *H*14), 6.49 (s, 1H, *H*6), 6.06 (d, *J* = 16.0 Hz, 1H, *H*15), 4.73 (s, 2H, 2 × *H*16), 3.62 (s, 2H, 2 × *H*7), 3.21 – 2.72 (m, 6H, 2 × *H*11, 2 *H*12, 2 × H9), 2.46 – 2.39 (m, 1H, $H13_a$), 2.19 (s, 4H, $H13_b$, ArCH_3), 1.48 (s, 9H, OC(CH_3)$_3$), 1.39 – 1.27 (m, 2H, 2 × *H*10).

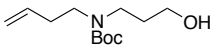
^{13}C NMR (126 MHz, toluene-d_8) δ_C 197.3 (*C*8), 157.4 (*C*1), 156.1 (N*C*(O)O*t*-Bu), 145.9 (*C*14), 138.2 (*C*17), 136.5 (*C*5), 135.5 (*C*3), 134.0 (*C*15), 128.3 (C19), 127.7 (*C*20), 126.8 (*C*18) , 125.8 (*C*2), 125.0 (*C*4), 111.6 (*C*6), 79.0 (O*C*(CH_3)$_3$), 69.9 (*C*16), 50.7 (*C*11), 50.3 (*C*12), 42.9 (*C*7), 30.3 (*C*13), 29.8 (*C*10), 28.5 (OC(*C*H_3)$_3$), 25.7 (*C*9), 21.1 (Ar*C*H_3).

HRMS (APCI) calcd for $C_{28}H_{34}NO_4^-$ $[M-H]^-$ 448.2493, found 448.2492.

ν_{max} (film)/cm^{-1} 2921, 1716, 1690, 1576, 1455, 1303, 1277, 1244, 1182, 1092, 801.



tert-Butyl but-3-en-1-yl(3-hydroxypropyl)carbamate



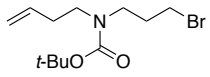
To a round-bottomed flask equipped with a stirrer bar was charged a solution of 4-bromo-1-butene (0.500 mL, 4.93 mmol, 1.0 eq) in MeOH (20.0 mL), 3-amino-1-propanol (1.10 mL, 14.8 mmol, 3.0 eq), and sodium iodide (185 mg, 1.23 mmol, 0.25 eq). The reaction was refluxed arbitrarily for 3 h. The reaction was then allowed to cool to rt, and the solvent was removed *in vacuo*. To the residue was added saturated aqueous NH_4CL (20 mL) and EtOAc (20 mL). The layers were separated. The aqueous layers were treated with 1.0 M aqueous NaOH solution until the pH paper indicated pH > 12. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The dark yellow crude residue (46.9 mg) was used in subsequent chemistry without further purification.

The crude residue (46.9 mg, assumed to be 0.364 mmol, 1.0 eq) was transferred to a round-bottomed flask equipped with a stirrer bar. The reaction flask was cooled to 0 °C. To the cooled reaction vessel was added CH_2Cl_2 (0.890 mL), 1.0 M aqueous NaOH (0.890 mL), and di-*tert*-butyl-dicarbonate (87.3 mg, 0.400 mmol, 1.1 eq). The resulting mixture was warmed to rt and stirred arbitrarily for 18 h. The layers were separated. The organic layer was washed with H_2O, dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was passed through a silica plug (eluting with MeOH/CH_2Cl_2 (1:9, v:v)), and the filtrate was concentrated concentrated *in vacuo*. The yellow crude residue (51.0 mg) was used in subsequent chemistry without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.83 – 5.66 (m, 1H, C*H*=CH_2), 5.08 – 4.97 (m, 2H, CH=C*H*$_2$), 3.57 – 3.47 (m, 2H, OC*H*$_2$), 3.41 – 3.30 (m, 2H, NC*H*$_2$), 3.21 – 3.11 (m, 2H), 2.26 (q, *J* = 7.4 Hz, 2H), 1.72 – 1.56 (m, 2H, $NCH_2CH_2CH_2$), 1.44 (s, 9H, OC(C*H*$_3$)$_3$).

These data are consistent with those previously published for this compound.[167]

tert-Butyl (3-bromopropyl)(but-3-en-1-yl)carbamate (290)



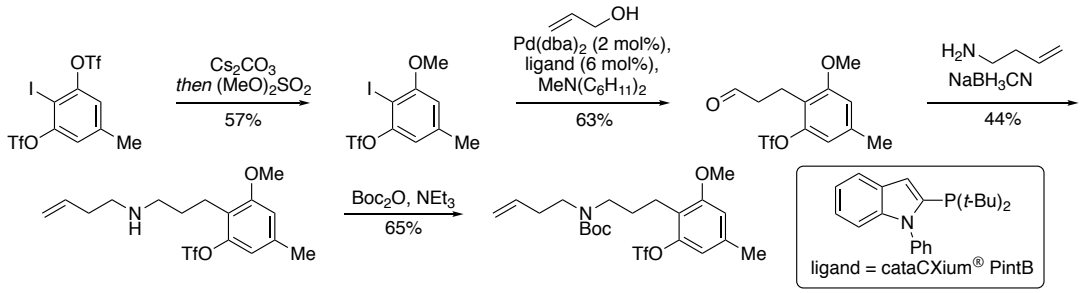
To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of *tert*-butyl but-3-en-1-yl(3-hydroxypropyl)carbamate (51.0 mg, assumed to be 0.222 mmol, 1.0 eq) in CH_2Cl_2 (0.740 mL). The reaction flask was cooled to 0 °C. To the cooled reaction vessel was added PPh_3 (89.8 mg, 0.342 mmol, 1.5 eq), and a solution of CBr_4 (114 mg, 0.342 mmol, 1.5 eq) in CH_2Cl_2 (0.430 mL). The resulting bright yellow mixture was warmed to rt and was stirred at this temperature for 1 h until complete consumption of the starting material, as indicated by TLC. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL), and was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as a colourless liquid (35.7 mg, 0.122 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.82 – 5.69 (m, 1H, C*H*=CH_2), 5.09 – 4.98 (m, 2H, CH=CH_2), 3.38 (t, *J* = 6.6 Hz, 2H, CH_2Br), 3.33 – 3.20 (m, 4H, CH_2NCH_2), 2.32 – 2.22 (m, 2H, CH_2=CHCH_2), 2.12 – 2.02 (m, 2H, C$H_2$$CH_2$Br), 1.44 (s, 9H, OC(C$H_3$)$_3$).

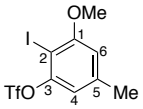
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.6 (N*C*O(O*t*-Bu), 135.5 (*C*H=CH_2), 116.8 (CH=*C*H_2), 79.7 (O*C*(CH_3)$_3$), 47.7 (N*C*H_2), 46.2 (N*C*H_2), 33.2 (CH_2=CH*C*H_2), 31.7 (*C*$H_2$$CH_2$Br), 30.9 (*C*$H_2$Br), 28.5 (OC(*C*$H_3$)$_3$).

HRMS (EI) cald for $C_{12}H_{22}{}^{79}BrNO_2Na^+$ $[M+Na]^+$ 314.0726, found 314.0727.

ν_{max} (film)/cm^{-1} 3077, 2975, 1689, 1641, 1477, 1158, 886.



2-Iodo-3-methoxy-5-methylphenyl trifluoromethanesulfonate (261)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **235** (12.4 g, 24.0 mmol, 1.0 eq) in DME (48.0 mL), and cesium carbonate (15.7 g, 48.1 mmol, 2.0 eq). The reaction mixture was heated at 80 °C for 3 h until complete consumption of starting material, as indicated by TLC. After this time, the reaction flask was cooled to 0 °C. To the cooled reaction was added dropwise dimethyl sulfate (3.18 mL, 33.7 mmol, 1.4 eq). The reaction mixture was allowed to warm to rt and was stirred for 1 h until complete consumption of the mono-deprotected intermediate, as indicated by TLC. After this time, the reaction mixture was cooled to 0 °C, and diethylamine (0.630 mL) was added to the reaction vessel to quench excess dimethyl sulfate. After stirring at 0 °C for 30 min, to the reaction mixture was added 1.0 M aqueous HCl solution (20 mL). The reaction mixture was then allowed to warm to rt, and the layers were separated. The aqueous layers were extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The crude residue was passed through a plug of silica, eluting with Et_2O/pet. ether (50 mL, 3:7, v:v), concentrated, and cooled until solidified. The cold residue was then triturated with cold hexane (0 °C, 50 mL) to afford the titled compound as a colourless powder (5.43 g, 13.7 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.78 (s, 1H, *H*4), 6.63 (s, 1H, *H*6), 3.90 (s, 3H, OCH_3), 2.38 (s, 3H, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 160.0 (Ar*C*), 151.1 (Ar*C*), 141.5 (Ar*C*), 118.9 (q, J_{CF} = 320 Hz, *C*F_3), 115.0 (Ar*C*), 111.4 (Ar*C*), 78.5 (Ar*C*), 57.0 (O*C*H_3), 21.8 (Ar*C*H_3).

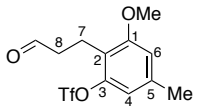
^{19}F NMR (377 MHz, $CDCl_3$) δ –73.2.

HRMS (APCI) calcd for $C_9H_8F_3IO_4S^+$ $[M]^+$ 395.9135, found 395.9135.

ν_{max} (film)/cm^{-1} 2944, 1598, 1407, 1216, 1079, 977, 813.

m.p. 76 – 78 °C.

3-Methoxy-5-methyl-2-(3-oxopropyl)phenyl trifluoromethanesulfonate (S13)



Following a modified procedure of Xiao *et al.*,[56] to a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged **261** (557 mg, 1.41 mmol, 1.0 eq), cataCXium® PintB (28.5 mg, 0.0844 mmol, 0.060 eq), and $Pd(dba)_2$ (16.2 mg, 0.0281 mmol, 0.020 eq). The Schlenk tube was evacuated and refilled with argon three times. To the Schlenk tube was added DMF (5.60 mL), allyl alcohol (0.110 mL, 1.51 mmol, 1.1 eq) and *N*,*N*-dimethylcyclohexylamine (0.330 mL, 1.51 mmol, 1.1 eq). The reaction mixture was stirred at 100 °C for 3 h until complete consumption of starting material, as indicated by TLC. The reaction flask was then cooled to rt. To the reaction mixture was added H_2O (10 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as an orange viscous oil (290 mg, 0.888 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.79 (br s, 1H, C*H*O), 6.70 (s, 1H, *H*4), 6.68 (s, 1H, *H*6), 3.83 (s, 3H, OCH_3), 2.97 (t, *J* = 7.4 Hz, 2H, 2 × *H*8), 2.67 (t, *J* = 7.4 Hz, 2H, 2 × *H*7), 2.36 (s, 3H, ArCH_3).

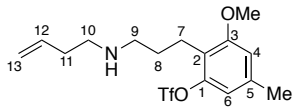
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.6 (*C*9), 158.6 (*C*1), 147.9 (*C*3), 139.0 (*C*5), 119.2 (*C*2), 118.6 (q, J_{CF} = 320 Hz, *C*F_3), 114.0 (*C*4), 111.3 (*C*6), 56.0 (O*C*H_3), 42.9 (*C*7), 21.7 (Ar*C*H_3), 17.1 (*C*8).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F –73.9.

HRMS (ESI) calcd for $C_{12}H_{14}F_3O_5S^+$ $[M+H]^+$ 327.0509, found 327.0511.

ν_{max} (film)/cm^{-1} 2976, 1727, 1626, 1465, 1415, 1209, 1138, 818.

2-(3-(But-3-en-1-ylamino)propyl)-3-methoxy-5-methylphenyl trifluoromethanesulfonate (S14)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S13** (50.0 mg, 0.153 mmol, 1.0 eq) in MeOH (0.610 mL), and but-3-en-1-amine (0.0150 mL, 0.169 mmol, 1.1 eq). The resulting reaction mixture was stirred at rt arbitrarily for 18 h. After this time, the reaction mixture was cooled to 0 °C, and sodium borohydride (9.3 mg, 0.245 mmol, 1.6 eq) was added. The ice-bath was removed, and the reaction was stirred for 10 min until the imine intermediate has been consumed, as indicated by TLC. The reaction was quenched with 1.0 M aqueous NaOH solution (1 mL), and mixture was extracted with Et_2O (3 × 1 mL). The combined organic layers were washed dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2/NEt_3 (5:95:0.1, v:v:v) afforded the title compound as an orange viscous oil (25.8 mg, 0.0673 mmol, 44%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 6.72 – 6.61 (m, 2H, *H*4, *H*6), 5.92 – 5.63 (m, 1H, *H*12), 5.19 – 4.92 (m, 2H, 2 × *H*13), 3.81 (s, 3H, OCH_3), 2.82 – 2.48 (m, 6H, 2 × *H*7, 2 × *H*9, 2 × *H*10), 2.48 – 1.94 (m, 5H, ArCH_3, 2 × *H*11), 1.84 – 1.64 (m, 2H, 2 × *H*8).

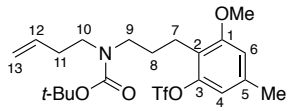
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.6 (*C*1), 148.2 (*C*3), 138.2 (*C*5), 136.4 (*C*12), 120.9 (*C*2), 118.5 (q, J_{CF} = 319 Hz, *C*F_3), 116.5 (*C*13), 113.7 (*C*4), 111.2 (*C*6), 55.9 (O*C*H_3), 49.4 (*C*10), 48.7 (*C*9), 34.3 (*C*11), 29.0 (*C*7), 21.8 (*C*8), 21.6 (Ar*C*H_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F –74.1.

HRMS (ESI) calcd for $C_{16}H_{23}F_3NO_4S^+$ $[M+H]^+$ 382.1294, found 382.1292.

ν_{max} (film)/cm^{-1} 2938, 1622, 1578, 1497, 1416, 1289, 1246, 1212, 1141, 1064, 819.

2-(3-(But-3-en-1-yl(*tert*-butoxycarbonyl)amino)propyl)-3-methoxy-5-methylphenyl trifluoromethanesulfonate (292)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **S14** (39.0 mg, 0.102 mmol, 1.0 eq) in CH_2Cl_2 (1.00 mL), triethylamine (17.0 μL, 0.122 mmol, 1.2 eq), and di-*tert*-butyl-dicarbonate (26.6 mg, 0.122 mmol, 1.2 eq). The reaction mixture was stirred at rt arbitrarily for 16 h. To the reaction mixture was added H_2O (2 mL), and the mixture was extracted with CH_2Cl_2 (3 × 2.0 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as a colourless oil (31.9 mg, 0.063 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.73 – 6.62 (m, 2H, *H*4, *H*6), 5.84 – 5.68 (m, 1H, *H*12), 5.11 – 4.96 (m, 2H, 2 × *H*13), 3.83 (s, 3H, OCH_3), 3.34 – 3.14 (m, 4H, 2 × *H*9, 2 × *H*10), 2.67 – 2.56 (m, 2H, 2 × *H*7), 2.35 (s, 3H, ArCH_3), 2.31 – 2.24 (m, 2H, 2 × *H*11), 1.79 – 1.67 (m, 2H, 2 × *H*8), 1.43 (s, 9H, OC(CH_3)$_3$).

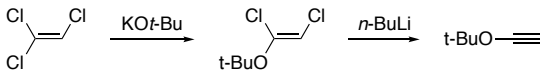
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.6 (*C*1), 155.7 (*C*(O)O*t*-Bu), 148.2 (*C*3), 138.3 (*C*5), 135.8 (*C*12), 120.9 (*C*2), 118.7 (q, J_{CF} = 320 Hz, *C*F_3), 116.5 (*C*13), 113.7 (*C*4), 111.2 (*C*6), 79.3 (O*C*(CH$_3$)$_3$), 56.0 (O*C*H$_3$), 46.8 (overlapping signals, *C*9, *C*10), 33.4 (*C*11, minor rotamer), 32.9 (*C*11, major rotamer), 28.5 (OC(*C*H$_3$)$_3$), 28.2 (*C*7, major rotamer), 27.6 (*C*7, minor rotamer), 21.7 (overlapping signals, *C*8, Ar*C*H$_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F –74.1.

HRMS (ESI) calcd for $C_{21}H_{30}F_3NO_6SNa^+$ $[M+Na]^+$ 504.1638, found 504.1630.

ν_{max} (film)/cm^{-1} 2980, 1693, 1642, 1467, 1416, 1213, 1143, 1067, 977, 819.

2-(Ethynyloxy)-2-methylpropane (295)



***CAUTION**: terminal ynol ethers should not be heated due to potential risk of explosion.*[112]

Following a procedure of Minehan and Tran,[113] to a flame-dried, argon-flushed Schlenk flask equipped with a stirrer bar was charged potassium *tert*-butoxide (7.10 g, 58.1 mmol, 1.0 eq). The solid was dried under high vacuum at 50 °C for 5 min. The flask was allowed to cool to rt and was charged with THF (94.0 mL). The resulting suspension was stirred and cooled to 0 °C, and to which was added dropwise trichloroethylene (5.70 mL, 58.1 mmol, 1.0 eq). The resulting brown mixture was slowly warmed to rt over 2 h. After this time, the flask was cooled down to 0 °C, and the reaction was quenched by the addition of H_2O (10 mL) and Et_2O (10 mL). The reaction was then warmed to rt. The layers were separated and the aqueous layers were extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. The crude brown oil was dissolved in pentane (5.0 mL), passed through a silica plug (eluting with pentane, 500 mL), and the filtrate was concentrated *in vacuo* to yield 1,2-dichlorovinyl *tert*-butyl ether as a colourless oil, which was used in subsequent chemistry without further purification.

The rest of this procedure was done behind a blast shield.

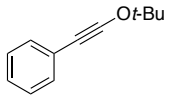
Following a modified procedure of Ready and Zhang,[112] crude 1,2-dichlorovinyl *tert*-butyl ether was transferred to an flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar, and was dissolved in THF (47.0 mL). The flask was cooled to –78 °C. To the cooled reaction vessel was added dropwise *n*-BuLi (2.5 M in hexanes, 76.0 mL, 174 mmol, 3.0 eq). The reaction was warmed to –40 °C, and was stirred at this temperature for 1 h. The reaction was quenched at –40 °C by the addition of H_2O (20 mL) and was then warmed to rt. The reaction was extracted with Et_2O (3 × 20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated on a nitrogen-flushed Buchi rotary evaporator over a cooled (25 °C) water bath, at 200 mbar, to afford the title compound as a light yellow liquid (6.72 g, 7.7% w:w in hexane and THF).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 1H, OCC*H*), 1.36 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 87.6, 86.0, 29.1, 26.9.

These data are consistent with those previously published for this compound.[168]

(*tert*-Butoxyethynyl)benzene

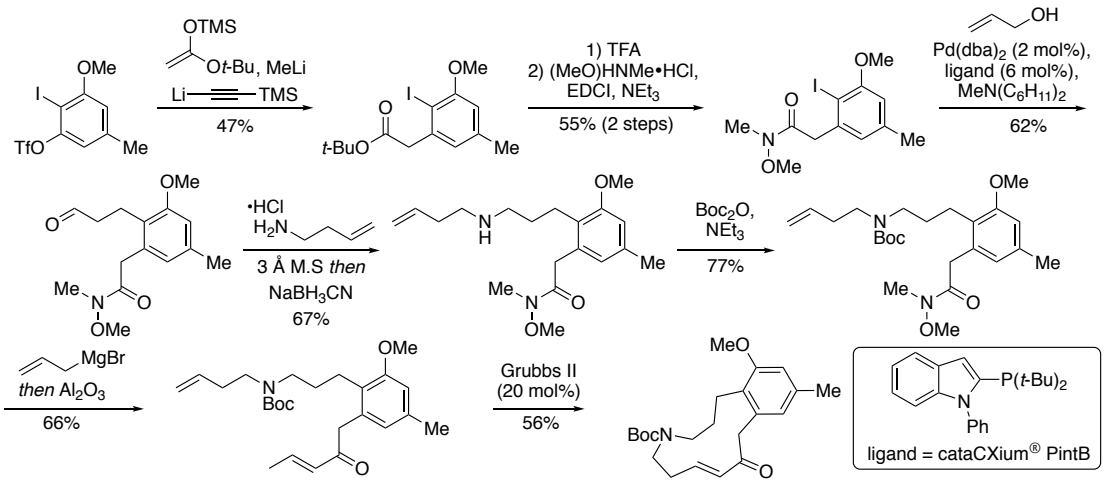


To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged $Pd(PPh_3)_4$ (25.0 mg, 0.0221 mmol, 0.10 eq), TBAI (122 mg, 0.331 mmol, 1.5 eq), CuI (4.2 mg, 0.0221 mmol, 0.10 eq), and powdered 4 Å molecular sieves (110 mg). The reaction flask was evacuated and refilled with argon three times. To the reaction vessel was added DMF (2.2 mL), NEt_3 (0.12 mL, 0.860 mmol, 4.0 eq), **295** (7.7% w:w in hexane and THF, 43.4 mg, 0.442 mmol, 2.0 eq), and phenyl trifluoromethanesulfonate (0.036 mL, 0.221 mmol, 1.0 eq). The resulting dark orange mixture was stirred at rt for 4 h, until complete consumption of starting material, as indicated by TLC. The reaction mixture was passed through an alumina plug (eluting with Et_2O/pet. ether (5:95, v:v), 5.0 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue *via* flash column chromatography eluting with pet. ether afforded the title compound as a yellow oil (27.0 mg, 0.155 mmol, 70% yield).

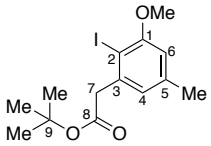
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.37 (m, 2H, 2 × Ar*H*), 7.31 – 7.28 (m, 3H, 3 × Ar*H*), 1.43 (s, 9H, $OC(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 131.5 (Ar*C*), 128.3 (Ar*C*), 126.4 (Ar*C*), 124.9 (Ar*C*), 94.3 (O*C*CPh), 87.6 ($OC(CH_3)_3$), 43.0 (OC*C*Ph), 27.4 ($OC(CH_3)_3$).

These data are consistent with those previously published for this compound.[112]



tert-Butyl 2-(2-iodo-3-methoxy-5-methylphenyl)acetate (262)



Following the procedure of Suzuki and Hamura,[73] to a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **229** (1.83 g, 3.85 mmol, 3.9 eq) in THF (35.0 mL). The reaction flask was cooled to 0 °C. To the cooled reaction vessel was added methyllithium (1.6 M in Et_2O, 5.89 mL, 9.42 mmol, 3.7 eq). The resulting solution was stirred at 0 °C for further 30 min, and was then cooled to –78 °C. To the cooled reaction mixture was added a solution of **261** (1.00 g, 2.52 mmol, 1.0 eq) in THF (35 mL), and ((trimethylsilyl)ethynyl)lithium (0.5 M in THF, 0.720 mL, 0.252 mmol, 0.10 eq, prepared by stirring a solution of ethynyltrimethylsilane (50.0 μL) in THF (0.700 mL) with *n*-BuLi (1.6 M in hexane, 0.220 mL) at –78 °C for 30 min). The resulting solution was warmed to –30 °C and was stirred at this temperature for further 2 h until complete consumption of starting material, as indicated by TLC. The reaction mixture was quenched with H_2O (20 mL) at –30 °C and was allowed to warm to rt. The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with Et_2O/pet. ether (1:9, v:v) afforded the title compound as a yellow oil (433 mg, 1.18 mmol, 47%).

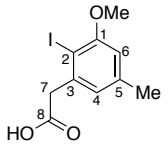
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.74 (s, 1H, *H*4), 6.53 (s, 1H, *H*6), 3.86 (s, 3H, OCH_3), 3.72 (s, 2H, 2 × *H*7), 2.32 (s, 3H, ArCH_3), 1.47 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.2 (*C*8), 158.3 (*C*1), 139.9 (*C*3), 139.4 (*C*5), 124.3 (*C*4), 110.6 (*C*6), 89.5 (*C*2), 81.2 (O*C*(CH$_3$)$_3$), 56.6 (O*C*H$_3$), 47.8 (*C*7), 28.2 (OC(*C*H$_3$)$_3$), 21.4 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{14}H_{19}IO_3Na^+$ $[M+Na]^+$ 385.0271, found 385.0270.

ν_{max} (film)/cm^{-1} 2978, 1730, 1574, 1453, 1146, 1087, 847.

2-(2-Iodo-3-methoxy-5-methylphenyl)acetic acid (S15)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **262** (425 mg, 1.17 mmol) in CH_2Cl_2 (0.730 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added dropwise trifluoroacetic acid (0.730 mL). The reaction was allowed to warm to rt and was stirred for 30 min until complete consumption of starting material, as indicated by TLC. After this time, the reaction mixture was diluted with EtOAc (2 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (1 mL), and the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl solution (1 mL). The combined aqueous layers were re-extracted with EtOAc (3 × 1 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as a colourless solid (337 mg, 1.10 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.90 (br s, COO*H*), 6.76 (s, 1H, *H*4), 6.56 (s, 1H, *H*6), 3.87 (s, 5H, OCH_3, 2 × *H*7), 2.33 (s, 3H, ArCH_3).

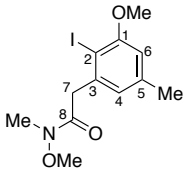
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.1 (*C*8), 158.3 (*C*1), 139.6 (*C*3), 138.5 (*C*5), 124.2 (*C*4), 111.0 (*C*6), 89.5 (*C*2), 56.6 (O*C*H$_3$), 46.4 (*C*7), 21.4 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{10}H_{11}IO_3Na^+$ $[M+Na]^+$ 328.9645, found 328.9645.

ν_{max} (film)/cm^{-1} 2921, 1709, 1574, 1451, 1408, 1179, 1087, 1014, 834.

m.p. 115 – 117 °C.

2-(2-Iodo-3-methoxy-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (267)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **S15** (303 mg, 0.990 mmol, 1.0 eq) in CH_2Cl_2 (5.90 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (145 mg, 1.48 mmol, 1.5 eq), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (285 mg, 1.48 mmol, 1.5 eq), and *N*,*N*-diisopropylethylamine (0.520 mL, 2.97 mmol, 3.0 eq). The reaction mixture was stirred at rt arbitrarily for 18 h. After this time, the reaction mixture was diluted with H_2O (10 mL). The layers were separated and the aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 1.0 M aqueous HCl (5 mL), brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as an off-white paste (203 mg, 0.584 mmol, 59%).

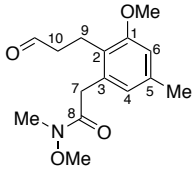
^{1}H NMR (200 MHz, $CDCl_3$) δ_H 6.75 (s, 1H, *H*4), 6.54 (s, 1H, *H*6), 3.95 (s, 2H, 2 × *H*7), 3.86 (s, 3H, ArOCH_3), 3.73 (s, 3H, NOCH_3), 3.23 (s, 3H, NCH_3), 2.31 (s, 3H, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.8 (*C*8), 158.2 (*C*1), 139.8 (*C*3), 139.4 (*C*5), 123.9 (*C*4), 110.7 (*C*6), 89.9 (*C*2), 61.6 (NOCH_3), 56.6 (ArOCH_3), 44.9 (*C*7), 32.6 (NCH_3), 21.5 (ArCH_3).

HRMS (ESI) calcd for $C_{12}H_{16}INO_3Na^+$ $[M+Na]^+$ 372.0067, found 372.0068.

ν_{max} (film)/cm^{-1} 2851, 1719, 1574, 1446, 1408, 1379, 1323, 1179, 1085, 835.

***N*-Methoxy-2-(3-methoxy-5-methyl-2-(3-oxopropyl)phenyl)-*N*-methylacetamide (269)**



Following a modified procedure of Xiao *et al.*,[56] to a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged with **267** (194 mg, 0.556 mmol, 1.0 eq), cataCXium® PintB (11.2 mg, 0.0333 mmol, 0.060 eq), and $Pd(dba)_2$ (6.39 mg, 0.0111 mmol, 0.020 eq). The Schlenk tube was evacuated and refilled with argon three times. To the Schlenk tube was added DMF (2.20 mL), allyl alcohol (40.0 μL, 0.611 mmol, 1.1 eq) and *N*,*N*-dimethylcyclohexylamine (0.130 mL, 0.611 mmol, 1.1 eq). The reaction mixture was stirred at 100 °C for 3 h until complete consumption of starting material, as indicated by TLC. The reaction mixture was then cooled to rt. To the reaction mixture was added H_2O (5.0 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (3 × 5 mL) and brine (5 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as an orange viscous oil (96.0 mg, 0.345 mmol, 62%).

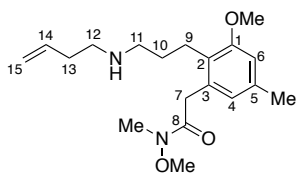
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.78 (s, 1H, C*H*O), 6.63 (s, 1H, *H*4), 6.59 (s, 1H, *H*6), 3.78 (s, 5H, ArOCH_3, 2 × *H*7), 3.66 (s, 3H, NOCH_3), 3.19 (s, 3H, NCH_3), 2.89 (t, *J* = 7.6 Hz, 2H, 2 × *H*10), 2.65 (t, *J* = 7.6 Hz, 2H, 2 × *H*9), 2.29 (s, 3H, ArCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 202.9 (*C*11), 172.5 (*C*8), 157.6 (*C*1), 136.9 (*C*3), 134.1 (*C*5), 124.8 (*C*2), 123.5 (*C*4), 110.2 (*C*6), 61.3 (NO*C*H_3), 55.3 (O*C*H_3), 43.7 (*C*10), 36.6 (*C*7), 32.4 (N*C*H_3), 21.5 (Ar*C*H_3), 19.2 (*C*9).

HRMS (ESI) calcd for $C_{15}H_{22}NO_4^+$ $[M+H]^+$ 280.1543, found 280.1547.

ν_{max} (film)/cm^{-1} 2983, 1719, 1661, 1582, 1461, 1413, 1326, 1281, 1145, 1101, 1003, 838.

2-(2-(3-(But-3-en-1-ylamino)propyl)-3-methoxy-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (S16)



To a flame-dried, argon-flushed vial equipped with a stirrer bar was added a solution of **269** (56.0 mg, 0.200 mmol, 1.0 eq) in MeOH (0.500 mL), activated 3 Å molecular sieves (103 mg), and 3-butenylamine hydrochloride (43.1 mg, 0.400 mmol, 2.0 eq). The resulting reaction mixture was stirred at rt for 30 min. To the vial was added sodium cyanoborohydride (31.5 mg, 0.501 mmol, 2.5 eq), and the resulting mixture was stirred at rt arbitrarily for 18 h. The reaction was then filtered through cotton wool (eluting with EtOAc, 2 mL), and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with $MeOH/CH_2Cl_2/NEt_3$ (1:9:0.1, v:v:v) afforded the title compound as a light yellow oil (45.2 mg, 0.134 mmol, 67%).

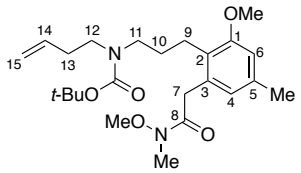
^1H NMR (400 MHz, $CDCl_3$) δ_H 6.60 (s, 2H, *H*4, *H*6), 6.11 (br s, 1H, N*H*), 5.76 – 5.59 (m, 1H, *H*14), 5.14 – 5.01 (m, 2H, 2 × *H*15), 3.83 – 3.71 (m, 5H, 2 × *H*7, ArOCH_3), 3.68 (s, 3H, NOCH_3), 3.21 (s, 3H, NCH_3), 2.88 – 2.82 (m, 4H, 2 × *H*11, 2 × *H*12), 2.67 (t, *J* = 7.3 Hz, 2H, 2 × *H*9), 2.34 (q, *J* = 7.0 Hz, 2H, 2 × *H*13), 2.28 (s, 3H, ArCH_3), 1.98 – 1.85 (m, 2H, 2 × *H*10).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.9 (*C*8), 157.9 (*C*1), 137.2 (*C*5), 134.1 (*C*3), 133.4 (*C*14), 124.8 (*C*2), 123.9 (*C*4), 118.3 (*C*15), 110.6 (*C*6), 61.6 (NO*C*H_3), 55.5 (ArO*C*H_3), 48.0 (overlapping signals, *C*11, *C*12), 36.7 (*C*7), 32.5 (N*C*H_3), 31.3 (*C*13), 25.8 (*C*10), 23.7 (*C*9), 21.5 (Ar*C*H_3).

HRMS (ESI) calcd for $C_{19}H_{31}N_2O_3^+$ $[M+H]^+$ 335.2329, found 335.2329.

ν_{max} (film)/cm^{-1} 2939, 1640, 1612, 1462, 1147, 1001, 842.

tert-Butyl but-3-en-1-yl(3-(2-methoxy-6-(2-(methoxy(methyl)amino)-2-oxoethyl)-4-methylphenyl)propyl)carbamate (271)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **S16** (247 mg, 0.741 mmol, 1.0 eq) in CH_2Cl_2 (7.70 mL), triethylamine (0.120 mL, 0.889 mmol, 1.2 eq), and di-*tert*-butyl-dicarbonate (194 mg, 0.889 mmol, 1.2 eq). The reaction mixture was stirred at rt arbitrarily for 16 h. To the reaction flask was added H_2O (10 mL), and the layers were separated. The aqueous layers

were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (3:7, v:v) afforded the title compound as a viscous light yellow oil (250 mg, 0.571 mmol, 77%).

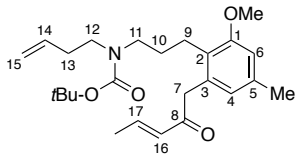
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.63 (s, 1H, *H*4), 6.58 (s, 1H, *H*6), 5.83 – 5.69 (m, 1H, *H*14), 5.09 – 4.96 (m, 2H, 2 × *H*15), 3.78 (s, 3H, ArOCH_3), 3.73 (s, 2H, 2 × *H*7), 3.61 (s, 3H, NOCH_3), 3.31 – 3.13 (m, 7H, 2 × *H*11, 2 × *H*12, NCH_3), 2.61 – 2.50 (m, 2H, 2 × *H*9), 2.31 – 2.23 (m, 5H, 2 × *H*13, ArCH_3), 1.71 – 1.60 (m, 2H, 2 × *H*10), 1.44 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.0 (*C*8), 157.7 (*C*1), 155.7 (N*C*(O)O*t*-Bu), 136.4 (*C*5), 135.9 (*C*14), 134.0 (*C*3), 126.4 (*C*2), 123.2 (*C*4), 116.4 (*C*15), 110.3 (*C*6), 79.1 (O*C*(CH$_3$)$_3$), 61.4 (NO*C*H$_3$), 55.5 (ArO*C*H$_3$), 47.8 (*C*11, major rotamer), 47.3 (*C*11, minor rotamer), 46.8 (*C*12), 36.6 (*C*7), 32.9 (*C*13), 32.5 (N*C*H$_3$), 28.6 (overlapping signals, *C*9, OC(*C*H$_3$)$_3$), 23.7 (*C*10), 21.6 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{24}H_{38}N_2O_5Na^+$ $[M+Na]^+$ 457.2673, found 457.2673.

ν_{max} (film)/cm^{-1} 2924, 1689 (broad), 1582, 1464, 1415, 1302, 1273, 1246, 1165, 1148, 1004, 912.

tert-Butyl (*E*)-but-3-en-1-yl(3-(2-methoxy-4-methyl-6-(2-oxopent-3-en-1-yl)phenyl)propyl)carbamate (273)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **271** (240 mg, 0.552 mmol, 1.0 eq) in THF (14 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added allylmagnesium bromide dropwise (1.0 M solution in Et_2O, 1.10 mL, 1.10 mmol, 2.0 eq). The ice-bath was removed and the resulting solution was stirred for 20 min until completion of starting material, as indicated by TLC. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL) at 0 °C. The resulting reaction mixture was warmed to room temperature. The layers were separated and the aqueous layers were extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and

the solvent removed *in vacuo*. The crude residue was then dissolved in Et_2O (5 mL), and to the solution was added alumina (200 mg). The reaction mixture was stirred at rt, arbitrarily for 16 h. After this time, the reaction mixture was filtered through a pad of Celite® (eluting with EtOAc, 10 mL), and the solvents were removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:9, v:v) afforded the title compound as a yellow oil (151 mg, 0.364 mmol, 66%).

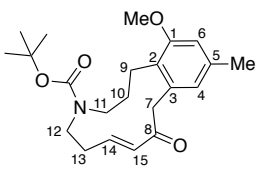
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.07 – 6.79 (m, 1H, *H*17), 6.63 – 6.51 (m, 2H, *H*4, *H*6), 6.28 – 6.08 (m, 1H, *H*16), 5.82 – 5.69 (m, 1H, *H*14), 5.08 – 4.96 (m, 2H, 2 × *H*15), 3.79 (s, 3H, OCH_3), 3.76 (s, 2H, 2 × *H*7), 3.29 – 3.14 (m, 4H, 2 × *H*11, 2 × *H*12), 2.55 – 2.42 (m, 2H, 2 × *H*9), 2.33 – 2.21 (m, 5H, ArCH_3, 2 × *H*13), 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H, CHCH_3), 1.68 – 1.58 (m, 2H, 2 × *H*10), 1.44 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 197.7 (*C*8, minor rotamer), 197.5 (*C*8, major rotamer), 157.8 (*C*1), 155.7 (N*C*(O)O*t*-Bu), 143.4 (*C*17), 136.6 (*C*5), 135.9 (*C*14), 133.8 (*C*3), 130.9 (*C*16, minor rotamer), 130.7 (*C*16, major rotamer), 126.6 (*C*2), 123.7 (*C*4), 116.4 (*C*15), 110.4 (*C*6), 79.2 (O*C*(CH$_3$)$_3$), 55.5 (O*C*H$_3$), 47.8 (*C*11, major rotamer), 47.3 (*C*11, minor rotamer), 46.9 (*C*12), 45.6 (*C*7, major rotamer), 45.4 (*C*7, minor rotamer), 33.5 (*C*13, minor rotamer), 33.0 (OC(*C*H$_3$)$_3$, minor rotamer), 32.9 (*C*13, major rotamer), 28.6 (overlapping signals, *C*10, OC(*C*H$_3$)$_3$, major rotamer), 23.9 (*C*9), 21.6 (Ar*C*H$_3$), 18.4 (CH*C*H$_3$).

HRMS (ESI) calcd for $C_{25}H_{37}NO_4Na^+$ $[M+Na]^+$ 438.2615, found 438.2613.

ν_{max} (film)/cm^{-1} 2973, 2931, 1689, 1629, 1581, 1415, 1364, 1163, 970, 835.

tert-Butyl (*E*)-14-methoxy-12-methyl-9-oxo-2,3,5,6,9,10-hexahydrobenzo[*e*][1]azacyclododecine-4(1*H*)-carboxylate (263)



To a flame-dried, argon-flushed 2-necked round-bottomed flask equipped with a stirrer bar and a condenser was added a solution of **273** (140 mg, 0.337 mmol, 1.0 eq) in freshly freeze-pump thawed

CH_2Cl_2 (45.0 mL). The solution was heated at 40 °C. To the refluxing solution was added dropwise a solution of Grubbs' 2nd Generation catalyst (57.0 mg, 0.0674 mmol, 0.22 eq) in freshly freeze-pump thawed CH_2Cl_2 (22.0 mL). The reaction was stirred at 40 °C arbitrarily for 16 h. The reaction mixture was allowed to cool to rt and filtered through a pad of Celite® (eluting with EtOAc, 10 mL) and the solvents removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as a yellow oil (71.0 mg, 0.188 mmol, 56%).

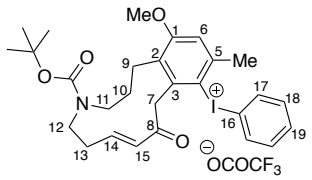
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.08 – 6.94 (m, 1H, *H*14), 6.84 (s, 1H, *H*6), 6.61 (s, 1H, *H*4), 6.24 – 6.15 (d, *J* = 15.0 Hz, 1H, *H*15), 3.83 – 3.73 (m, 5H, OCH_3, 2 × *H*7), 3.40 – 3.26 (m, 4H, 2 × *H*11, 2 × *H*12), 2.76 – 2.57 (m, 4H, 2 × *H*9, 2 × *H*13), 2.32 – 2.27 (m, 3H, ArCH_3), 1.53 – 1.47 (11H, 2 × *H*10, OC(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 199.6 (*C*8, minor rotamer), 199.5 (*C*8, major rotamer), 158.2 (*C*1, minor rotamer), 158.1 (*C*1, major rotamer), 156.7 (N*C*(O)O*t*-Bu, minor rotamer), 156.2 (N*C*(O)O*t*-Bu, major rotamer), 147.0 (*C*14, major rotamer), 146.4 (*C*14, minor rotamer), 136.9 (*C*5, major rotamer), 136.7 (*C*5, minor rotamer), 134.5 (*C*3, major rotamer), 134.1 (*C*3, minor rotamer), 133.9 (*C*15, minor rotamer), 133.8 (*C*15, major rotamer), 126.2 (*C*2, minor rotamer), 125.8 (*C*2, major rotamer), 125.0 (*C*4, major rotamer), 124.8 (*C*4, minor rotamer), 110.4 (*C*6, minor rotamer), 110.4 (*C*6, major rotamer), 79.9 (O*C*(CH$_3$)$_3$, minor rotamer), 79.8 (O*C*(CH$_3$)$_3$, major rotamer), 55.5 (O*C*H$_3$), 50.9 (*C*12, major rotamer), 50.4 (*C*12, minor rotamer), 50.3 (*C*11, major rotamer), 49.6 (*C*11, minor rotamer), 42.9 (*C*7, major rotamer), 42.6 (*C*7, minor rotamer), 31.6 (*C*13, minor rotamer), 30.4 (*C*13, major rotamer), 28.8 (*C*10), 28.6 (OC(*C*H$_3$)$_3$), 25.3 (*C*9, major rotamer), 25.2 (*C*9, minor rotamer), 21.5 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{22}H_{31}NO_4Na^+$ $[M+Na]^+$ 396.2145, found 396.2146.

ν_{max} (film)/cm^{-1} 2972, 2930, 1689 (broad signal), 1577, 1464, 1365, 1091, 982, 860, 732.

(*E*)-(4-(*tert*-Butoxycarbonyl)-14-hydroxy-12-methyl-9-oxo-1,2,3,4,5,6,9,10-octahydrobenzo[*e*][1]azacyclododecin-11-yl)(phenyl)iodonium 2,2,2-trifluoroacetate (283)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged **263** (11.0 mg, 0.0295 mmol, 1.0 eq), [bis(trifluoroacetoxy)iodo]benzene (13.9 mg, 0.0325 mmol, 1.1 eq), and $(CF_3)_2CHOH$ (0.150 mL). The resulting deep red solution was stirred at rt for 2 h until complete consumption of starting material, as indicated by TLC. The solvent was removed *in vacuo*, and the crude residue purified *via* column chromatography eluting with $MeOH/CH_2Cl_2$ (5:95, v:v) to afford the title compound as a bright yellow wax (9.8 mg, 0.0142 mmol, 48% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.99 – 7.85 (m, 2H, 2 × *H*17), 7.47 – 7.44 (m, 1H, *H*19), 7.36 – 7.34 (m, 2H, 2 × *H*18), 7.23 – 7.14 (m, 1H, *H*14), 6.73 (s, 1H, *H*6), 6.21 (d, *J* = 15.9 Hz, 1H, *H*15), 4.62 – 4.32 (m, 2H, 2 × *H*7), 3.81 – 3.77 (m, 3H, OCH_3), 3.43 – 3.23 (m, 4H, 2 × *H*11, 2 × *H*12), 2.93 – 2.56 (m, 4H, 2 × *H*9, 2 × *H*13), 2.40 – 2.39 (m, 3H, ArCH_3), 1.57 – 1.51 (m, 9H, OC(CH_3)$_3$), 1.43 – 1.35 (m, 2H, 2 × *H*10).

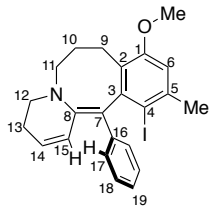
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 198.4 (*C*8), 160.8 (*C*1), 156.6 (N*C*(O)O*t*-Bu), 150.5 (*C*14), 142.4 (*C*5), 138.7 (*C*3), 133.6 (*C*17), 133.2 (*C*15), 131.5 (*C*18), 131.1 (*C*19), 129.3 (*C*2), 118.9 (*C*4), 117.4 (*C*16), 116.74 (q, *J* = 295 Hz, *C*F_3), 112.6 (*C*6), 80.4 (O*C*(CH$_3$)$_3$), 55.9 (O*C*H$_3$), 50.8 (N*C*H$_2$), 50.7 (N*C*H$_2$), 42.9 (*C*7), 31.8 (*C*13), 29.0 (*C*10), 28.7 (OC(*C*H$_3$)$_3$), 27.7 (Ar*C*H$_3$), 26.7 (*C*9).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F –75.2.

HRMS (ESI) calcd for $C_{28}H_{35}INO_4^+$ $[M]^+$ 576.1605, found 576.1601.

ν_{max} (film)/cm^{-1} 2974, 1683 (broad), 1585, 1461, 1415, 1318, 1271, 1090, 719.

(*Z*)-12-Iodo-9-methoxy-11-methyl-13-phenyl-3,6,7,8-tetrahydro-4*H*-benzo[*d*]pyrido[1,2-*a*]azocine (284)



^{1}H NMR (700 MHz, $CDCl_3$) δ_H 7.19 – 7.07 (m, 5H, 2 × *H*17, 2 × *H*18, *H*19), 6.72 (s, 1H, *H*6), 6.43 – 6.40 (m, 1H, *H*15), 5.99 – 5.95 (m, 1H, *H*14), 3.84 (s, 3H, OCH_3), 3.45 – 3.40 (m, 1H, $H9_a$), 3.21 – 3.13 (m, 2H, $H11_a$, $H12_a$), 3.05 – 3.00 (m, 1H, $H12_b$), 2.78 – 2.71 (m, 1H, $H11_b$), 2.61 – 2.55 (m, 1H, $H9_b$), 2.34 (s, 3H, $ArCH_3$), 2.33 – 2.26 (m, 1H, $H13_a$), 2.25 – 2.16 (m, 1H, $H13_b$), 2.01 – 1.93 (m, 1H, $H10_a$), 1.36 – 1.28 (m, 1H, $H10_b$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 155.9 (*C*1), 148.2 (*C*3), 141.8 (*C*8), 140.7 (*C*16), 140.3 (*C*5), 133.0 (*C*18), 128.6 (overlapping signals, *C*2, *C*7), 128.4 (*C*14), 126.7 (*C*19), 125.5 (*C*15), 125.3 (*C*17), 110.9 (*C*6), 98.0 (*C*4), 55.8 (OCH_3), 51.7 (*C*12), 50.4 (*C*11), 30.2 ($ArCH_3$), 26.5 (*C*10), 24.9 (*C*9), 23.1 (*C*13).

HRMS (ESI) calcd for $C_{23}H_{25}INO^+$ $[M+H]^+$ 458.0975, found 458.0973.

ν_{max} (film)/cm^{-1} 2919, 1684, 1593, 1456, 1327, 1158, 1091, 772.

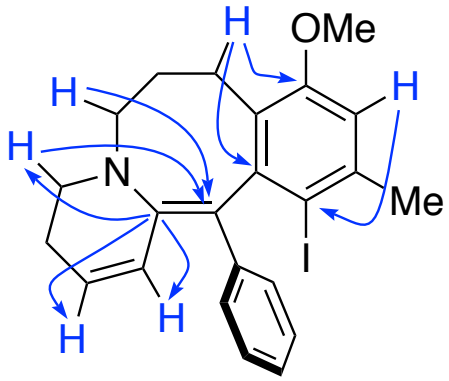


Figure 6.1 Selected HMBC correlations to elucidate the fused ring system.

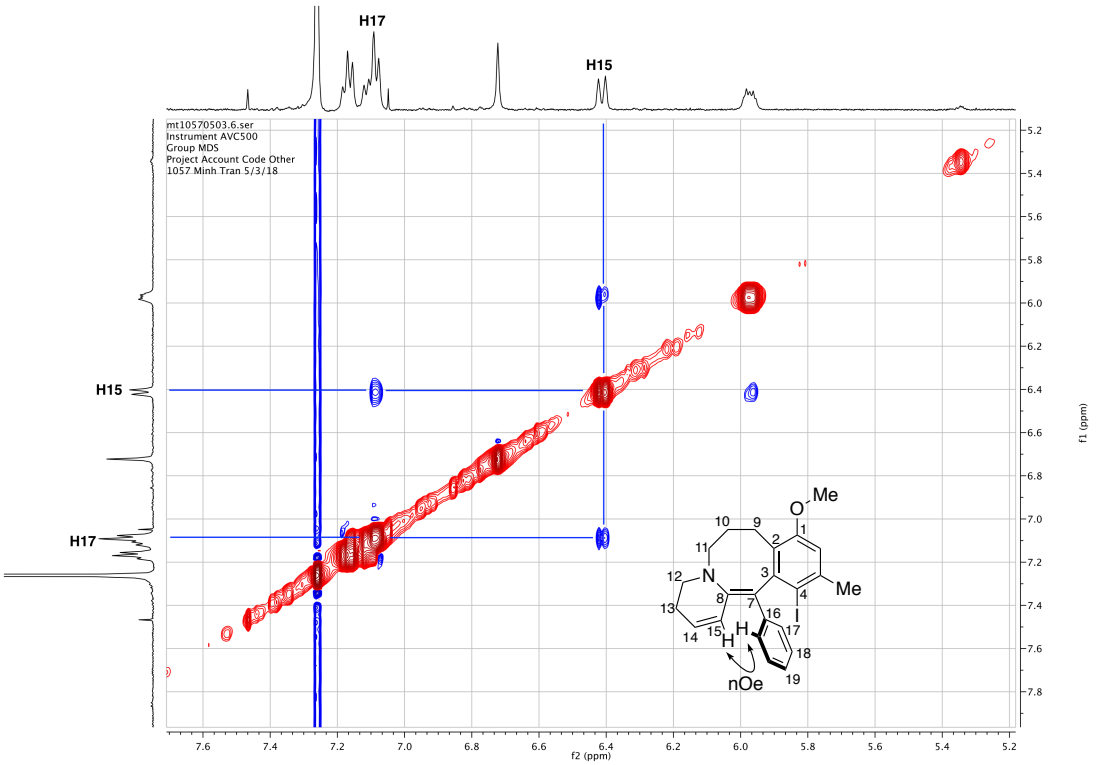
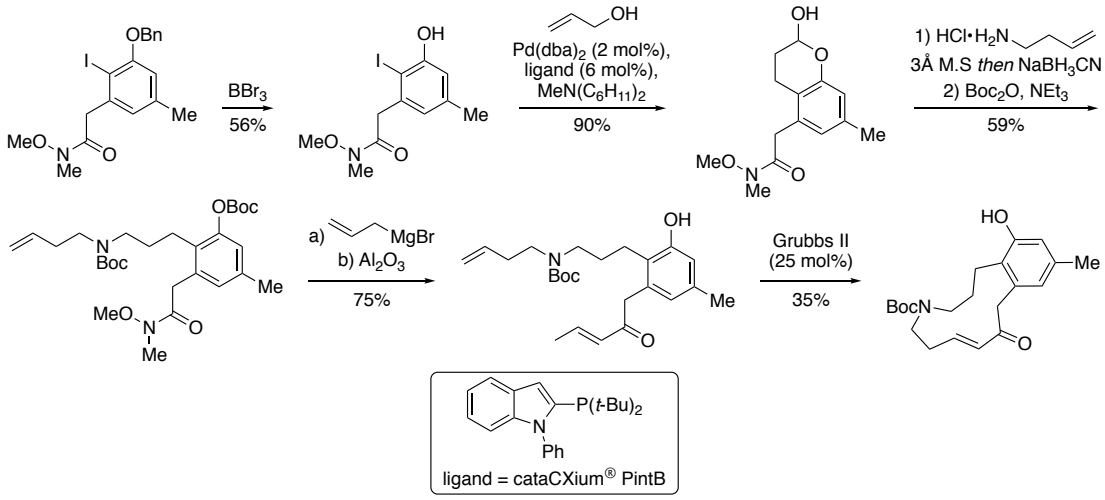
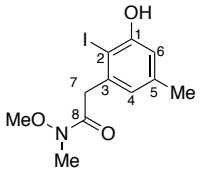


Figure 6.2 nOe correlations between H17 and H15 to show the spatial proximity of the phenyl ring to the fused ring system.



2-(3-Hydroxy-2-iodo-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (303)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **266** (2.50 g, 5.88 mmol, 1.0 eq) in CH_2Cl_2 (59.0 mL). The reaction vessel was cooled to –78 °C. To the cooled reaction flask was added BBr_3 (1.0 M solution in CH_2Cl_2, 7.10 mL, 7.05 mmol, 1.2 eq) dropwise. The reaction was stirred at –78 °C for 10 min until completion of starting material, as indicated by TLC. The reaction was quenched by the addition of H_2O (30 mL). The resulting reaction mixture was allowed to warm to rt, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:1, v:v) afforded the title compound as a yellow solid (1.11 g, 3.29 mmol, 56%).

^{1}H NMR (500 MHz, CD_3CN) δ_H 7.37 (s, 1H, O*H*), 6.68 – 6.63 (m, 1H, *H*4), 6.63 – 6.59 (m, 1H, *H*6), 3.88 (s, 2H, 2 × *H*7), 3.75 (s, 3H, OCH_3), 3.15 (s, 3H, NCH_3), 2.23 (s, 3H, $ArCH_3$).

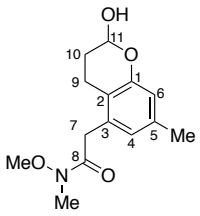
^{13}C NMR (126 MHz, CD_3CN) δ_C 172.2 (*C*8), 156.9 (*C*1), 141.4 (*C*3), 140.2 (*C*5), 124.6 (*C*4), 114.7 (*C*6), 88.3 (*C*2), 62.0 (OCH_3), 45.1 (*C*7), 32.8 (NCH_3), 20.8 ($ArCH_3$).

HRMS (ESI) calcd for $C_{11}H_{14}INO_3Na^+$ $[M+Na]^+$ 357.9911, found 357.9910.

ν_{max} (film)/cm^{-1} 3223, 1640, 1586, 1327, 1175, 1101, 848.

m.p. 173 – 175 °C.

2-(2-Hydroxy-7-methylchroman-5-yl)-*N*-methoxy-*N*-methylacetamide (304)



Following a modified procedure of Xiao *et al*.,[56] to a flame-dried, argon-flushed Schlenk tube equipped with a stirrer bar was charged **303** (1.20 g, 3.57 mmol, 1.0 eq), cataCXium® PintB (72.3 mg, 0.214 mmol, 0.060 eq) and $Pd(dba)_2$ (41.1 mg, 0.0714 mmol, 0.020 eq). The Schlenk tube was evacuated and refilled with argon three times. To the Schlenk tube was added DMF (14.0 mL), distilled allyl alcohol (0.270 mL, 3.93 mmol, 1.1 eq) and distilled *N*,*N*-dimethylcyclohexylamine (0.840 mL, 3.93 mmol, 1.1 eq). The reaction mixture was stirred at 100 °C for 3 h until completion of starting material, as indicated by TLC. The reaction mixture was then cooled to rt. To the reaction mixture was added H_2O (20 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (6:4, v:v) afforded the title compound as a yellow oil (848 mg, 3.21 mmol, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.64 (s, 1H, *H*4), 6.57 (s, 1H, *H*6), 5.51 (br s, 1H, *H*11), 3.70 (br s, 2H, 2 × *H*7), 3.62 (s, 3H, OCH_3), 3.44 (br s, 1H, O*H*), 3.21 (s, 3H, NCH_3), 2.83 – 2.70 (m, 1H, $H9_a$), 2.69 – 2.57 (m, 1H, $H9_b$), 2.24 (s, 3H, ArCH_3), 2.07 – 1.93 (m, 2H, 2 × *H*10).

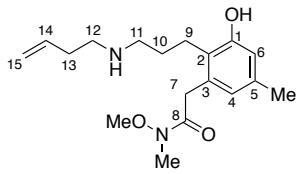
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.6 (*C*8), 152.2 (*C*1), 137.1 (*C*5), 133.9 (*C*3), 123.7 (*C*4), 118.2 (*C*2), 116.7 (*C*6), 91.8 (*C*11), 61.4 (OCH_3), 36.4 (*C*7), 32.5 (NCH_3), 27.3 (*C*10), 21.2 (ArCH_3), 17.9 (*C*9).

HRMS (ESI) calcd for $C_{14}H_{19}NO_4Na^+$ $[M+Na]^+$ 288.1206, found 288.1204.

ν_{max} (film)/cm^{-1} 3387, 1640, 1578, 1457, 1296, 1136, 1058, 850.

2-(2-(3-(But-3-en-1-ylamino)propyl)-3-hydroxy-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide

(S17)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged **304** (838 mg, 3.16 mmol, 1.0 eq), 3 Å molecular sieves (400 mg), but-3-en-1-amine hydrochloride (510 mg, 1.5 eq), and MeOH (6.30 mL). The reaction mixture was stirred at rt for 30 min, before being cooled to 0 °C. To the reaction was added odium cyanoborohydride (496 mg, 7.90 mmol, 2.5 eq). The resulting mixture was allowed to warm to rt, and arbitrarily stirred for 16 h. The solvent was removed *in vacuo* and the residue purified *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (0.5:9.5 to 1:9, v:v) afforded the title compound as a viscous colourless oil (773 mg, 2.40 mmol, 76%).

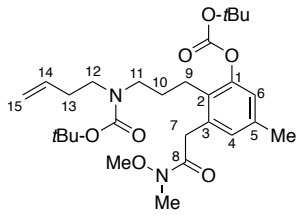
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.62 (s, 1H, *H*6), 6.51 (s, 1H, *H*4), 5.70 – 5.64 (m, 1H, *H*14), 5.20 – 5.09 (m, 2H, 2 × *H*15), 3.76 – 3.70 (m, 5H, 2 × *H*7, OCH_3), 3.23 (s, 3H, NCH_3), 2.87 (t, *J* = 7.3 Hz, 2H, 2 × *H*12), 2.80 (t, *J* = 6.2 Hz, 2H, 2 × *H*11), 2.65 (t, *J* = 6.8 Hz, 2H, 2 × *H*9), 2.39 (q, *J* = 7.3 Hz, 2H, 2 × *H*13), 2.18 (s, 3H, ArCH_3), 1.93 (t, *J* = 6.8 Hz, 2H, 2 × *H*10).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 173.0 (*C*8), 154.9 (*C*1), 137.5 (*C*5), 134.3 (*C*3), 132.4 (*C*14), 124.0 (*C*4), 122.1 (*C*2), 119.5 (*C*15), 115.9 (*C*6), 61.7 (O*C*H_3), 47.6 (*C*12), 47.3 (*C*11), 36.1 (*C*7), 32.6 (N*C*H_3), 30.7 (*C*13), 25.4 (*C*10), 22.2 (*C*9), 21.1 (Ar*C*H_3).

HRMS (ESI) calcd for $C_{18}H_{29}N_2O_3^+$ $[M+H]^+$ 321.2173, found 321.2175.

ν_{max} (film)/cm^{-1} 3500, 2983, 1643, 1588, 1458, 1121, 1030, 788.

tert-Butyl but-3-en-1-yl(3-(2-((_tert_-butoxycarbonyl)oxy)-6-(2-(methoxy(methyl)amino)-2-oxoethyl)-4-methylphenyl)propyl)carbamate (305)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of di-*tert*-butyl-dicarbonate (1.09 g, 5.60 mmol, 2.2 eq) in CH_2Cl_2 (3.00 mL), 4-dimethylaminopyridine (278 mg, 2.27 mmol, 1.0 eq), and a solution of **S17** (728 mg, 2.27 mmol, 1.0 eq) in CH_2Cl_2 (20 mL). The resulting reaction mixture was stirred at rt arbitrarily for 16 h. To the reaction mixture was added H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (3:7, v:v) afforded the title compound as a viscous yellow oil (925 mg, 1.82 mmol, 78%).

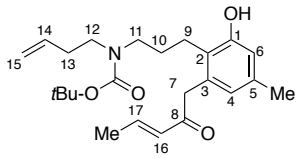
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.91 (s, 1H, *H*4), 6.81 (s, 1H, *H*6), 5.81 – 5.66 (m, 1H, *H*14), 5.10 – 4.88 (m, 2H, 2 × *H*15), 3.74 (s, 2H, 2 × *H*7), 3.64 – 3.49 (m, 3H, OCH_3), 3.30 – 3.12 (m, 7H, 2 × *H*11, 2 × *H*12, NCH_3), 2.55 – 2.47 (m, 2H, 2 × *H*9), 2.31 – 2.17 (m, 5H, ArCH_3, 2 × *H*13), 1.71 – 1.60 (m, 2H, *H*10), 1.53 (s, 9H, OC(CH_3)$_3$), 1.42 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.4 (*C*8), 155.5 (NC(O)O*t*-Bu), 152.4 (NC(O)O*t*-Bu), 149.5 (*C*1), 136.7 (*C*5), 135.6 (*C*14), 134.6 (*C*3), 129.8 (*C*2), 128.9 (*C*4), 121.6 (*C*6), 116.5 (*C*15), 83.2 (O*C*(CH$_3$)$_3$), 79.2 (OC(*C*H$_3$)$_3$), 61.3 (O*C*H$_3$), 46.8 (*C*11), 46.4 (*C*12), 36.6 (*C*7), 33.3 (*C*13), 32.4 (N*C*H$_3$), 28.6 (*C*10), 28.5 (OC(*C*H$_3$)$_3$), 27.8 (OC(*C*H$_3$)$_3$), 24.2 (*C*9), 21.0 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{28}H_{44}N_2O_7^+$ $[M+H]^+$ 521.3221, found 521.3225.

ν_{max} (film)/cm^{-1} 2979, 1753, 1687, 1463, 1414, 1367, 1247, 1159, 1002, 874, 775.

tert-Butyl (_E_)-but-3-en-1-yl(3-(2-hydroxy-4-methyl-6-(2-oxopent-3-en-1-yl)phenyl)propyl)carbamate (306)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **305** (903 mg, 1.73 mmol, 1.0 eq) in Et_2O (43.0 mL). The reaction vessel was cooled to 0 °C. To the cooled flask was added allylmagnesium bromide (1.0 M in Et_2O, 5.20 mL, 5.19 mmol, 3.0 eq). The reactioni was stirred at 0 °C for 15 min until complete consumption of starting material, as indicated by TLC. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) at 0 °C. The layers were separated and the aqueous layers were extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*.

The yellow crude residue was dried under high vacuum in a round bottom flask equipped with a stirrer bar. The reaction flask was flushed with argon, and was charged with Et_2O (20 mL) and alumina (400 mg). The resulting reaction mixture was stirred at rt arbitrarily for 16 h. The reaction mixture was filtered through a plug of Celite® (eluting with Et_2O, 20 mL), and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:8, v:v) afforded the title compound as a yellow oil (521 mg, 1.30 mmol, 75%).

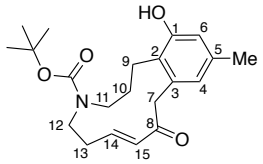
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.07 – 6.79 (m, 1H, *H*17), 6.61 – 6.46 (m, 2H, *H*6, *H*4), 6.19 (dd, *J* = 15.6, 1.7 Hz, 1H, *H*16), 5.90 – 5.60 (m, 1H, *H*14), 5.10 – 4.98 (m, 2H, 2 × *H*15), 3.75 (s, 2H, 2 × *H*7), 3.22 (t, *J* = 7.2 Hz, 4H, 2 × *H*12, 2 × *H*11), 2.51 (t, *J* = 7.5 Hz, 2H, 2 × *H*9), 2.32 – 2.21 (m, 5H, ArCH_3, 2 × *H*13), 1.88 (dd, *J* = 6.9, 1.7 Hz, 3H, CHCH_3), 1.79 – 1.58 (m, 2H, 2 × *H*10), 1.45 (s, 9H, OC(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 197.8 (*C*8), 156.2 (N*C*(O)O*t*-Bu), 154.7 (*C*1), 143.5 (*C*17), 136.9 (*C*5), 135.6 (*C*14), 134.1 (*C*3), 130.6 (*C*16), 124.4 (*C*2), 124.0 (*C*4), 116.6 (*C*15), 115.7 (*C*6), 79.8 (O*C*(CH_3)$_3$), 47.1 (overlapping signals, *C*12, *C*11), 45.8 (*C*7), 33.2 (*C*13), 28.6 (*C*10), 28.4 (OC(*C*H_3)$_3$), 23.6 (*C*9), 21.1 (Ar*C*H_3), 18.4 (CH*C*H_3).

HRMS (ESI) calcd for $C_{24}H_{35}NO_4Na^+$ $[M+Na]^+$ 424.2458, found 424.2456.

ν_{max} (film)/cm^{-1} 3342, 2977, 1686, 1663, 1586, 1420, 1250, 1164, 969, 772.

tert-Butyl (_E_)-14-hydroxy-12-methyl-9-oxo-2,3,5,6,9,10-hexahydrobenzo[_e_][1]azacyclododecine-4(1_H_)-carboxylate (289)



To a flame-dried, argon-flushed 2-necked round-bottomed flask equipped with a condenser was added a solution of **306** (507 mg, 1.26 mmol, 1.0 eq) in freshly freeze-pump thawed CH_2Cl_2 (200 mL), and a solution of Grubbs' 2nd Generation catalyst (268 mg, 0.316 mmol, 0.25 eq) in CH_2Cl_2 (53 mL). The reaction was stirred at 40 °C arbitrarily for 16 h. The reaction mixture was allowed to cool to rt and filtered through a pad of Celite® (eluting with EtOAc, 20 mL) and the solvents removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (3:7, v:v) afforded the title compound as a yellow oil (157 mg, 0.441 mmol, 35%).

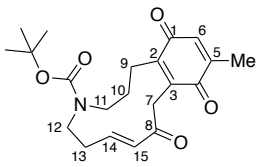
^{1}H NMR (500 MHz, CD_3CN) δ_H 6.86 – 6.69 (m, 1H, *H*14), 6.61 (s, 1H, *H*4), 6.52 (s, 1H, *H*6), 6.19 (d, *J* = 16.0 Hz, 1H, *H*15), 3.73 (s, 2H, 2 × *H*7), 3.47 – 3.10 (m, 4H, 2 × *H*11, 2 × *H*12), 2.75 – 2.49 (m, 4H, 2 × *H*10, 2 × *H*13), 2.20 (s, 3H, ArCH_3), 1.54 – 1.45 (m, 9H, OC(CH_3)$_3$), 1.46 – 1.39 (m, 2H, 2 × *H*9).

^{13}C NMR (126 MHz, CD_3CN) δ_C 200.2 (*C*8), 157.6 (N*C*(O)O*t*-Bu), 156.2 (*C*1), 147.9 (*C*14), 137.3 (*C*5), 136.5 (*C*3), 134.7 (*C*15), 125.4 (*C*4), 125.1 (*C*2), 115.3 (*C*6), 79.9 (O*C*(CH_3)$_3$), 51.3 (*C*11), 50.9 (*C*12), 32.3 (*C*13), 29.6 (*C*9), 28.7 (OC(*C*H_3)$_3$), 25.9 (*C*10), 20.9 (Ar*C*H_3).

HRMS (ESI) calcd for $C_{21}H_{29}NO_4Na^+$ $[M+Na]^+$ 382.1989, found 382.1990.

ν_{max} (film)/cm^{-1} 3343 (broad), 2973, 1664 (broad), 1583, 1479, 1416, 1366, 1303, 1247, 1168, 775.

tert-Butyl (_E_)-12-methyl-9,11,14-trioxo-2,3,5,6,9,10,11,14-octahydrobenzo[_e_][1]azacyclododecine-4(1_H_)-carboxylate (310)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **289** (7.0 mg, 0.0195 mmol, 1.0 eq) in $(CF_3)_2CHOH$ (0.200 mL), anhydrous potassium carbonate (5.4 mg, 0.0399 mmol, 2.0 eq), (diacetoxyiodo)benzene (6.90 mg, 0.0214 mmol, 1.1 eq) and H_2O (0.390 μL, 0.0215 mmol, 1.1 eq). The resulting solution was stirred at rt for 5 h until complete consumption of the starting material, as indicated by TLC. To the reaction mixture was added H_2O (1 mL). The mixture was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (3:7, v:v) afforded the title compound as a yellow oil (2.0 mg, 5.27 μmol, 27%).

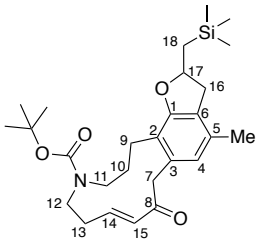
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.95 – 6.82 (m, 1H, *H*14), 6.62 – 6.51 (m, 1H, *H*6), 6.27 (d, *J* = 15.7 Hz, 1H, *H*15), 3.86 (s, 2H, 2 × *H*7), 3.40 – 3.24 (m, 4H, 2 × *H*11, 2 × *H*12), 2.74 – 2.63 (m, 1H, $H13_a$), 2.63 – 2.45 (m, 3H, $H13_b$, 2 × *H*10), 2.08 (s, 3H, CH_3), 1.50 (s, 9H, OC(CH_3)$_3$), 1.40 – 1.31 (m, 2H, 2 × *H*9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 197.3 (*C*8), 187.4 (*C*1), 186.4 (*C*4), 156.7 (N*C*(O)O*t*-Bu), 147.3 (*C*14), 145.7 (*C*5), 144.9 (*C*3), 139.5 (*C*2), 134.3 (*C*15), 133.4 (*C*6), 80.2 (O*C*$(CH_3)_3$), 50.4 (overlapping signals, *C*11, *C*12), 35.0 (*C*7), 30.5 (*C*13), 28.7 (OC(*C*H_3)$_3$), 28.6 (*C*9), 26.3 (*C*10), 16.4 (*C*H_3).

HRMS (ESI) calcd for $C_{21}H_{27}NO_5Na^+$ $[M+Na]^+$ 396.1781, found 396.1782.

ν_{max} (film)/cm^{-1} 2917, 1785, 1687 (broad), 1462, 1416, 1247, 1163, 1103, 720.

tert-Butyl (_E_)-4-methyl-7-oxo-2-((trimethylsilyl)methyl)-2,3,6,10,11,13,14,15-octahydrobenzofuro[7,6-_e_][1]azacyclododecine-12(7_H_)-carboxylate (312)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **289** (10.0 mg, 0.0278 mmol, 1.0 eq) in $(CF_3)_2CHOH$ (70.0 μL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added allyltrimethylsilane (27.0 μL, 0.167 mmol, 6.0 eq), anhydrous potassium carbonate (5.8 mg, 0.0417 mmol, 1.5 eq) and a solution of (diacetoxyiodo)benzene (13.4 mg, 0.0417 mmol, 1.5 eq) in $(CF_3)_2CHOH$ (0.060 mL). The reaction was stirred at 0 °C for 10 min and then allowed to warm to rt and was stirred arbitrarily for a further 10 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (3:7, v:v) afforded the title compound as a colourless paste (1.7 mg, 21%). Starting material (3.0 mg, 8.34 μmol, 30%) was also isolated.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.05 – 6.91 (m, 1H, *H*14), 6.66 (s, 1H, *H*4), 6.19 (dd, *J* = 23.0, 15.9 Hz, 1H, *H*15), 4.92 – 4.79 (m, 1H, *H*17), 3.86 – 3.65 (m, 2H, 2 × *H*7), 3.47 – 3.22 (m, 4H, 2 × *H*11, 2 × *H*12), 3.22 – 3.09 (m, 1H, $H13_a$), 2.76 – 2.46 (m, 5H, $H13_b$, 2 × *H*16, 2 × *H*9), 2.17 (s, 3H, ArCH_3), 1.55 – 1.49 (m, 11H, OC(CH_3)$_3$, 2 × *H*10), 1.28 – 1.19 (m, 1H, $H18_a$), 1.13 – 1.02 (m, 1H, $H18_b$), 0.08 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 199.6 (*C*8), 158.6 (*C*1), 155.9 (N*C*(O)O*t*-Bu), 146.5 (*C*14), 133.8 (*C*15), 132.8 (*C*3), 132.1 (*C*5), 124.8 (*C*4), 124.7 (C6), 119.2 (*C*2), 81.9 (*C*17), 79.6 (O*C*(CH_3)$_3$), 50.4 (overlapping signals, *C*11, *C*12), 42.4 (*C*7), 37.7 (*C*16), 30.4 (*C*13), 28.8 (*C*10), 28.6 (OC(CH_3)$_3$), 25.7 (*C*18), 25.3 (*C*9), 18.7 (Ar*C*H$_3$), –0.76 (Si(CH_3)$_3$).

HRMS (ESI) calcd for $C_{27}H_{41}NO_4SiNa^+$ $[M+Na]^+$ 494.2697, found 494.2694.

ν_{max} (film)/cm^{-1} 2957, 2918, 1694, 1671, 1654, 1471, 1463, 1412, 1365, 1355, 1301, 1281, 1258, 1247, 1192, 1170, 1157, 1133, 1105, 1082, 1065, 1037, 1032, 102, 859, 728.

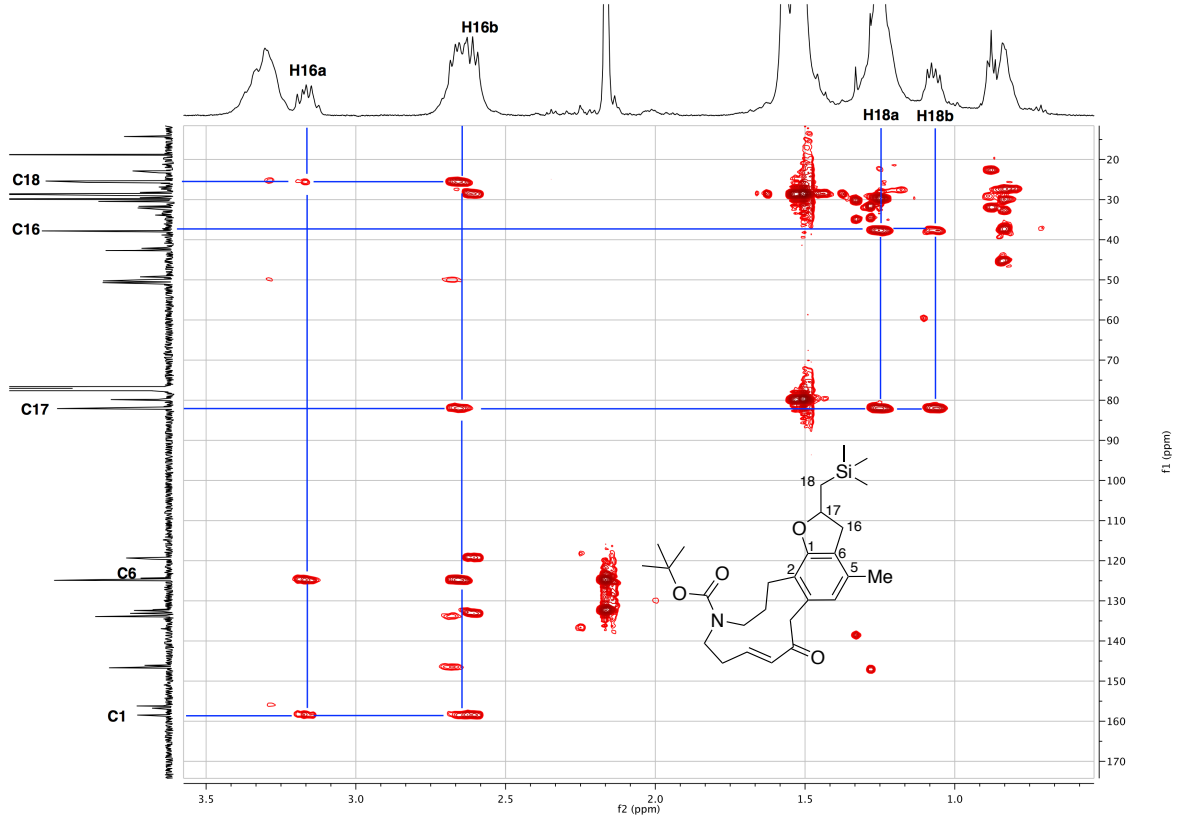
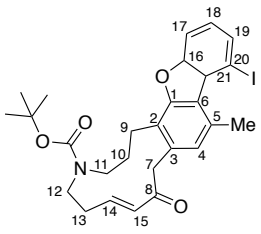


Figure 6.3 Selected HMBC correlations to elucidate the top right hand part of **312**.

tert-Butyl (12b*R*,16a*R*,*E*)-13-iodo-12-methyl-9-oxo-2,3,5,6,9,10,12b,16a-octahydrobenzo[2,3]benzofuro[7,6-*e*][1]azacyclododecine-4(1*H*)-carboxylate (314)



^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.05 – 6.92 (m, 1H, *H*14), 6.89 – 6.78 (m, 2H, *H*4, *H*19), 6.24 – 6.13 (m, 2H, *H*15, *H*17), 6.02 – 5.90 (m, 1H, *H*18), 4.81 (dd, *J* = 8.3, 5.5 Hz, 1H, *H*16), 4.08 (d, *J* =

8.3 Hz, 1H, *H*21), 4.04 – 3.54 (m, 2H, 2 × *H*7), 3.53 – 3.07 (m, 4H, 2 × *H*11, 2 × *H*12), 2.88 – 2.50 (m, 7H, 2 × *H*9, 2 × *H*13, ArCH_3), 1.70 – 1.53 (m, 11H, OC(CH_3)$_3$, 2 × *H*10).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 199.5 (*C*8), 158.8 (*C*1), 156.2 (N*C*(O)O*t*-Bu), 146.9 (*C*14), 135.0 (*C*19), 133.8 (*C*15), 133.7 (*C*3), 133.5 (*C*5), 129.1 (*C*18), 127.1 (*C*4), 126.4 (*C*6), 120.8 (*C*17), 119.8 (*C*2), 103.1 (*C*20), 80.5 (*C*16), 79.9 (O*C*(CH$_3$)$_3$), 50.6 (*C*11), 50.0 (*C*12), 48.6 (*C*21), 42.2 (*C*7), 30.4 (*C*13), 29.8 (*C*10), 28.7 (OC(*C*H$_3$)$_3$), 25.3 (*C*9), 21.6 (Ar*C*H$_3$).

HRMS (ESI) calcd for $C_{27}H_{32}INO_4Na^+$ $[M+Na]^+$ 584.1268, found 584.1268.

ν_{max} (film)/cm^{-1} 2917, 2849, 1689, 1628, 1464, 1365, 1302, 1276, 1168, 1137, 1108, 917.

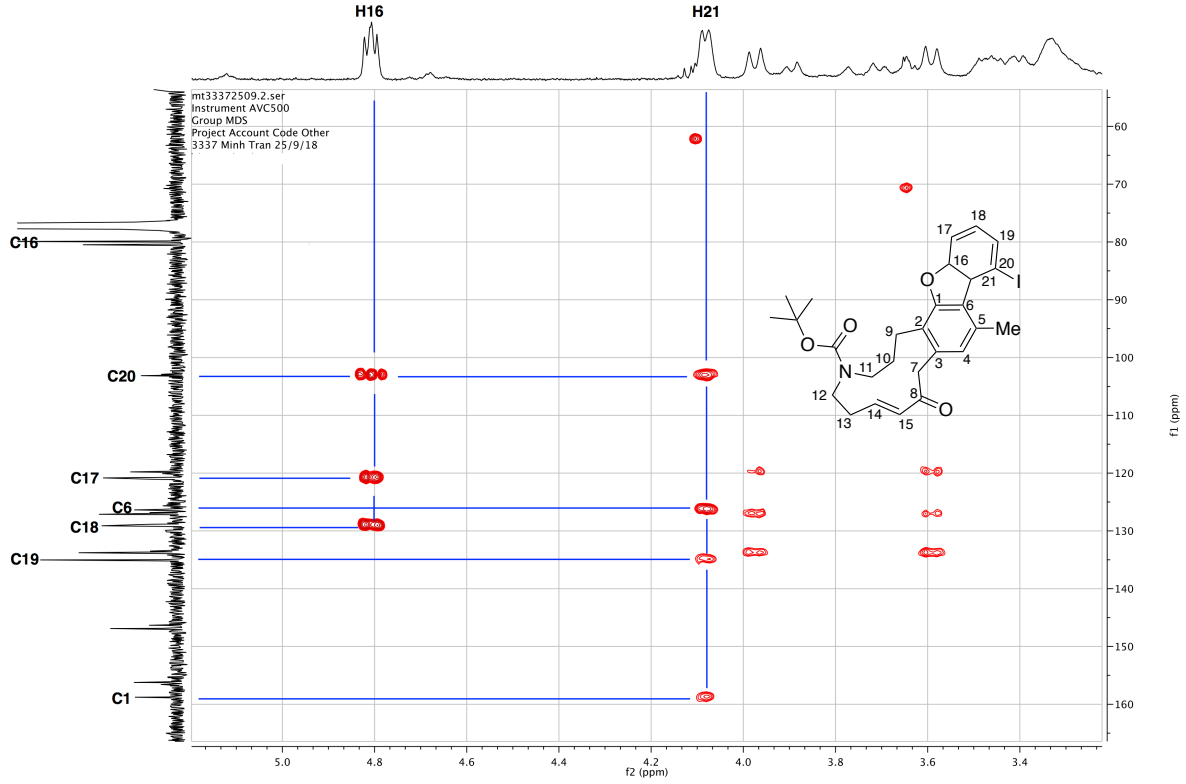
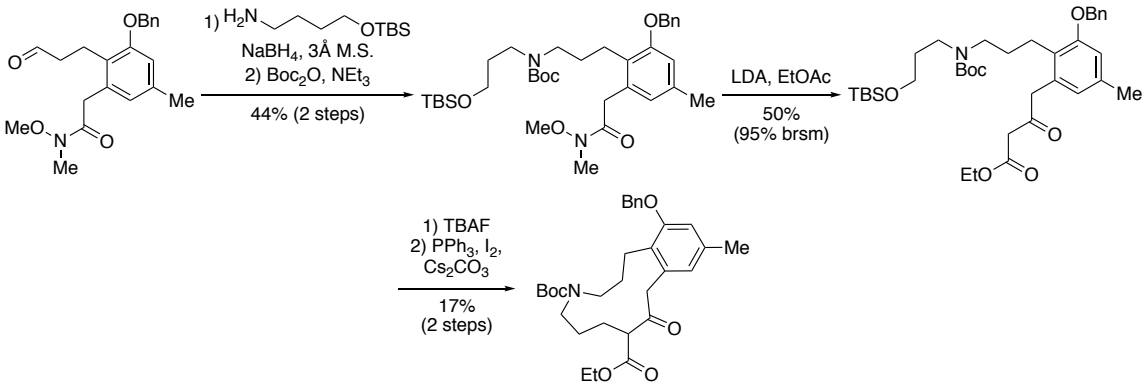
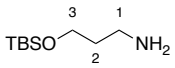


Figure 6.4 Selected HMBC correlations to elucidate the top right hand part of **314**.



4-((*tert*-Butyldimethylsilyl)oxy)butan-1-amine (325)



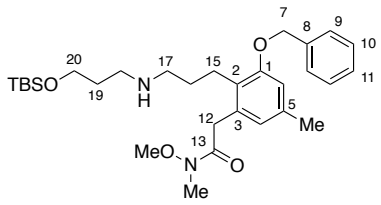
Following a modified procedure by Gothelf *et al*.,[169] to a round-bottomed flask equipped with a stirrer bar was charged a solution of 3-amino-1-propanol (0.460 mL, 6.00 mmol, 1.0 eq) in CH_2Cl_2 (6.40 mL), triethylamine (0.740 mL, 5.29 mmol, 1.5 eq), and *tert*-butyldimethylsilyl chloride (995 mg, 6.6 mmol, 1.1 eq). The resulting mixture was stirred arbitrarily for 16 h at rt. The reaction mixture was washed with H_2O (3 × 2 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield a yellow crude residue (730 mg) which was used in subsequent chemistry without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.57 (t, J = 6.7 Hz, 2H, 2 × *H*3), 2.66 (t, J = 6.7 Hz, 2H, 2 × *H*1), 1.55 – 1.50 (m, 2H, 2 × *H*2), 0.84 (s, 9H, SiC(CH_3)$_3$), 0.00 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 60.8 (*C*3), 39.5 (*C*1), 36.0 (*C*2), 25.8 (Si*C*), 18.8 (C*C*H$_3$), -5.7 (Si*C*H$_3$).

These data are consistent with those previously published for this compound.[169]

2-(3-(Benzyloxy)-2-(3-((3-(((*tert*-butyldimethylsilyl)oxy)propyl)amino)propyl)-5-methylphenyl)-*N*-methoxy-*N*-methylacetamide (S18)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **268** (1.05 g, 2.96 mmol, 1.0 eq) in MeOH (14.8 mL), 3 Å molecular sieves (500 mg), and **325** (728 mg, assumed to be 3.84 mmol, 1.3 eq). The reaction mixture was stirred at rt arbitrarily for 18 h. The reaction vessel was cooled to 0 °C and sodium borohydride (168 mg, 4.44 mmol, 1.5 eq) was added in one portion to the reaction. The ice bath was removed and the reaction was stirred for 10 min until complete consumption of the starting material, as indicated by TLC. The reaction was cooled to 0 °C and quenched with 1.0 M aqueous NaOH solution (5 mL), and H_2O (10 mL). The mixture was warmed to rt and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (1:9, v:v) afforded the title compound as a viscous light yellow oil (697 mg, 1.33 mmol, 45%).

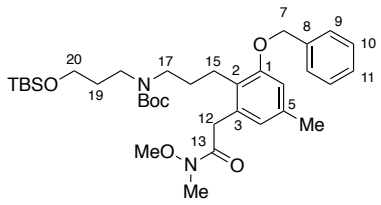
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44 – 7.28 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.70 – 6.62 (m, 2H, *H*4, *H*6), 5.03 (s, 2H, 2 × *H*7), 3.77 (s, 2H, 2 × *H*12), 3.65 – 3.59 (m, 5H, OCH_3, 2 × *H*20), 3.21 (s, 3H, NCH_3), 2.78 – 2.68 (m, 6H, 2 × *H*18, 2 × *H*17, 2 × *H*15), 2.28 (s, 3H, ArCH_3), 1.87 – 1.77 (m, 2H, 2 × *H*16), 1.77 – 1.65 (m, 2H, 2 × *H*19), 0.86 (s, 9H, OSi$(CH_3)_2$C$(CH_3)_3$), 0.02 (s, 6H, OSi$(CH_3)_2$C$(CH_3)_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.9 (*C*13), 157.0 (*C*1), 137.5 (*C*8), 136.7 (*C*5), 134.4 (*C*3), 128.7 (*C*10), 128.0 (*C*11), 127.4 (*C*9), 126.3 (*C*2), 123.9 (*C*4), 111.6 (*C*6), 70.3 (*C*7), 61.7 (*C*20), 61.5 (O*C*H_3), 49.2 (*C*17), 47.0 (*C*18), 36.7 (*C*12), 32.5 (N*C*H_3), 31.4 (*C*19), 28.4 (*C*16), 26.0 (OSi$(CH_3)_2$C$(CH_3)_3$), 23.8 (*C*15), 21.6 (Ar*C*H_3), 18.4 (OSi$(CH_3)_2$*C*$(CH_3)_3$), –5.3 (OSi$(CH_3)_2$C$(CH_3)_3$).

HRMS (ESI) calcd for $C_{30}H_{49}N_2O_4Si^+$ $[M+H]^+$ 529.3456, found 529.3456.

ν_{max} (film)/cm^{-1} 3500, 1664, 1579, 1461, 1381, 1254, 1175, 1094, 777.

tert-Butyl (3-(2-(benzyloxy)-6-(2-(methoxy(methyl)amino)-2-oxoethyl)-4-methylphenyl)propyl)(3-((_tert_-butyldimethylsilyl)oxy)propyl)carbamate (326)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of di-*tert*-butyl-dicarbonate (334 mg, 1.53 mmol, 1.2 eq) in CH_2Cl_2 (3 mL), 4-dimethylaminopyridine (78.0 mg, 0.638 mmol, 0.5 eq), and a solution of **S18** (675 mg, 1.28 mmol, 1.0 eq) in CH_2Cl_2 (10 mL). The resulting reaction mixture was stirred at rt arbitrarily for 16 h. To the reaction mixture was added H_2O (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (2:8 to 3:7, v:v) afforded the title compound as a viscous yellow oil (494 mg, 0.781 mmol, 61%).

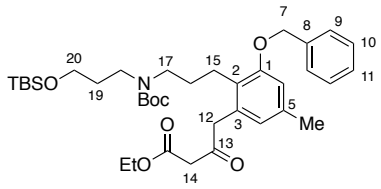
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.45 – 7.28 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.69 – 6.61 (m, 2H, *H*4, *H*6), 5.04 (s, 2H, 2 × *H*7), 3.75 (s, 2H, 2 × *H*12), 3.69 – 3.48 (m, 5H, OCH_3, 2 × *H*20), 3.31 – 3.05 (m, 7H, NCH_3, 2 × *H*17, 2 × *H*18), 2.68 – 2.59 (m, 2H, 2 × *H*15), 2.28 (s, 3H, ArCH_3), 1.75 – 1.58 (m, 4H, 2 × *H*16, 2 × *H*19), 1.46 – 1.31 (m, 9H, O(CH_3)$_3$), 0.87 (s, 9H, OSi(CH$_3$)$_2$C(CH_3)$_3$), 0.02 (s, 6H, OSi(CH_3)$_2$C(CH$_3$)$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 172.9 (*C*13), 156.8 (*C*(O)O*t*-Bu), 155.7 (*C*1), 137.7 (*C*8), 136.4 (*C*5), 134.2 (*C*3), 128.6 (*C*10), 127.8 (*C*11), 127.2 (*C*9), 126.7 (*C*2), 123.4 (*C*4), 111.5 (*C*6), 79.0 (O*C*(CH$_3$)$_3$), 70.1 (*C*7), 61.4 (O*C*H$_3$), 61.0 (*C*20), 47.7 (*C*17), 44.1 (*C*18), 36.5 (*C*12), 32.5 (N*C*H$_3$), 31.6 (*C*19), 28.6 (overlapping signals, *C*16, OC(*C*H$_3$)$_3$), 26.1 (OSi(CH$_3$)$_2$C(*C*H$_3$)$_3$), 23.9 (*C*15), 21.6 (Ar*C*H$_3$), 18.4 (OSi(CH$_3$)$_2$*C*(CH$_3$)$_3$), –5.2 (OSi(*C*H$_3$)$_2$C(CH$_3$)$_3$).

HRMS (ESI) calcd for $C_{35}H_{56}N_2O_6Si^+$ $[M+H]^+$ 629.3980, found 629.3978.

ν_{max} (film)/cm^{-1} 2929, 1689 (broad), 1580, 1463, 1365, 1301, 1252, 1174, 1096, 1029, 984, 776.

Ethyl 4-(3-(benzyloxy)-2-(3-((*tert*-butoxycarbonyl)(3-((*tert*-butyldimethylsilyl)oxy)propyl)amino)propyl)-5-methylphenyl)-3-oxobutanoate (327)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of diisopropylamine (70.0 μL, 0.496 mmol, 2.2 eq) in THF (0.660 mL). The reaction flask was cooled to –78 °C. To the cooled reaction vessel was added *n*-BuLi (2.0 M in hexanes, 0.250 mL, 0.496 mmol, 2.2 eq), and the reaction was stirred for 15 min at –78 °C. To the cooled reaction was added a solution of EtOAc (50.0 μL, 0.496 mmol, 2.2 eq) in THF (0.330 mL). The resulting reaction mixture was stirred for 15 min before the addition of a solution of **326** (145 mg, 0.226 mmol, 1.0 eq) in THF (0.330 mL). The reaction was stirred arbitrarily for 3 h at –78 °C, and quenched at –78 °C by the addition of saturated aqueous NH_4Cl solution (1 mL), and was warmed to rt. The mixture was extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as a yellow oil (61.0 mg, 0.0904 mmol, 40%), and starting material (50.0 mg, 0.0779 mmol, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.46 – 7.29 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.68 (s, 1H, *H*4), 6.58 (s, 1H, *H*6), 5.05 (s, 2H, 2 × *H*7), 4.23 – 4.07 (m, 2H, OCH_2CH_3), 3.81 (s, 2H, 2 × *H*12), 3.60 – 3.52 (m, 2H, 2 × *H*20), 3.50 – 3.41 (m, 2H, 2 × *H*14), 3.30 – 3.06 (m, 4H, 2 × *H*17, 2 × *H*18), 2.63 – 2.51 (m, 2H, 2 × *H*15), 2.28 (s, 3H, $ArCH_3$), 1.81 – 1.57 (m, 4H, 2 × *H*19, 2 × *H*16), 1.50 – 1.32 (m, 9H, $OC(CH_3)_3$), 1.26 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.87 (s, 9H, $OSi(CH_3)_2C(CH_3)_3$), 0.02 (s, 6H, $OSi(CH_3)_2C(CH_3)_3$).

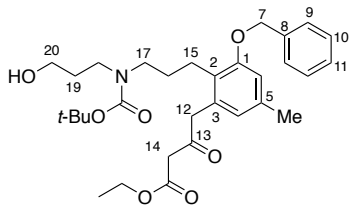
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 200.8 (*C*13), 167.3 (*C*(O)OEt), 157.1 (*C*1), 155.7 (*C*(O)O*t*-Bu), 137.5 (*C*8), 136.6 (*C*5), 132.5 (*C*3), 128.7 (*C*10), 127.9 (*C*11), 127.0 (*C*9), 126.9 (*C*2), 124.0 (*C*4), 112.0 (*C*6), 79.1 ($OC(CH_3)_3$), 70.1 (*C*7), 61.5 (OCH_2CH_3), 58.9 (*C*20), 47.4 (*C*12), 47.8 (*C*14), 47.3

(*C*17), 44.1 (*C*18), 31.8 (*C*19), 28.6 (OC(CH_3)$_3$), 26.1 (OSi(CH_3)$_2$C(CH_3)$_3$), 23.9 (*C*15), 21.6 (*C*16), 21.5 (ArCH_3), 18.4 (OSi(CH_3)$_2$*C*(CH_3)$_3$), 14.2 (OCH_2CH_3), –5.2 (OSi(CH_3)$_2$C(CH_3)$_3$).

HRMS (ESI) calcd for $C_{37}H_{57}NO_7Si^+$ $[M+H]^+$ 656.3977, found 656.3976.

ν_{max} (film)/cm^{-1} 2929, 1745, 1720, 1691, 1581, 1469, 1252, 1223, 1176, 1096, 836.

Ethyl 4-(3-(benzyloxy)-2-(3-((*tert*-butoxycarbonyl)(3-hydroxypropyl)amino)propyl)-5-methylphenyl)-3-oxobutanoate (329)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of **327** (45.6 mg, 0.0696 mmol, 1.0 eq) in THF (0.700 mL). The reaction vessel was cooled to 0 °C. To the cooled reaction flask was added TBAF (1.0 M solution in THF, 0.100 mL, 0.104 mmol, 1.5 eq). The resulting mixture was warmed to rt and was stirred arbitrarily for 16 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with MeOH/CH_2Cl_2 (0.5:9.5, v:v) afforded the title compound as a yellow oil (30.1 mg, 0.0557 mmol, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.47 – 7.30 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.70 (s, 1H, *H*4), 6.60 (s, 1H, *H*6), 5.04 (s, 2H, 2 × *H*7), 4.18 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 3.82 (s, 2H, 2 × *H*14), 3.54 – 3.41 (m, 4H, 2 × *H*20, 2 × *H*12), 3.32 – 3.07 (m, 4H, 2 × *H*17, 2 × *H*18), 2.60 – 2.49 (m, 2H, 2 × *H*15), 2.30 (s, 3H, ArCH_3), 1.72 – 1.61 (m, 2H, 2 × *H*16), 1.61 – 1.49 (m, 2H, 2 × *H*19), 1.39 (s, 9H, OC(CH_3)$_3$), 1.34 – 1.20 (m, 3H, OCH$_2$CH_3).

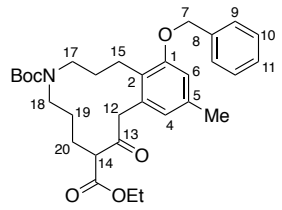
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 200.8 (*C*13), 167.3 (*C*(O)OEt), 157.2 (*C*(O)O*t*-Bu), 157.1 (*C*1), 137.3 (*C*8), 137.1 (*C*5), 132.7 (*C*3), 128.7 (*C*10), 128.0 (*C*11), 127.3 (*C*9), 126.8 (*C*2), 124.1 (*C*4), 112.0 (*C*6), 80.0 (O*C*(CH_3)$_3$), 70.1 (*C*7), 61.5 (OCH_2CH$_3$), 58.4 (*C*20), 48.2 (*C*12), 48.1 (*C*14), 47.3

(*C*17), 42.4 (*C*18), 30.6 (*C*19), 28.5 (*C*16), 28.4 (OC(CH$_3$)$_3$), 24.0 (*C*15), 21.5 (ArCH$_3$), 14.2 (OCH$_2$$CH_3$).

HRMS (ESI) calcd for $C_{31}H_{44}NO_7^+$ $[M+H]^+$ 542.3112, found 542.3114.

ν_{max} (film)/cm^{-1} 3454, 2924, 1745, 1718, 1665, 1580, 1454, 1303, 1249, 1165, 1091, 739.

4-(*tert*-Butyl) 8-ethyl 14-(benzyloxy)-12-methyl-9-oxo-2,3,5,6,7,8,9,10-octahydrobenzo[*e*][1]azacyclododecine-4,8(1*H*)-dicarboxylate (330)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a solution of PPh_3 (20.3 mg, 0.0775 mmol, 1.4 eq) in CH_2Cl_2 (0.170 mL). The reaction vessel was cooled to 0 °C. To the reaction flask was added imidazole (6.03 mg, 0.0886 mmol, 1.6 eq) and iodine (19.7 mg, 0.0775 mmol, 1.4 eq). The resulting mixture was stirred for 5 min at 0 °C, followed by the addition of a solution of **329** (30.0 mg, 0.0554 mmol, 1.0 eq) in CH_2Cl_2 (0.170 mL) at 0 °C. The resulting reaction mixture was stirred for 5 h at 0 °C until complete consumption of the starting material, as indicated by TLC. The reaction mixture was warmed to rt, and washed with saturated aqueous $Na_2S_2O_3$ solution (1 mL) and the solvent removed *in vacuo* to yield a yellow crude residue (32.0 mg), which was used in subsequent chemistry without further purification.

The crude residue (32.0 mg, assumed to be 0.0491 mmol) was dried under high vacuum in a round-bottomed flask equipped with a stirrer bar. The reaction flask was flushed with argon, and was charged with Cs_2CO_3 (41.0 mg, 0.116 mmol, 2.1 eq), and THF (7.90 mL). The resulting mixture was stirred at 37 °C arbitrarily for 16 h before being cooled to rt. To the reaction was added H_2O (10 mL). The mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as a yellow oil (6.0 mg, 0.0103 mmol, 21%).

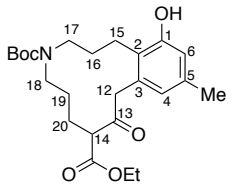
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.45 – 7.28 (m, 5H, 2 × *H*9, 2 × *H*10, *H*11), 6.69 (s, 1H, *H*4), 6.59 (s, 1H, *H*6), 5.05 (s, 2H, 2 × *H*7), 4.24 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.12 – 4.03 (m, 1H, $H12_a$), 3.75 – 3.52 (m, 3H, $H12_b$, *H*14, $H17_a$), 3.44 – 3.28 (2 × *H*18), 3.25 – 3.09 (m, 1H, $H17_b$), 2.77 – 2.66 (m, 1H, $H15_a$), 2.63 – 2.53 (m, 1H, $H15_b$), 2.33 – 2.15 (m, 4H, $ArCH_3$, $H20_a$), 2.16 – 2.05 (m, 1H, $H20_b$), 1.68 – 1.61 (m, 4 H, 2 × *H*16, 2 × *H*19), 1.52 (s, 9H, $OC(CH_3)_3$), 1.31 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 203.8 (*C*13), 170.0 (*C*(O)OEt), 157.3 (*C*1), 156.9 (*C*(O)O*t*-Bu), 137.7 (*C*8), 136.4 (*C*5), 132.6 (*C*3), 128.6 (*C*10), 127.7 (*C*11), 126.9 (*C*9), 126.5 (*C*2), 125.6 (*C*4), 112.0 (*C*6), 79.8 ($OC(CH_3)_3$), 69.9 (*C*7) 61.5 (OCH_2CH_3), 59.2 (*C*14), 49.7 (*C*18), 49.2 (*C*17), 44.2 (*C*12), 31.0 (*C*16), 28.6 ($OC(CH_3)_3$), 27.1 (*C*19), 25.9 (*C*20), 24.9 (*C*15), 21.6 ($ArCH_3$), 14.3 (OCH_2CH_3).

HRMS (ESI) calcd for $C_{31}H_{42}NO_6^+$ $[M+H]^+$ 524.3007, found 524.3012.

ν_{max} (film)/cm^{-1} 2918, 1733 (broad), 1687, 1577, 1540, 1462, 1417, 1246, 1165, 1093, 773.

4-(*tert*-Butyl) 8-ethyl 14-hydroxy-12-methyl-9-oxo-2,3,5,6,7,8,9,10-octahydrobenzo[*e*][1]azacyclododecine-4,8(1*H*)-dicarboxylate (319)

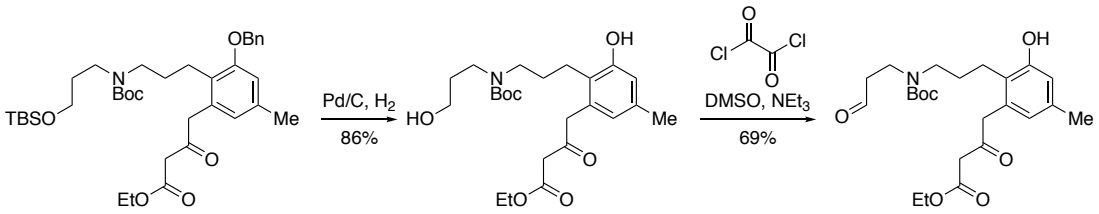


To a round-bottomed flask equipped with a stirrer bar was charged a solution of **330** (5.0 mg, 9.55 μmol, 1.0 eq) in EtOAc (0.100 mL), and palladium on carbon (10 wt. % loading on carbon, 1.0 mg, 0.939 μmol, 0.098 eq). The reaction vessel was purged with a balloon of hydrogen gas, and was kept under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred at 40 °C for 48 h, until complete consumption of starting material, as indicated by TLC. The reaction mixture was cooled to rt, and filtered through a plug of Celite® (eluting with EtOAc, 2 mL), and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (2:8, v:v) afforded the title compound as a colourless paste (1.0 mg, 2.29 μmol, 24%).

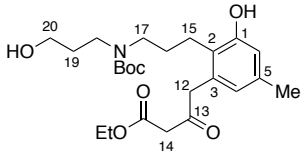
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.56 – 6.49 (m, 2H, *H*4, *H*6), 4.77 (br s, O*H*), 4.24 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 4.09 – 4.00 (m, 1H, *H*12$_a$), 3.73 – 3.54 (m, 4H, *H*12$_b$, *H*14, NC*H*$_2$), 3.27 – 3.14 (m, 2H, NC*H*$_2$), 2.65 – 2.44 (m, 2H, 2 × *H*16), 2.25 (s, 4H, ArC*H*$_3$, *H*20$_a$), 2.15 – 2.06 (m, 1H, *H*20$_b$), 1.72 – 1.66 (m 2H, 2 × *H*15), 1.62 – 1.59 (m, 2H, 2 × *H*19), 1.52 (s, 9H, OC(C*H*$_3$)$_3$), 1.32 – 1.29 (m, 3H, OCH$_2$C*H*$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 203.8 (*C*13), 170.0 (*C*(O)OEt), 156.9 (N*C*(O)O*t*-Bu), 154.2 (*C*1), 136.6 (*C*5), 133.0 (*C*3), 125.8 (*C*4), 124.0 (*C*2), 115.5 (*C*6), 79.9 (O*C*(CH$_3$)$_3$), 61.5 (O*C*H$_2$CH$_3$), 59.1 (*C*14), 49.5 (N*C*H$_2$), 49.1 (N*C*H$_2$), 44.1 (*C*12), 30.3 (*C*15), 28.6 (OC(*C*H$_3$)$_3$), 27.0 (*C*19), 25.9 (*C*20), 24.6 (*C*16), 21.1 (Ar*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$).

HRMS (ESI) calcd for $C_{24}H_{35}NO_6Na^+$ $[M+Na]^+$ 456.2357, found 456.2356.



Ethyl 4-(2-(3-((*tert*-butoxycarbonyl)(3-hydroxypropyl)amino)propyl)-3-hydroxy-5-methylphenyl)-3-oxobutanoate (328)



To a round-bottomed flask equipped with a stirrer bar was charged a solution of **327** (27.0 mg, 0.0411 mmol, 1.0 eq) in EtOAc (0.400 mL), and palladium on carbon (10 wt. % loading on carbon, 10.0 mg, 9.40 μmol, 0.23 eq). The reaction vessel was purged with a balloon of hydrogen gas, and was kept under an atmosphere of hydrogen (balloon pressure). The resulting mixture was stirred at rt arbitrarily for 16 h. The reaction mixture was filtered through a plug of Celite® (eluting with EtOAc, 5 mL), and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (7:3, v:v) afforded the title compound as a yellow oil (16.0 mg, 0.0353 mmol, 86%).

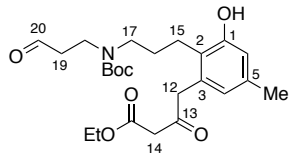
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.55 (s, 1H, *H*4), 6.51 (s, 1H, *H*6), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.77 (s, 2H, 2 × *H*12), 3.64 – 3.51 (m, 2H, 2 × *H*20), 3.43 (s, 2H, 2 × *H*14), 3.40 – 3.27 (m, 2H, 2 × *H*18), 3.25 – 3.14 (m, 2H, 2 × *H*17), 2.54 – 2.45 (m, 2H, 2 × *H*15), 2.22 (s, 3H, $ArCH_3$), 1.77 – 1.62 (m, 4H, 2 × *H*16, 2 × *H*19), 1.45 (s, 9H, $OC(CH_3)_3$), 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 201.3 (*C*13), 167.4 (*C*(O)OEt), 157.3 (N*C*(O)O*t*-Bu), 154.8 (*C*1), 137.1 (*C*5), 132.8 (*C*3), 124.6 (*C*2), 123.7 (*C*4), 115.7 (*C*6), 80.3 ($OC(CH_3)_3$), 61.6 (OCH_2CH_3), 58.6 (*C*20), 48.3 (*C*12), 48.1 (*C*14), 47.5 (*C*17), 43.0 (*C*18), 30.9 (*C*19), 29.8 (OCH_2CH_3), 28.5 ($OC(CH_3)_3$), 28.4 (*C*15), 23.7 (*C*16), 21.0 ($ArCH_3$).

HRMS (ESI) calcd for $C_{24}H_{37}NO_7Na^+$ $[M+Na]^+$ 474.2462, found 474.2460.

ν_{max} (film)/cm^{-1} 3325, 2933, 1735, 1717, 1661, 1587, 1476, 1421, 1306, 1249, 1165, 667.

Ethyl 4-(2-(3-((*tert*-butoxycarbonyl)(3-oxopropyl)amino)propyl)-3-hydroxy-5-methylphenyl)-3-oxobutanoate (322)



To a flame-dried, argon-flushed round-bottomed flask equipped with a stirrer bar was charged a cooled solution of freshly distilled oxalyl chloride (3.0 μL, 0.0354 mmol, 1.0 eq) in CH_2Cl_2 (60.0 μL). The reaction flask was cooled to −78 °C. To the cooled reaction vessel was added dropwise a solution of DMSO (5.00 μL, 0.0709 mmol, 2.0 eq) in CH_2Cl_2 (0.170 mL). The resulting solution was stirred for 5 min at −78 °C before the dropwise addition of a solution of **328** (16.0 mg, 0.0354 mmol, 1.0 eq) in CH_2Cl_2 (0.100 mL), and triethylamine (25.0 μL, 0.177 mmol, 5.0 eq) to the reaction vessel. The reaction mixture was stirred at −78 °C for a further 10 min before being warmed to rt slowly over 45 min, until complete consumption of the starting material, as indicated by TLC. The reaction was quenched by the addition of H_2O (1 mL) at rt and the resulting mixture was stirred for further 15 min. The mixture was diluted with CH_2Cl_2 (5 mL), and was washed with 1.0 M aqueous HCl solution (1 mL), saturated aqueous $NaHCO_3$ solution (1 mL), and brine (1 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification of the residue *via* flash column chromatography eluting with EtOAc/pet. ether (1:4, v:v) afforded the title compound as a yellow oil (11.0 mg, 0.0244 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.78 (s, 1H, *H*20), 6.56 (s, 1H, *H*6), 6.53 (s, 1H, *H*4), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.78 (s, 2H, 2 × *H*12), 3.58 – 3.49 (m, 2H, 2 × *H*19), 3.44 (s, 2H, 2 × *H*14), 3.30 – 3.09 (m, 2H, 2 × *H*17), 2.76 – 2.61 (m, 2H, 2 × *H*18), 2.57 – 2.41 (m, 2H, 2 × *H*15), 2.23 (s, 3H, $ArCH_3$), 1.82 – 1.54 (m, 2H, 2 × *H*16), 1.44 (s, 9H, $OC(CH_3)_3$), 1.37 – 1.27 (m, 3H, OCH_2CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 201.3 (*C*20), 201.2 (*C*13), 167.4 (*C*(O)OEt), 155.9 (N*C*(O)O), 154.6 (*C*1), 137.2 (*C*5), 132.9 (*C*3), 124.5 (*C*2), 124.1 (*C*4), 116.0 (*C*6), 80.3 ($OC(CH_3)_3$), 61.6 (OCH_2CH_3), 48.2 (overlapping signal, *C*12, *C*14), 47.8 (*C*17), 43.7 (*C*18), 41.5 (*C*19), 28.7 (*C*15), 28.5 ($OC(CH_3)_3$), 23.5 (*C*16), 21.0 ($ArCH_3$), 14.3 (OCH_2CH_3).

HRMS (ESI) calcd for $C_{24}H_{34}NO_7^-$ $[M-H]^-$ 448.2341, found 448.2337.

ν_{max} (film)/cm^{-1} 2923, 2850, 1716 (broad), 1662, 1586, 1457, 1305, 1260, 1033, 797.

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